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Sleep and circadian rhythms in cancer patients and relationship with quality of life

Edited by
Joy Perrier, Ali Amidi, Lisa Maria Wu, Bénédicte Giffard and Josée Savard

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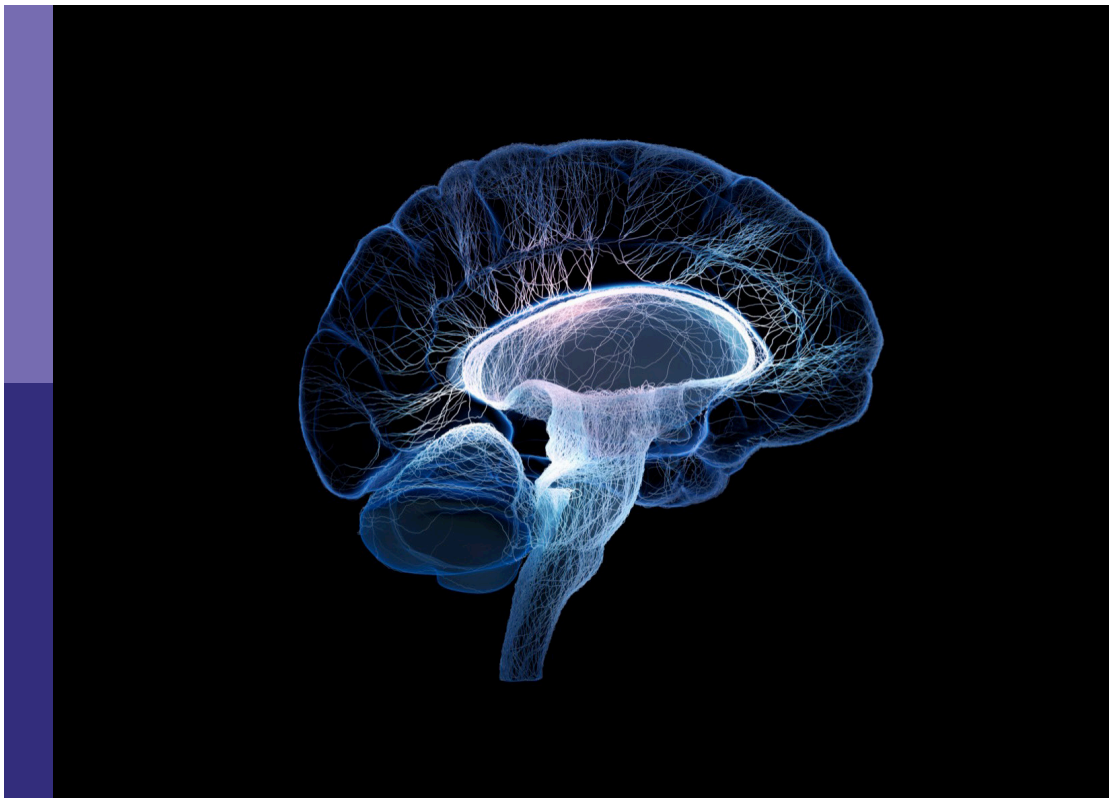

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Sleep and circadian rhythms in cancer patients and relationship with quality of life

Topic editors

Joy Perrier — INSERM U1077 Neuropsychologie et Imagerie de la Mémoire Humaine, France

Ali Amidi — Aarhus University, Denmark

Lisa Maria Wu — Aarhus University, Denmark

Bénédicte Giffard — INSERM U1077 Neuropsychologie et Imagerie de la Mémoire Humaine, France

Josée Savard — Laval University, Canada

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Table of contents

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Claude Gronfier,
Institut National de la Santé et de la Recherche Médicale (INSERM), France

*CORRESPONDENCE
Joy Perrier
joy.perrier@unicaen.fr

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Editorial: Sleep and circadian rhythms in cancer patients and their relationship with quality of life

Joy Perrier[1]*, Bénédicte Giffard[1,2], Lisa M. Wu[3,4,5], Josée Savard[6,7,8] and Ali Amidi[5]

[1]Normandie Université, UNICAEN, PSL Université, EPHE, INSERM, U1077, CHU de Caen, GIP Cyceron, Neuropsychologie et Imagerie de la Mémoire Humaine, Caen, France, [2]Cancer and Cognition Platform, Ligue Nationale Contre le Cancer, Caen, France, [3]Department of Medical Social Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL, United States, [4]Aarhus Institute of Advanced Studies, Aarhus University, Aarhus, Denmark, [5]Sleep & Circadian Psychology Research Group, Department of Psychology and Behavioural Sciences, Aarhus University, Aarhus, Denmark, [6]School of Psychology, Université Laval, Quebec City, QC, Canada, [7]CHU de Québec-Université Laval Research Center, Quebec City, QC, Canada, [8]Laval University Cancer Research Center, Quebec City, QC, Canada

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Editorial on the Research Topic
Sleep and circadian rhythms in cancer patients and their relationship with quality of life

We spend around one third of our lives sleeping and a good night of sleep is critical for many important functions such as learning and memory, brain restoration and plasticity, and immune functioning. Furthermore, inadequate sleep and insomnia are linked to numerous illnesses including metabolic and cardiovascular diseases. Cancer patients have frequent complaints of insomnia, with a high prevalence of 30–60% before, during and after treatment (Savard et al., 2011). There is also emerging evidence of circadian disruption associated with cancer and cancer treatments, which may underlie and exacerbate commonly reported symptoms of depressed mood, fatigue, cognitive complaints and sleep disturbances (ANSES, 2016; Labrèche et al., 2019; Martin et al., 2021; Milanti et al., 2021; Amidi and Wu, 2022). Despite the important impact of sleep on mental and physical health, until recently, sleep disturbances following cancer and its treatment were often neglected by both clinicians and researchers.

This Research Topic aims to elucidate sleep and circadian rhythm disturbances associated with cancer and cancer treatments, as well as their impact on quality of life and survivorship. The high quality of the manuscripts published in this Research Topic highlights the increased interest in the field of sleep/circadian rhythms and cancer and the broad scope of work in the area. Three reviews highlighted the importance of sleep and circadian rhythms in cancer patients as potential drivers of quality-of-life sequelae,

five papers investigated quality of life and sleep and circadian rhythm biomarkers in cancer patients and, two papers focused on innovative approaches to tackle sleep and circadian rhythm alterations in cancer patients.

Sleep disruption and cancer: Beyond quality of life

The first review perfectly exemplifies the current debate in the scientific literature about sleep and cancer with the so-called "chicken or the egg" question. Berisha et al. present an elegant review that discusses existing evidence about sleep disruption both as a consequence or as a potential risk factor of cancer. After describing sleep disruption-induced changes in systemic physiology and associated changes in the central nervous system, the authors explain the clinical implications of these findings, as well as the need to better manage sleep disruption in cancer patients, such as through the use of melatonin. Finally, unanswered questions and future directions are discussed in order to pave the way for future studies.

Two more reviews give additional insights into the same "chicken or the egg" question, but are not able to definitively conclude that a causal relationship exists between sleep disruption and quality of life/prognosis outcomes. The systematic review and meta-analysis by Strom et al. focuses on associations between sleep/sleep-wake activity and prognostic outcomes in cancer patients. Among the 26 studies included in their review, 19 report associations between poorer sleep, and a poorer response to treatment, shorter time to progression, and/or reduced overall survival. However, the authors also highlight several limitations of the studies reviewed, such as the high heterogeneity of sleep measures across studies that weaken comparability, and the small number of studies that used objective measures of sleep with the remainder relying primarily on single-item questionnaires. The authors conclude that disturbed sleep during treatment may be a relevant behavioral marker of poor cancer prognosis that warrants further investigation.

The systematic review by Helligsoe et al. describes the nature of sleep disorders in survivors of childhood central nervous system tumor and explores the association between tumor location and diagnosed sleep disorder. Only 11 studies are included in the review, pointing to the scarcity of studies that have objectively assessed sleep disorders using polysomnography with proper diagnosis in brain tumor patients. Analyses show that sleep disorders are common among children who have survived a central nervous system tumor with the most common being sleep-related breathing disorders (i.e., obstructive sleep apnea) and central disorders of hypersomnolence (i.e., narcolepsy).

Links between sleep/circadian rhythm dysregulation and quality of life in cancer

Four papers examine associations between sleep and sleep-wake rhythms and aspects of cognitive functioning and quality of life. Trivedi et al. investigate post-treatment sleep-wake rhythm outcomes using actigraphy in non-central nervous system cancer (including endometrial and breast cancer and melanoma). Results show that greater sleep regularity is associated with better quality of life and better physical functioning highlighting the need for interventions to help maintain sleep-wake rhythm regularity in cancer patients. Using a large cohort of patients, Garland et al. investigate longitudinal associations between insomnia symptoms and perceived cognitive impairments in cancer patients using validated questionnaires. Results show that the presence of both insomnia and perceived cognitive impairments is significantly greater within 2 months after surgery than later on during treatment. The authors also identify important factors that are related to a higher risk of reporting comorbid insomnia and cognitive impairment. Duivon et al.'s study investigates prospective memory, i.e., the memory for future intentions in breast cancer patients treated with surgery, radiotherapy followed or not by endocrine therapy. They detect subtle changes in cortical activity (EEG) related to memory consolidation during sleep but that are not related to memory performance itself. In the study by Olsthoorn et al., caregivers of 83 pediatric brain tumor survivors were surveyed about their children's sleep difficulties. Results show that at least one sleep-related item was scored as "somewhat true" for 68% of the children and a higher level of sleep disturbance is related to worse sluggish cognitive tempo (i.e., confusion, slowed behavior and low motivation). Finally, Oliva et al. focus on inflammatory biomarkers, as assessed with plasma samples, and their relationships with self-reported sleep quality in cancer patients both before and during oncological treatments. Results indicate that, across treatments, higher sleep complaints are associated with increased levels of a number of pro-inflammatory biomarkers 3 months after treatment initiation. Authors emphasize the need to evaluate biomarkers and self-reported sleep at multiple time-points across treatment instead of single point measurements.

Targeting sleep/circadian rhythm dysregulation in cancer patients

Two intervention trials are presented that aim to improve sleep and circadian rhythm disruption in cancer patients. These

studies highlight movement in the field toward prevention and regulation of disrupted sleep and circadian rhythms in cancer patients to improve quality of life and prognostic outcomes. One study is a Phase II randomized controlled trial by Rissling et al. in which they test whether morning exposure to bright white light would maintain or improve sleep and circadian activity rhythms in breast cancer patients undergoing chemotherapy when compared with a dim red light comparison condition. Results show that morning exposure to bright light is associated with longer night-time sleep, fewer sleep disturbances, fewer and shorter daytime naps, and less activity at night and more activity during the day by the end of cycle 4 of chemotherapy. These results show promise for the use of bright light therapy in cancer patients in order to reduce sleep and circadian rhythms disturbances, although larger scale trials are still necessary. Finally, Fox et al. present a study protocol focused on gynecologic cancer patients, a patient population that has been neglected in sleep studies as compared with breast cancer patients. The authors propose a two-part protocol guided by the Multiphase Optimization Strategy (MOST) framework. The first part will serve to identify barriers to and facilitators of intervention adherence. In the second part of the protocol, that will test the efficacy of the intervention, participants will be randomized to one of eight conditions (i.e., stimulus control, sleep restriction and bright light therapy either alone or in combination) and will complete assessments from baseline up to 3 months post-intervention. Measurements will include subjective and objective (i.e., actigraphy) sleep measures as well as questionnaires related to symptom burden, quality of life, fatigue and urine samples to analyze urinary 6-sulfatoxymelatonin, the primary urinary metabolite of melatonin. The ultimate goal of this study is to propose a framework to develop an efficient and effective, minimally burdensome behavioral sleep intervention.

Conclusion

Studies published in this Research Topic clearly underscore the significance of sleep and circadian rhythms disruptions in cancer patients and their possible impact on quality of life and perhaps even prognostic outcomes. Future research would benefit from deeper and integrative investigations of sleep and circadian rhythms over longer periods. Indeed, although actigraphy can provide information about rest-activity rhythms, it can be influenced by many parameters, including the quality of sleep and daytime sleepiness, and by environmental factors such as light exposure. It is thus, highly suggested to evaluate sleep and circadian processes in a multimodal manner that, in addition to questionnaires and actigraphy, includes the assessment of circadian physiology and other parameters (e.g., dim light melatonin onset, light exposure, and sleep hygiene behaviors). For instance, the use of polysomnography (when possible) would help better understanding changes to sleep architecture that occur in cancer patients. Moreover, using polysomnography would facilitate the study of memory consolidation during sleep, known to be altered during wake in cancer (Perrier et al., 2020; Duivon et al., 2021). Moreover, additional studies of sleep and circadian rhythms are needed in relation to cancer treatments beyond chemotherapy, such as endocrine- and immune therapies, with the former being proposed to most breast cancer patients for at least 5 years and that may also impact cognitive functioning (Wu and Amidi, 2017). Finally, there is an increasing number of interventional studies targeting sleep problems or aiming to improve circadian rhythms in cancer patients being published (Garland et al., 2014; Wu et al., 2018, 2022; Savard et al., 2022). Future investigations will hopefully determine the optimal approach to administer cancer treatments informed by circadian biology, such as tailoring the timing of treatments to individuals' chronotype (e.g., Innominato et al., 2022; Printezi et al., 2022).

Author contributions

JP wrote the first draft of the manuscript. BG, LW, JS, and AA provide revisions and comments. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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Irregular Sleep/Wake Patterns Are Associated With Reduced Quality of Life in Post-treatment Cancer Patients: A Study Across Three Cancer Cohorts

*Ritu Trivedi[1], Hong Man[1], Ayey Madut[1], Marius Mather[2], Elisabeth Elder[3,4], Haryana M. Dhillon[5,6], Alison Brand[3,7], Julie Howle[3,8,9], Graham Mann[3,9,10], Anna DeFazio[3,7,10,11], Terence Amis[1,3,11,12], Sean W. Cain[13], Andrew J. K. Phillips[13] and Kristina Kairaitis[1,3,11,12]**

[1] Ludwig Engel Centre for Respiratory Research, The Westmead Institute for Medical Research, Westmead, NSW, Australia, [2] Sydney Informatics Hub, The University of Sydney, Camperdown, NSW, Australia, [3] Westmead Clinical School, Faculty of Medicine and Health, The University of Sydney, Sydney, NSW, Australia, [4] Westmead Breast Cancer Institute, Westmead Hospital, Westmead, NSW, Australia, [5] Centre for Medical Psychology and Evidence-Based Decision-Making, School of Psychology, Faculty of Science, The University of Sydney, Camperdown, NSW, Australia, [6] Psycho-Oncology Cooperative Research Group, School of Psychology, Faculty of Science, The University of Sydney, Camperdown, NSW, Australia, [7] Department of Gynecological Oncology, Westmead Hospital, Westmead, NSW, Australia, [8] Crown Princess Mary Cancer Centre, Westmead and Blacktown Hospitals, Sydney, NSW, Australia, [9] Melanoma Institute Australia, The University of Sydney, Sydney, NSW, Australia, [10] Centre for Cancer Research, The Westmead Institute for Medical Research, Westmead, NSW, Australia, [11] Sydney West Translational Cancer Research Centre, Westmead, NSW, Australia, [12] Department of Respiratory and Sleep Medicine, Westmead Hospital, Westmead, NSW, Australia, [13] Turner Institute for Brain and Mental Health, School of Psychological Sciences, Monash University, Clayton, VIC, Australia

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Josée Savard,
Laval University, Canada

Reviewed by:
Jessica R. Lunsford-Avery,
Duke University, United States
Stefano Bastianini,
University of Bologna, Italy

***Correspondence:**
Kristina Kairaitis
kristina.kairaitis@sydney.edu.au

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Background: Cancer patients often describe poor sleep quality and sleep disruption as contributors to poor quality of life (QoL). In a cross-sectional study of post-treatment breast, endometrial, and melanoma cancer patients, we used actigraphy to quantify sleep regularity using the sleep regularity index (SRI), and examined relationships with reported sleep symptoms and QoL.

Methods: Participants were recruited post-primary treatment (35 diagnosed with breast cancer, 24 endometrial cancer, and 29 melanoma) and wore an actigraphy device for up to 2 weeks and SRI was calculated. Self-report questionnaires for cancer-related QoL [European Organization for Research and Treatment of Cancer EORTC (QLQ-C30)] were completed. Data were compared using analysis of variance (ANOVA) or Chi-Square tests. Multivariate linear regression analysis was used to determine independent variable predictors for questionnaire-derived data.

Results: Age distribution was similar between cohorts. Endometrial and breast cancer cohorts were predominantly female, as expected, and body mass index (BMI) was higher in the endometrial cancer cohort, followed by breast and melanoma. There were no differences between tumor groups in: total sleep time, sleep onset latency, bedtime, and SRI (breast 80.9 ± 8.0, endometrial 80.3 ± 12.2, and melanoma 81.4 ± 7.0) (all $p > 0.05$). A higher SRI was associated with both better functional and symptom scores,

including increased global QoL, better physical functioning, less sleepiness and fatigue, better sleep quality, and associated with less nausea/vomiting, dyspnea, and diarrhea (all $p < 0.05$).

Conclusion: In cancer patients post-treatment, greater sleep regularity is associated with increased global QoL, as well as better physical functioning and fewer cancer related symptoms. Improving sleep regularity may improve QoL for cancer patients.

Keywords: sleep quality, sleep regularity, quality of life, cancer, cancer symptoms, endometrial cancer, breast cancer, melanoma

INTRODUCTION

Sleep disturbance is a common symptom associated with cancer and its treatment, with up to 95% of people with cancer (Fortner et al., 2002; Langford et al., 2012) reporting disturbed sleep. Sleep disturbance has a negative impact on quality of life (QoL) in this population (Sun and Lin, 2016). For some people with cancer, the negative impact of poor sleep persists post-treatment (Ancoli-Israel et al., 2014) and has been associated with poorer cancer outcomes and QoL. In women with a history of breast cancer, perceived poor sleep quality post-treatment is a predictor for a poorer survival outcome (Palesh et al., 2014). Long sleep duration and frequent sleep difficulties are associated with increased breast cancer mortality in women with a history of breast cancer (Palesh et al., 2014; Trudel-Fitzgerald et al., 2017). Understanding and addressing sleep problems in people with cancer may result in improvements in long-term well-being and survival.

Sleep is often assessed using subjective metrics derived from questionnaires designed to probe an individual's perception of their at-home sleep experience over time. Actigraphy is a well-established, non-invasive, objective methodology for evaluating sleep across a variety of settings including cancer populations (Smith et al., 2018). Actigraphic metrics are highly correlated with gold-standard sleep assessment *via* polysomnography (PSG; Madsen, 2015). Actigraphy studies of cancer populations have usually quantified sleep in terms of sleep duration and sleep efficiency (Fernandes et al., 2006; Ancoli-Israel et al., 2014; Lévi et al., 2014; Palesh et al., 2014; Palesh, 2017). However, these metrics do not adequately capture other dimensions of sleep disturbance, including day-to-day variability in sleep patterns (Bei et al., 2016).

The sleep regularity index (SRI; Phillips et al., 2017) is a recently developed sleep metric that quantifies the consistency of an individual's daily sleep/wake pattern by computing the percentage probability of an individual being in the same state (sleep vs. wake) at any two time-points 24 h apart, averaged across the study period. The metric effectively measures the degree of overlap in sleep/wake patterns between consecutive days, with values theoretically ranging from 0 (random) to 100 (completely regular). In practice, SRI values typically range from approximately 30 to 95, with a smaller number indicating less regular sleep (Phillips et al., 2017). Recent studies have reported that, compared with the standard actigraphy metrics of sleep duration and sleep efficiency, SRI has a stronger association with increased cardiometabolic risk (Lunsford-Avery et al., 2018), poorer mood (Pye et al., 2021), and poorer academic performance (Phillips et al., 2017).

Sleep/wake patterns in people with cancer are characterized by fragmented sleep, difficulty falling and staying asleep, waking up earlier than intended, unrestorative sleep (Roth, 2007), daytime napping, and low activity during the day (Davidson, 2002; Arndt, 2006; Kotronoulas, 2012; Lowery-Allison, 2018). These sleep patterns are likely to result in day-to-day variability in sleep/wake patterns, and contribute to a lower SRI score. Mood disorders (Mitchell et al., 2011), and cardiovascular death are common among cancer survivors due to shared risk factors (Sturgeon et al., 2019). Despite the recognition of increased mood disorders, cardiovascular risk, subjective poor sleep, and sleep fragmentation in cancer populations, SRI has not been quantified in any cancer population. In addition, the association with QoL in any population has not been examined. The aim of this study was to quantify the SRI, across three post-treatment cancer cohorts (breast, endometrial, and melanoma) using actigraphy and examine associations with subjective measurements of QoL and sleep. We hypothesized that irregular sleep/wake patterns in patients with a history of cancer, quantified using the SRI would be associated with a reduced QoL, and to subjective sleep.

MATERIALS AND METHODS

The study was approved by the Western Sydney Local Health District Ethics Committee (AU RED HREC/15/WMEAD/369). Written, informed consent was obtained from all participants.

Participants

Participants were recruited from either breast (n = 35), endometrial (n = 24), or melanoma (n = 28) outpatient cancer clinics at Westmead Hospital between 2017 and 2019. Potential participants were approached in person by the investigators, and invited to participate in a study on sleep in cancer. Participants were included if they: (1) were at least 18 years of age; (2) had a confirmed diagnosis of breast cancer, endometrial cancer, or melanoma; and (3) had completed treatment (e.g., chemotherapy, radiotherapy, or surgery) either 2 months (endometrial cancer), 3 months (melanoma) or 12 months (breast cancer) previously. Timing of recruitment was chosen to mitigate against the acute impacts of a recent diagnosis or treatment regime. Participants were excluded if they: (1) had any serious or active medical or psychiatric comorbidities that would likely interfere with

their assessment, or compliance with the protocol; (2) were unable/unlikely to comply with the study requirements for any reason; or (3) were pregnant. Twenty one of the breast cancer patients and 17 of the endometrial cancer patients had participated in a previous study (Madut et al., 2021).

Data Collection and Study Procedures

We collected demographic data, menopausal status, cancer history, including histopathology and treatment, and current medications from participants medical records. We did not collect information on sleeping environment.

Questionnaires

Subjective sleep symptoms and sleep quality were assessed at recruitment using the following validated questionnaires: (1) Pittsburgh Sleep Quality Index (Carpenter, 1998; Backhaus, 2002; Beaudreau, 2012) (PSQI), (2) Epworth Sleepiness Scale (Johns, 1992) (ESS), and (3) Insomnia Severity Index (Savard et al., 2005) (ISI). QoL was assessed using the validated European Organization for Research and Treatment of Cancer Quality of Life Core (Fayers, 2002) (EORTC QLQ-C30) questionnaire. The EORTC QLQ-30 produces subscales of Global QoL, Functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning) and Symptom scales (fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties).

Actigraphy

Participants wore an *Actiwatch-2* (Philips Respironics, Bend, OR, United States) on their non-dominant wrist for up to 14 consecutive days, except when showering. Data were downloaded into proprietary software (Actiware, Phillips Respironics, Bend, OR, United States) for analysis. Automatically analyzed data for 30-s epochs were reviewed, quality checked, and manually adjusted. Rest periods were identified as the absence of light with continued activity, and sleep time identified as reduction in both light and activity. Time periods where the actiwatch was not worn by the participant with a complete absence of activity were excluded from analysis. Total sleep time, sleep onset latency, sleep effectiveness, wake after sleep onset (WASO), number of awakenings, get up, and bedtime were determined using the proprietary software algorithms.

Sleep Regularity Index Calculation

The SRI was calculated using the established method (Phillips et al., 2017). The SRI was calculated as SRI = 200×Agreement/Cases−100, where Agreement is the number of valid (non-missing) epochs 24 h apart in the same sleep/wake state across the actigraphy recording, while Cases is the number of valid (non-missing) epochs 24 h apart. Patients were not included for SRI calculation if there were fewer than 5 days (120 h) of valid overlapping epochs of actigraphy (n = 6 patients). Five valid overlapping days is the minimum required data to obtain an accurate estimate of sleep regularity (Fischer et al., 2021).

Statistical Analyses

Statistical analyses were conducted using R version 3.6.2. $P < 0.05$ was considered significant. Univariate comparisons were performed using ANOVA for continuous variables and Chi-Squared Tests for categorical variables. Multivariate analysis was performed using linear regression models to determine independent variable predictors for questionnaire-derived data (dependent variables). Each of the subscales of the EORTC QLQ-C30 were included. Regression models were run using complete cases only. Actigraphy measures were entered into these models as potential predictors with $\log_{10}$ transformation for skewed variables (reported below). The regression models controlled for the covariates of age, BMI, neck circumference, gender, and cancer type. Bed time was coded with midnight as zero, with times between midday and midnight coded as negative values (number of h away from midnight), and those between midnight and midday as positive. All numeric predictors were mean centered and scaled. To avoid issues with collinearity, time in bed, and get up time were not included as predictors in these models, as they were linearly dependent on other variables already included (sleep onset time and wake time, respectively). Given the inherent correlation between some of the actigraphy measures, Variance Inflation Factors were also checked to diagnose collinearity (Johnston et al., 2018). The breast cancer cohort was used as the reference group for all linear regression models.

RESULTS

Participant Demographics

Participant demographics are shown in **Table 1**. Average age was not significantly different between cancer cohorts (p = 0.489). As expected, endometrial and breast cancer cohorts were almost exclusively female. The majority of women were post-menopausal, apart from one endometrial cancer and four melanoma patients. Nineteen breast cancer patients were taking anti- oestrogen therapy (tamoxifen or an aromatase inhibitor). Of the melanoma cohort, 69% were male. Endometrial cancer patients had a higher BMI relative to the other groups (p = 0.001).

Cancer Grade/Stage and Treatment Modalities and Sleep Assessment

Cancer grade/stage data and classification of treatment modalities are provided in **Supplementary Table 1**. Most of the breast cancer patients had Grade 2/3 malignancies treated with a combination of surgery, radiation, chemotherapy, and endocrine treatments. The majority of endometrial (Grade 1/Stage 1a) and melanoma participants (Stage Ia + Ib) had less advanced malignancies and were treated with surgery alone (hysterectomy and bilateral salpingo-oophorectomy and excision, respectively). For the breast cancer patients, actigraphy was performed an average of 2 years after initial diagnosis, endometrial cancer patients were assessed around 7 months after diagnosis and melanoma was assessed around 14 months after initial diagnosis (**Supplementary Table 1**).

TABLE 1 | Patient demographics.

Group		Breast cancer	Endometrial cancer	Melanoma	Total	*p*
n		35	24	29	88	
Gender *n* (%)	F	34 (97.1)	24 (100.0)	9 (31.0)	67 (76.1)	<0.001
	M	1 (2.9)	0 (0.0)	20 (69.0)	21 (23.9)	
Mean (STD)						
Age (years)		62.1 (9.5)	62.5 (9.1)	59.5 (11.8)	61.3 (10.2)	0.49
BMI (kg/m^2)		28.4 (5.7)	34.3 (7.4)	30.8 (4.7)	30.8 (6.3)	0.001

Standard Actigraphy Metrics

Data for standard actigraphy metrics for each of the three cohorts are shown in **Table 2**. Breast cancer participants had, on average, 6 and 14 min greater WASO than the endometrial and melanoma groups, respectively ($p = 0.018$). There were no other significant cancer cohort differences for other standard actigraphy metrics (all $p > 0.22$; **Table 2**).

Sleep Regularity Index

Sleep regularity index could not be measured in six subjects (three breast cancer patients, one endometrial cancer patient, and two melanoma patients), as actigraphy data collection time was less than 5 overlapping days. For the 82 subjects in whom we measured SRI, actigraphy data for an average of 11.2 ± 2.0 days (range 5.9–13.2 days) was analyzed, and only one subject did not have a weekend day included. For those excluded from analysis, average actigraphy data collection was 3.46 ± 0.97 days (range 1.9–4.6 days). The SRI values ranged from 34.3 to 95.6, with left-skewed distributions, particularly in the endometrial and breast cancer cohorts (**Figure 1**). Group mean values for SRI were not significantly different ($p = 0.09$) between cancer cohorts (breast cancer: 80.9 ± 8.0; endometrial cancer: 80.3 ± 12.2; and melanoma cancer: 81.4 ± 7.0).

Questionnaire Data

Data by cancer cohort for each questionnaire, including QoL, functional, and symptoms scores from the QLQ-C30 questionnaire, are shown in **Figure 2** and **Supplementary Table 2**. There were no significant differences between the cancer cohorts for the majority of questionnaire results. However, the breast cancer cohort had a significantly higher PSQI score ($p = 0.007$) than endometrial or melanoma cancer cohorts (**Figure 2B**). The ISI score tended to be highest in the breast cancer cohort, although the difference was not significant (**Figure 2C** and **Supplementary Table 2**; $p = 0.066$). Similarly, sleep disturbance symptoms assessed *via* the QLQ-C30 sleep item were significantly higher for the breast cancer cohort (**Supplementary Table 2**; $p = 0.012$) compared with the endometrial or melanoma cohorts. No other questionnaire data were significantly different between cancer cohorts (all $p > 0.20$).

Multivariate Linear Regression Models

Variables included were bedtime, sleep onset latency (log-transformed), WASO, number of awakenings (log-transformed), SRI, age, BMI, gender (male), endometrial cancer, and melanoma. Full statistical models are presented in **Supplementary Tables 3–20**, while results for significant predictor variables only are shown in **Table 3** (all $p < 0.05$).

QLQ-C30 Quality of Life, Function, and Symptom Scales

Quality of life score

Sleep regularity index and male sex were associated with a higher QoL score, while being a member of the melanoma cohort was associated with a lower QoL score (see **Table 3**). No other independent variable was associated with QoL score (all $p > 0.1$; **Supplementary Table 3**). **Figure 3** shows estimated regression coefficients for linear regression models for predictors of the QLQ-C30 QoL score.

Physical functioning score

Sleep regularity index and being a member of the endometrial cancer cohort were significantly positively associated with a higher Physical Functioning Score, while greater age was associated with a lower Physical Functioning Score (see **Table 3**). No other independent variable was associated with Physical Functioning Score (all $p > 0.08$; **Supplementary Table 4**).

Emotional functioning score

Male sex was associated with higher levels of Emotional Functioning (see **Table 3**). However, no other independent variable tested was associated with Emotional Functioning (all $p > 0.07$; **Supplementary Table 6**).

Symptom scores

Lower symptom scores for fatigue, nausea/vomiting, dyspnea, and diarrhea were associated with higher SRI values; while lower nausea/vomiting, diarrhea, and financial difficulty scores associated with increased sleep onset latency (log-transformed). Constipation was associated with a later bed time, while appetite loss, and diarrhea were associated with shorter total sleep time. Lower sleep and diarrhea symptoms scores were predicted in males, while lower scores for financial difficulties were in endometrial cancer (all $p < 0.05$, **Table 3**).

Role, cognitive, and social functioning scores

No independent variable tested was associated with the role, cognitive, and social functioning scores (all $p > 0.07$; **Supplementary Tables 5**, **7**,**8**).

Pittsburgh Sleep Quality Index

Lower PSQI scores (better sleep quality) were predicted by a higher SRI score, a longer sleep onset latency, and in endometrial

TABLE 2 | Standard actigraphy metrics.

Variable	Breast cancer	Endometrial cancer	Melanoma	*p*
n	35	24	29	
Mean (SD)				
Sleep time (h)	7.5(1.0)	7.3(0.8)	7.3(1.1)	0.701
Onset latency (min)	29.7(21.8)	28.8(18.2)	34.1(25.2)	0.634
Sleep efficiency (%)	82.4(5.3)	82.6(4.5)	82.6(7.4)	0.980
Wake after sleep onset (min)	54.5(20.9)	48.1(15.3)	41.6(15.7)	0.018
Number of awakenings (*n*)	39.5(11.5)	35.4(10.4)	35.1(11.3)	0.218
Getup time (h)	07 : 16(00 : 13)	07 : 03(00 : 18)	07 : 07(00 : 16)	0.727
Bed time (h)	22 : 12(00 : 19)	22 : 19(00 : 31)	22 : 05(00 : 37)	0.918

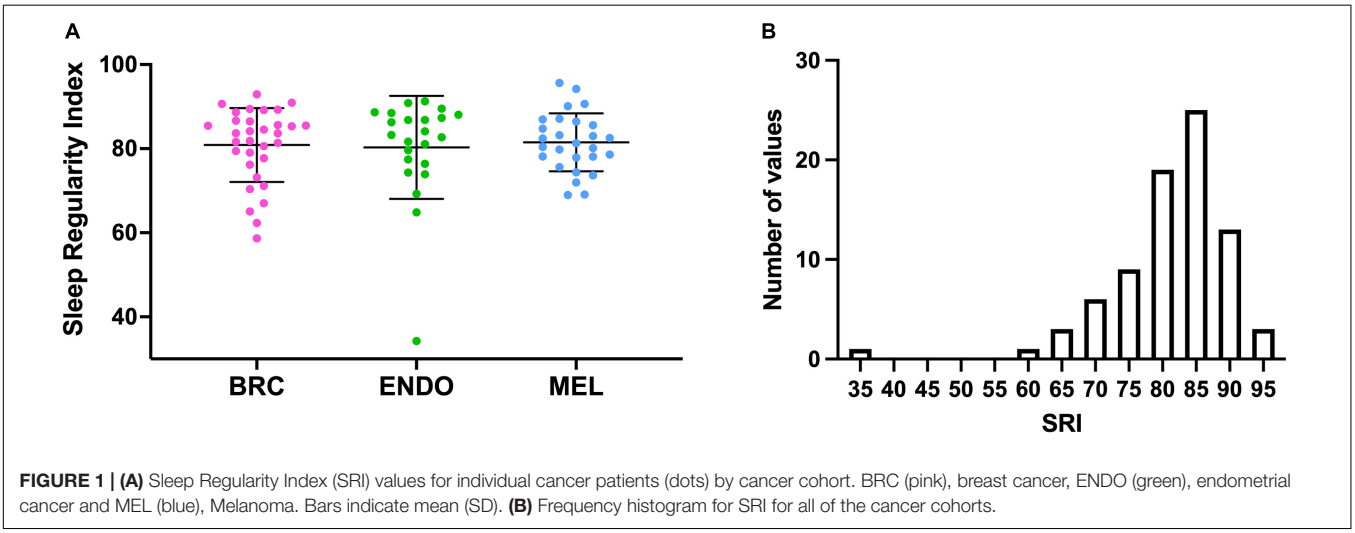

FIGURE 1 | (A) Sleep Regularity Index (SRI) values for individual cancer patients (dots) by cancer cohort. BRC (pink), breast cancer, ENDO (green), endometrial cancer and MEL (blue), Melanoma. Bars indicate mean (SD). **(B)** Frequency histogram for SRI for all of the cancer cohorts.

cancer cohorts. No other independent variable emerged as a significant predictor for the PSQI Score (all $p > 0.09$; **Supplementary Table 18**).

Insomnia Severity Index

Lower ISI scores (less insomnia symptoms) were predicted by a higher SRI value, male sex, and endometrial cancer (see **Table 3**). No other independent variable tested was a significant predictor for the ISI Score (all $p > 0.1$; **Supplementary Table 19**).

Epworth Sleepiness Scale

Lower ESS scores were predicted by later bedtimes and higher SRI values (see **Table 3**). No other independent variable tested emerged as a significant predictor for the ESS Score (all $p > 0.2$; **Supplementary Table 19**).

DISCUSSION

We found that greater sleep regularity is associated with higher QoL in melanoma, breast, and endometrial cancer patients. Sleep regularity was superior in predicting QoL relative to other actigraphic metrics of sleep, including sleep duration, sleep efficiency, and sleep timing. Greater sleep regularity was also a predictor of higher sleep quality, fewer insomnia symptoms, and less sleepiness. When the subscales of the cancer QoL questionnaires were examined, sleep regularity was also associated with better physical functioning, less fatigue, less dyspnoea and less nausea, and vomiting. These findings have important implications for assessing and improving sleep in cancer patients and may have implications for improving longer-term cancer survival.

In this group of cancer patients, the SRI was associated with many of the subjective cancer symptoms measured. Other predictors were also important, including: (1) male sex, which was associated with better QoL, emotional functioning, fewer diarrhea symptoms, and less insomnia severity; (2) shorter sleep onset latency, which was a predictor of less nausea and diarrhea symptoms, and fewer financial difficulties; (3) longer total sleep time, which was a predictor of more diarrhea symptoms and greater appetite loss; and (4) later sleep onset time, which was associated with less sleepiness. The relationship between less physical symptoms such as gastrointestinal symptoms, breathlessness, and better sleep regularity is a novel finding. These associations may be explained by the presence of circadian rhythms in all biological processes. Gastro-intestinal functions have clear circadian variation (Voigt et al., 2019), and similarly, breathlessness has demonstrated circadian rhythmicity (Tsai et al., 2007). The negative associations between nausea and vomiting, diarrhea and sleep onset latency

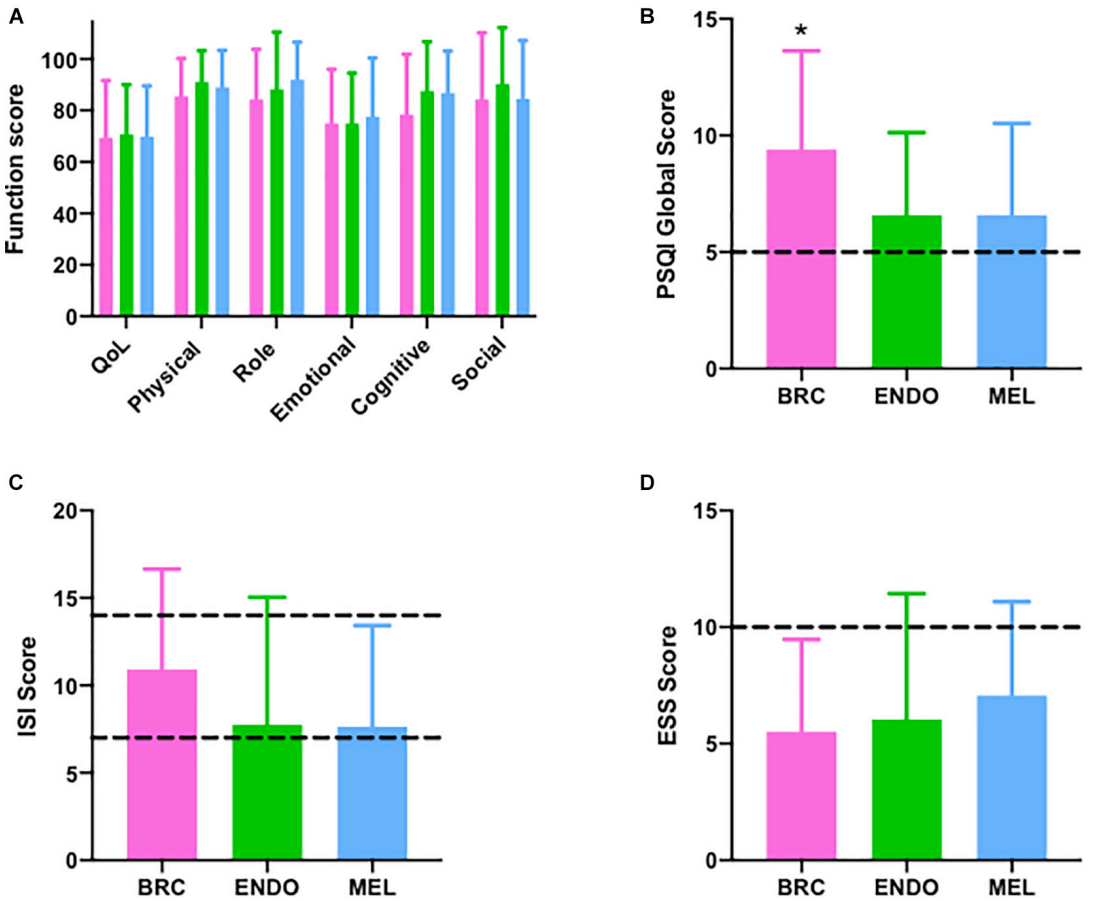

FIGURE 2 | Questionnaire outcomes in breast (pink; $n = 35$), endometrial (green; $n = 24$), and melanoma (blue; $n = 29$) cancer patients. **(A)** European Organization for Research and Treatment of Cancer EORTC QLQ-C30) questionnaire with quality of life (QoL) and individual function scores (physical, role, emotional, cognitive, and social), **(B)** Pittsburgh Sleep Quality Index (PSQI) >5 indicates poor sleep quality **(C)** Insomnia Severity Index (ISI) (Dashed lines ISI > 8 sub-threshold insomnia, >14 clinical insomnia), **(D)** Epworth Sleepiness Scale (Dashed lines: ESS > 10 indicated daytimes sleepiness). BRC, breast cancer; ENDO, endometrial cancer; and MEL, melanoma cancer, $^*p < 0.009$.

may similarly be circadian rhythms, or alternatively sleep may be delayed due to gastrointestinal symptoms. Circadian rhythms and relationships to sleep regularity are discussed in more detail below. Relationship between sleep onset latency to financial difficulties would seem to be most likely a consequence of anxiety (Vahtera et al., 2007). No previous studies have examined the associations between regular sleep and cancer symptoms.

In addition to cancer symptoms and QoL, sleep regularity was also a better predictor of other sleep symptoms in these cancer patients than any other actigraphic metric of sleep. A higher SRI was associated with better sleep quality (as measured by the PSQI), less insomnia (as measured by the ISI), and less sleepiness (as measured by the ESS). Most participants slept for around 7 h with average sleep efficiency of 82%, similar to previous reports in breast (Berger and Higginbotham, 2000; Ancoli-Israel et al., 2006; Palesh et al., 2014) and endometrial cancer patients (Armbruster, 2018). However, the objective actigraphic measurement most closely predicting sleep symptoms was the SRI.

Sleep regularity has emerged recently as a powerful predictor of a range of health outcomes. Sleep regularity has not been measured in the general population, however, in an older group of healthy patients is reported to be around 86.4 (Pye et al., 2021). Our cancer cohorts have similar values for SRI to older patients with current depression (Pye et al., 2021). Recent studies have found lower SRI to be associated with depression (Pye et al., 2021), insomnia, post traumatic stress disorder (PTSD) (Mascaro et al., 2021), poorer mood (Sano et al., 2015), cardiometabolic dysfunction (Lunsford-Avery et al., 2018; Fritz et al., 2020), and poorer functional outcomes in autism (Cohen et al., 2017) and delayed sleep-wake phase disorder (Murray et al., 2019). The SRI has also been found to improve with treatment for alcohol dependence (Brooks et al., 2020). Our findings show that SRI is also a strong predictor for measures of QoL in cancer populations, including both functional and symptom scores. The broad utility of the SRI is likely due to its composite nature. Rather than being based on variability in any one dimension of sleep (e.g., variability in sleep onset time or total sleep time), the

TABLE 3 | Coefficients from linear regression models predicting questionnaire variables [European Organization for Research and Treatment of Cancer Quality of Life Core (EORTC QLQ-C30) quality of life (QoL) scores, functional scores, and symptoms scales; Pittsburgh Sleep Quality Index (PSQI); Insomnia Severity Index (ISI); and Epworth Sleepiness Scale (ESS)].

Variable	*b*	95% CI	*p*
Quality of life (*n* = 79)			
Sleep regularity index	10.28	4.86 to 15.69	<0.001
Gender: male	31.73	10.49 to 52.97	0.0040
Melanoma	−14.63	−28.86 to −0.39	0.044
Physical functioning (*n* = 80)			
Sleep regularity index	6.55	2.88 to 10.22	<0.001
Age (years)	−4.57	−7.78 to −1.36	0.0059
Endometrial cancer	12.30	4.81 to 19.78	0.0017
Emotional functioning (*n* = 79)			
Gender: male	31.26	7.14 to 55.39	0.012
Fatigue (*n* = 80)			
Sleep regularity index	−7.50	−12.76 to −2.24	0.0059
Nausea/vomiting (*n* = 80)			
Onset latency (log-transformed)	−3.63	−7.21 to −0.04	0.048
Sleep regularity index	−3.88	−7.64 to −0.11	0.044
Dyspnoea (*n* = 80)			
Sleep regularity index	−5.53	−10.92 to −0.13	0.045
Insomnia (*n* = 80)			
Gender: male	−37.01	−70.28 to −3.75	0.030
Appetite loss (*n* = 80)			
Sleep time (h)	4.55	0.16 to 8.94	0.042
Constipation (*n* = 80)			
Bed time	5.89	0.87 to 10.91	0.022
Diarrhea (*n* = 79)			
Sleep time (h)	2.97	0.25 to 5.69	0.033
Onset latency (log-transformed)	−6.18	−9.47 to −2.88	<0.001
Sleep regularity index	−3.58	−6.96 to −0.21	0.037
Gender: male	−17.47	−30.7 to −4.25	0.010
Financial difficulties (*n* = 79)			
Onset latency (log-transformed)	−8.93	−15 to −2.86	0.0045
Endometrial cancer	−16.50	−29.21 to −3.8	0.012
PSQI (*n* = 80)			
Onset latency (log-transformed)	−1.14	−2.19 to −0.08	0.035
Sleep regularity index	−1.51	−2.62 to −0.4	0.0082
Endometrial cancer	−3.11	−5.37 to −0.85	0.0076
ISI (*n* = 80)			
Sleep regularity index	−2.77	−4.45 to −1.09	0.0016
Gender: male	−6.90	−13.49 to −0.31	0.041
Endometrial cancer	−4.17	−7.59 to −0.74	0.018
ESS (*n* = 80)			
Bedtime	−1.15	−2.08 to −0.22	0.016
Sleep regularity index	−2.86	−3.96 to −1.76	<0.001

*Only significant predictors are shown; for complete results, refer to **Supplementary Tables 3–20**. Numeric predictors were centered and scaled. Coefficients reflect the increase in scores for a one standard deviation increase in the predictor for continuous variables, or difference from the reference level for categorical variables, holding other variables constant.*

SRI compares the overall degree of overlap in sleep/wake patterns between consecutive days. Consequently, it is sensitive to many aspects of sleep disruption, including variation in sleep onset time, wake time, sleep duration, WASO, and napping. Given sleep disruption manifests in various forms across different health conditions, the SRI may have general clinical utility as a predictor of multiple outcomes.

The day-to-day variability of sleep/wake patterns is a consequence of factors including behavioral influences, social settings, circadian rhythms, and light sensitivity. Circadian

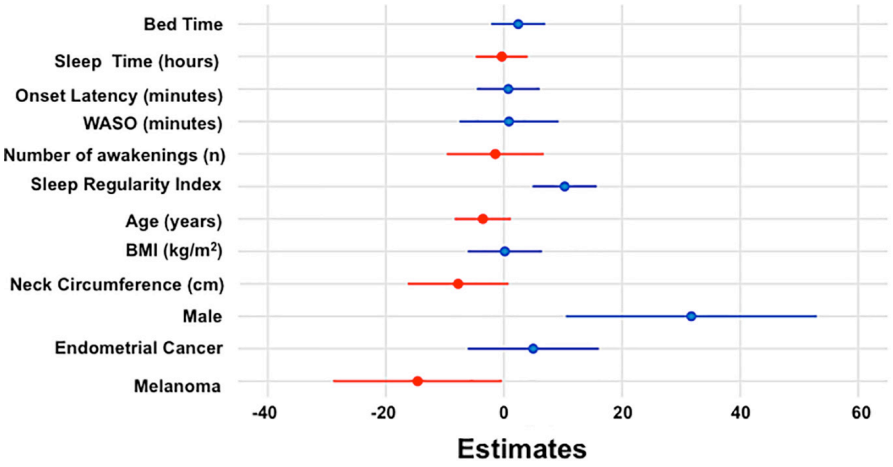

FIGURE 3 | Estimated regression coefficients (dots) with 95% confidence intervals (bars) from linear regression model for QoL are shown with positive and negative coefficients represented in blue and red, respectively.

rhythms are daily cycles that occur in virtually all biological processes, centrally co-ordinated and controlled by the brain's master clock, the suprachiasmatic nucleus (SCN). Less regular sleep is associated with later onset of melatonin production (Phillips et al., 2017) and less stable timing of melatonin onset (Watson et al., 2020). Recent studies have shown significant variability in the population in light-related suppression of SCN outputs (Phillips et al., 2019), and home lighting exposures are in the range of light likely to suppress SCN outputs (Phillips et al., 2019; Cain et al., 2020). Our study has not examined which mechanisms are contributing in these cancer cohorts. This knowledge may lead to approaches to improve sleep regularity, which may in turn improve QoL, physical functioning, and cancer-related symptoms. Measurement of sleep regularity in cancer patients is relatively simple, uses standard clinical tools that are relatively available such as actigraphy. Addressing and improving sleep regularity may even result in better cancer outcomes in the longer term; at least in breast cancer patients sleep disruption and extreme sleep duration are associated with increased long-term mortality (Trudel-Fitzgerald et al., 2017). Whether improvements in sleep regularity will improve short or long term cancer outcomes is as yet unknown.

This is a relatively small study of a restricted number of cancer cohorts. The study is cross- sectional, and demonstrates associations rather than causation. An alternative interpretation may be that physical symptoms such as pain, breathlessness, and gastrointestinal disturbance can result in irregular sleep. In addition, the majority of participants were women, a group with more sleep-related symptoms, and all the male participants had melanoma. However, results for each of the symptom questionnaires, as well as actigraphy, were similar to those reported in larger, more diverse cancer populations. Actigraphy was analyzed without the assistance of a sleep diary. It has been demonstrated that there are small systematic differences in measured sleep duration and sleep onset latency when automatic analysis of actigraphy is compared with a sleep diary, resulting in slightly longer sleep duration with automatic analysis (van Hees et al., 2018). This may have impacted on the sleep regularity measurement, although as it is a systematic error this effect is unlikely to be large. Another important factor is that many of the patients may have had other sleep disorders, such as obstructive sleep apnea (OSA), that may have influenced sleep regularity and may be an important mediator of the effects of low SRI on outcomes in this population. In particular, we have recently demonstrated that nearly two-thirds of women with breast or endometrial cancer have moderate to severe OSA (Madut et al., 2021), which would be expected to associate with lower SRI due to frequent awakenings. Many of the patients in this study were also involved in this earlier study, and 41% all participants had a history of snoring. In addition, we did not collect information on sleeping environments such as bed partners, or employment status which may result in structured or unstructured days, and in turn have influenced sleep regularity. Despite these limitations, this small pilot study is suggestive of an important role for sleep regularity in QoL, physical functioning, and cancer-related symptoms in patients with a history of cancer.

In summary, in this novel investigation of sleep regularity in cancer cohorts, we found that sleep regularity is an important predictor for QoL. There is growing appreciation for considering other dimensions of sleep, including sleep regularity, in measuring sleep and circadian disruption, and predicting the downstream effects on health. Parallel to findings in other populations, sleep regularity was a stronger predictor of many key outcomes than other sleep-related metrics. These findings suggest we need to enrich traditional quota-based assessments of total sleep time and sleep efficiency with measures of sleep regularity for a fuller picture of health. Moreover, attention to measuring sleep regularity using widely available actigraphic methods including consumer devices, and management strategies aimed at improving sleep regularity (e.g., potentially *via* controlled lighting exposures) may provide a pathway to better sleep and QoL outcomes for cancer patients in the clinical setting.

DATA AVAILABILITY STATEMENT

The data analyzed for this study are available at: https://hdl.handle.net/2123/26161.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Western Sydney Local Health District Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

RT: data curation, formal analysis, and writing original draft. HM and AM: data curation and investigation. MM: formal analysis. EE, AB, JH, and AD: conceptualization, funding acquisition, resources, and writing review and editing. HD: conceptualization, funding acquisition, and writing review and editing. GM: conceptualization, funding acquisition, and resources. TA and KK: conceptualization, formal analysis, funding acquisition, investigation, methodology, project administration, supervision, and writing review and editing. AP and SC: conceptualization, formal analysis, methodology, and writing review and editing. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2021.700923/full#supplementary-material

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Prospective Rates, Longitudinal Associations, and Factors Associated With Comorbid Insomnia Symptoms and Perceived Cognitive Impairment

Sheila N. Garland[1,2], *Hans Ivers*[3,4,5] *and Josée Savard*[3,4,5]*

[1] Department of Psychology, Faculty of Science, Memorial University, St. John's, NL, Canada, [2] Discipline of Oncology, Faculty of Medicine, Memorial University, St. John's, NL, Canada, [3] School of Psychology, Université Laval, Quebec City, QC, Canada, [4] CHU de Québec-Université Laval Research Center, Quebec City, QC, Canada, [5] Laval University Cancer Research Center, Quebec City, QC, Canada

Background: Insomnia and cognitive impairment are both common conditions experienced by people diagnosed with cancer. Individually, these conditions have negative impacts on functioning, but the combined burden has yet to be evaluated. The purpose of this research was to estimate rates of comorbid insomnia and perceived cognitive impairments, examine the longitudinal associations between these two conditions, and identify demographic and clinical factors associated with reporting both insomnia and perceived cognitive impairment.

Methods: In this secondary analysis, a heterogeneous sample of 962 patients completed the Insomnia Severity Index (ISI) and the Cognitive Failures Questionnaire (CFQ) at the time of their cancer surgery (baseline; T1) and then again at 2 (T2), 6 (T3), 10 (T4), 14 (T5), and 18 (T6) months. Correlations and partial correlations, controlling for age and education level, were computed at each time point to assess the relationship between ISI and CFQ scores. Cross-lagged correlations assessed associations between ISI and CFQ scores over time. Proportions of patients with comorbid insomnia and cognitive impairments were calculated and logistic regressions investigated changes over time in these proportions. ANOVAs, logistic regressions, ordinal regressions, and multinomial regressions were used to identify risk factors of having comorbid insomnia and cognitive difficulties.

Results: Significant and bidirectional correlations between ISI and CFQ scores were observed at each time point and over time. The proportion of patients having both clinical levels of insomnia and perceived cognitive difficulties ranged from 18.73 to 25.84% across time points and this proportion was significantly greater at T1 and T2 than T4, T5, and T6. Participants who reported comorbid insomnia and cognitive impairment were more likely to be younger, female, not currently working, currently receiving chemotherapy, with clinical levels depression and anxiety, and using antidepressants or anxiolytics.

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Seockhoon Chung,
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Shawn D. Youngstedt,
Arizona State University, United States

***Correspondence:**
Josée Savard
josee.savard@psy.ulaval.ca

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Conclusion: Comorbid insomnia and perceived cognitive impairment affects around one in five patients and is more frequent at the beginning of the cancer care trajectory. The relationship between insomnia and cognitive impairment appears to be bidirectional. Insomnia may represent an important patient level vulnerability that when identified and treated can improve perception of cognitive function.

Keywords: cancer, cognition, impairment, insomnia, sleep

INTRODUCTION

Insomnia is a prevalent and persistent condition in people diagnosed with cancer throughout their treatment trajectory (Palesh et al., 2010; Leysen et al., 2019). Insomnia is defined as dissatisfaction with sleep quality or quantity characterized by difficulty initiating or maintaining sleep that causes significant distress and impairment in functioning (American Psychiatric Association, 2013). When symptoms occur at least 3 times per week and have been present for at least 3 months, the diagnostic criteria for insomnia disorder are met. Estimates suggest that roughly 40–60% of patients will present with insomnia symptoms and that around 20% will meet the criteria for a disorder at the time of diagnosis (Savard et al., 2011; Fleming et al., 2018; Harrold et al., 2020). Even after treatment completion, the prevalence of insomnia symptoms or disorder remains up to three times greater than in the general population, with a prevalence of insomnia symptoms of 47% at 12 months (Fleming et al., 2018) and 36% at 18 months (Savard et al., 2011) compared to roughly 6–10% (Ohayon, 2002; Buysse, 2013). Patients who experience insomnia at the time of their cancer diagnosis are significantly more likely to report persistent insomnia, compared to those who identify as good sleepers (Savard et al., 2011), which emphasizes the importance of early identification and intervention. Factors associated with cancer-related insomnia include younger age (Harrold et al., 2020), having a diagnosis of a breast or gynecological cancer (Savard et al., 2011; Harrold et al., 2020), receiving chemotherapy (Fleming et al., 2018), and experiencing comorbid anxiety or depression (Hoang et al., 2019; Maguire et al., 2019). Insomnia in cancer survivors has been associated with greater overall symptoms burden including higher levels of pain, fatigue, anxiety, and depression (Nishiura et al., 2015). Insomnia has also been linked to an increased risk of infections (Ruel et al., 2015), worse long-term quality of life (Lowery-Allison et al., 2018), and poorer treatment response and greater overall mortality (Innominato et al., 2015), although the latter needs to be demonstrated in more studies. As such, insomnia is an important treatment target to optimize short and long-term cancer recovery.

Cognitive impairment is also a common, but less well-understood, complaint of people diagnosed and treated for cancer. Compared to non-cancer controls, neuropsychological testing demonstrates a range of objective deficits in memory, concentration, information processing and executive functioning in some but not all cancer survivors (Ahles and Root, 2018; Janelsins et al., 2018). A systematic review of 101 cross-sectional, longitudinal, and randomized controlled studies reported more cancer-related cognitive alterations for subjective measures than performance tasks (Bray et al., 2018). In a prospective observational study, 45% of women with breast cancer 6 months post-chemotherapy (n = 581) reported a clinically meaningful decline in perceived cognition, compared to 12% of non-cancer controls (n = 334) (Janelsins et al., 2017). As with insomnia, younger age and higher levels of anxiety and depression are also associated with greater cognitive complaints. Cognitive impairment has a significant negative impact on quality of life, including return to work, social relationships, and self-confidence (Lange et al., 2019), which makes the identification of potentially modifiable risk factors a research and clinical imperative.

In the general population, insufficient quality and quantity of sleep has been found to be associated with numerous cognitive deficits including impaired psychomotor and cognitive speed, attention, learning, memory, and executive function (Goel et al., 2009). More specifically, insomnia is associated with worse working memory, attention, and perceived cognitive impairment (Brownlow et al., 2020). The cognitive effects of insomnia in cancer patients has not been well studied. An early cross-sectional study of women with breast cancer found that those with an insomnia disorder had worse verbal episodic memory and executive functioning assessed objectively (Caplette-Gingras et al., 2013). In a more recent cross sectional online survey of 1,393 breast cancer survivors, 47% showed current cognitive complaints and those who reported sleep difficulties were twice as likely to report cognitive impairments (Boscher et al., 2020). When assessed prospectively in a different sample of 98 women with breast cancer from the time of diagnosis to 12 months, rates of perceived cognitive impairments were stable at roughly 36% (Rodriguez et al., 2021). While fatigue and insomnia were associated with greater perceived cognitive impairment, insomnia did not significantly predict future cognitive impairment (Rodriguez et al., 2021). In men with prostate cancer, insomnia symptoms significantly mediated the relationship between receiving androgen deprivation therapy and perceived cognitive function and satisfaction with cognition (Garland et al., 2021b). In sum, although existing research suggests an association between cancer-related insomnia and both objective and perceived cognitive impairment, it is not yet clear the extent to which insomnia precedes or follows cognitive impairments, how commonly these symptoms co-exist and what factors may influence this co-morbidity. Further, studies have investigated only a few specific groups of cancer patients, often breast cancer, which limits the generalizability of results.

The objectives of this secondary analysis were to estimate rates of comorbid insomnia and perceived cognitive impairments and examine the longitudinal associations between these two

conditions in the 18 months following a cancer surgery. Further, we sought to identify factors that are associated with reporting both insomnia and perceived cognitive impairment, compared to those individuals who only report one of the symptoms or none.

MATERIALS AND METHODS

Participants

This is a secondary analysis of a larger study on the epidemiology of cancer-related insomnia (for details, see Savard et al., 2009, 2011). Patients were eligible if they were scheduled to undergo a surgery with a curative intent for a first non-metastatic cancer, were between 18 and 80 years old and were able to read and understand French. They were excluded if they had received a neoadjuvant treatment for cancer, the surgery was part of brachytherapy for prostate cancer, had severe cognitive impairments (e.g., Alzheimer's disease) or a severe psychiatric disorder (e.g., psychosis, bipolar disorder), had received a diagnosis for a sleep disorder other than insomnia (including sleep apnea), and had severe visual, hearing or language defects. A total of 3,196 patients were solicited, 1,677 were eligible (52.5% of solicited patients), and 962 agreed to participate (57.4% of eligible patients).

Procedure

Patients were approached by a research assistant to participate to the study on the day of their pre-operative visit at L'Hôtel-Dieu de Québec and the Hôpital du St-Sacrement of the CHU de Québec-Université Laval. The study was approved by the ethics review boards of both hospitals. After the study goals and procedures were explained, agreeing patients were invited to provide written consent to participate. They also received a battery of self-report scales to be completed within the next 2 weeks (baseline; T1) and received by mail the same questionnaires to fill out 2 (T2), 6 (T3), 10 (T4), 14 (T5), and 18 (T6) months later. Of note, 81.2% of the participants completed baseline measures after the surgery (20 days after on average).

Measures

Data on cancer and treatment-related information was abstracted from patients' medical charts. Participants self-reported other demographic variables.

Insomnia Severity Index (ISI): The ISI contains 7 items designed to specifically assess the severity of insomnia symptoms, their impact on daytime functioning, and the amount of associated distress in the past week (Savard et al., 2005). The ISI is summed to compute a total score with a range of 0–28. Higher values indicate more severe insomnia severity and a score of ≥ 8 indicates the presence of clinical levels of insomnia.

Cognitive Failures Questionnaire (CFQ): The CFQ is a 25-item measure of self-reported failures in perception, memory, and motor function in the past 6 months at T1 and since the last questionnaire completion from T2 to T6 (Broadbent et al., 1982). Responses are rated on a 5 point scale from 0 (never) to 5 (very often), yielding a total score of 0–100. The higher the score, the more cognitive impairment. The psychometric qualities of this questionnaire are satisfactory (Broadbent et al., 1982) and this measure is frequently used to assess self-reported cognition in cancer patients (Bray et al., 2018). While there is no universally agreed upon cutoff score to distinguish clinically significant levels of perceived cognitive impairment using this instrument in cancer patients, past research in cardiac patients have used scores ≥ 26 (Moulaert et al., 2017), > 32 (Boyce-van der Wal et al., 2015), and > 44 (Steinbusch et al., 2017). We decided to use a cutoff > 32, which appeared to be a good compromise between having a too liberal or a too conservative criterion.

Statistical Analyses

Correlations and partial correlations, controlling for age and education level, were computed at each time point to assess the relationship between insomnia (ISI) and cognitive functioning (CFQ) scores. Cross-lagged correlations of ISI scores with subjective cognitive functioning (CFQ) were also computed between one variable at one time point and the other variable at the previous time point, and this, by including in the calculation all five possible combinations of a time point and the previous time point (i.e., T1-T2, T2-T3, T3-T4, T4-T5, and T5-T6). Descriptive analyses (frequencies, percentages) were conducted to estimate, at each time point, the proportion of patients who had both clinical levels of insomnia (ISI ≥ 8) and perceived cognitive impairments (CFQ > 32), who had only one condition and who had none. Logistic regressions with repeated measures, including a random effect for patients, were computed to investigate changes over time in these proportions. Finally, to identify risk factors of having comorbid insomnia and cognitive difficulties, ANOVAs (for continuous variables), logistic regressions (for dichotomous variables), ordinal regressions (for ordinal variables) and multinomial regressions (for categorical variables with more than two categories) were conducted to compare patients having both conditions to the remaining on: age, sex, education, marital status, occupation, income, cancer type, cancer stage, current and past chemotherapy, current and past radiation therapy, current hormone therapy, medical comorbidity, menopausal status (for females), presence of clinical levels of depression and anxiety, and the use of antidepressants and anxiolytics. With the exception of education and income, for which baseline data were used, all models included data at all time points and a random patient effect to take into account the dependence between data collected from the same patient throughout the study.

RESULTS

Participants' Characteristics

The mean age was 57.0 years old (SD = 9.9; range: 23–79) and 64.4% of the sample was composed of females. Time since cancer diagnosis was 2.2 months on average (range: 0.1–7.1). The cancer types were breast (48.3%), prostate (27.3%), gynecological (11.5%), urinary and gastro-intestinal (7.2%), and other (5.7%). Most commonly, patients had Stage 1 (35.2%) or Stage 2 (37.2%) disease. More information is available elsewhere (Savard et al., 2009, 2011).

Associations Between Insomnia and Perceived Cognitive Impairments

Correlations obtained between ISI and CFQ scores and partial correlations controlling for age and education are presented in **Table 1**. Correlations were all significant (all *p*s < 0.0001) and varied between 0.25 and 0.35 across time, while partial correlations were also all significant (all *p*s < 0.0001) and ranged from 0.23 to 0.37. In both cases, the lowest correlation coefficients were found at baseline (T1).

Significant cross-lagged partial correlations, controlling for age and education, were obtained between ISI and CFQ scores, where ISI scores at one time point was significantly associated with CFQ scores at the previous time point (previous CFQ → current ISI: $r = 0.30$, $p < 0.001$) and CFQ scores at one assessment was significantly correlated with ISI scores at the previous time point (previous ISI → current CFQ; $r = 0.31$, $p < 0.001$).

Mean Scores and Rates of Insomnia and Perceived Cognitive Impairments Across Time

Participants obtained mean ISI scores of 8.89 (*SD* = 6.1) at T1, 8.83 (*SD* = 5.6) at T2, 7.65 (*SD* = 5.7) at T3, 6.99 (*SD* = 5.4) at T4, 6.85 (*SD* = 5.4) at T5, and 6.47 (*SD* = 5.1) at T6. The mean CFQ scores were 29.23 (*SD* = 12.6), 29.04 (*SD* = 13.6), 29.30 (*SD* = 13.2), 29.19 (*SD* = 13.4), 28.90 (*SD* = 13.3), and 28.69 (*SD* = 13.0), respectively. Rates of clinical levels of cognitive impairments varied from 37.18 to 39.88% with little change over time, while rates of clinical insomnia ranged from 35.63 to 55.88% with the highest proportions found at T1 (see **Table 2**).

Comorbidity of Insomnia and Perceived Cognitive Impairments

The proportion of patients having both clinical levels of insomnia and perceived cognitive difficulties ranged from 18.73 to 25.84% across time points (see **Table 2**). Most participants had scores under the clinical cutoff for both insomnia and cognitive impairments (from 31.51 to 45.92%). Having clinical levels of cognitive impairments with no clinical levels of insomnia was the least frequent situation (from 12.12 to 18.57%). The proportion of patients having comorbid insomnia and cognitive impairments significantly changed over time, $F(5, 1{,}972) = 5.20$, $p < 0.0001$. Pairwise comparisons indicated that this proportion was significantly greater at T1 and T2 than T4, T5, and T6.

TABLE 1 | Correlations and partial correlations, controlling for age and education, between ISI and CFQ scores.

Time	Correlation	Partial correlation
T1 (0 month)	0.25****	0.23****
T2 (2 months)	0.35****	0.35****
T3 (6 months)	0.32****	0.32****
T4 (10 months)	0.35****	0.35****
T5 (14 months)	0.34****	0.37****
T6 (18 months)	0.33****	0.33****

ISI, Insomnia Severity Index; CFQ, Cognitive Failures Questionnaires.
*****p < 0.0001.*

TABLE 2 | Rates (n;%) of clinical levels of insomnia and perceived cognitive impairments and comorbidity rates.

	With clinical cognitive impairments	Without clinical cognitive impairments	Total with clinical insomnia
T1 (*n* = 952)			
With clinical insomnia	246 (25.84%)	286 (30.04%)	**532 (55.88%)**
Without clinical insomnia	120 (12.61%)	300 (31.51%)	
Total with clinical cognitive impairments	**366 (38.45%)**		
T2 (*n* = 850)			
With clinical insomnia	219 (25.76%)	247 (29.06%)	**466 (54.82%)**
Without clinical insomnia	103 (12.12%)	281 (33.06%)	
Total with clinical cognitive impairments	**322 (37.88%)**		
T3 (*n* = 810)			
With clinical insomnia	185 (22.84%)	173 (21.36%)	**358 (44.20%)**
Without clinical insomnia	138 (17.04%)	314 (38.77%)	
Total with clinical cognitive impairments	**323 (39.88%)**		
T4 (*n* = 769)			
With clinical insomnia	158 (20.55%)	140 (18.21%)	**298 (38.75%)**
Without clinical insomnia	138 (17.95%)	333 (43.30%)	
Total with clinical cognitive impairments	**296 (38.49%)**		
T5 (*n* = 727)			
With clinical insomnia	148 (20.36%)	128 (17.61%)	**276 (37.96%)**
Without clinical insomnia	135 (18.57%)	316 (43.47%)	
Total with clinical cognitive impairments	**283 (38.93%)**		
T6 (*n* = 710)			
With clinical insomnia	133 (18.73%)	120 (16.90%)	**253 (35.63%)**
Without clinical insomnia	131 (18.45%)	326 (45.92%)	
Total with clinical cognitive impairments	**264 (37.18%)**		

The bold refers to the total number of participants with clinical levels of insomnia or cognitive impairment.

A significant time effect was also found on rates of clinical insomnia only, $F(5, 797.8) = 17.77$, $p < 0.0001$. Pairwise comparisons revealed that rates obtained as T1 and T2 were significantly greater than those observed from T3 to T6. The proportion of patients with clinical cognitive impairments only significantly changed over time, $F(5, 2{,}665) = 13.90$, $p < 0.0001$, with significantly lower rates at T1 and T2 than from T3-T6. Finally, a significant time effect was shown on rates of patients with absence of clinical levels on any of the symptoms, $F(5, 914.8) = 16.83$, $p < 0.0001$. Pairwise comparisons indicated that these proportions were significantly lower from T1 to T3 than from T4 and T6 and that they were significantly lower at T1 and T2 than T3 and T5.

Risk Factors for Comorbid Insomnia and Perceived Cognitive Impairments

Among all possible risk factors investigated, differences between patients with and without comorbid insomnia-perceived cognitive impairments were significant on age, sex, occupation, current chemotherapy, the presence of clinical levels of depression and anxiety, and the use of antidepressants and

anxiolytics. More specifically, patients with comorbidity were significantly younger, $F(1, 3{,}701) = 21.81$, $p < 0.0001$ (57.46 vs. 57.63), more likely to be females, $F(1, 4{,}816) = 7.20$, $p < 0.01$ (83.32% vs. 73.28%), to be currently receiving chemotherapy $F(1, 1{,}747) = 6.22$, $p < 0.05$ (4.98% vs. 3.63%), and to use antidepressants, $F(1, 4{,}635) = 6.90$, $p < 0.01$ (8.35% vs. 5.47%) and anxiolytics, $F(1, 4{,}635) = 36.30$, $p < 0.0001$ (29.77% vs. 16.02%). They were also less likely to work, $F(1, 4{,}801) = 7.03$, $p < 0.01$ (24.22% vs. 30.58%) and to report a clinical level of depression, $F(1, 4{,}804) = 7.70$, $p < 0.01$ (95.64% vs. 97.35%), and anxiety, $F(1, 4{,}806) = 26.00$, $p < 0.0001$ (96.94% vs. 99.12%).

DISCUSSION

To our knowledge, this is the first study to prospectively assess the comorbidity of insomnia symptoms and perceived cognitive impairment in a large, heterogeneous sample of cancer patients. Over an 18-month period post-surgery, the prevalence of both perceived clinically significant insomnia and cognitive impairment was highest at baseline at 25.84% and lowest at 18 months at 18.73%. We observed strong associations between subjectively assessed insomnia and cognitive functioning, independent of patient age and education. Further, the association between insomnia and cognitive impairments was bidirectional, wherein the presence of one at a single timepoint was significantly associated with the other at the following timepoint. Having comorbid insomnia and cognitive impairment was associated with a few demographic and clinical variables.

In non-cancer samples, there is a large body of experimental evidence to support the insomnia (or sleep deprivation) → perceived cognitive impairment relationship. Sufficient quality and quantity of sleep is essential for optimal attention, concentration, memory, and executive functions (Walker, 2009; Raven et al., 2018). There are several biological mechanisms that have been proposed in an effort to establish the pathways by which sleep disturbances may contribute to cognitive impairment. These include, but are not limited to, changes in neurotransmitter systems involved in sleep (Bekinschtein et al., 2008; Havekes et al., 2012), neural disruptions and reduction in the volume of the hippocampus (Riemann et al., 2007; Meerlo et al., 2009), changes in the functioning of the hypothalamic-pituitary-adrenal (HPA) axis (van Dalfsen and Markus, 2018), and changes in functionality of different brain regions involved in working memory (Mu et al., 2005; Chee et al., 2006). This suggests that an intervention designed to target insomnia may have a secondary benefit of improving perceived cognitive function, but this remains to be tested in cancer survivors (Garland et al., 2021a). Less is known about why perceived or objectively assessed cognitive impairment might be associated with future insomnia, but it is possible that the distress caused by the perception of cognitive impairment (Myers, 2013) might increase insomnia at a subsequent timepoint. Alternatively, there may be some third variable or common etiology (e.g., HPA axis dysregulation) that may explain both (Balbo et al., 2010), but this requires further investigation.

The prevalence of both perceived clinically significant insomnia and cognitive impairment was highest at baseline and declined thereafter, albeit modestly. This is likely due to the acute impact of the distress caused by receiving a cancer diagnosis (Kaiser et al., 2019) or the impacts of a recent surgery (and hospitalization) on sleep (Ida et al., 2019) and cognitions (Wu et al., 2019). The prevalence of clinical levels of perceived cognitive impairment ranged from 37.18 to 39.88% across the 18 months, whereas the prevalence for clinically relevant insomnia symptoms ranged from 35.63 to 55.88%. Our findings further support previous cross-sectional and longitudinal studies demonstrating that roughly 30 percent of breast cancer patients experience perceived cognitive impairment prior to even starting treatment (Wefel et al., 2004; Hermelink et al., 2007). Our results also suggest that perceived cognitive impairment can persist past treatment and remission, in line with past research that up to 35 percent of patients report cognitive impairments from 6 months to 20 years following treatment (Yamada et al., 2010; Koppelmans et al., 2012). We observed that clinical levels of insomnia were more frequent than clinical levels of cognitive impairments, and rates obtained are consistent with past estimates placing the prevalence of cancer-related insomnia to be between 30 and 60%, depending on the type and timing of measurement (Savard and Morin, 2001; Davidson et al., 2002; Savard et al., 2011). The prevalence and relative stability of these two symptoms have important implications for overall health and functioning. Both insomnia and cognitive failures (as measured by the CFQ) have been associated with workplace (Daley et al., 2009; Day et al., 2012) and traffic (Allahyari et al., 2008; Leger et al., 2014) accidents. Research has also demonstrated a direct relationship of insomnia on impaired workplace functioning, including greater absenteeism and presenteeism (Brossoit et al., 2019). Those patients who experience both insomnia and perceived cognitive impairment may be at greater risk for these and other negative impacts on their health and functioning.

A few demographic and clinical variables were significantly associated with the presence of comorbid insomnia and cognitive impairment. Patients with this comorbidity were younger, more likely to be female, and currently undergoing chemotherapy. Previous research has reported associations between younger age and female sex and higher levels of insomnia and perceived cognitive impairment (Oertelt-Prigione et al., 2021). There is also robust evidence to support the association between chemotherapy and both insomnia and perceived cognitive impairment, that persists past treatment completion (Hermelink et al., 2007; Lindner et al., 2014; Janelsins et al., 2017; Yao et al., 2017; Kim et al., 2020). Those who experienced comorbid insomnia and cognitive impairment were also significantly less likely to work than those without clinical levels of insomnia and/or cognitive complaints. This supports the greater combined occupational impacts of having these two conditions. Interestingly, patients with both conditions were less likely to have clinical levels of depression and anxiety, but this can be explained by their greater likelihood of using a psychotropic medication to manage these disorders. None of the other clinical characteristics, including cancer type, or demographic variables were associated with comorbidity.

There are a number of limitations that need to be considered. First, this was a secondary analysis of a larger study designed to assess insomnia over time and not cognitive function. This limited the ability to assess more specific indices of cognitive function. The inclusion of objective measures of cognition would not have been practically feasible with a sample this large. The absence of neuropsychological tests does not allow us to draw conclusions about specific domains of cognitive function associated with insomnia. Further, the measure we used, the CFQ, has a high test-retest reliability which makes it hard to determine whether the relative stability of problems we observed were a result of persistent problems or the measures insensitivity to detect change. Other studies in cancer samples have also not found significant change over time using this measure (Bray et al., 2018). In addition, empirically validated cutoffs for the CFQ have not been established in people diagnosed with cancer. Although patients with an existing diagnosis of a sleep disorder other than insomnia, e.g., sleep apnea, were excluded from this study, those with an undiagnosed sleep disorder may have been undetected. Sleep disorders other than insomnia have also been associated with cognitive complaints. As such, we cannot fully rule out the potential influence of other sleep-related factors in the results observed. Finally, the intervals between time points were fairly long (2 and 4 months) making it more difficult to conclude with certainty about the direction of the relationship between insomnia and cognitive impairment. Additional prospective and clinical studies using both objective and subjective measures of cognitive functioning and shorter time intervals are needed.

Comorbid insomnia and perceived cognitive impairment affects around one in five patients and is more frequent at the beginning of the cancer care trajectory. Reporting these symptoms simultaneously has the potential to exacerbate the overall symptom burden and impact on individual functioning. All patients should be regularly screened for insomnia, cognitive concerns, along with other survivorship issues, followed by a more careful assessment and/or a referral for neuropsychological testing if warranted (Van Dyk and Ganz, 2021). Insomnia may represent an important patient level vulnerability that when identified, can be effectively treated with cognitive-behavioral therapy for insomnia (Johnson et al., 2016), which can improve not only insomnia but also co-occurring fatigue (Heckler et al., 2016), mood disturbance (Peoples et al., 2019), and possibly cognitive impairment.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Research Ethics Committees of the Centre Hospitalier Universitaire de Québec, the Centre Hospitalier Affilié Universitaire de Québec, and the Université Laval. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SG: conceptualization, methodology, and writing and editing the original draft. HI: data curation, formal analysis, and editing. JS: funding acquisition, conceptualization, methodology, writing, and editing. All authors contributed to the article and approved the submitted version.

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frontiers in Neuroscience

SYSTEMATIC REVIEW
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Systematic Review: Sleep Disorders Based on Objective Data in Children and Adolescents Treated for a Brain Tumor

Anne Sophie Lind Helligsoe[1,2], Kathrine Synne Weile[1,2], Line Kenborg[3], Louise Tram Henriksen[1,2], Yasmin Lassen-Ramshad[4], Ali Amidi[5], Lisa Maria Wu[5,6], Jeanette Falck Winther[1,2,3], Line Pickering[7] and René Mathiasen[8]*

[1] Department of Pediatrics and Adolescent Medicine, Aarhus University Hospital, Aarhus, Denmark, [2] Department of Clinical Medicine, Faculty of Health, Aarhus University, Aarhus, Denmark, [3] Childhood Cancer Research Group, Danish Cancer Society Research Center, Copenhagen, Denmark, [4] Danish Centre for Particle Therapy, Aarhus University Hospital, Aarhus, Denmark, [5] Unit for Psychooncology and Health Psychology, Department of Psychology and Behavioural Sciences, Aarhus University, Aarhus, Denmark, [6] Department of AIAS, Aarhus Institute of Advanced Studies, Aarhus University, Aarhus, Denmark, [7] Department of Clinical Neurophysiology, Danish Center for Sleep Medicine, Rigshospitalet, University of Copenhagen, Glostrup, Denmark, [8] Department of Paediatrics and Adolescent Medicine, The University Hospital Rigshospitalet, Copenhagen, Denmark

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Maria Paola Mogavero, Scientific Clinical Institute Maugeri (ICS Maugeri), Italy
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***Correspondence:**
Anne Sophie Lind Helligsoe
aslf@dadlnet.dk
orcid.org/0000-0003-4956-4897

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Background: Tumors of the central nervous system (CNS) are the most common solid childhood malignancy. Over the last decades, treatment developments have strongly contributed to the improved overall 5-year survival rate, which is now approaching 75%. However, children now face significant long-term morbidity with late-effects including sleep disorders that may have detrimental impact on everyday functioning and quality of life. The aims of this study were to (1) describe the symptoms that lead to polysomnographic evaluation; (2) describe the nature of sleep disorders diagnosed in survivors of childhood CNS tumor using polysomnography (PSG); and (3) explore the association between tumor location and diagnosed sleep disorder.

Methods: An extensive literature search following the Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines (PRISMA) was conducted. Inclusion criteria were children and adolescents diagnosed with a CNS tumor age <20 years having a PSG performed after end of tumor treatment. The primary outcome was sleep disorder confirmed by PSG.

Results: Of the 1,658 studies identified, 11 met the inclusion criteria. All the included articles were appraised for quality and included in the analysis. Analyses indicated that sleep disorders commonly occur among childhood CNS tumor survivors. Symptoms prior to referral for PSG were excessive daytime sleepiness (EDS), fatigue, irregular breathing during sleep and snoring. The most common sleep disorders diagnosed were sleep-related breathing disorders (i.e., obstructive sleep apnea) and central disorders of hypersomnolence (i.e., narcolepsy).

Conclusion: Our findings point to the potential benefit of systematically registering sleep disorder symptoms among CNS tumor patients together with tumor type and treatment information, so that at-risk patients can be identified early. Moreover, future rigorous and larger scale controlled observational studies that include possible modifiable confounders of sleep disorders such as fatigue and obesity are warranted.

Clinical Trial Registration: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021243866, identifier [CRD42021243866].

Keywords: childhood, CNS tumor, sleep, polysomnography, sleep disorder

BACKGROUND

Tumors of the central nervous system (CNS) are the most common solid childhood malignancy (Grabas et al., 2020). Over the last decades, treatment developments have contributed to a markedly improved overall 5-year survival rate approaching 75% (Lannering et al., 2009; Gatta et al., 2014; Desandes et al., 2020). However, children now face significant long-term morbidity, including sleep disorders, with detrimental impact on everyday functioning and quality of life (Pickering et al., 2017; Jeon et al., 2021) that may be due to the tumor type, tumor location, or treatment (typically a combination of surgery, chemotherapy, and/or radiotherapy).

Sleep disorders are associated with decreased health-related quality of life in the general pediatric and adolescent population (Hart et al., 2005; Owens, 2014). Sleep disorders, sleep disturbances, and excessive daytime sleepiness (EDS) have been reported in children with cancer and associated with an increased risk of hospitalizations (Mulrooney et al., 2008; Kenborg et al., 2019). Furthermore, sleep disturbances can adversely affect social functioning (Walsh et al., 2020) and impair scholastic achievement (Lahteenmaki et al., 2007). In general, CNS tumor survivors have an increased risk of socioeconomic adverse effects compared with other childhood cancer survivors (Frederiksen et al., 2019).

During the cancer trajectory, sleep disturbances may occur during cancer treatments and the year after (Hinds et al., 2007; Daniel et al., 2017) but it is unclear whether childhood CNS tumor survivors are likely to experience sleep disorders later in life. Such diagnostic information would not only be important for cancer survivors to be aware of, but also to inform treatment options.

Research in childhood cancer survivors has primarily focused on sleep disorders captured by self-report data (Mulrooney et al., 2008). Yet, an increasing number of studies are encouraging the evaluation of sleep disorders using polysomnography (PSG) in childhood CNS tumor survivors in order to better understand the nature of their dysfunction (Kaleyias et al., 2012). Therefore, the present study aimed to systematically review the literature to: (1) describe the symptoms that lead to polysomnographic evaluation in survivors of childhood CNS tumor; (2) describe the nature of sleep disorders diagnosed in this group using PSG; and (3) explore the association between tumor location and diagnosed sleep disorder.

MATERIALS AND METHODS

The Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines (PRISMA) were followed (Page et al., 2021). A systematic review protocol was designed, and the research group agreed on the search strategy and *a priori* defined inclusion and exclusion criteria. The study protocol was registered with Prospero (registration number CRD 42021243866).

Search Strategy

We conducted a comprehensive literature search with no restrictions with respect to language or year of publication including (1) electronic searches of PubMed/MEDLINE, Embase/Ovid, Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) and (2) searches of reference lists of identified studies, related reviews, and clinical trial registries (ClinicalTrials.gov registry). Our search strategy consisted of three individual blocks combining sleep, CNS tumor, and children. The search strategy for the MEDLINE search is available in **Supplementary Table 1**. The search was repeated before submission on November 1st, 2021.

Study Selection, Inclusion, and Exclusion Criteria

Studies were included based on the following inclusion criteria: (a) CNS tumor diagnosis before the age of 20 years; (b) PSG performed after the end of treatment; (c) randomized controlled trial (RCT) or observational study with or without a control group; (d) primary outcomes were symptoms leading to PSG and diagnosed sleep disorders; and (e) the association of tumor location and diagnosed sleep disorder was described. Studies were excluded if only (a) electroencephalography or (b) actigraphy were performed, and if they were (c) case reports, case series or small sample studies in which data were not aggregated. Studies where only some of the patients fulfilled the inclusion criteria were included and data on the included individuals were extracted. Two review authors (ASLH, KSW) independently screened and selected studies based on title and abstract using Covidence. The same reviewers subsequently performed

full-text screening and data extraction independently. Non-English studies were translated by a translator to decide whether inclusion criteria were met. Disagreements were resolved with discussion. Duplicates were excluded.

Data Extraction

For each included study, we recorded the first author's name, year of publication, country, study design, age at diagnosis, age at PSG, time since diagnosis, CNS tumor location, treatment, symptoms leading to PSG, and diagnosed sleep disorder based on the International Classification of Sleep Disorders (Sateia, 2014). Studies were grouped according to study design and diagnosed sleep disorder. Central sleep apnea is characterized by a lack of drive to breathe during sleep and can be influenced by tumor location, pharmacological treatment, and surgery to the area and thus interruption of the neurologic circuit (Eckert et al., 2007). Obstructive sleep apnea is characterized by repeated upper airway collapse during sleep leading to desaturation and thereby disrupted sleep (Jordan et al., 2014).

Quality Assessment

All studies were appraised for quality by two independent researchers (ASLH, KSW) using the standardized Newcastle-Ottawa Scale (Wells et al., 2021) for assessing risk of bias in observational studies as recommended by the Cochrane Collaboration (Higgins et al., 2017). The scale is based on a star rating system with a maximum of nine stars. Risk of bias was assessed in both case control as well as cohort studies according to three criteria: (1) selection of study groups, (2) comparability of the study and control group, and (3) ascertainment of outcome.

For the criteria "selection of groups," representativeness of the group, selection, and ascertainment of exposure were assessed. For the criteria "comparability between groups" we defined age as a factor of particular relevance for adjustment, as age affects the diagnostic criteria of sleep disorders made after PSG. For the criteria "ascertainment of outcome," we defined a threshold for minimum follow-up length after end of treatment of 1 year.

RESULTS

Characteristics of Included Studies

A total of 1,658 studies were identified and after removal of 247 duplicates, the remaining 1,411 studies were screened using the inclusion and exclusion criteria (**Figure 1**). After the screening of title and abstract, 1,319 studies did not meet eligibility criteria. Seventy studies were excluded as they did not meet inclusion criteria after full-text screening, and 12 were case reports or case series. One study was hand searched. Eleven studies, published between 1991 and 2021, were included in our analyses. All studies included PSG. One study included polygraphic evaluation of sleep disorders combined with data on respiratory rhythm, and was therefore included in our analyses (Fagioli et al., 1991).

Reasons for exclusion after full-text screening were: Sleep evaluation by cassette recording and not PSG (Palm et al., 1992); ongoing treatment (Chuang et al., 2013; Delrosso et al., 2014); duplicates (Mendez, 1992; Khan et al., 2017); and in one case, the same population had been used twice, thus, we only included the most recent publication (Rosen and Brand, 2011). We did, however, include one study, where only some of the patients met the inclusion criteria (Crowley et al., 2011).

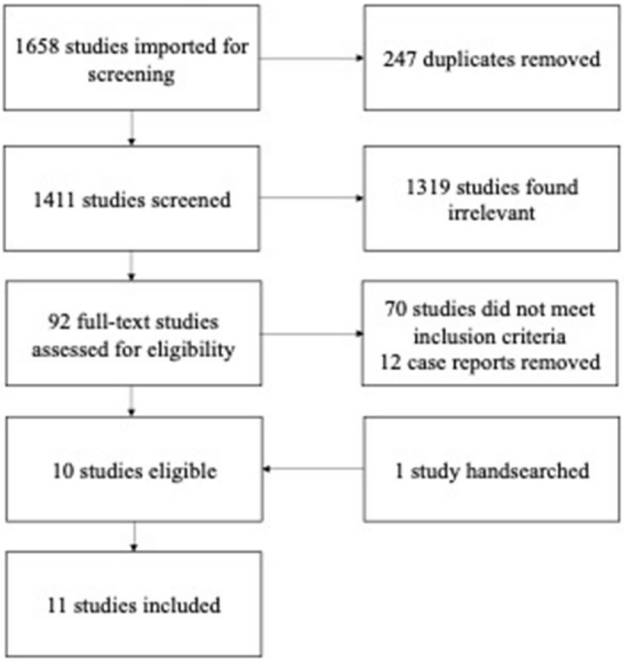

FIGURE 1 | PRISMA flow chart. A total of 1,658 studies were produced. Of these 247 duplicates were removed, and the remaining 1,411 studies were screened. After screening title and abstract 1,319 studies were found irrelevant, as they did not meet eligibility criteria. Seventy studies were excluded as they did not meet inclusion criteria after full-text screening, and 12 were case reports or case series. Finally 11 studies were included.

The 11 studies included represented 261 patients with a median age range at diagnosis from 5.6 to 10.1 years, at PSG from 12.4 to 40.5 years, and time from diagnosis from 0.75 year to 10.2 years (**Table 1**). The studies varied widely by tumor type, age at PSG, sample size and study setting. Tumor treatment consisting of either surgery, chemotherapy, and/or radiation had been completed in all studies except one (Rosen and Brand, 2011) where 25% of the patients were still receiving treatment. Three studies were conference abstracts (Müller et al., 2006; Pilotto et al., 2019; Johnson et al., 2020) and eight studies were full text articles. In four studies ($n = 39$), the patients had been diagnosed with craniopharyngioma (Müller et al., 2006; O'Gorman et al., 2010; Crowley et al., 2011; Manley et al., 2012) and in seven studies ($n = 222$), the population consisted of different CNS tumor diagnoses (Fagioli et al., 1991; Rosen and Brand, 2011; Mandrell et al., 2012; Khan et al., 2017; Pilotto et al., 2019; Johnson et al., 2020; Pickering et al., 2021). In three studies, the patients were diagnosed with both craniopharyngioma and obesity (Müller et al., 2006; O'Gorman et al., 2010; Crowley et al., 2011). In one study (Crowley et al., 2011), only 25% of the study sample ($n = 7$) were diagnosed in childhood and

TABLE 1 | Characteristics of studies according to country, number of participants, age at diagnosis, age at polysomnography, and quality assessment following the Newcastle-Ottawa Scale.

Author, Year	Country	Total number of participants	Subjects meeting eligibility criteria	Age at diagnosis (median, years)	Age at PSG (median, years)	Time since diagnosis (years)	Quality Assessment (0–9 stars)
Crowley et al. (2011)	Ireland	28	7	NA	40.5	NA	5
Fagioli et al. (1991)	France	19	19	6.8	NA	NA	5
Johnson et al. (2020) (abstract)	USA	12	12	NA	14	9-72 months	2
Khan et al. (2017)	USA	39	39	10.1	NA	10.2	6
Mandrell et al. (2012)	USA	31	31	7.4	14.3	NA	5
Manley et al. (2012)	USA	19	9 (data on 7)	8	17.5	9	5
Müller et al. (2006)	Germany	115	10	NA	NA	NA	5
O'Gorman et al. (2010)	Canada	15	15	NA	15.5	NA	7
Pickering et al. (2021)	Denmark	61	61	5.6	12.4	5.3	6
Pilotto et al. (2019) (abstract)	Italy	16	12	9.3	12.5	NA	2
Rosen and Brand (2011)	USA	70	48	NA	NA	NA	4

specific sleep disorder data for those individuals could not be separately extracted.

Regarding study design, no RCTs were identified, but five publications included control or comparison groups (O'Gorman et al., 2010; Crowley et al., 2011; Mandrell et al., 2012; Khan et al., 2017; Pickering et al., 2021). Due to heterogeneity and the risk of bias, it was only possible to narratively describe the results with a focus on symptoms that led to PSG, the sleep disorders diagnosed after PSG, and their association with tumor location.

Quality Assessment

Risk of bias assessment is summarized in **Table 2**. The quality scale ranged from 0 to 9, where scores below seven was indicative of low quality (Wells et al., 2021). The 11 studies had an average score of 4.7, and only one study (O'Gorman et al., 2010) met criteria for high quality due to its high scores with respect to comparability between groups. In general, studies received the lowest scores with respect to "selection of study groups" and "comparability between groups" and highest scores in "ascertainment of outcome."

Symptoms Leading to Polysomnography

In seven (64%) studies, symptoms prior to referral for PSG were presented (**Table 3**). The patients reported EDS, fatigue, irregular breathing during sleep, and snoring.

Sleep Disorders Diagnosed After Polysomnography

Findings from the PSGs are listed in **Table 3**. Seven studies (O'Gorman et al., 2010; Crowley et al., 2011; Rosen and Brand, 2011; Mandrell et al., 2012; Khan et al., 2017; Pilotto et al., 2019; Pickering et al., 2021) reported that the PSG was performed in accordance with guidelines from the American Academy of Sleep Medicine (Iber et al., 2007). In eight studies, specific diagnoses of sleep disorders were noted (Müller et al., 2006; Crowley et al., 2011; Rosen and Brand, 2011; Mandrell et al., 2012; Manley et al., 2012; Khan et al., 2017; Johnson et al., 2020; Pickering et al., 2021). We grouped these in accordance with the International Classification of Sleep Disorders (Sateia, 2014) into: (1) sleep-related breathing disorders, (2) central disorders of hypersomnolence, (3) parasomnias, and (4) sleep-related movement disorders (**Table 4**), as no other diagnostic categories of sleep disorders were captured in the included studies.

Sleep-Related Breathing Disorders

In four studies (Crowley et al., 2011; Mandrell et al., 2012; Manley et al., 2012; Pickering et al., 2021), 83/129 (64%) patients were diagnosed with sleep-related breathing disorders that included obstructive, central, and mixed sleep apnea (Sateia, 2014). The majority of the patients in the four studies (79/129) had hypothalamic tumor involvement. The largest study of the four (Pickering et al., 2021) reported on 61 patients (respiratory data on 59 patients), of whom 51 of the children were diagnosed with sleep apnea (obstructive $n = 29$, mixed $n = 7$, central $n = 5$). The most common symptoms prior to referral for PSG were EDS, irregular breathing during sleep, snoring, and fatigue. In the second largest study (Mandrell et al., 2012), EDS was confirmed by a short mean sleep latency of 3 min measured by a multiple sleep latency test (MSLT). The MSLT is an objective test of the tendency to fall asleep under controlled conditions (Arand and Bonnet, 2019).

Daytime sleepiness and sleep apnea were assessed in one study with patients with craniopharyngioma (Crowley et al., 2011), and almost 40% (11/28) of the patients with craniopharyngioma presented with EDS and were diagnosed with obstructive sleep apnea. Furthermore, they were treated with continuous positive airway pressure and modafinil and four out of 11 (36%) benefitted from the treatment.

Central Disorders of Hypersomnolence

In six studies (Müller et al., 2006; Rosen and Brand, 2011; Mandrell et al., 2012; Khan et al., 2017; Johnson et al., 2020;

TABLE 2 | Quality appraisal of the ten studies included according to Newcastle Ottawa Scale.

Study author, Year	Design	Selection 1	Selection 2	Selection 3	Selection 4	Comparability 1	Exposure/ Outcome 1	Exposure/ Outcome 2	Exposure/ Outcome 3	Total
Crowley et al. (2011)	Case control	1	0	0	1	1	1	1	0	5
Fagioli et al. (1991)	Cohort	1	NA	1	0	NA	1	1	1	5
Johnson et al. (2020)	Cohort	0	NA	1	0	NA	1	1	0	2
Khan et al. (2017)	Case control	1	1	0	1	2	1	1	1	6
Mandrell et al. (2012)	Cohort	1	NA	1	0	NA	1	0	1	5
Manley et al. (2012)	Cohort	1	NA	1	0	NA	1	1	1	5
Müller et al. (2006)	Cohort	1	NA	1	0	NA	1	0	1	5
O'Gorman et al. (2010)	Case control	1	1	0	1	2	1	1	1	7
Pickering et al. (2021)	Cohort	1	NA	1	0	2	0	1	1	6
Pilotto et al. (2019)	Cohort	1	NA	0	0	NA	1	1	0	2
Rosen and Brand (2011)	Cohort	1	NA	1	0	NA	1	0	0	4
Mean										4,7

Exposure was related to case-control studies, whereas outcome was related to cohort studies. The questions related in every column refer to the Newcastle Ottawa Scale. Not assessed (NA) is noted when there was no comparison group (Selection 1 = "Adequate case definition/Representativeness of cohort", Selection 2 = "Representativeness of cases/Selection of non-exposed cohort", Selection 3 = "Selection of controls/Ascertainment of exposure", Selection 4 = "Definition of controls/Outcome of interest", Comparability 1 = "Comparability of cases and controls/cohorts", Exposure/Outcome 1 = "Ascertainment of exposure/Assessment of outcome", Exposure/Outcome 2 = "Method of ascertainment/Long enough follow-up", Exposure/Outcome 3 = "Non-response rate/Adequacy of follow-up").

Pickering et al., 2021), 63 patients complaining of EDS prior to PSG were subsequently diagnosed with either hypersomnia or narcolepsy. In two studies, EDS was assessed by questionnaire with the Epworth Sleepiness Scale (Khan et al., 2017) or the Pediatric Daytime Sleepiness Scale (Pickering et al., 2021). The presence of cataplexy was reported in three studies (Mandrell et al., 2012; Khan et al., 2017; Pickering et al., 2021), and hypocretin levels were not reported in any studies.

Four out of the six studies involved tumors predominantly located in the hypothalamus (Müller et al., 2006; Rosen and Brand, 2011; Mandrell et al., 2012; Pickering et al., 2021), one study with tumors in different locations (Khan et al., 2017), and one with tumors in unknown locations (Johnson et al., 2020).

As expected, the prevalence of EDS and narcolepsy was higher in childhood brain tumor survivors compared with the general population, and in more than 50% of cases (40/77), a diagnosis led to treatment of the sleep disorder (Khan et al., 2017; Pickering et al., 2021). In one study, narcolepsy was diagnosed between 9 and 72 months after cancer treatment (Khan et al., 2017).

Somnolence together with sleep apnea was assessed in one study with patients with craniopharyngioma (Crowley et al., 2011), and as described, almost 40% (11/28) of the patients with craniopharyngioma presented with EDS and were diagnosed with obstructive sleep apnea.

Tumor Location and Sleep Disorder

Four studies included only patients diagnosed with a suprasellar tumor ($n = 62$), and they were diagnosed with obstructive sleep apnea ($n = 11$), narcolepsy/hypersomnia ($n = 7$), central or obstructive sleep apnea ($n = 3$), and sleep-related breathing disorder ($n = 2$) (Müller et al., 2006; O'Gorman et al., 2010; Crowley et al., 2011; Manley et al., 2012). One study observed an association between central sleep apnea and tumor location in cerebellum suggesting an impact of posterior fossa tumor involvement on sleep and ventilatory control (Pilotto et al., 2019).

Two studies (Fagioli et al., 1991; Pilotto et al., 2019) included patients with cerebellar tumors and found shorter sleeping times and more awakenings compared with normative data. In one study, two patients were diagnosed with non-rapid eye movement (NREM) parasomnias after partial resection of a pilocytic astrocytoma and a ganglioglioma, respectively. One patient was diagnosed with rapid eye movement (REM) sleep parasomnia after partial resection of a diffuse astrocytoma (Pickering et al., 2021). One study reported restless legs syndrome after diagnosis of craniopharyngioma in three out of seven patients (Manley et al., 2012). Two studies reported no specific diagnoses of sleep disorders (Fagioli et al., 1991; O'Gorman et al., 2010).

Other PSG Findings

One study investigated growth hormone secretion in relation to sleep (Fagioli et al., 1991), and another study reported a higher frequency of sleep disordered breathing in obese patients with craniopharyngiomas than obese controls (O'Gorman et al., 2010).

DISCUSSION

The present systematic review of 11 published studies indicates that sleep disorders may occur after surviving a childhood CNS tumor. From these studies we found that the symptoms leading to PSG were heterogeneous, and we found no clear association between tumor location and sleep disorder. However, these studies reported a high occurrence of sleep disorders among their patients. By using the diagnostic classification system from the International Classification of Sleep Disorders (Sateia, 2014), the

TABLE 3 | Characteristics of population, symptoms leading to polysomnography, tumor location, and findings after polysomnography.

Author	Number of participants	Population	Tumor location	Symptoms	Findings after PSG
Fagioli et al. (1991)	19 (18)	Mix of CNS tumors	Cerebellum/4th ventricle ($n = 18$),	NA	Shorter sleeping time and more awakenings compared to controls.
Johnson et al. (2020)	12	Mix of CNS tumors	NA	NA	High risk of sleep wake cycle disorder in early survivorship (9-72 months post treatment). Morning melatonin and biomarker correlates with fatigue 7 clinical sleep disorders, 2 hypersomnia, 1 narcoplepsy.
Khan et al. (2017)	39	Mix of CNS tumors	Cortical ($n = 4$), midline ($n = 26$), paramedian ($n = 4$), posterior fossa ($n = 5$)	Hypersomnia	13 hypersomnia and 26 narcoplepsy without cataplexy. 11/39 abnormal PSG. 37 patients received treatment.
Mandrell et al. (2012)	31	Mix of CNS tumors	Fossa posterior/4th ventricle ($n = 4+4$), sellar/parasellar/hypothalamic (n = 17), optic nerve ($n = 2$), pineal gland ($n = 1$), spinal ($n = 1$), thalamus ($n = 1$), brainstem ($n = 1$)	Excessive daytime sleeping, fatigue, snoring, irregular breathing during sleep	14 obstructive sleep apnea, 4 central sleep apnea, 4 hypersomnia, 3 narcolepsy without cataplexy.
Pickering et al. (2021)	61 (59)	Mix of CNS tumors	Thalamus, hypothalamus, basal forebrain ($n = 25$), fossa posterior ($n = 16$), brain stem ($n = 5$), ventricles ($n = 3$), pineal gland ($n = 2$), optic nerve ($n = 2$), other ($n = 9$)	Sleep disordered breathing, emotional problems, fatigue	51/59 sleep apnea (obstructive, n=29, central, n=5, mixed, n=7), 5/59 narcolepsy, 2/59 NREM parasomnia, 1/59 REM sleep parasomnia.
Pilotto et al. (2019)	16	Mix of CNS tumors	Sub tentorial tumor ($n = 8$)	NA	Increased central apnea index with cerebellum localization.
Rosen and Brand (2011)	48	Mix of CNS tumors	Hypothalamus/brainstem ($n = 35$), posterior fossa ($n = 7$), cortex ($n = 6$)	Sleepiness, fatigue, respiratory insufficiency, snoring	9/14 excessive daytime sleepiness, 5 of them with positive PSG of narcolepsy.
Crowley et al. (2011)	7 (28)	Craniopharyngioma	Suprasellar/Hypothalamic	Somnolence	11/28 obstructive sleep apnea. Somnolence can be due to obstructive sleep apnea in patients with craniopharyngioma.
Manley et al. (2012)	9 (7)	Craniopharyngioma	Suprasellar/Hypothalamic	Day time fatigue, sleep dysfunction	3 obstructive or central sleep apnea, arousal index 11.0, 3 restless legs syndrome. Sleep dysfunction is multifactorial, PSG should be performed more often.
Müller et al. (2006)	10	Craniopharyngioma	Suprasellar/Hypothalamic	Obesity, increased daytime sleepiness	2 sleep related breathing disorder, 4 repeated episodes of SOREM (sleep onset rapid eye movement), 3 hypersomnia, 9 were acutely obese.
O'Gorman et al. (2010)	15	Craniopharyngioma	Suprasellar/Hypothalamic	NA	Obstructive hypopnea apnea index was increased in patients with craniopharyngioma. Sleep disordered breathing is more frequent in patients with craniopharyngioma and obesity compared with BMI matched controls.

two most common sleep diagnoses captured by the included studies were obstructive sleep apnea and narcolepsy categorized in sleep related breathing disorders and central disorders of hypersomnolence, respectively.

Symptoms Before PSG

Patients commonly reported EDS, fatigue, irregular breathing during sleep, and snoring prior to PSG. These symptoms were not associated with specific sleep disorders, but fatigue and sleepiness

TABLE 4 | Sleep disorders classified according to International Classification of Sleep Disorders, Third edition.

Diagnostic group	Sleep disorders	Authors	Number of patients with sleep disorders/ total of patients included
Sleep-related breathing disorders	Obstructive, central or mixed sleep apnea	Pickering et al.	51/59
	Obstructive or central sleep apnea	Manley et al.	3/7
	Obstructive sleep apnea	Mandrell et al.	14/31
	Central sleep apnea	Mandrell et al.	4/31
	Central sleep apnea	Pilotto et al.	*n* was unknown
Central disorders of hypersomnolence	Narcolepsy	Pickering et al.	5/61
	Narcolepsy or hypersomnolence	Khan et al.	37/39
	Narcolepsy, hypersomnolence	Mandrell et al.	7/31
	Narcolepsy, hypersomnolence + unknown sleep disorder	Johnson et al.	2+5/12
	Narcolepsy, hypersomnolence	Müller et al.	7/10
Parasomnias	NREM parasomnia	Pickering et al.	2/59
	REM sleep parasomnia		1/59
Sleep-related movement disorders	Restless legs syndrome	Manley et al.	3/7
Delayed sleep phase	Delayed sleep phase syndrome	Rosen et al.	1/48

are recognized late effects for childhood cancer survivors and can persist years after end of cancer treatment and lead to psychosocial challenges (Verberne et al., 2012). Central nervous system tumor survivors have an increased risk of EDS compared with children, who have survived other childhood malignancies (van Deuren et al., 2020).

Sleep Disorder Diagnoses and the Association With Tumor Location

The different types of sleep disorders may be associated with specific tumor locations. Overall, studies reported tumors in a variety of locations including suprasellar, posterior fossa, and brain stem. Indeed, five of the 11 included studies included patients with suprasellar tumors (O'Gorman et al., 2010; Crowley et al., 2011; Mandrell et al., 2012; Manley et al., 2012; Pickering et al., 2021). The most common type of sleep disorder observed in survivors of CNS tumors was sleep apnea. Adenotonsillar hypertrophy is the most important risk factor for obstructive sleep apnea in general pediatric populations (Gislason and Benediktsdóttir, 1995; Dayyat et al., 2009). Obesity increases the risk of obstructive sleep apnea in adolescents and likely also children with specific medical conditions and comorbidities such as children with brain tumors (Jordan et al., 2014). Prior studies have reported that patients with tumor involvement of the hypothalamus may suffer from hypothalamic obesity due to underlying mechanisms causing a combination of increased energy intake and reduced physical activity (Harz et al., 2003; Park et al., 2013).

Narcolepsy was another sleep disorder diagnosed in CNS tumor survivors. In such studies, tumor locations included the hypothalamus, brain stem, or posterior fossa. This association is posited to be due to disruption of sleep- and wakefulness-promoting neural networks caused by the tumor itself or by subsequent treatments such as surgery and/or radiotherapy (Sakuta et al., 2012). Specifically, sleep and wakefulness are regulated by neuronal networks of the thalamus, hypothalamus, basal forebrain and brain stem, and an ascending reticular activation system originating from the upper brainstem and basal forebrain activates the cortex and modulates wakefulness (Saper et al., 2005). Thus, damage to this network or to any of the central nuclei may potentially result in disturbed sleep (Saper, 2013). Manifestation of narcolepsy in CNS tumor survivors due to lack of hypocretin may also relate to the flip-flop switch that mediates transitions between wakefulness and sleep (Saper et al., 2005). The switch is stabilized by orexin produced by neurons located in the lateral hypothalamus. A deficiency of orexin, as seen in patients with narcolepsy type 1, causes undesired switches between sleep and wakefulness resulting in sleep attacks and fragmented sleep pattern. Furthermore, orexin suppresses REM sleep which explains the REM sleep dissociation events observed in these patients. Among patients with CNS tumors, numerous studies have reported secondary/comorbid narcolepsy in those patients with tumors involving the hypothalamic area or close to the third ventricle (Kanbayashi et al., 2006; Sakuta et al., 2012; Madan et al., 2021). Mogavero et al. propose that a diagnosis of neurodegenerative disease may decrease the risk of cancer i.e., the inverse comorbidity mechanism (Mogavero et al., 2020, 2021). Narcolepsy type 1 results from an autoimmune destruction of the orexin producing neurons in the lateral hypothalamus. An interconnection between narcolepsy and cancer, based on genetic and immunological factors, may therefore be hypothesized. As orexin deficiency is the pathological feature in narcolepsy type 1, orexin may play a role in some tumor types. Numerous studies have reported on secondary/comorbid narcolepsy in patients with brain tumors, which may be due to an involvement of the orexin producing neurons or their projections (Marcus et al., 2002; Mandrell et al., 2012). In children with brain tumors, comorbid narcolepsy was observed in 8% and sleep apnea in 86% (Pickering et al., 2021). In comparison, the prevalence of narcolepsy type 1 in the general population is about 0.03% (Longstreth et al., 2007) and sleep apnea 1–10% (Tsukada et al., 2018). On that note, a brain tumor diagnosis does not seem to provide protection against sleep disorders.

Where the cerebellum has a key role in central respiratory control (Stoodley et al., 2012), the brainstem plays an important modulating role (Feldman and Del Negro, 2006). In our study, few patients with brainstem tumors were included, but they were often diagnosed with either hypersomnolence or narcoplepsy (Rosen and Brand, 2011; Mandrell et al., 2012; Pickering et al., 2021). Other studies have described sleep disordered breathing associated with brainstem tumors (Osanai et al., 1994; Ito et al., 1996).

In this review, one study reported sleep-related movement disorder in three out of seven patients with restless legs syndrome (Manley et al., 2012). Another study reported of periodic leg movement, which did not interfere with sleep and thus not classified as a sleep disorder (Khan et al., 2017). Only a few patients in this review were diagnosed with parasomnias, although it has been reported in case reports previously (Cordani et al., 2021). Moreover, none of the 11 studies included described insomnia among their patients. Activity of the ventrolateral preoptic nucleus located in the anterior hypothalamus is central to sleep promotion and it has been reported that involvement of the area results in insomnia (Nofzinger et al., 2004), and insomnia is prevalent both in childhood CNS tumor survivors as well as in the general population (Morin et al., 2011). However, insomnia may be underreported in this review, due to our inclusion criteria of PSG, as insomnia is typically captured using patient-reported outcome measures (Ohayon and Reynolds, 2009).

Patients in our systematic review were all diagnosed before the age of 20 years but underwent PSG between 12.4 and 40.5 years of age. The study population is therefore heterogenous with respect to age, and different sleep disorders are prevalent in different age groups just as one sleep disorder may change across the life span (Lividini et al., 2021). Importantly, PSG was scored in relation to age (Berry et al., 2012). Sleep architecture and the amount of sleep needed changes from childhood into adulthood (Kahn et al., 1996; Quan et al., 2003; McLaughlin Crabtree and Williams, 2009; Owens and Weiss, 2017). In adolescence, altered psychosocial life and maturing of biological processes regulating sleep/wake systems can alter the homeostatic process that works together with the circadian timing system, and this maturation of the biological processes leads to a lower total sleep time in adulthood compared to childhood (Carskadon et al., 2004). Furthermore, delayed sleep phase in adolescents can be debilitating and complicate the diagnosis of other sleep disorders (Thorpy et al., 1988).

Strengths and Limitations

To the best of our knowledge, this is the first systematic review undertaken of studies on PSG-diagnosed sleep disorders in childhood CNS tumor survivors. In addition, we examined associations between sleep disorders and tumor location, the results of which can inform researchers, health care providers and patients about this important late effect during the cancer trajectory.

This review highlights a number of limitations across research in this area. First, all but one of the studies were rated with a high risk of bias. The studies were heterogenous when comparing study population and design, and only five studies included a control group. Second, the included studies were published between the years 1991 and 2021, during which cancer treatment improved significantly, further reducing comparability between studies. In addition, several potential confounders such as fatigue and obesity were also not investigated in depth (Mulrooney et al., 2008; Crabtree et al., 2010). Third, some studies only conducted PSG on selected patients with specific symptoms, such as EDS, while other studies conducted PSG on all included patients independently of symptoms of a sleep disorder. Fifth, PSG evaluations of children can be limited by the lack of normative data for children under 18 years (Ng and Chan, 2013). Lastly, the majority of sleep disorders in children are diagnosed based on medical history combined with validated sleep questionnaires. Polysomnography is mandatory only when diagnosing obstructive sleep apnea, PSG combined with MSLT for narcolepsy and actigraphy for diagnosing circadian rhythm disorders. Therefore, children diagnosed with either questionnaires or actigraphy were not included in this review.

It is also important to note that we did not consider the effects of specific treatments on the diagnosis of sleep disorders, and we know that treatment alone can have an effect on the developing brain (Mogavero et al., 2020). Furthermore, patient reported outcome measures may better capture other sleep disorders, such as insomnia that commonly occur in cancer survivors (Merz and Tomfohr-Madsen, 2018; Tonning Olsson et al., 2020). Thus, an overall evaluation of the frequency of the full range of sleep disorders in childhood CNS survivors could not be determined from this review.

Conclusion, Research Implications, and Perspectives

In conclusion, the identification of symptoms of a PSG-diagnosed sleep disorder and potential associations with tumor location can provide important information regarding this important late effect that can impair quality of life for childhood CNS tumor survivors. In the future, it will benefit health care practitioners and patients to systematically register sleep disorder symptoms together with tumor type and treatment information in patients, with an awareness of known discrepancies between subjective and objective sleep evaluations (Jackowska et al., 2011; Lubas et al., 2021). By doing so, clinicians can better identify patients who are likely to need referral for PSG. Furthermore, more rigorous and larger scale controlled observational studies are warranted focusing on possible modifiable confounders of sleep disorders such as fatigue and obesity. Overall, capturing sleep disorder symptoms would inform the development of interventions for affected children, with the ultimate goal of improving social functioning, educational attainment and health related quality of life in childhood CNS tumor survivors.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

AH designed the study, collected, analyzed, and interpreted the data, wrote and edited the manuscript. KW designed the study, analyzed and interpreted the data, and critically reviewed the manuscript. LK, LH, YL-R, AA, LW, JW, LP, and RM designed the study, interpreted the data, and critically reviewed the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2022.808398/full#supplementary-material

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METHODS
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Optimizing a Behavioral Sleep Intervention for Gynecologic Cancer Survivors: Study Design and Protocol

Rina S. Fox[1,2,3], Julia S. Gaumond[3], Phyllis C. Zee[4,5], Karen Kaiser[3,6], Edward J. Tanner[6,7], Sonia Ancoli-Israel[8], Juned Siddique[6,9], Frank J. Penedo[10], Lisa M. Wu[3,11], Kathryn J. Reid[4,5], Sairam Parthasarathy[12,13], Terry A. Badger[1,2], Christine Rini[3,6] and Jason C. Ong[4,5,14]*

[1] Division of Community and Systems Health Science, University of Arizona College of Nursing, Tucson, AZ, United States, [2] University of Arizona Cancer Center, Tucson, AZ, United States, [3] Department of Medical Social Sciences, Northwestern University Feinberg School of Medicine, Chicago, IL, United States, [4] Department of Neurology, Northwestern University Feinberg School of Medicine, Chicago, IL, United States, [5] Center for Circadian and Sleep Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, United States, [6] Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL, United States, [7] Department of Obstetrics and Gynecology, Northwestern University Feinberg School of Medicine, Chicago, IL, United States, [8] Department of Psychiatry, University of California, San Diego, San Diego, CA, United States, [9] Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, United States, [10] Department of Medicine and Psychology and Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL, United States, [11] Aarhus Institute of Advanced Studies, Aarhus University, Aarhus, Denmark, [12] Division of Pulmonary, Allergy, Critical Care, and Sleep Medicine, Department of Medicine, University of Arizona, Tucson, AZ, United States, [13] University of Arizona Health Sciences – Center for Sleep and Circadian Science, University of Arizona, Tucson, AZ, United States, [14] Nox Health, Suwanee, GA, United States

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***Correspondence:**
Rina S. Fox
rsfox@arizona.edu

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Sleep difficulties, particularly symptoms of insomnia and circadian disruption, are among the primary complaints of gynecologic cancer survivors before, during, and after treatment. Moreover, difficulty sleeping has been linked to poorer health-related quality of life and elevated symptom burden in this population. Although leading behavioral sleep interventions have demonstrated efficacy among cancer survivors, up to 50% of survivors are non-adherent to these treatments, likely because these interventions require labor-intensive behavior and lifestyle changes. Therefore, there is a need for more effective and acceptable approaches to diminish sleep disturbance among cancer survivors. This manuscript describes the methodology of a two-part study guided by the Multiphase Optimization Strategy (MOST) framework to identify a streamlined behavioral sleep intervention for gynecologic cancer survivors. Three candidate intervention components previously shown to decrease sleep disturbance will be evaluated, including sleep restriction, stimulus control, and systematic bright light exposure. Participants will be adult women with a history of non-metastatic gynecologic cancer who have completed primary treatment and who report current poor sleep quality. Fifteen participants will be recruited for Part 1 of the study, which will utilize qualitative methods to identify barriers to and facilitators of intervention adherence. Results will inform changes to the delivery of the candidate intervention components to promote adherence in Part 2, where 80 participants will be recruited and randomized to one of eight conditions reflecting every possible combination of the three candidate intervention components in a full factorial design. Participants will complete assessments at baseline, post-intervention, and 3-months post-intervention. Part 2 results will identify the combination of candidate intervention components that yields

the most efficacious yet efficient 6-week intervention for diminishing sleep disturbance. This is the first known study to apply the MOST framework to optimize a behavioral sleep intervention and will yield a resource-efficient treatment to diminish sleep disturbance, improve health-related quality of life, and decrease symptom burden among gynecologic cancer survivors. ClinicalTrials.gov Identifier: NCT05044975.

Keywords: sleep disturbance, gynecologic cancer, behavioral sleep intervention, optimization, cancer survivorship

INTRODUCTION

Sleep Disturbance in Cancer Survivorship

Sleep difficulties, particularly symptoms of insomnia and circadian disruption, are common among gynecologic cancer survivors (Westin et al., 2016; Campbell et al., 2019; Palagini et al., 2021), with recent research demonstrating an estimated prevalence greater than 80% (Pozzar et al., 2021). Sleep disturbance has also been associated with poorer health-related quality of life (HRQOL) and higher symptom burden in this population (Ross et al., 2020). Difficulty sleeping is often treated with Cognitive Behavioral Therapy for Insomnia (CBT-I), the gold-standard treatment for insomnia, including among those with comorbid conditions (Schutte-Rodin et al., 2008; Qaseem et al., 2016; van Straten et al., 2017). CBT-I is a multicomponent behavioral intervention consisting of cognitive restructuring, sleep restriction, stimulus control, sleep hygiene education, and relaxation therapy (Morin and Benca, 2012). Sleep restriction and stimulus control are generally recognized as the core components driving treatment effects (Morin et al., 2006). A recent meta-analysis evaluating the efficacy of CBT-I specifically in cancer survivors found that the intervention improved multiple sleep outcomes, including sleep efficiency, sleep onset latency, wake after sleep onset, and insomnia symptom severity (Johnson et al., 2016). Another recent meta-analysis supported the efficacy of CBT-I among cancer survivors regardless of whether the intervention was delivered in-person or remotely (Ma et al., 2021). However, although CBT-I can be highly efficacious, up to 50% of cancer survivors do not adhere to the treatment as it is currently packaged, and thus do not benefit maximally from it (Matthews et al., 2012, 2013; McChargue et al., 2012; Garland et al., 2014). This may be because the intervention requires patients to make multiple, simultaneous, and often intrusive behavioral and lifestyle changes (Agnew et al., 2021). A less burdensome alternative is systematic bright light exposure, which has recently been explored as another strategy for improving sleep disturbance in cancer survivors (Wu et al., 2018, 2021; Fox et al., 2021). Results suggest systematic bright light exposure in the morning may have a beneficial impact on sleep disturbance among cancer survivors. However, effects are generally not as strong as they are for CBT-I, with research thus far limited to small pilot studies where the mechanisms underlying the effects of bright light have not been well explored.

A leading theory of sleep-wake regulation is the two-process model (Borbely et al., 2016), which posits that sleep timing and intensity depend on the interaction of a homeostatic process and a circadian process, which function independently. According to this model, the homeostatic process reflects the body's attempts to maintain balance, in that more time spent awake leads to increased pressure to fall asleep (Deboer, 2018). The circadian process, a pacemaker managed by the suprachiasmatic nucleus of the hypothalamus, determines one's daily rhythm for sleep and wake, leading to increased sleepiness at certain times of the day and increased alertness at others (Deboer, 2018). Thus, sleep-wake cycles and circadian rhythms separately influence sleep (Borbely et al., 2016). Sleep restriction and stimulus control, the two core components of CBT-I, both target the homeostatic process. Conversely, systematic bright light exposure targets the circadian process. Therefore, combining sleep restriction, stimulus control, and bright light may have additive or even interactive effects. One known study is currently exploring this hypothesis (Bean et al., 2020); however, it is doing so exclusively among patients undergoing chemotherapy for breast cancer. Thus, the applicability of results to cancer survivors who have completed primary treatment will be unclear. Additionally, this known study is adding systematic bright light exposure to CBT-I as a packaged intervention, thus increasing the burden associated with this already challenging treatment. To maximize benefit from the available evidence-based treatments, studies are needed that can determine what combination of behavioral sleep intervention components yields the most effective intervention while also maximizing adherence to optimize impact.

Intervention Optimization

Multicomponent behavioral interventions are traditionally developed and evaluated as pre-bundled treatment packages and assessed *via* randomized controlled trial (RCT; Guastaferro and Collins, 2019). This is an effective and important scientific approach to identify how an intervention performs relative to a control or comparison. However, this approach is unable to identify which components of the intervention, if any, could be changed or removed to increase efficiency and decrease burden. That is to say, the effects of the individual components of the intervention, both independently and interactively, remain unknown. To address this challenge, Collins and colleagues developed the Multiphase Optimization Strategy (MOST) framework (Collins et al., 2005; Collins, 2018). MOST is grounded in engineering theory and involves three phases. Like traditional RCT-based intervention science, the MOST framework involves a Preparation phase that includes developing a conceptual model, selecting candidate intervention

components based on theory and evidence, and conducting pilot testing. It also includes an Evaluation phase, in which components are bundled into a final intervention package that is then evaluated, typically *via* RCT.

What sets MOST apart is the inclusion of an Optimization phase, which occurs between the Preparation and Evaluation phases, in which candidate intervention components are evaluated using randomized experimentation to determine the impact of components individually and in various combinations. This enables identification of which components make valuable contributions to the overall program effects and what combination of components yields the greatest impact. The result is an intervention that has been optimized according to specific criteria (e.g., effectiveness, efficiency, cost) and that can achieve desired results with fewer resources and less participant burden. Of note, factorial designs are frequently used in the Optimization phase because they provide an economical framework for testing multiple components in a single study.

The Present Study

This paper describes the procedures and methodology of a two-part study guided by the MOST framework. The first part, which is consistent with the Preparation phase of the framework, will employ a qualitative approach to identify barriers to and facilitators of adherence to sleep restriction, stimulus control, and systematic bright light exposure, three evidence-based candidate intervention components previously shown to decrease sleep disturbance among cancer survivors. The second part, which is consistent with the Optimization phase of the framework, will employ a factorial design to identify the best combination of these three components, enhanced to promote adherence per the results of Part 1, to yield a resource-efficient behavioral sleep intervention with exclusively active components. Feasibility, acceptability, and adherence will also be examined, and the potential mediating roles of sleep disturbance and circadian markers on intervention effects will be explored. This work will yield an optimized behavioral sleep intervention to diminish sleep disturbance, improve HRQOL, and reduce symptom burden among gynecologic cancer survivors.

MATERIALS AND METHODS

Participants and Recruitment

Across both parts of the study, participants will be survivors of a non-metastatic gynecologic cancer who have completed primary treatment, are between the ages of 18 and 74, and report poor sleep quality. Part 1 of the study will include 15 participants and Part 2 will include 80, for a total sample size of 95 participants to be enrolled over 5 years. Participants will be recruited from the Robert H. Lurie Comprehensive Cancer Center of Northwestern University and the University of Arizona Cancer Center, two comprehensive cancer centers located in Chicago, IL and Tucson, AZ, United States, respectively. All potential participants will provide verbal consent to complete screening for study eligibility. Those who are eligible and subsequently enroll will provide written informed consent prior to engaging in any study activities.

Eligibility

Potential participants will be identified through a combination of physician referral and electronic medical record screening. Study eligibility will be confirmed by participant self-report *via* a telephone screening interview. To be eligible for the study, participants must endorse or demonstrate: (1) a history of a non-metastatic ovarian, uterine, vaginal, vulvar, or cervical cancer; (2) English language proficiency; (3) age 18–74 years; (4) typical sleep onset between 9:00pm and 3:00am; (5) poor sleep quality [i.e., score $>$ 5 on the Pittsburgh Sleep Quality Index [PSQI] (Buysse et al., 1989)]; and (6) reliable telephone and internet access.

Participants who meet any of the following criteria will be excluded: (1) diagnosis of a second primary cancer other than a non-melanoma skin cancer; (2) diagnosis of significant neurological, physiological or psychological dysfunction that could impact study participation [e.g., active psychosis, glaucoma, HIV, epilepsy, current substance abuse, active suicidality]; (3) diagnosis of sleep apnea, restless legs syndrome, periodic limb movement disorder, or narcolepsy per self-report and medical record review; (4) completion of primary anti-cancer treatment (e.g., chemotherapy, radiation therapy) $<$30 days prior to participation or surgical intervention $<$60 days prior to participation; (5) significant mental or physical decline (i.e., $\geq$2 mistakes on the six-item version of the Mini Mental Status Exam [MMSE] (Callahan et al., 2002) or Eastern Cooperative Oncology Group [ECOG] (Oken et al., 1982) performance status score $>$ 1); (6) shift work; and (7) plans to travel across meridians during participation. Exclusion criteria were selected due to their known impact on study outcomes or because of potential interference with study participation.

Candidate Intervention Components and Intervention Delivery

The three candidate intervention components to be evaluated were selected according to the two-process model of sleep-wake regulation (Borbely et al., 2016). To further minimize burden, only the sleep restriction and stimulus control components of CBT-I will be evaluated while sleep hygiene education, cognitive restructuring, and relaxation therapy will not, as sleep restriction and stimulus control have been identified as primary mechanisms of CBT-I efficacy among adherent patients (Morin et al., 2006).

Sleep Restriction

Sleep restriction involves limiting one's opportunity for sleep to the amount of time reported sleeping on an average night plus 30 min. For this study, wake time will be determined by asking participants to identify the earliest time they need to awaken on any given day based on their individual lifestyles. The prescribed bedtime will then be identified by working backward from this wake time. The initial sleep opportunity window will be informed by 7 days of sleep diaries completed immediately prior to beginning the intervention. This window will then be adjusted weekly based on participants' sleep efficiency (i.e., ratio of time asleep to time in bed at night), calculated from

weekly sleep diaries, as is the gold standard recommendation (Spielman et al., 1987).

Stimulus Control

Based on classical and operant conditioning, stimulus control aims to disassociate non-sleep behaviors from the bedroom and reinforce the association of the bedroom with sleep-related stimuli (e.g., bed). Instructions include not going to bed until sleepy, getting out of bed if unable to fall asleep or fall back to sleep within approximately 20 min, avoiding behaviors other than sleep and sexual activity in the bedroom, waking up at the same time each day, and avoiding daytime naps (Bootzin et al., 1991).

Systematic Bright Light Exposure

Bright light will be systematically delivered by wearable Re-Timer™ glasses. The Re-Timer™ glasses are a small ($7.9'' \times 5.5'' \times 2.2''$), lightweight (2.64 oz.) device that delivers green-blue light from below to replicate the natural pathway of light to the eyes. Participants will be instructed to wear the glasses on the highest setting for 30 min every morning during the intervention period, initiating this time within 30 min of awakening and completing light exposure prior to noon. Re-Timer™ glasses can be worn over traditional eyeglasses as long as the eyeglasses do not have photochromatic or tinted lenses.

Intervention Delivery

Prior to the initiation of the intervention period, research staff will provide an intervention orientation to participants. This orientation, which will last approximately 30–60 min, will be completed either in-person or over video conference, and will include general sleep education as well as an explanation of the intervention components the participant will receive and the rationale behind them. After this orientation, participants will implement their assigned intervention components at home daily for 6 weeks.

The candidate intervention components will be administered *via* weekly emails. All participants will monitor their sleep by completing a daily sleep diary for the duration of the 6-week intervention period. All participants will also receive a weekly email from the study team with a reminder to complete and return the sleep diary. Sleep diaries will be returned electronically. For participants receiving stimulus control, the weekly email will also contain a reminder of the stimulus control instructions. For participants receiving systematic bright light exposure, the weekly email will also contain a reminder of how to use the Re-Timer™ glasses. For participants receiving sleep restriction, the weekly email will also contain a reminder of the sleep restriction instructions and the prescribed sleep schedule for the coming week, which will be determined by a licensed clinical psychologist with specialized training in behavioral sleep intervention (RSF) based on the prior week's sleep diary. Participants receiving more than one candidate intervention component will receive a single weekly email containing the information relevant to all components being delivered. The study team will be available to participants throughout the intervention period to answer questions, troubleshoot, and provide support as needed.

Study Design

This two-part study is guided by the MOST framework. Participants in Part 1 will not be randomized, but rather will receive all three candidate intervention components simultaneously. It is well established that greater adherence predicts behavioral sleep intervention efficacy; however, knowledge of how best to increase adherence is limited (Matthews et al., 2012, 2013; Agnew et al., 2021). Therefore, upon completion of the intervention in Part 1, individual semi-structured interviews will be conducted with participants and analyzed to identify barriers to and facilitators of adherence to the three candidate intervention components. Results will inform the design and delivery of the components in Part 2 to enhance adherence. Subsequently, in Part 2, a full factorial experiment will be completed that involves eight experimental conditions (**Table 1**). It is important to note that this study is not an eight-arm RCT and the purpose is not to compare outcomes across each of the eight conditions directly. Rather, each main effect and interaction estimate will use data from participants in all of the experimental conditions. For example, the main effect of sleep restriction will be estimated by comparing the mean for the 40 participants in conditions 1 through 4 to the mean for the 40 participants in conditions 5 through 8 in **Table 1**. A detailed explanation of how factorial study designs maintain power has been previously published (Collins et al., 2009).

Hypotheses

We hypothesize that gynecologic cancer survivors will be able to engage with each of the three candidate intervention components and that each component will be deemed acceptable. We further hypothesize that the optimal combination of intervention components will yield stronger effects for diminishing sleep disturbance, improving HRQOL, and reducing symptom burden than each individual component.

DATA COLLECTION AND MEASURES

Data Collection

Data to be collected include sociodemographic information, medical information, patient-reported outcome measures, qualitative patient feedback, urine samples, and objective sleep information recorded by actigraphy. Throughout the study, the REDCap (Harris et al., 2009) data collection platform will be used to capture and store participant data. This platform is

TABLE 1 | Experimental conditions.

Experimental condition	Sleep restriction	Stimulus control	Bright light
1	Yes	Yes	Yes
2	Yes	Yes	No
3	Yes	No	Yes
4	Yes	No	No
5	No	Yes	Yes
6	No	Yes	No
7	No	No	Yes
8	No	No	No

optimized for secure research data collection and storage and allows for HIPPA-compliant export and analysis. Data will be entered into REDCap either directly by participants or by the research team. All study assessments will be completed in-person or remotely *via* videoconference.

Across both Part 1 and Part 2 of the study, the screening questionnaire will be administered by telephone to determine eligibility. Eligible and interested participants will then provide informed consent before completing a baseline assessment where they will provide sociodemographic and medical information and complete questionnaires related to their sleep, HRQOL, and symptom burden. Participants will also collect urine the night before this baseline assessment, wear a wrist actigraph, and complete sleep diaries for the 7 days leading up to the assessment. Immediately after completing the 6-week intervention period, participants will complete a follow-up assessment that mirrors the baseline plus an additional measure of acceptability. In addition to the baseline and post-intervention assessments, participants in Part 1 will complete a semi-structured interview and accompanying survey within 2 weeks of completing the intervention to provide information about barriers to and facilitators of protocol adherence. In contrast, participants in Part 2 will complete an additional follow-up assessment 3 months after completing the intervention that mirrors the baseline and post-intervention assessments to measure longitudinal intervention effects.

Measures

Feasibility and Acceptability

In both Part 1 and Part 2, study feasibility will be assessed according to established procedures (Bowen et al., 2009), including documenting the number of eligible participants, participant willingness to be enrolled, attrition, reported reasons for withdrawing, and self-reported protocol adherence.

Acceptability of the candidate intervention components will be assessed with items from the Functional Assessment of Chronic Illness Therapy – Treatment Satisfaction – General scale (FACIT-TS-G) (Peipert et al., 2014), which will be administered at the post-intervention assessment only. The FACIT-TS-G includes eight items that utilize Likert-type response scales, were developed as stand-alone single items, and are scored individually. Higher item scores indicate greater acceptability.

Covariates

Sociodemographic and Medical Information

Sociodemographic and medical information will be gathered through participant self-report and medical chart review at screening, baseline, post-intervention, and 3-month follow-up. Sociodemographic data will include age, education, income, racial background, ethnicity, employment status, and relationship status. Medical data will include information about exclusionary and comorbid medical conditions, prescription medication use, and cancer-related information (e.g., time since diagnosis, stage at diagnosis, treatment history). Participants will also complete the Self-Administered Comorbidity Questionnaire (Sangha et al., 2003).

Sleep Apnea Risk

The Berlin questionnaire (Netzer et al., 1999) will assess risk for sleep apnea at baseline. This screener consists of nine items reflecting known clinical features of sleep apnea and yields scores in three categories related to the risk of having sleep apnea. Participants are classified as High Risk or Low Risk based on their responses to individual items and their overall scores in the symptom categories.

Pain

An 11-item numerical rating scale, ranging from 0 (*No pain*) to 10 (*Worst imaginable pain*), will evaluate pain intensity (Ferreira-Valente et al., 2011) at baseline, post-intervention, and 3-month follow-up. The numerical rating scale is one of the most commonly used measures of pain intensity and has been shown to be responsive to pain (Ferreira-Valente et al., 2011).

Treatment Expectancy

Following the baseline assessment and orientation session and prior to the start of the 6-week intervention period, participants will complete the Credibility/Expectancy Questionnaire (Devilly and Borkovec, 2000). This six-item measure was developed for clinical studies to measure treatment expectancy and rationale credibility. It yields two subscale scores reflecting affectively based expectancy and cognitively based credibility.

Primary Outcomes

Objectively Measured Sleep

The Actiwatch Spectrum Plus (Mini Mitter/Phillips/Respironics) will be used to objectively measure sleep/wake activity at baseline, post-intervention, and 3-month follow-up. In addition to sleep/wake activity, the Actiwatch Spectrum Plus records information about amount and duration of ambient white light luminance in units of lux. Participants will wear the device, which is similar in size to a watch, on the non-dominant wrist for 7 consecutive days immediately prior to each assessment. Actiwatch Spectrum Plus data will be scored and analyzed with Actiware Sleep v6.1.2 (Phillips-Respironics, Mini Mitter, Bend, OR, United States) to calculate sleep outcomes, such as total sleep time, percent sleep, total wake time, number and duration of nighttime awakenings, sleep mid-point, and number and duration of daytime naps (defined as a minimum of 10 consecutive min of inactivity). These data will also be used to calculate circadian activity rhythms (Marler et al., 2006) and the sleep regularity index (Phillips et al., 2017), which are indicators of circadian rhythm robustness. Participants will be instructed to press the event marker on the Actiwatch when initiating sleep effort at the start of the main sleep period, when discontinuing sleep effort upon final awakening, and when taking daytime naps. When wearing the Actiwatch, participants will also complete an actigraphy log in which they will record instances of and reasons for Actiwatch removal, which will be used to inform editing of the actigraphy data (Ancoli-Israel et al., 2015).

Subjectively Measured Sleep

Consensus Sleep Diary. Participants will complete the Consensus Sleep Diary (Carney et al., 2012) daily during the intervention period and whenever wearing the Actiwatch Spectrum Plus. The

Consensus Sleep Diary includes questions about time to bed, time to sleep, number and duration of nighttime awakenings, time of final awakening, time out of bed, and overall sleep quality. Diary data will guide the weekly sleep opportunity window for those receiving sleep restriction. It will also be used in conjunction with the actigraphy log to facilitate actigraphy scoring, as described above (Ancoli-Israel et al., 2015).

Perceived Sleep Quality. The eight-item Patient Reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance Short Form 8a (Yu et al., 2012) will be used to assess perceived sleep quality at baseline, post-intervention, and 3-month follow-up. Respondents rate the quality of their sleep over the prior 7 days on a five-point scale ranging from *Very poor* to *Very good* and rate the frequency with which they experienced different sleep symptoms on a five-point scale ranging from *Not at all* to *Very much*. Higher scores reflect worse sleep quality. All PROMIS assessments generate *T* scores that are standard scores with a mean of 50 and a standard deviation of 10 based on the reference population in which the measure was developed. For many PROMIS measures this is the general United States population; however, the Sleep Disturbance scale was developed with a population enriched for chronic illness. Thus, a score of 50 on this scale represents the average for individuals slightly more impaired than the general population.

Sleep-Related Daytime Impairment. The eight-item PROMIS Sleep-related Impairment Short Form 8a (Yu et al., 2012) will assess perceived impairment during wake associated with sleep problems at baseline, post-intervention, and 3-month follow-up. Respondents rate the frequency with which they experienced daytime sleep-related symptoms over the prior 7 days on a five-point scale ranging from *Not at all* to *Very much*. Higher scores indicate greater daytime impairment. The PROMIS Sleep-related Impairment scale was also developed with a population enriched for chronic illness, and thus scores can be interpreted similarly to the Sleep Disturbance scale.

Secondary Outcomes

Health-Related Quality of Life

The 27-item Functional Assessment of Cancer Therapy – General (FACT-G) (Webster et al., 2003) will measure HRQOL at baseline, post-intervention, and 3-month follow-up. Participants indicate the extent to which each item has applied to them over the past week using a five-point scale ranging from *Not at all* to *Very much*, with higher scores indicating better HRQOL. The measure yields four subscales reflecting physical, social, emotional, and functional well-being, which can be summed to yield a total score.

Symptom Burden

The Memorial Symptom Assessment Scale. The 32-item Memorial Symptom Assessment Scale (MSAS; Portenoy et al., 1994) will evaluate overall symptom burden at baseline, post-intervention, and 3-month follow-up. The MSAS measures the prevalence of, severity of, and distress associated with 32 physical and psychological symptoms over the course of the past week. Frequency of symptoms is rated on a four-point scale ranging from *Rarely* to *Almost constantly*, severity of symptoms is rated on a four-point scale ranging from *Mild* to *Very severe*, and symptom-related distress is measured on a five-point scale ranging from *Not at all* to *Very much*. The measure yields three sub-scales reflecting physical symptom burden, psychological symptom burden, and overall distress. A total score can also be computed, with higher scores indicating greater symptom burden.

Patient Reported Outcomes Measurement Information System-Cancer Computer Adaptive Tests

Symptoms of fatigue (Lai et al., 2011), anxiety (Pilkonis et al., 2011), and depression (Pilkonis et al., 2011, 2014) will be assessed at baseline, post-intervention, and 3-month follow-up with PROMIS-Cancer computer adaptive tests. The PROMIS-Cancer scales were derived from established PROMIS item banks and were refined to increase the cancer-relevance of the measures (Garcia et al., 2007). For all constructs, respondents rate their symptom experience over the past 7 days on a five-point scale ranging from *Never* to *Always*. Select items in the Fatigue item bank use a five-point scale ranging from *Not at all* to *Very much* or from *None* to *Very*. Across all item banks higher scores indicate greater symptom burden.

Urine

Urinary 6-sulfatoxymelatonin (aMT6s), the primary urinary metabolite of melatonin, will be measured at baseline, post-intervention, and 3-month follow-up as a marker of circadian rhythms. The night prior to each assessment participants will collect three urine samples: pre-bedtime, overnight including the first morning void, and approximately 3 h after the first morning void (Cook et al., 2000). For each sample, total volume will be recorded, aMT6s and creatinine will be determined, and the concentration of aMT6s will be calculated and expressed as μg/g Cr (Schernhammer and Hankinson, 2009).

Adherence

In Part 1 of the study, participants will provide information about protocol adherence in the semi-structured interview and accompanying survey. In both parts of the study, adherence to sleep restriction and stimulus control instructions will be gathered by self-report and from the Consensus Sleep Diaries that participants will complete daily during the 6-week intervention period. Re-Timer^{TM} usage and reasons for non-adherence will be recorded on a daily Re-Timer^{TM} log (Fox et al., 2021).

Analytic Plan

Across both parts of the study, descriptive statistics will be used to characterize the sample.

Part 1: Qualitative Approach

For Part 1 of the study, two coders will review the semi-structured interview transcripts and independently generate a preliminary list of themes regarding barriers and facilitators of treatment adherence using a constant comparative approach (Glaser and Strauss, 1967). The coders will meet regularly to

discuss and compare themes. Redundant and irrelevant themes will be removed, and a coding dictionary will be developed for the remaining analysis. Coders will use this dictionary to code all transcripts, and data saturation will be evaluated. Past work indicates that saturation often occurs within the first 12 interviews, and basic themes may be identifiable as early as the sixth interview (Guest et al., 2006). Therefore, 15 interviews will be conducted to increase the likelihood of reaching saturation. Results, consisting of the most prevalent and important themes and corresponding quotations from participants, will inform any needed modifications to the delivery of the candidate intervention components to enhance adherence in Part 2.

Part 2: Intervention Optimization

For Part 2, we will use benchmarks of 80% recruitment (i.e., 80% of eligible survivors) and 80% retention to demonstrate feasibility. We will use a benchmark of 60% protocol adherence for each candidate intervention component, based on prior studies of CBT-I and bright light in cancer survivors (Berger et al., 2003; Ancoli-Israel et al., 2012). Descriptive statistics will be applied to the FACIT-TS-G items to examine acceptability.

To identify the optimal combination of candidate intervention components, longitudinal mixed effects models will be fit to the data with primary and secondary outcomes evaluated in separate models. All study time points will be included in these models, and fixed effects will include time (a nominal variable with three levels, which will be entered as two indicator variables), each candidate intervention component, and two-way interactions among components. The effect of a component at post-intervention and 3-month follow-up will be assessed based on that component's interaction with time. Candidate intervention components will be defined using effect coding (absence: -1, presence: $+1$) so effects remain uncorrelated (Kugler et al., 2012). Models will also adjust for hypothesized covariates as outlined above, as well as demographic and baseline clinical characteristics found to significantly differ across conditions. Further analyses will evaluate if the presence of multiple candidate intervention components has a greater effect on each outcome than single components. To do this, an additional variable will be created to indicate the number of components to which a participant was exposed (0, 1, 2, 3). This variable will be included as a fixed effect in these models, along with its interaction with time.

In addition to optimizing the intervention, we will also explore the potential mediating role of circadian markers (i.e., aMT6s, circadian activity rhythms, sleep regularity) on the effects of candidate intervention components. The potential mediating role of sleep disturbance on the relationships of intervention components to HRQOL and symptom burden will also be evaluated. Given the exploratory nature of this analysis, interpretation will focus on effect sizes rather than statistical significance.

Power analyses for Part 2 were conducted using the Factorial Power Plan Macro for SAS (Dziak et al., 2013) to detect an effect size $\geq$0.40 for main effects and two-way interactions with 80% power and two-sided alpha = 0.05. Analyses will be conducted using a maximum likelihood estimation approach, which provides valid inference in the presence of missing data under a missing at random assumption (Enders and Bandalos, 2001). Once all data are collected, they will be imported into SPSS (IBM, Armonk, NY, United States) (IBM Corp, 2020) for cleaning. Data will then be analyzed in SPSS (IBM Corp, 2020), and MPlus (Muthén & Muthén, Los Angeles, CA, United States) (Muthén and Muthén, 1998-2017).

DISCUSSION

The goal of this study is to optimize a behavioral intervention to decrease sleep disturbance, improve HRQOL, and diminish symptom burden among survivors of gynecologic cancers. While efficacious when adhered to, current leading behavioral sleep intervention packages are burdensome and often have low adherence among oncologic samples. Part 1 of the study will address this concern by utilizing qualitative methods to identify barriers to and facilitators of intervention adherence, with results informing subsequent treatment delivery to maximize participant engagement. Additionally, delivering bundled treatment packages without assessing their individual components can lead to unnecessary burden and inefficient use of resources, because inactive components may be included in these treatments. By leveraging the MOST framework, Part 2 of this study will efficiently test the efficacy of three candidate intervention components independently and in combination to identify a resource-efficient, maximally effective, evidence-based behavioral sleep intervention for gynecologic cancer survivors that consists of exclusively active components. Feasibility, acceptability, and adherence will also be explored.

The primary limitation of this study is that intervention components that were not examined could be important to sleep disturbance, HRQOL, and/or symptom burden. However, we selected the components under evaluation because, taken together, they directly address both components of the two-process model of sleep-wake regulation (Borbely et al., 2016), emphasize the most well-supported components of CBT-I, and include a lower-burden systematic bright light exposure component that has shown promising efficacy and acceptability in past studies. Nonetheless, future research may benefit from examining other candidate intervention components. Additionally, it is possible that participants with non-insomnia sleep disorders may be recruited, as diagnostic sleep interviews are not being conducted as part of screening. However, to minimize the likelihood of this occurring we will assess past diagnosis of a sleep disorder by both self-report and medical record review.

To our knowledge, this is the first study that will apply the MOST framework to develop an efficient, minimally burdensome behavioral sleep intervention. Select prior studies have attempted to disentangle multicomponent sleep interventions like CBT-I using a comparative treatment design, in which participants

receive an intervention component in isolation, a combination of components, or a control (Epstein et al., 2012; Harvey et al., 2014). However, unlike the present study, this approach has not supported exploration of interactions among components. The present study will use optimization strategies so the final treatment includes only active components, and intervention delivery will be adapted to promote treatment adherence. Given the notable impact and implications of sleep disturbance among gynecologic cancer survivors, there is a great need to identify non-pharmacological treatments to address symptoms with as little burden as possible. If the components ultimately included in the optimized intervention prove to be feasible and acceptable, this work will yield a resource-efficient behavioral intervention that is primed for evaluation in a subsequent, large, fully powered RCT. This in turn could identify an effective treatment package to diminish the highly prevalent and understudied problem of sleep disturbance among survivors of gynecologic cancers.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

RF, PZ, KK, ET, SA-I, JS, FP, LW, KR, CR, and JO contributed to the conception and design of the study. RF wrote the first draft of the manuscript. JG wrote the sections of the manuscript. All authors contributed to manuscript revision, and read and approved the submitted version.

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Preventing Sleep Disruption With Bright Light Therapy During Chemotherapy for Breast Cancer: A Phase II Randomized Controlled Trial

*Michelle Rissling[1], Lianqi Liu[2], Shawn D. Youngstedt[3], Vera Trofimenko[4], Loki Natarajan[5,6], Ariel B. Neikrug[7], Neelum Jeste[8], Barbara A. Parker[2,6] and Sonia Ancoli-Israel[1,6]**

[1] Department of Psychiatry, University of California, San Diego, San Diego, CA, United States, [2] Department of Medicine, University of California, San Diego, San Diego, CA, United States, [3] Edson College of Nursing and Health Innovation, Arizona State University, Phoenix, AZ, United States, [4] St. Joseph Hospital, Orange, CA, United States, [5] Family Medicine and Public Health, University of California, San Diego, San Diego, CA, United States, [6] Moores Cancer Center, University of California, San Diego, San Diego, CA, United States, [7] Department of Psychiatry and Human Behavior, University of California, Irvine, Irvine, CA, United States, [8] Johnson & Johnson, San Diego, CA, United States

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***Correspondence:**
Sonia Ancoli-Israel
sancoliisrael@health.ucsd.edu

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Purpose: The goal of this study was to examine whether daily increased morning light exposure would maintain or improve sleep and the circadian pattern of relatively more activity in the day and less during the night in women undergoing chemotherapy for breast cancer.

Patients and Methods: Participants were 39 women with newly diagnosed breast cancer, randomized to either 30-mins of daily morning bright white light (BWL) or dim red light (DRL). Sleep/wake was measured objectively for 72-h with wrist actigraphy and subjectively with the Pittsburgh Sleep Quality Index (PSQI) prior to and during chemotherapy cycles 1 and 4. The study was registered with the National Institutes of Health ClinicalTrials.gov (Clinical Trials number: NCT00478257).

Results: Results from actigraphy suggested that compared to the DRL group, women in the BWL group had longer night-time sleep, fewer sleep disturbances during the night, and had fewer and shorter daytime naps at the end of cycle 4 of chemotherapy as well as exhibiting less activity at night and more activity during the day by the end of cycle 4. Results from PSQI indicated that components of sleep quality improved but daytime dysfunction deteriorated during cycle 4 treatment in the BWL group; meanwhile the DRL group used more sleep medications in the treatment weeks which might have led to the improved sleep quality during the recovery weeks of both cycles.

Conclusion: These results suggest that bright white light therapy administered every morning on awakening may protect women undergoing chemotherapy for breast cancer from nighttime sleep and daytime wake disruption. Randomized clinical trials in larger samples are needed to confirm these findings.

Keywords: breast cancer, light therapy, sleep, actigraphy, PSQI, activity

INTRODUCTION

Disturbed sleep is one of the most common and distressing complaints among patients with breast cancer, occurring in 30–50% of patients undergoing chemotherapy (Savard and Morin, 2001). Nighttime sleep disruptions, such as difficulty falling asleep, staying asleep, and frequent awakenings, are aggravated in women with breast cancer undergoing chemotherapy (Ancoli-Israel et al., 2006; Berger et al., 2007; Palesh et al., 2010). Patients with cancer also complain of increased daytime napping (Engstrom et al., 1999) described as longer and more frequent daytime naps as treatment progresses (Berger and Farr, 1999; Young-McCaughan et al., 2003; Levin et al., 2005; Wielgus et al., 2009), which has been associated with decreased daytime activity that, in turn, has been found to predict higher cancer-related fatigue (CRF) (Berger and Farr, 1999; Wielgus et al., 2009).

Many studies measuring sleep in cancer have used actigraphs, a wrist worn device which measures activity which can be used to estimate sleep and wake. Despite the ability of actigraphy to simultaneously measure both sleep and activity (Berger et al., 2008), relatively few studies have evaluated both outcomes in patients with breast cancer undergoing chemotherapy (Young-McCaughan et al., 2003; Berger et al., 2007).

Previous research in our laboratory found that women with breast cancer have decreased daytime light exposure both before and during chemotherapy, with the most pronounced decrease in light exposure during the treatment infusion weeks of chemotherapy (Liu et al., 2005). Synchronized endogenous circadian activity rhythms are related to exposure to diurnal bright light (Kripke et al., 2007); low diurnal illumination levels have been associated with nocturnal sleep dysfunction (Terman et al., 1995; Ancoli-Israel et al., 2002). Sleep and mood disruptions have been successfully treated with morning exposure to increased artificial bright light in other populations, including individuals with winter depression (Rosenthal et al., 1985; Terman and Terman, 2005), non-seasonal depression (Al-Karawi and Jubair, 2016), anxiety (Youngstedt and Kripke, 2007), and PTSD (Youngstedt et al., 2021). Our laboratory has shown that morning bright light therapy prevents cancer related fatigue from getting worse, prevents circadian activity rhythms from deteriorating and improves quality of life in women undergoing chemotherapy for breast cancer (Ancoli-Israel et al., 2011; Neikrug et al., 2012; Jeste et al., 2013). Morning light therapy has been combined with cognitive behavioral therapy to improve sleep in women undergoing chemotherapy (Bean et al., 2020); however, there are no studies evaluating just bright light therapy on sleep or activity in this group. Thus, we evaluated whether administration of bright light upon awakening in the morning would alleviate the poor nighttime sleep and lower daytime alertness experienced during chemotherapy in women with breast cancer.

MATERIALS AND METHODS

We conducted a small phase II randomized clinical pilot study comparing bright white light (BWL) therapy to dim red light (DRL) therapy in women diagnosed with breast cancer undergoing four cycles of adjuvant or neo-adjuvant chemotherapy. The study was conducted between July 2005 and June 2007

Patients

Data were collected from the same women reported in previous publications on the effect of light on fatigue, circadian activity rhythms and quality of life (Ancoli-Israel et al., 2011; Neikrug et al., 2012; Jeste et al., 2013). As reported in those studies, 58 women were referred by physicians for the study (see **Figure 1**). Of those referred, 17 were ineligible after screening and 41 were consented and randomized. Of the 41 randomized, two participants (one from each group) dropped out immediately and were not included in the analysis; eight women from the BWL and three women from the DRL dropped during the treatment phase and were included in the analysis. Therefore, data are presented from 39 women (mean age = 53.95 years, *SD* = 9.06, range = 32–70 years).

Inclusion and Exclusion Criteria

Participants were referred by medical oncologists in the San Diego community or from the UCSD Moores Cancer Center. Inclusion criteria were having a new diagnosis of stage I–III breast cancer and scheduled to receive at least four cycles of adjuvant or neoadjuvant chemotherapy. Exclusion criteria were being pregnant, having metastatic or IIIB (including inflammatory) breast cancer, significant pre-existing anemia, or confounding underlying medical illnesses or any other physiological or psychological impairments that would have limited participation. Breast cancer disease staging was based on the American Joint Committee on Cancer Staging Manual 5th Edition (Greene, 2002). Menopausal status was determined using self-report of the occurrence of menses (Rissling et al., 2011).

After referral from the oncologist, informed consent, HIPAA, and release of information were obtained by the study coordinator. Pertinent medical information [e.g., stage of disease and estrogen/progesterone receptor status (ER/PR)] was abstracted from each participant's medical record prior to participation in the study.

Approval for this study was received from the University of California San Diego Office of IRB Administration and by the UC San Diego Moores Cancer Center's Protocol Review and Monitoring Committee. All women provided written informed consent before participation. The study was registered with the National Institutes of Health ClinicalTrials.gov (Clinical Trials number: NCT00478257).

Study Design

Figure 2 shows the study design which included a baseline assessment, treatment randomization prior to the start of chemotherapy followed by daily morning light treatment for four cycles of chemotherapy. After baseline, actigraphy and questionnaires were repeated only during the treatment and recovery weeks of cycles 1 and 4 of chemotherapy. Each chemotherapy cycle was either 2 or 3 weeks as the recommended

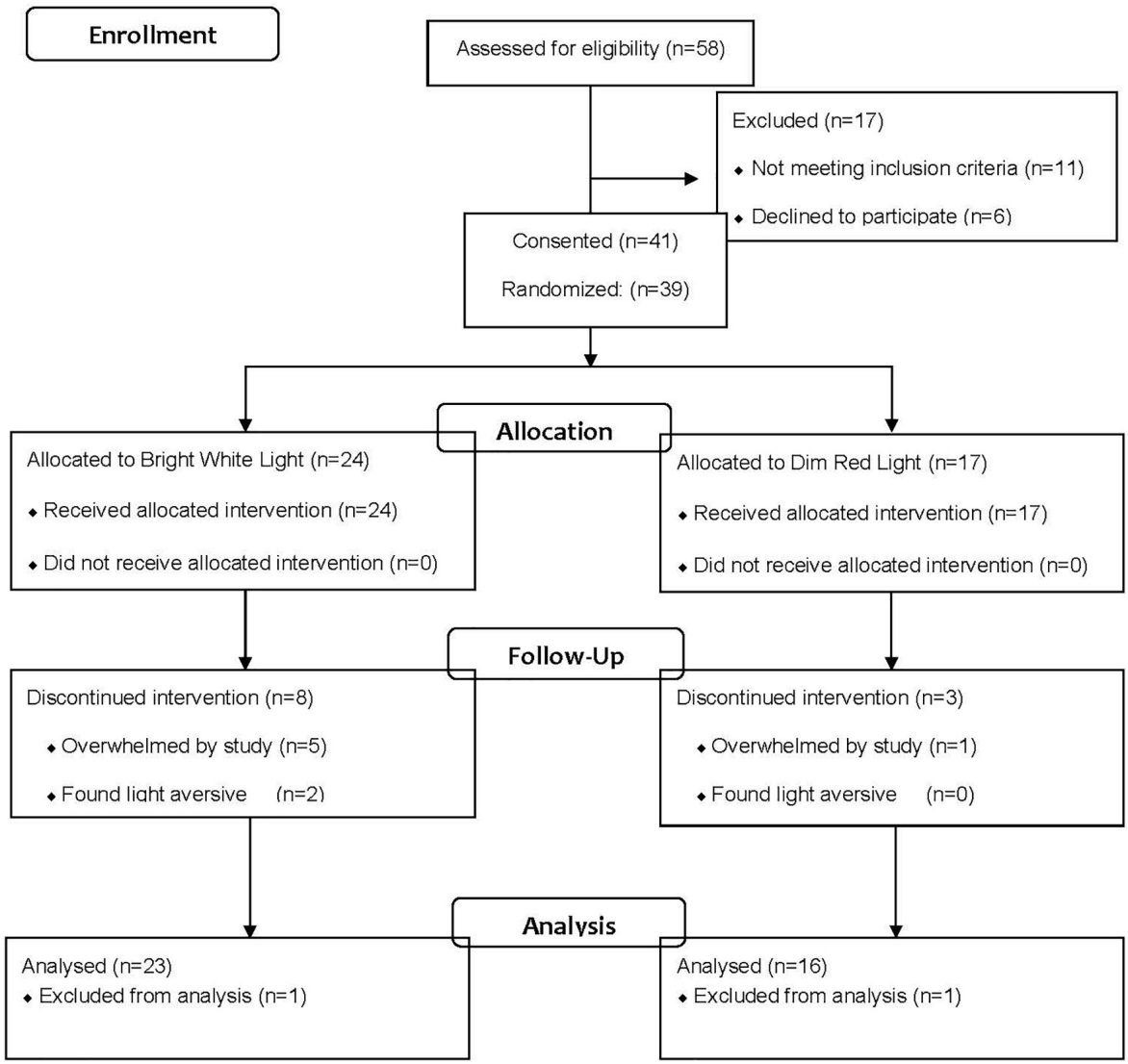

FIGURE 1 | Consort table depicting sample sizes at each point of the study.

chemotherapy regimen changed in the middle of our study. Wrist actigraphs were worn for three consecutive 24-h periods (72-h) at each of the five time-points: prior to the start of chemotherapy (baseline), chemotherapy treatment week of cycle 1 (C1TW), recovery week of cycle 1 (C1RW), chemotherapy treatment week of cycle 4 (C4TW), and recovery week of cycle 4 (C4RW). Actigraphy periods coincided with each participant's scheduled weekday chemotherapy infusions. All questionnaires could be filled out any time during the 3 days that actigraphy data were collected. The actigraph and the questionnaires were all picked up together.

Results of questionnaire data assessing fatigue, mood, quality of life, functional outcome, menopausal status and climacteric symptoms have been previously published (Liu et al., 2009, 2012; Ancoli-Israel et al., 2011; Rissling et al., 2011; Neikrug et al., 2012; Jeste et al., 2013).

Randomization

The randomization sequence was generated by the study statistician using the R statistical software package.[1] A blocked design with a 2:3 allocation to dim red light (DEL; n = 16) versus bright white treatment (BWL; n = 23) using a block size of 4. Our hypothesis was that BWL would be more beneficial; and therefore, more participants were randomized to BWL to provide a larger sample with this treatment. Both treatments were non-invasive. The study coordinators were blinded to the randomization allocation of participants.

Instructions to Participants

Each participant was provided with a Litebook®, a demonstration of proper operation, a paper tape measure and digital timer.

[1] http://cran.r-project.org/

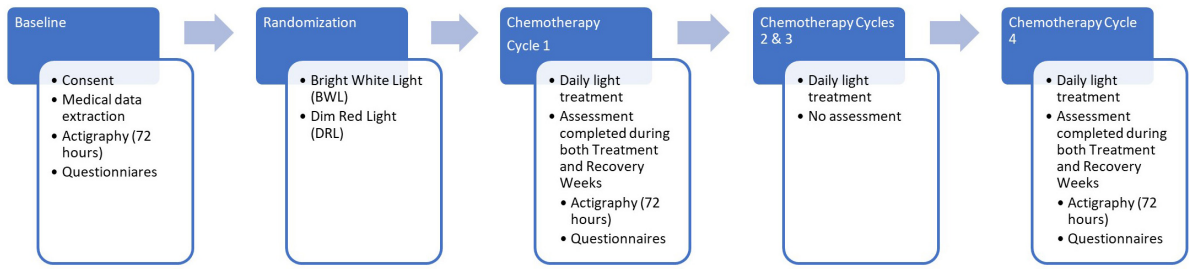

FIGURE 2 | Flow diagram depicting study procedures including timing of actigraphy and questionnaire assessments.

Participants were instructed how to position the Litebook® and to operate it for 30 continuous minutes immediately upon awakening every day throughout their four cycles of chemotherapy. The goal of the study was described to participants by the study coordinators as an evaluation of two frequencies of light therapy (red or white) for improving sleep and fatigue during chemotherapy.

Light

Light was administered *via* a Litebook® 1.2 (Litebook Ltd., Medicine Hat, AB, Canada). The Litebook® is a small ($6'' \times 5'' \times 1''$) and lightweight (8 oz.) light box designed to be placed on a table about $18''$ from the patient's head and within a 45° visual field. As previously published (Ancoli-Israel et al., 2011; Neikrug et al., 2012), light was administered with the Litebook® 1.2 (Litebook Ltd., Medicine Hat, AB, Canada). The Litebook® utilizes 60 white light-emitting diode (LED) lights with a distribution of energy particularly concentrated in the middle and long wavelengths (Desan et al., 2007) and which mimic the visible spectrum of sunlight (about 1,500 lux) for minimum glare and maximum eye comfort, without emitting ultraviolet (UV) light. Two women randomized into the BWL group reported the light aversive and dropped out during treatment; however, these data are included in the analysis. An identical-appearing device utilizing red LEDs emitting dim red light at <50 lux was used for the comparison DRL group. No participants reported the dim red light aversive.

The Litebooks® were modified to include an integrated meter which allowed for monitoring treatment adherence by recording operation time and duration. Partial adherence data were available for 30 participants (BWL $n = 17$; DRL $n = 13$); analysis indicated similar frequency of use (BWL = 55.0%; DRL = 70.2% of days assigned) and duration of use [BWL = 31.5 min (SD = 9.89); DRL = 33.9 min (SD = 10.93) per day used] with no significant difference between the groups.

Measures

Pittsburgh Sleep Quality Index

Sleep quality was measured with the Pittsburgh Sleep Quality Index (PSQI), a 19-item questionnaire which rates patients' reports of sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication and daytime dysfunction (Buysse et al., 1989). The total PSQI scores range from 0 to 21 with high scores reflecting poor sleep quality. A total score above 5 is generally considered poor sleep. Due to the timeline of the data collection, in consultation with Dan Buysse, the developer of the PSQI (personal communication), the PSQI was modified to assess sleep over the past week.

Actigraphy

Wrist actigraphy devices were used for obtaining objective measures of nighttime and daytime sleep as well as for activity levels. Wrist actigraphy measures motion over time by recording the amount of electrical deflection during a fixed interval (e.g., minute by minute) (Ancoli-Israel et al., 2003; Ancoli-Israel et al., 2015). In the current study, two similar actigraphy devices were used. The Actillume® was used with the first 11 participants (Ambulatory Monitoring, Inc., Ardsley, NY, United States). Actillume® data were analyzed using the Action-3 software program (Ambulatory Monitoring Inc., Ardsley, NY, United States). Actillume® data for nine participants (BWL = 5; DRL = 4) are included in these analyses. The Actiwatch-Light® (Mini-Mitter| Respironics/Philips, Eindhoven, Netherlands) was used in the remainder of the participants ($n = 28$). Actiwatch-Light® data were analyzed using the Actiware® 5 sleep and activity monitoring software program (Mini-Mitter| Respironics). Activity sensitivity threshold was set to medium. Both devices record continuous acceleration data on the non-dominant wrist using a battery-operated microprocessor that senses motion with a piezoelectric beam and detects movement in all three axes. As previously published, device equivalency was evaluated by comparing data collected by paired devices worn simultaneously for 72-h by eight healthy adult volunteers (Liu et al., 2005, 2013a,b; Ancoli-Israel et al., 2014). The software-scored sleep/wake data based on the two types of activity count were highly correlated (both r's > 0.85, both p's < 0.0001), therefore, these variables were deemed equivalent for the purpose of this study. Data from 39 participants (BWL = 23, DRL = 16) are included in analyses.

Actigraphic sleep variables were derived from a mean of three continuous sleep and wake (night/day) periods using 1-min epochs. Self-report *via* sleep log was used to edit actigraphy data and determine daytime and nighttime sleep and wake periods. Nighttime variables included: nighttime average activity counts per minute, sleep percentage (%sleep), nighttime total sleep time (TST) and nighttime total waketime (TWT). Daytime variables included: daytime average activity counts per minute, mean nap duration (mNAP), number of daytime naps (nNAP), and total nap time (TNT). A daytime sleep episode, or nap, was defined

as any period of 10 or more minutes of consecutive actigraphic inactivity (i.e., sleep) during the period between final out of bedtime in the morning and into bedtime the following night.

Statistical Analyses

Descriptive statistics were calculated for the entire sample as well as separately for the two treatment groups. Group differences were assessed with *t*-tests at baseline for possible confounders (i.e., demographic variables, clinical characteristics, and chemotherapy regimen). Variables that significantly differed between the treatment groups at a 0.05 significance level were controlled for in the inferential analysis.

Linear mixed-effects models were used for analyzing changes of subjective sleep quality, objective activity count and sleep/wake variables before and during chemotherapy, with group, time and group-by-time interaction included as fixed covariate effects. Baseline was the reference time point and the DRL group was the reference group. Each of the outcome variables were modeled separately. If a significant group, time or group-x-time interaction was found, further *post hoc* tests were conducted using appropriate contrasts: between group differences at each time point, and/or within group changes from Baseline to the other time points. Linear mixed-effects models and restricted maximum likelihood methods (Diggle et al., 1996) were employed for analyzing and comparing sleep and activity variables for each treatment group. This paradigm relies on the "missing at random" assumption (Diggle et al., 1996) and allows for modeling partial data where the number of measures per person could vary and participants with missing time points could still be included in the analysis. Thus, mixed model protects from a "completers only" bias.

RESULTS

Demographics

Table 1 shows the sociodemographic characteristics of our sample. There were no significant differences between the treatment groups in age, BMI, race, income, education, marital status, ER/PR status, or stage of disease.

Objective Sleep Measures

Nighttime Sleep

At baseline, the BWL group had significantly less TST than the DRL group ($p = 0.01$), thus the baseline TST was adjusted in all linear mixed-effects models. No other group differences were found at baseline (both p's > 0.2 for %sleep and TWT).

While controlling for baseline differences, a significant group-by-time interaction was found for TST at both C4TW ($p = 0.042$) and C4RW ($p = 0.012$; **Figure 3A**). Compared with baseline, the BWL group had significant increases in TST at C4TW and C4RW (p's < 0.03), whereas the DRL group had no significant changes in TST at these time points.

Significant group-by-time interactions were found for %sleep and TWT at C4RW (**Figures 3B,C**). Compared with baseline, the DRL had a significant decrease in %sleep ($p < 0.05$) and a significant increase in TWT ($p < 0.05$) at C4RW, whereas

TABLE 1 | Demographic and medical characteristics at baseline ($N = 39$).

Variable	BWL ($n = 23$)	DRL ($n = 16$)	p value[a]
Age: mean years (*SD*)	54.26 (9.31)	53.50 (8.96)	0.799
BMI (*SD*)	29.03 (7.78)	29.58 (8.25)	0.836
Marital status: [*n* (%)]			0.882
Never married	1 (4.4)	1 (6.3)	
Divorced	7 (30.4)	3 (18.8)	
Widowed	2 (8.7)	1 (6.3)	
Married	13 (56.5)	11 (68.8)	
Ethnicity/race [*n* (%)]			0.952
African American Black	4 (17.4)	2 (12.5)	
Asian	2 (8.7)	1 (6.3)	
Caucasian	15 (65.2)	13 (81.3)	
Other	2 (8.7)	0 (0.0)	
Education [*n* (%)]			0.879
Some high school or less	2 (8.7)	0 (0.0)	
Completed high school	6 (26.01)	6 (37.5)	
Some college	8 (34.8)	4 (25.0)	
College degree	7 (30.4)	6 (37.5)	
Annual family income [*n* (%)]			0.222
≤$15,000	5 (21.7)	3 (18.8)	
≤$30,000	6 (26.1)	0 (0.0)	
≤$50,000	1 (4.4)	2 (12.5)	
≤$100,000	4 (17.4)	2 (12.5)	
>$100,000	5 (21.7)	6 (37.5)	
Did not Answer	2 (8.7)	3 (18.8)	
Menopausal status pre-chemotherapy [*n* (%)]			0.982
Premenopausal	5 (21.7)	4 (25.0)	
Perimenopausal	3 (13.0)	2 (12.5)	
Postmenopausal	8 (34.8)	7 (43.8)	
Post-hysterectomy	6 (26.1)	3 (18.8)	
Unknown	1 (4.4)	0 (0.0)	
Cancer stage [*n* (%)]			0.789
Stage I	4 (17.4)	5 (31.3)	
Stage II	10 (43.5)	6 (37.5)	
Stage III	4 (17.4)	2 (12.5)	
Unknown	5 (21.7)	3 (18.8)	
Surgery [*n* (%)]			0.750
Lumpectomy	7 (30.4)	8 (50.0)	
Mastectomy	9 (39.1)	6 (37.5)	
Double mastectomy	4 (17.4)	1 (6.3)	
Pre-op chemotherapy	2 (8.7)	1 (6.3)	
Unknown	1 (4.4)	0 (0.0)	
Chemotherapy regimen [*n* (%)]			0.162
Exactly four cycles of AC	3 (13.0)	3 (18.8)	
Exactly four cycles of AC + Taxotere	5 (21.7)	0 (0.0)	
Exactly four cycles of AC + Taxol	6 (26.1)	2 (12.5)	
6 cycles of TAC	2 (8.7)	4 (25.0)	
Other regimen	4 (17.4)	6 (37.5)	
Unknown	3 (13.0)	1 (6.3)	
Prior use of hormone replacement therapy [*n* (%)]			0.155
Yes	2 (8.7)	4 (25.0)	

(Continued)

TABLE 1 | (Continued)

Variable	BWL (n = 23)	DRL (n = 16)	p value[a]
No	13 (56.5)	10 (62.5)	
Unknown	8 (34.8)	2 (12.5)	

BWL, bright white light; DRL, dark red light; BMI, body mass index.
[a]*Two sample T test for continuous variables and Fisher's Exact test for categorical variables.*

the BWL had no significant changes in these variables at these time points.

Daytime Sleep

No group differences in daytime sleep at baseline were detected (all p's > 0.3). A significant group-by-time interaction for nNAP was found at both C4TW and C4RW (p's < 0.05; **Figure 4A**). Compared with baseline, nNAP increased significantly at C4TW (p < 0.03) and C4RW (p = 0.0003) in the DRL group, whereas the BWL group had no significant changes in nNAP at these time points.

Significant group-by-time interactions for TNT were found at C4TW and C4RW (ps < 0.05; **Figure 4B**). Compared with baseline, in the DRL group, TNT increased significantly at C4TW (p = 0.0003) and but changes during C4RW were not significant. In the BWL group there were no significant changes in TNT.

Significant group-by-time interactions for mNAP were found at C1TW (p < 0.03), C4TW (p < 0.05), and C4RW (p < 0.05; **Figure 4C**). Compared with baseline, mNAP increases significantly at C1TW (p < 0.0003) and C4TW (p < 0.05) and non-significantly at C4RW (p < 0.05) in the DRL group, whereas compared with baseline, mNAP had a small (non-significant) increase at C1TW, and small (non-significant) decreases at C4TW and C4RW in the BWL group.

Activity

Activity During the Nighttime Sleep Period

As shown in **Figure 5A**, activity counts during the nighttime sleep period did not differ between groups at baseline (p = 0.16). At C4RW a significant group-by-time interaction was found (p = 0.047). Compared with baseline, at C4RW the DRL group had a significant increase in nighttime sleep period activity (p = 0.033), whereas the BWL group showed a non-significant decrease in nighttime sleep activity count. No other group-by-time effect was found for activity during the night period.

Activity During the Daytime Wake Period

As shown in **Figure 5B**, activity counts during the daytime wake period did not differ between groups at baseline (p = 0.35). A significant group-by-time interaction was observed at C4TW (p = 0.013). Compared with baseline, at C4TW the DRL group had significantly less activity counts (p < 0.001), whereas the BWL did not have a significantly change in activity count. A similar pattern was observed during C1TW; compared with baseline, activity counts decreased in the DRL group (p < 0.001) but did not change significantly in the BWL group. However, the group-by-time interaction was not significant at C1TW, nor for other assessment times.

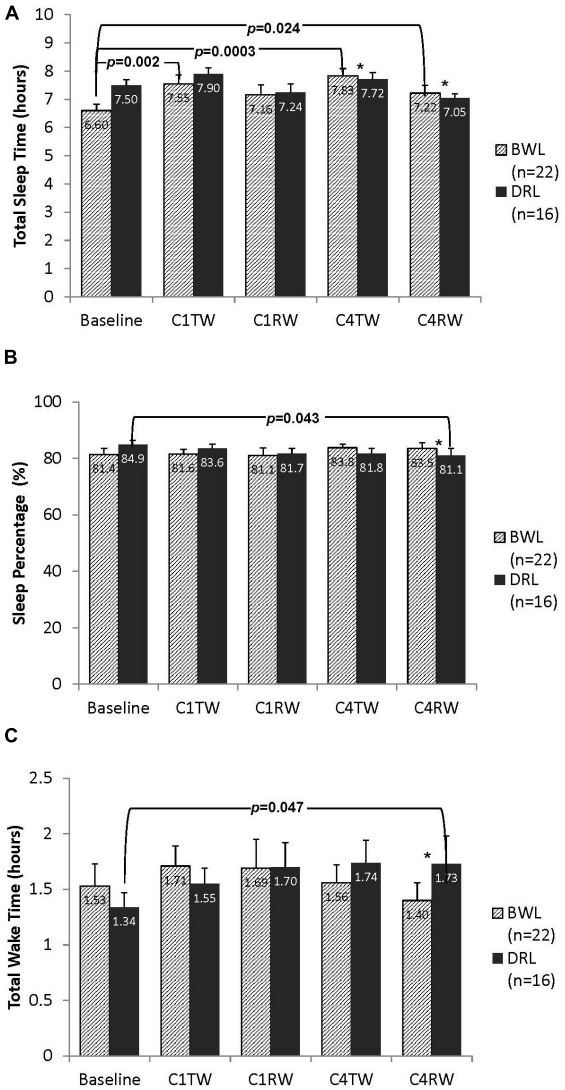

FIGURE 3 | Bar graphs depicting nighttime **(A)** total sleep time, **(B)** sleep percentage, and **(C)** total wake time for both bright white light (BWL) and dim red light (DRL) treatment groups from baseline through the treatment weeks (TW) and recovery weeks (RW) of chemotherapy cycles 1 and 4. With the exception of recovery week of cycle 1 (C1RW), the BWL group demonstrated longer total sleep time **(A)** compared to baseline. On the other hand, DRL group demonstrated longer total wake time **(C)** and lower sleep percentage **(B)** during the recovery week of cycle 4 (C4RW). *p < 0.05 for group-by-time interaction, indicating that compared to DRL group, BWL group had significant longer total sleep time during cycle 4 (both C4TW and C4RW), significant higher sleep percentage and shorter total wake time during C4RW.

Subjective Sleep Quality

Pittsburgh Sleep Quality Index global and component scores are listed in **Table 2**. There were no significant differences in the PSQI global or component scores between the BWL group and the DRL group at baseline (all p's > 0.05), and also no significant

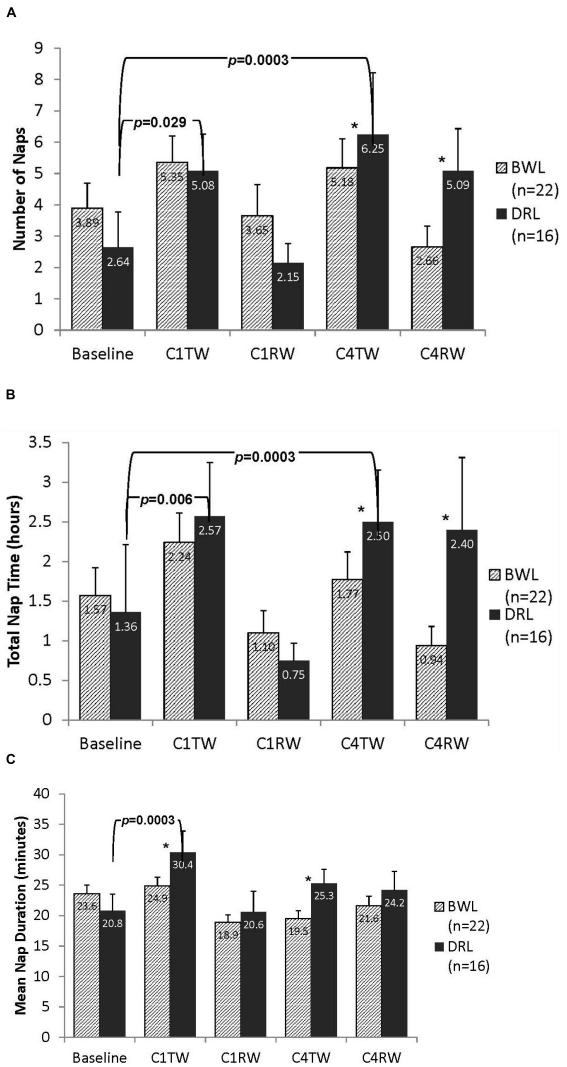

FIGURE 4 | Bar graphs depicting daytime **(A)** number of naps, **(B)** total nap time, and **(C)** mean nap duration for both BWL and DRL treatment groups from baseline through the TW and RW of chemotherapy cycles 1 and 4. With the exception of recovery weeks (C1RW and C4RW), the DRL group demonstrated more frequent **(A)** and longer **(B)** naps as chemotherapy treatment progressed. Mean nap duration **(C)** also increased at C1TW for the DRL group, $^*p < 0.05$ for group-by-time interaction, indicating that compared to DRL group, BWL group had significant fewer naps and shorter total nap time during cycle 4 (both C4TW and C4RW).

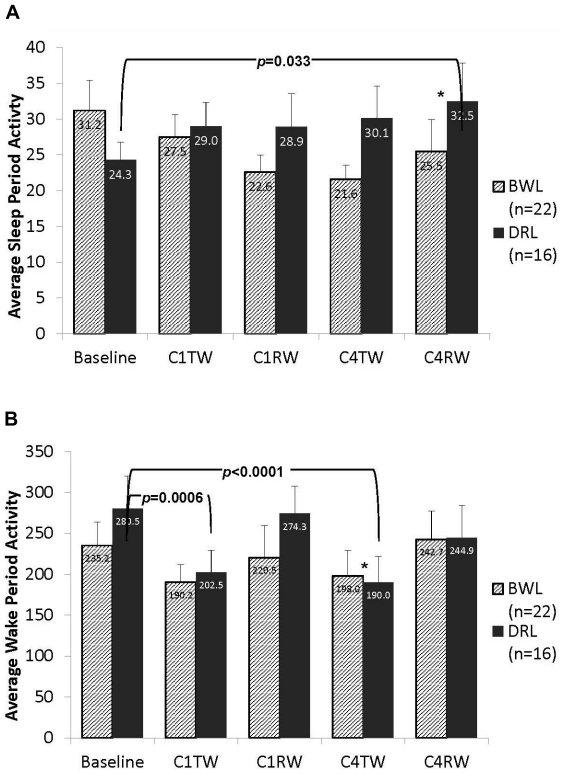

FIGURE 5 | Bar graphs depicting average counts per minute for both **(A)** the nighttime sleep period and **(B)** the daytime wake period activity in the BWL and DRL treatment groups from baseline through the TW and RW of chemotherapy cycles 1 and 4. As depicted in panel **(A)**, the average nighttime activity decreased in the BWL group while the DRL increased from baseline to the end of cycle 4 (C4RW). Conversely, as depicted in panel **(B)**, the average daytime activity decreased in the DRL group from baseline to the treatment weeks of cycle 1 (C1TW) and cycle 4 (C4TW). $^*p < 0.05$ for group-by-time interaction, indicating that compared to DRL group, BWL group had significant less daytime activity decrease during C4TW.

group-by-time interactions for the global or component scores during either cycle (all p's > 0.05). Within the BWL group, compared to baseline, there were significantly lower scores in three subscales (i.e., improvement in subjective sleep quality, sleep duration, sleep disturbances) during C4RW, however, the daytime dysfunction component score increased (i.e., worse daytime function) during both weeks of cycle 4 (both p's < 0.05). Within the DRL, compared to baseline, the subjective sleep quality component score decreased during the recovery weeks of both cycles (i.e., sleep quality improved) but the use of sleeping medication increased during the treatment weeks of both cycles (all p's < 0.05).

DISCUSSION

The results of this study suggest that morning bright white light administered daily during chemotherapy to women with breast cancer may help reduce deterioration of nighttime sleep and sleep quality and reduce daytime sleepiness.

During the weeks of chemotherapy administration, the weeks of greatest distress, the women in both treatment groups took more and longer naps. During the recovery week of cycle 1, both groups returned to the pre-chemotherapy levels. However, by the fourth cycle, the cumulative effects of chemotherapy resulted in less sleep at night and more and longer naps during the day in the women in the DRL group while women in the BWL group showed an increase in nighttime sleep and a return to pre-chemotherapy levels of napping.

TABLE 2 | Mean (*SE*) Pittsburgh sleep quality index (PSQI) total and component scores by group condition and mixed model analysis.

PSQI	Bright white light					Dim red light				
	Baseline *N* = 16	C1TW *N* = 14	C1RW *N* = 13	C4TW *N* = 12	C4RW *N* = 14	Baseline *N* = 22	C1TW *N* = 17	C1RW *N* = 18	C4TW *N* = 16	C4RW *N* = 15
Global	8.9 (0.9)	9.1 (0.8)	8.6 (1.0)	8.5 (0.9)	6.9 (0.9)	7.9 (0.9)	8.1 (1.1)	7.1 (1.3)	7.9 (0.9)	6.9 (1.1)
Subjective sleep quality	1.3 (0.2)	1.4 (0.2)	1.0 (0.2)	0.9 (0.2)	0.4** (0.1)	1.6 (0.2)	1.4 (0.3)	1.0* (0.3)	1.1 (0.2)	0.9* (0.2)
Sleep latency	1.4 (0.2)	1.4 (0.2)	1.4 (0.2)	0.9 (0.3)	0.8 (0.3)	1.5 (0.3)	1.1 (0.3)	1.2 (0.3)	1.0 (0.3)	1.3 (0.3)
Sleep duration	1.3 (0.2)	0.9 (0.2)	0.9 (0.2	0.9 (0.2)	0.9* (0.2)	0.8 (0.1)	0.8 (0.2)	0.5 (0.2)	0.4 (0.2)	0.5 (0.1)
Habitual sleep efficiency	1.8 (0.3)	1.9 (0.3)	1.3 (0.3)	1.6 (0.3)	1.1 (0.3)	1.3 (0.3)	0.9 (0.3)	0.9 (0.3)	1.2 (0.4)	0.7 (0.3)
Sleep disturbances	1.5 (0.1)	1.4 (0.2)	1.2 (0.1)	1.3 (0.2)	1.1* (0.2)	1.6 (0.1)	1.5 (0.2)	1.4 (0.1)	1.7 (0.2)	1.5 (0.1)
Use of sleeping medication	1.1 (0.3)	1.4 (0.4)	1.7 (0.3)	1.8 (0.4)	1.6 (0.4)	0.7 (0.3)	1.5* (0.4)	1.3 (0.4)	1.4* (0.4)	1.2 (0.4)
Daytime dysfunction	0.6 (0.2)	0.8 (0.2)	0.9 (0.2)	1.1* (0.1)	1.0* (0.2)	0.6 (0.2)	0.9 (0.2)	0.7 (0.2)	1.0 (0.2)	0.8 (0.2)

*Compared to Baseline in each group: *p < 0.05, **p < 0.01; there were no significant group by time interactions for both groups at any time point (all p's > 0.1).*

Similar results were observed in sleep quality. While no significant group by time interaction was observed by the end of cycle 4 chemotherapy, compared to baseline, the BWL group reported improvement in nighttime sleep quality (subjective sleep quality, sleep duration and sleep disturbance components). Reports of daytime dysfunction, however, increased. This deterioration of daytime functioning during the fourth cycle of treatment might be attributed not only to disturbed sleep, but also to the cumulative side-effects of cancer treatment. The finding that the DRL group reported improved sleep quality during the treatment weeks of both cycles may be explained by the concurrent increase in sleep medication use (Huedo-Medina et al., 2013). Taken together, the objective sleep and subjective sleep quality results suggest that overall, the bright white light resulted in less deterioration of sleep.

In addition to the effects on sleep, significant changes in the amount of activity both during the sleep period and the wake period were observed. Berger et al. (2009) showed that there is little distinction between night and day activity, as measured by actigraphy during chemotherapy, which suggested both disrupted sleep at night and disrupted wake during the day (2009). Having high actigraphic activity counts during the wake period and low counts during the sleep period has been associated with higher survival (Mormont et al., 2000; Innominato et al., 2009), better quality of life (Innominato et al., 2009), and lower levels of depression (Du-Quiton et al., 2010) and fatigue (Innominato et al., 2009) in patients with cancer. Having a more robust circadian pattern of acigraphic activity and better sleep has also been predictive of less cognitive decline in women with breast cancer (Ancoli-Israel et al., 2021). In the current study, women exposed to dim red light had decreased wake-time activity during chemotherapy treatment weeks of cycle 1 and cycle 4, as might be expected during chemotherapy, while those exposed to bright white light had no significant changes in daytime activity compared to baseline. During the sleep period, those in the BWL group showed less activity than those in the DRL group. These data suggest that bright white light also protected the women from the deterioration in wake-time physical activity usually experienced during chemotherapy. Nonetheless, activity levels during the wake period are considered low (Kwan et al., 2020). Even modest increases in physical activity could potentially elicit improvements in sleep (Mercier et al., 2017) and in circadian synchronization (Youngstedt et al., 2019).

The impetus for this study was the prior observation that women undergoing chemotherapy receive progressively less bright light exposure as treatment progresses, particularly in the days following chemotherapy infusion, and that this decrease is associated with fatigue and sleep disturbances (Liu et al., 2005). Previously reported data from this sample demonstrated that bright light therapy prevented cancer-related fatigue (Ancoli-Israel et al., 2011) and prevented deterioration of both the circadian activity rhythm (Neikrug et al., 2012) and subjective quality of life during chemotherapy (Jeste et al., 2013). The current results demonstrate not only a lack of deterioration of sleep and activity in the bright white light group but also improvement in daytime sleep and nighttime activity compared to pre-chemotherapy levels.

We believe that the most likely mechanisms mediating sleep improvement reported in the present study are the indications of better circadian entrainment by light (Neikrug et al., 2012). Bright light entrains the circadian system by stimulating retinal photoreceptors in the retina, which interact with the SCN *via* a monosynaptic pathway, as well as multi-synaptic pathways from the retina to the ventral lateral geniculate nucleus and intergeniculate nucleus (Golombek and Rosenstein, 2010). Effects of bright light on alertness and sleepiness (Badia et al., 1991) also might have contributed to better nighttime sleep, as well as reduced napping noted in the present study. However, whether

the observed benefit of bright light therapy was due to the alerting effect of light, to the improvement in circadian activity rhythms or some other unobserved mechanism, cannot be determined from this study.

While there have been a few other studies examining the effect of bright light treatment on sleep in cancer survivors (Johnson et al., 2016, 2018; Starreveld et al., 2018; Valdimarsdottir et al., 2018; Wu et al., 2018; Fox et al., 2020), to our knowledge, this is the first randomized controlled trial examining the effect of bright light therapy on sleep (measured both objectively and subjectively) and activity during chemotherapy in women with breast cancer. Berger et al. (2009) found a positive effect on sleep in a similar population using a modified behavioral therapy that included both nighttime and daytime sleep restriction; however, the improvement in the treatment group was limited to an improvement in subjective sleep quality and fewer objectively measured awakenings at night (daytime sleep was not reported). While these results are suggestive that targeting both nighttime and daytime sleep disruption using a behavioral treatment may be beneficial during chemotherapy, the lack of objective improvement in sleep also suggests that additional intervention may be needed.

Notwithstanding the significant group-by-time effects for several of the variables, the clinical significance of some of these effects was minimal. While bright light has been shown to be highly effective in fatigue, circadian rhythms and quality of life in these same women (Ancoli-Israel et al., 2011; Neikrug et al., 2012; Jeste et al., 2013), the percent sleep remained low and total wake time remained high at all time points. Combining bright light with other treatments, such as cognitive behavioral treatment for insomnia (Bean et al., 2020) or exercise (Mercier et al., 2017) may have additive benefits with greater clinical efficacy.

The strengths of the current study include the randomized controlled and longitudinal design; in particular, the inclusion of a baseline prior to chemotherapy in addition to data collection during chemotherapy. Additional strengths include the inclusion of both subjective and objective measures of sleep and the utilization of the mixed model statistical analysis which allowed for partially complete subject records (i.e., missing data at some time-points), thereby avoiding the biases of "completers only" analysis.

However, there are also limitations to the study. The first major limitation is the small sample size. With a larger sample size, trends such as the deterioration found in the DRL group may have been statistically significant. However, this was a preliminary study intended to provide Phase II data for a larger randomized trial. Secondly, the physical activity results should be interpreted with caution as we did not employ waist actigraphy. Our main interest was on sleep for which wrist actigraphy is a reliable measure (Ancoli-Israel et al., 2003; Ancoli-Israel et al., 2015). More detailed assessment of physical activity and exercise is needed in future work. A third limitation may be the 72-h period of actigraphy data collection. This shorter period was chosen to both reduce patient burden and to ensure sufficient time for baseline data collection as often the time period between recruitment and the start of chemotherapy was less than 1 week.

In summary, the breast cancer chemotherapy group receiving dim red light showed expected and progressive deterioration during chemotherapy, particularly in daytime sleepiness and inactivity during the day during cycle 4. The bright white light group, however, showed significantly less deterioration and were less sleepy and more active during the day at cycle 4 showing a greater ability to recover from the cumulative negative effects of chemotherapy. Larger studies are needed to replicate these findings; however, the study suggests that morning bright light, an easy, non-invasive, non-harmful behavioral treatment, may at least prevent deterioration of nighttime sleep and promote daytime activity and alertness in women undergoing chemotherapy for breast cancer.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of California San Diego Office of IRB Administration and by the UC San Diego Moores Cancer Center's Protocol Review and Monitoring Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SA-I was the PI of the study. MR led the writing of the manuscript and contributed to the data collection and interpretation. LL contributed to the study conception, design, material preparation, and commenting on all versions of the manuscript. SY contributed to writing and commenting on previous versions of the manuscript. VT and LN contributed to the study conception, design, material preparation, and writing and commenting on previous versions of the manuscript. LN performed the statistical analyses. AN contributed to material preparation, data collection, and commenting on all versions of the manuscript. SA-I, NJ, and BP contributed to the study conception, design, material preparation, and writing and commenting on all versions of the manuscript. All authors read and approved the final manuscript.

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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SYSTEMATIC REVIEW
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Sleep During Oncological Treatment – A Systematic Review and Meta-Analysis of Associations With Treatment Response, Time to Progression and Survival

Louise Strøm[1], Josefine T. Danielsen[1], Ali Amidi[1], Ana Lucia Cardenas Egusquiza[2], Lisa Maria Wu[1,3] and Robert Zachariae[1,4]*

[1] *Unit for Psycho-Oncology and Health Psychology, Department of Psychology and Behavioral Sciences, Aarhus University, Aarhus, Denmark,* [2] *Department of Psychology and Behavioral Sciences, Center for Autobiographical Memory Research, Aarhus University, Aarhus, Denmark,* [3] *Aarhus Institute of Advanced Studies, Aarhus University, Aarhus, Denmark,* [4] *Department of Oncology, Aarhus University Hospital, Aarhus, Denmark*

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Jeremy Borniger, Stanford University, United States

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****Correspondence:***
Louise Strøm
louisestroem@psy.au.dk

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Introduction: Disrupted sleep and sleep-wake activity are frequently observed in cancer patients undergoing oncological treatment. These disruptions are often associated with aggravated symptom burden and diminished health-related quality of life that in turn may compromise treatment adherence and, thus, effectiveness. In addition, disrupted sleep has been linked to carcinogenic processes, which ultimately could result in worse prognostic outcomes.

Aims: Our aim was to systematically review and conduct a meta-analysis of studies examining the associations between sleep and sleep-wake activity and prognostic outcomes in cancer patients undergoing oncological treatment.

Methods: A comprehensive systematic search of English language papers was undertaken in June 2020 using PubMed, The Cochrane Library, and CINAHL. Two reviewers independently screened 4,879 abstracts. A total of 26 papers were included in the narrative review. Thirteen papers reporting hazard ratios reflecting associations between a dichotomized predictor variable (sleep) and prognostic outcomes were subjected to meta-analysis.

Results: Nineteen of the 26 eligible studies on a total of 7,092 cancer patients reported associations between poorer sleep and poorer response to treatment, shorter time to progression, and/or reduced overall survival, but were highly heterogeneous with respect to the sleep and outcome parameters investigated. Meta-analysis revealed statistically significant associations between poor self-reported sleep and reduced overall survival (HR = 1.33 [95% CI 1.09–1.62], k = 11), and shorter time to progression (HR = 1.40 [95% CI 1.23–1.59], k = 3) and between poor objectively assessed sleep and reduced overall survival (HR = 1.74 [95% CI 1.05–2.88], k = 4).

Conclusion: The current findings indicate that disturbed sleep during treatment may be a relevant behavioral marker of poor cancer prognosis. The limited number of studies, the common use of single item sleep measures, and potential publication bias highlight the need for further high quality and longitudinal studies.

Keywords: cancer patients, sleep, sleep-wake activity, survival, time to progression, treatment response

INTRODUCTION

Disturbances and alterations in sleep architecture and behavior commonly occur when individuals experience medical illness (Opp and Krueger, 2015), and cancer is no exception (Clevenger et al., 2012; Sharma et al., 2012; Loh et al., 2018). Such sleep disturbances are often associated with aggravation of symptom burden (Palesh et al., 2010; George et al., 2016) and impairments to quality of life (Trudel-Fitzgerald et al., 2014; Nho et al., 2017). Additionally, accumulating evidence highlights the important role of healthy sleep in cell genome stability (Lamia, 2017), efficient immune responses (Fondell et al., 2011; De Lorenzo et al., 2015), and sufficient melatonin secretion that can mitigate carcinogenic processes (Schernhammer and Schulmeister, 2004; Mirza-Aghazadeh-Attari et al., 2020). Hence, sleep disturbances and disorders have been linked to various pathologies, including increased risk of cancer (Erren et al., 2016; Mogavero et al., 2021), all-cause mortality in the general population (Dew et al., 2003), and tumor progression in mouse models (Papagiannakopoulos et al., 2016; De Lorenzo et al., 2018). Moreover, once diagnosed with cancer, the cancer itself may serve as an indirect factor influencing sleep, through various pathophysiological processes, including inflammation, which has been proposed as an underlying biological mechanism of sleep disturbance (Raison et al., 2010; Irwin et al., 2016; Besedovsky et al., 2019). This suggests that the cancer-related inflammatory response may be an additional contributor to alterations in cancer patients' sleep (Mantovani et al., 2008). Apart from biological mechanisms, psychological symptoms, such as heightened stress, depression, and anxiety may also play an important role in the manifestation of sleep disturbance (Ancoli-Israel, 2009; Liu et al., 2009). In addition, persistent behavioral problems, including those arising from pediatric cancers, may contribute to long-term sleep disturbance (Mogavero et al., 2020). However, both psychologically and biologically driven sleep disturbances are most likely bi-directionally related, both contributing to the perpetuation and exacerbation of sleep and sleep-wake irregularity (Krueger et al., 2003, 2009; Meier-Ewert et al., 2004; Rockstrom et al., 2018; Ashok Kumar et al., 2019), which makes the relationship between sleep, sleep-wake activity, tumorigenesis and cancer progression highly complex.

While sleep disturbances may be present in cancer patients already prior to treatment (Zhou et al., 2018), many patients undergoing oncological treatment, especially chemotherapy and radiotherapy, experience sleep problems with prevalence estimates ranging from 30% to 75% (Ancoli-Israel et al., 2001; Savard et al., 2009, 2015; Palesh et al., 2010; Costa et al., 2014). Cancer prognosis has improved for most cancers, especially with the introduction of new targeted therapies like immune checkpoint inhibitors (Kennedy and Salama, 2020). However, sleep disturbances during treatment in these patients could challenge response to treatment and compromise survival, by potentially aggravating symptom burden, hence compromising adherence to treatment (Kidwell et al., 2014), as well as potentially disrupting immunological and endocrine processes in protecting the body against cancer development (Eismann et al., 2010). In a meta-analysis by Stone et al. (2019), long sleep duration was found to be associated with increased cancer-specific mortality for all-cancers, and all-cause mortality for breast cancer. While this review added to the field by highlighting the long-term risks of sleep duration on cancer-specific mortality, it focused on sleep duration in cancer survivors both pre-diagnosis and years after treatment completion. Other meta-analyses investigating sleep and cancer-mortality have been limited, primarily focusing on general population samples (Gallicchio and Kalesan, 2009; Ma et al., 2016). Thus, to the best of our knowledge, no review has been published on the association between sleep disturbance during oncological treatment and the subsequent response to treatment, time to progression and survival. However, this is an important time period in the trajectory of cancer patients, since an increased symptom burden including sleep disturbance may have prognostic consequences.

Therefore, the primary aim of the present review was to systematically review and conduct a meta-analysis of available studies examining associations between disturbed sleep and sleep-wake activity and cancer prognostics, e.g., treatment response, time to progression, and survival in a population of cancer patients undergoing oncological treatment.

Improving our knowledge about the association between sleep during treatment and treatment response and survival, could enable the development of targeted interventions to support patients' recovery, at a critical time in the course of their disease.

METHODS

Registration and Search Strategy

This present systematic review and meta-analysis adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009), and was pre-registered in PROSPERO (Page et al., 2018) (registration ID: CRD42020189880). A broad systematic search of English language papers was undertaken by the first author and a librarian in June 2020 using PubMed, The Cochrane Library, and CINAHL. The following search terms were used, including MeSH-terms or MeSH-term equivalents: (Sleep OR insomnia OR "circadian rhythm" OR rhythm) AND (immunotherapy OR

immunotherapies OR "checkpoint inhibitor" OR "checkpoint inhibitors" OR ICI OR ICIs OR "PD-1" OR "PD-L1" OR nivolumab OR pembrolizumab OR chemotherapeutic OR chemotherapy OR "cancer treatment*" OR cytostatic) AND (effect OR effects OR outcome OR outcomes OR "clinical response" OR "clinical effect" OR response OR "response to treatment" OR survival OR mortality OR prognos*) AND (cancer OR neoplasms OR neoplasm). No publication date restriction was imposed.

Selection Criteria and Screening

Identified records were imported to the review software Covidence (Kellermeyer et al., 2018). Two authors (LS and JTD) independently screened 4,879 abstracts, according to predefined hierarchically displayed inclusion criteria based on the PICO framework (Sackett et al., 1996) and adapted to meet our research question: "Is sleep and sleep-wake activity in cancer patients receiving oncological treatment associated with response to treatment, time to progression and survival?". Inclusion criteria were: (1) cancer patients regardless of diagnosis, who have received approved oncological treatment, except for transplantation; (2) all sleep-related measures (self-reported and objective) represented by at least one quantified item, assessed after diagnosis, and immediately prior to or during cancer treatment; (3) outcome evaluated in relation to a sleep measure (4) outcome constitutes clinical response to oncological treatment, overall survival or time-to-progression after oncological treatment; and (5) all types of observational and controlled trial studies of adult humans (≥18 years), except for Phase 1 studies.

If abstracts reported both a sleep measure and measure of treatment response or survival indicating that results on a possible association could be found in the full text, studies were considered eligible for full text review. Full texts were independently screened by two authors (LS and JTD), and reasons for exclusion were documented. Conflicts were resolved at consensus meetings with a third author (RZ). Subsequently, reference lists of included studies and relevant reviews were screened for papers missed by the systematic database search. Moreover, included studies were objects for citation searches.

Quality Assessments

Methodological quality and risk of bias assessment, was undertaken independently by two authors (LS and JTD) for all included studies, using the NIH Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (National Heart Lung, 2014). Although 12 studies based their results on samples obtained in randomized controlled trails, the measurement of sleep data and outcome met criteria for observational designs.

Data Extraction and Synthesis

Data extraction was performed independently by two authors (LS and AC). The data extraction form included: name of first author, year of publication, title of paper, study design, number of participants, age and gender of participants, diagnosis of participants, treatment regimens, treatment-naivety, method used for assessing sleep or sleep-wake activity (i.e., subjective/objective assessment), time of reported sleep measure (i.e., prior to treatment, during treatment), sleep measure (actigraphy measure, sleep scale or sleep item), number of assessments, outcome measure (i.e., response rate, response classification, time to progression/progression free survival, and overall survival) results, and median follow-up time. In case of missing data, the corresponding author of set paper was contacted for this information. A narrative method was applied to synthesize the findings, and an *a priori* decision was made to perform a meta-analysis if a minimum of three studies reported comparable predictor and outcome measures. Analyses were grouped according to the predictor being self-reported or objective and according to the reported treatment outcome (i.e., overall survival, time-to-progression and response to treatment).

Meta-Analytic Strategy

A total of 13 studies were subjected to meta-analysis to ascertain the pooled overall effect estimate and its precision. Eligibility criteria were results of unadjusted analyses reported as hazard ratios reflecting associations between a dichotomized predictor variable (sleep) and the outcome. One study reporting only adjusted analyses (Sullivan et al., 2006), was also included. To aid the interpretation of the results, we conducted a Bayesian Model-Averaged meta-analysis, as a supplement to the conventional frequentist meta-analysis (Gronau et al., 2017). The frequentist analyses were performed using Comprehensive Meta-Analysis, version 3 (Borenstein et al., 2013). The supplementary Bayesian analyses were conducted with JASP Version 0.12.2 (JASP Team, 2022).

Pooling Effects

An inverse variance-weighted random-effects model considering the precision of each study was used in all analyses, with hazard ratios larger than 1.0 taken to indicate an effect in the hypothesized direction, i.e., poor sleep associated with a shorter time to progression or shorter overall survival. Three studies reported survival outcomes for several sleep variables (Palesh et al., 2014; Cash et al., 2018; Gottfried et al., 2020). For these studies, the results were combined into one pooled weighted result to ensure independence of effects included in the meta-analysis.

Heterogeneity

Heterogeneity was investigated using Q and I^2 statistics (Higgins et al., 2019). Heterogeneity tests aim at determining to which degree the variation in effect sizes reflects true differences (heterogeneity) or sampling error. The I^2 value is an estimate of the between-study variance in a pooled effect estimate that is accounted for by heterogeneity of the effect sizes in the included studies and is assumed to be relatively unaffected by the number of studies (Higgins et al., 2003). If the results indicated heterogeneity ($I^2 > 0.0$), we calculated the 95% prediction interval, which estimates the expected range of true effects in 95% of similar future studies (IntHout et al., 2016).

Publication Bias

The possibility of publication bias was assessed using funnel plots and Egger's test (Egger et al., 1997). If results were suggestive of possible publication bias, sensitivity analyses were conducted by imputing the "missing studies" and calculating adjusted effect estimates using the Duval and Tweedie trim-and-fill method (Duval and Tweedie, 2000).

Moderator Analysis

To explore possible sources of heterogeneity ($I^2 > 0.0$), we examined the role on the effect size of four possible moderators with meta-regression based on random-effects models and estimated with maximum likelihood method. The moderators included percent women, median follow-up time in months, mean sample age, and cancer stage (advanced vs. mixed). If associations were found between the moderators, this was adjusted for in the analysis.

Bayesian Analysis

A supplementary Bayesian Model-Averaged meta-analysis (Gronau et al., 2017) of the associations between sleep and overall survival and time-to-progression, respectively, examined the results of four models: (a) fixed-effect null hypothesis (fH_0), (b) fixed-effect alternative hypothesis (fH_1), (c) random-effects null hypothesis (rH_0), and (d) random effects alternative hypothesis (rH_1). Bayesian Model-Averaged analysis thus avoids selecting either a fixed- or random-effects model and addresses two questions in light of the observed data: What is the plausibility that the overall effect is non-zero and is there between-study variability in the effect size? We chose an uninformed prior probability, i.e., 25%, of each of the four models and 2,000 iterations. Concerning parameter distributions, we chose previously recommended defaults (Gronau et al., 2017). We thus used a zero-centered Cauchy prior with a scale of 0.707 for the effect size. To have zero indicating the null effect, the hazard ratios and the upper and lower limits were log-transformed. For the between-study variation, we used an empirically informed prior distribution of non-zero between-study deviation estimates based on effect sizes from 705 meta-analyses published in Psychological Bulletin between 1990 and 2013 (van Erp et al., 2017). This distribution has been approximated by an Inverse-Gamma (1, 0.15) prior on the standard deviation (Tau) (Gronau et al., 2017).

RESULTS

Search Results

A total of 4,879 studies were identified after duplicate removal and 10 additional studies were identified by other sources (two studies through reference list screenings, and eight studies by citation search) of which five were eligible for full text screening. A total of 105 papers were eligible for full text screening with 26 studies being included for analysis. Exclusion of the 79 studies upon full-text screening were primarily attributed to the exclusion criteria "not relating a sleep measure to one of the predefined outcome measures, e.g., response to treatment, time to progression or overall survival" (67%). A table of all excluded studies following full-text screening including reasons for exclusion are provided in the **Supplementary Table 1**. Level of conflict following the abstract screening was 103 out of 4,879 screenings corresponding to a 97.9% agreement between reviewers. Following full text, agreement was 93.3% (Cohen's Kappa 0.82). Full-text conflicts were mainly concerned with which primary exclusion criterion to apply. Screening and selection process is provided in the PRISMA flow diagram in **Figure 1**.

Study Characteristics

Characteristics of the 26 included studies are shown in **Table 1** and described in the sections below.

Diagnosis and Stage

A total of 13 different cancer diagnoses were represented in the 26 studies. The most frequently investigated cancers were colorectal cancer reported in six studies (Mormont et al., 2000; Maisey et al., 2002; Innominato et al., 2009, 2012, 2015; Lévi et al., 2014), non-small cell lung cancer in six studies (Naughton et al., 2002; Braun et al., 2011; Zhao et al., 2013; Chang and Lin, 2014; Gottfried et al., 2020; Kuo et al., 2020), and breast cancer in five studies (Geels et al., 2000; Kramer et al., 2000; Zhao et al., 2013; Chang and Lin, 2014; Palesh et al., 2014). In four studies, the sample consisted of mixed cancer populations (Zhao et al., 2013; Chang and Lin, 2014; Collins et al., 2017; Chandra et al., 2019). Twenty-four studies included patients with advanced disease, of which 10 studies included mixed cancer stages, and two studies failed to report cancer stage (Geels et al., 2000; Chandra et al., 2019).

Study Samples

The sample sizes ranged from 33 to 1,194 (median = 190). Three studies reported data from the same trial, but had different study objectives and no overlapping data (Innominato et al., 2009, 2012, 2015). Thus, they were considered independent samples. One paper (Lévi et al., 2014) reported a pooled sample, consisting of three different samples. Two of these samples were already represented in our review (Mormont et al., 2000; Innominato et al., 2009), thus, only the third and newly obtained sample from the paper was included. One study (Robinson et al., 2012) reported separate data for two independent samples of women with ovarian and endometrial cancer.

Study Design and Treatment Regimen

Twelve of the studies reported their sample to be subsamples from Phase III randomized controlled trials and were therefore combined samples in which different treatment regimens were utilized. Treatment regimens were reported in 20 studies, of which 18 reported having different regimens within the same study, including systemic treatment (i.e., hormonal and chemotherapy), radiation or surgery. Seven of the 26 study samples included treatment-naive participants at study entry. Thus, in the majority of studies, participants had received oncological treatment prior to participation.

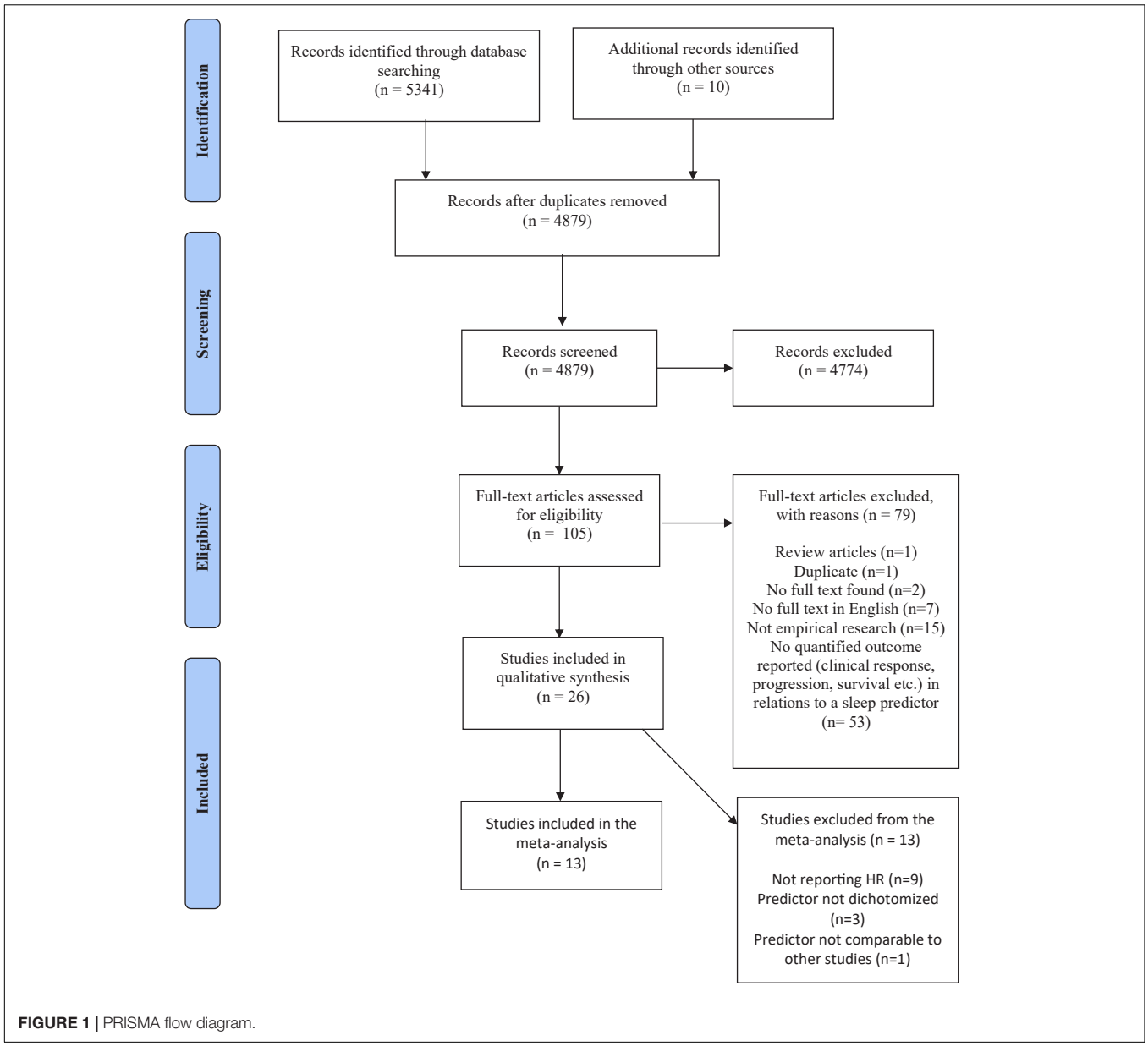

FIGURE 1 | PRISMA flow diagram.

Quality Assessments

Supplementary Table 2 provides an overview of the quality ratings for the individual studies. Overall, the ratings indicated high quality regarding clear definitions of research question, study population, exposure and outcome measures, and high quality in assessing exposure prior to outcome, as well as including a sufficient timeframe between the two. However, assessment of sleep more than once had low-quality ratings in all but five studies, and although all studies meet criteria for examining effects of different levels of sleep disturbance on outcome, levels were converted to a dichotomous variable in 16 studies, whereas six studies used quartiles, composite scores or change in symptom score between two assessments. Continuous variables were used in four studies. Moreover, power justifications were only reported in two studies.

Sleep Parameters

Both self-reported (k = 19) and objective (k = 7) measures were used to evaluate sleep, and one study (Palesh et al., 2014) reported a self-reported measure verified by an objective measure. Of the 18 studies only using self-reported sleep measures, the majority (k = 13) were based on a single item regarding sleep disturbances from the European Organization for the Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30), a validated quality of life instrument for cancer patients (Aaronson et al., 1993). In this item cancer patients respond to the following question about their sleep: "During the past week, have you had trouble sleeping?". The four available response categories are; "Not at all," "a little," "quite a bit," and "very much" (Aaronson et al., 1993). The Pittsburgh Sleep Quality Index (PSQI), a 19-item self-rated questionnaire that assesses

TABLE 1 | Study characteristics.

Study	Cancer type	Study design	N in analysis (% women)	Sleep (predictor) (S) = Self-report (O) = Objective	Timing of sleep assessment	Prognostic outcomes	Median follow-up (months)	Analysis and predictor	Results (Direction of association[1])	Included in meta-analysis (+)
Braun et al., 2011	Non-small cell lung cancer	Observational – retrospective	1194 (49.7%)	EORTC QLQ-C30 (S)	Pre-treatment	Overall survival	NR	**Unadjusted:** Insomnia **Adjusted:** NR	 ns	
Braun et al., 2012	Prostate cancer	Observational – retrospective	673 (0%)	EORTC QLQ-C30 (S)	Pre-treatment	Overall survival	NR	**Unadjusted:** Insomnia **Adjusted:** Insomnia	 ns ns	
Cash et al., 2018	Head and neck cancer	Observational – prospective	38 (40%)	Actigraphy (O)	Pre-treatment	Overall survival Response to treatment Overall survival	24	**Unadjusted:** Sleep-wake activity (r24) Sleep-wake activity (I < 0) Sleep-wake activity (I < 0) **Adjusted:** Sleep-wake activity (I < 0)	 + + +	+
Chandra et al., 2019	Hematological malignancy and lymphoma	Observational – prospective	66 (40.90%)	PSQI (S)	Pre-treatment	Overall survival	6	**Unadjusted:** Sleep quality **Adjusted:** NR	 +	
Chang and Lin, 2014	Lung, breast, gastro and liver, head and neck cancer, hematology, genitourinary	Observational – retrospective	68 (50%)	Actigraphy (O) PSQI (S)	During treatment	Overall survival	84	**Unadjusted:** Sleep-wake activity (I < 0) Sleep quality **Adjusted:** Sleep-wake activity (I < 0) Sleep quality	 + + + ns	+
Collette et al., 2004	Prostate cancer	RCT	388 (0%)	EORTC QLQ-C30 (S)	Pre-treatment	Overall survival	NR	**Unadjusted:** Insomnia **Adjusted:** Insomnia	 + +	+
Collins et al., 2017	Hepatobiliary-pancreatic system cancers as primary cancers or metastases from other primary cancers	Observational – retrospective	292 (36%)	PSQI (S)	NR	Overall survival	NR	**Unadjusted:** Sleep latency Sleep efficiency Shorter sleep duration Shorter and longer sleep duration **Adjusted:** Shorter sleep duration Shorter and longer sleep duration	 ns ns + + + +	

(Continued)

TABLE 1 | (Continued)

Study	Cancer type	Study design	N in analysis (% women)	Sleep (predictor) (S) = Self-report (O) = Objective	Timing of sleep assessment	Prognostic outcomes	Median follow-up (months)	Analysis and predictor	Results (Direction of association[1])	Included in meta-analysis (+)
								Unadjusted:		
Geels et al., 2000	Breast cancer	RCT	198 (NR)	QoL and CRF (case report forms) (S)	Pre- and during treatment	Response to treatment	NR	Insomnia (QoL)	ns	
								Insomnia (CRF)	ns	
								Adjusted:		
								NR		
								Unadjusted:		
Gottfried et al., 2020	Lung cancer	Registry-based	404 (40.80%)	Single sleep question (S)	Pre-treatment	Overall survival	26	Difficulty falling asleep	ns	+
								Frequent arousals at night	+	
								Both of the above combined	+	
								Adjusted models:		
								Sleep abnormalities	+	
								Unadjusted:		
Innominato et al., 2009	Colorectal cancer	RCT	130 (43.10%)	Actigraphy (O)	Pre- and during treatment	Overall survival	72	Sleep-wake activity (I < 0)	+	
								Sleep-wake activity (r24)	+	
								Mean rest-activity rhythm	ns	
						Response to treatment		Sleep-wake activity (I < 0 and r24)	ns	
						Progression free survival		Sleep-wake activity (I < 0 and r24)	ns	
								Adjusted models:		
						Overall survival		Sleep-wake activity (I < 0)	+	
								Unadjusted:		
Innominato et al., 2012	Colorectal cancer	RCT	77 (35.10%)	Actigraphy (O)	During treatment	Overall survival	77.2	Sleep-wake activity (I < 0)	+	+
						Response to treatment & Progression free survival		Sleep-wake activity (I < 0)	ns	
								Adjusted:		
						Overall survival		Sleep-wake activity (I < 0)	+	
								Unadjusted:		
Innominato et al., 2015	Colorectal cancer	RCT	361 (38.80%)	EORTC QLQ-C30 (S)	Pre- and during treatment	Overall survival	89.2	Insomnia	+	+
						Time to progression		Insomnia	+	
						Response to treatment		Insomnia	+	
								Adjusted:		
						Overall survival		Insomnia	+	

(Continued)

TABLE 1 | (Continued)

Study	Cancer type	Study design	N in analysis (% women)	Sleep (predictor) (S) = Self-report (O) = Objective	Timing of sleep assessment	Prognostic outcomes	Median follow-up (months)	Analysis and predictor	Results (Direction of association[1])	Included in meta-analysis (+)
Kramer et al., 2000	Breast cancer	Observational – retrospective	187 (100%)	EORTC QLQ-C30 (S)	Pre-treatment	Overall survival Response to treatment	42.2	**Unadjusted:** Insomnia Insomnia **Adjusted:** NR	 ns ns	+
Kuo et al., 2020	Lung cancer	Observational – prospective	33 (18.20%)	Actigraphy (O)	Pre-treatment	Overall survival	6.15	**Unadjusted:** Sleep-wake activity (I < 0) **Adjusted:** Sleep-wake activity (I < 0)	 + +	+
Lévi et al., 2014 (Cohort III)[2]	Colorectal cancer	RCT	436 (37.40%)	Actigraphy (O)	Pre-treatment	Overall survival Progression-free survival (PFS) Overall survival	NR	**Unadjusted:** Sleep-wake activity (I < 0) Sleep-wake activity (I < 0) **Adjusted:** Sleep-wake activity (I < 0)	 + + +	
Maisey et al., 2002	Colorectal cancer	RCT	501 (37%)	EORTC QLQ-C30 (S)	Pre-treatment	Overall survival	34.1	**Unadjusted:** Insomnia **Adjusted:** Insomnia	 + +	+
Merli et al., 2004	Non-Hodgkin's lymphoma	RCT	91 (66%)	EORTC QLQ-C30 (S)	Pre-, during and post-treatment	Treatment response	NR	**Unadjusted:** Insomnia **Adjusted:** NR	 +	
Mormont et al., 2000	Colorectal cancer	Observational – prospective	192 (33%)	Actigraphy (O)	Pre-treatment	Overall survival Objective response Overall survival	24	**Unadjusted:** Sleep-wake activity (I < 0) Sleep-wake activity (I < 0) Sleep-wake activity (r24) **Adjusted:** Sleep-wake activity (I < 0) Sleep-wake activity (r24) Mean sleep-wake activity	 + + + + + +	
Naughton et al., 2002	Small-cell lung cancer	RCT – companion study	67 (29%)	Sleep Quality Scale – four items (S)	Pre- and during treatment	Overall survival	NR	**Unadjusted:** Sleep quality **Adjusted:** NR	 ns	

(Continued)

TABLE 1 | (Continued)

Study	Cancer type	Study design	N in analysis (% women)	Sleep (predictor) (S) = Self-report (O) = Objective	Timing of sleep assessment	Prognostic outcomes	Median follow-up (months)	Analysis and predictor	Results (Direction of association[1])	Included in meta-analysis (+)
Nowak et al., 2004	Pleural mesothelioma	Phase II trial single-arm	53 (15%)	EORTC QLQ-C30 (S)	Pre-treatment	Overall Survival	NR	**Unadjusted:** Insomnia **Adjusted:** NR	 ns	
Palesh et al., 2014	Breast cancer	Observational – prospective	97 (100%)	Sleep logs and actigraphy (S), (O)	NR	Overall survival	72	**Unadjusted:** Sleep efficiency Time in bed WASO Wake episodes Wake episode duration Sleep latency **Adjusted:** Sleep efficiency WASO Wake episodes Wake episodes duration	 **+** ns **+** **+** **+** ns + + + +	+
Robinson et al., 2012	Endometrial and ovarian cancer	Cross-sectional	453 (100%)	EORTC QLQ-C30 (S)	During and after treatment	Overall survival	NR	**Unadjusted:** Insomnia (Ovarian cancer) Insomnia (Endometrial cancer) **Adjusted:** Insomnia (Ovarian cancer) Insomnia (Endometrial cancer)	 ns ns ns ns	+
Roychowdhury et al., 2003	Bladder cancer	RCT	363 (20.80%)	EORTC QLQ-C30 (S)	Pre-treatment	Overall survival Time to progression Time to treatment failure	NR	**Unadjusted:** Insomnia Insomnia Insomnia **Adjusted:** NR	 **+** **+** ns	+
Sullivan et al., 2006	Prostate cancer	RCT	765 (0%)	EORTC QLQ-C30 (S)	Pre- and during treatment	 Overall survival Time to progression	NR	**Unadjusted:** NR **Adjusted:** Insomnia Change in insomnia Change in insomnia	 ns **+** **+**	+
Teunissen et al., 2004	Gastro-entero-pancreatic cancers	Observational – prospective	42 (56%)	EORTC QLQ-C30 (S)	Pre- and post-treatment	Treatment response	1.2	**Unadjusted:** Change in insomnia **Adjusted:** NR	 **+**	

(Continued)

TABLE 1 | (Continued)

Study	Cancer type	Study design	N in analysis (% women)	Sleep (predictor) (S) = Self-report (O) = Objective	Timing of sleep assessment	Prognostic outcomes	Median follow-up (months)	Analysis and predictor	Results (Direction of association[1])	Included in meta-analysis (+)
Zhao et al., 2013	Breast, lung, lymphoma, alimentary tract or nasopharynx cancer	Observational – Open label trial	240 (47%)	PSQI (S)	Pre- and post-treatment	Treatment response	NR	**Unadjusted:** Sleep quality Change in sleep quality **Adjusted:** NR	+ +	

[1]Please note that + = Poor sleep → worse prognosis. − = Poor sleep → improved prognosis; ns, non-significant association. [2]Reported on the independent sample in the study, to avoid sample overlap with other studies. EORTC-QLQ-30, European Organization for the Research and Treatment of Cancer Core Quality of Life Questionnaire; NR, not reported; PSQI, The Pittsburgh Sleep Quality Index; RCT, randomized controlled trial; WASO, wake after sleep onset; Sleep-wake activity (r24), autocorrelation coefficient at 24 h (regularity and reproducibility of activity pattern); Sleep-wake activity (I < 0), dichotomy index (relative ratio of activity in and out of bed).

sleep quality and disturbances over a 1-month period was used in three studies (Zhao et al., 2013; Collins et al., 2017; Chandra et al., 2019). One study (Gottfried et al., 2020) reported sleep based on one of two questions: "difficulty falling asleep?" and "frequent arousals at night?". The last study (Naughton et al., 2002) assessed sleep using a single item about "trouble sleeping", but this was not clearly described.

In all of the studies with objective evaluations of sleep (k = 7), the sleep outcome was sleep-wake activity measured with actigraphy [i.e., a small non-invasive wrist-worn activity logger (Ancoli-Israel et al., 2003)]. Sleep-wake activity was evaluated using the dichotomy index I < 0, measuring the relative amount of activity in bed versus out of bed (Ortiz-Tudela et al., 2014). Three studies included an additional evaluation—the autocorrelation coefficient r24— measuring the regularity of the activity pattern over 24 h (Ortiz-Tudela et al., 2014).

Associations Between Sleep, Treatment Response, Time to Progression and Survival

Reported prognostic outcomes included treatment response, time to progression or overall survival. Survival was the most frequent outcome (k = 22), and nine of the 26 studies reported on more than one outcome. Overall, 19 of 26 studies found poor sleep to be significantly associated with poorer survival or worse treatment response, while seven studies found no associations. Poor sleep was assessed from both self-reported (e.g., insomnia symptoms, poor sleep quality) and actigraphy-derived sleep outcomes (e.g., sleep-wake activity, nighttime restfulness, wake after sleep onset, sleep latency, sleep efficiency, and wake episodes). No studies found associations between better sleep and poorer treatment response, shorter time to progression or poorer survival. Effect sizes and sample sizes differed significantly with hazard ratios ranging from 1.10 to 13.70, and sample sizes ranging from 33 to 1,194. Only two studies examined sleep duration. In one study of patients with advanced cancers affecting the hepatobiliary and pancreatic systems, both short and long sleep duration were associated with increased mortality (linear term: hazard ratio = 0.485; quadratic term: hazard ratio = 1.064) (Collins et al., 2017), but in another study of women with advanced breast cancer, there was no linear or quadratic association between sleep duration and survival (Palesh et al., 2014).

Adjusted models were reported in 16 of the 26 papers. However, covariates were neither comparable in characteristic nor in number, and only selected models were subjected to adjustments. In all but one study (Chang and Lin, 2014) results of the adjusted models remained statistically significant.

Meta-Analytic Results

Association Between Self-Reported Sleep and Overall Survival

As seen in **Table 2** and **Figure 2**, the overall combined hazard ratio for the 11 studies investigating self-reported sleep and overall survival in a total of 3,050 patients was 1.33, indicating that poorer self-reported sleep was statistically significantly associated with reduced overall survival (95% CI: 1.09–1.62;

$p = 0.005$). A sensitivity analysis omitting Sullivan et al. (2006), which had only used an adjusted model, resulted in a similar pooled effect size (HR = 1.30; 95% CI: 1.06–1.59; $p = 0.012$). A visual inspection of the funnel plot and the statistically significant Egger's test ($p = 0.012$) suggested the possibility of publication bias in the direction of an association in the hypothesized direction. As seen in **Figure 3**, the trim and fill method yielded five "missing" studies, which, when imputing these values, resulted in a smaller effect reduced to statistical non-significance. The high I^2 (87.6%) suggests that a considerable proportion of the variance is explained by systematic differences between studies rather than sampling error. When exploring the influence of possible between-study differences on the association between poorer self-reported sleep and reduced overall survival with meta-regression, the associations were significantly weaker in studies with a larger percentage of women (Slope: −0.006: $p < 0.001$). As seen in **Table 3**, the association was maintained when adjusting for cancer stage. While cancer stage was not a significant moderator of the association when adjusting for the percentage of women in the studies, a statistically weaker association (slope: −0.24; $p = 0.032$) was found between poorer sleep and reduced overall survival in studies of patients with advanced cancer, compared to studies with mixed samples. The remaining moderating factors explored did not reach statistical significance. The findings of the frequentist analysis were supported by the supplementary Bayesian Model-Averaged meta-analysis, which provided strong evidence for a non-zero effect of poor self-reported sleep on overall survival corresponding to a Bayes Factor (BF) (Duval and Tweedie, 2000) of 10.2, i.e., indicating that the alternative hypothesis is 10.2 times more likely than the null-hypothesis. The Bayesian analysis provided very strong evidence concerning heterogeneity of the effects. The BF for heterogeneity was 10^{12} indicating that the probability that the effect sizes are heterogeneous are extremely likely.

Associations Between Self-Reported Sleep and Time to Progression

As seen in **Table 2** and **Figure 4**, the overall combined hazard ratio for the three studies investigating self-reported sleep and time to disease progression in a total of 1,489 patients showed that poor self-reported sleep was statistically significantly associated with shorter time to progression (HR: 1.40; 95% CI: 1.23–1.59; $p < 0.001$). The findings of the frequentist analysis were supported by the supplementary Bayesian Model-Averaged meta-analysis, which provided strong evidence for a non-zero effect of poor self-reported sleep on time to progression corresponding to a BF (Duval and Tweedie, 2000) of 20.9, i.e., indicating that the alternative hypothesis is more than 20 times more likely than the null-hypothesis. The BF for non-heterogeneity was 2.5, providing only anecdotal evidence for non-heterogeneous effect sizes. Due to the small number of studies, publication bias and moderator analyses were not conducted.

Associations Between Objectively Assessed Sleep and Overall Survival

As seen in **Table 2** and **Figure 5**, the overall combined hazard ratio for the four studies investigating objectively assessed sleep and overall survival in a total of 216 patients showed that poor objective sleep was statistically significantly associated with reduced overall survival (HR: 1.74; 95% CI: 1.05–2.88; $p = 0.032$). However, a sensitivity analysis omitting an outlier with a HR (5.57) approaching two standard deviations from the pooled HR, resulted in a smaller, and non-significant, effect. The supplementary Bayesian meta-analysis provided only anecdotal evidence for a non-zero effect of poor objectively assessed sleep on overall survival corresponding to a BF (Duval and Tweedie, 2000) of 2.3, i.e., indicating that the alternative hypothesis is only 2.3 times more likely than the null-hypothesis. The Bayesian analysis provided strong evidence for heterogeneity of the effects with a BF of 10.3. Due to the small number of studies, publication bias and moderator analyses were not conducted.

DISCUSSION

Summary of Main Findings

To the best of our knowledge, this is the first systematic review of literature on associations between sleep immediately prior to or during treatment in cancer patients and prognostic indicators, thus filling a knowledge gap on the role of sleep during a critical period in the cancer trajectory. Overall, the findings of the narrative part of this review suggests that disturbances in sleep and sleep-wake activity immediately prior to or during treatment are associated with reduced overall survival, poorer response to treatment, and shorter time to progression. Traditional frequentist meta-analyses with Bayesian meta-analysis, provided evidence in support of poorer self-reported sleep being associated with reduced overall survival and shorter time to progression. However, these findings should be interpreted with caution due to the indications of possible publication bias with respect to the analyses of self-reported sleep, and less robust results with respect to the association between objective sleep and overall survival. Moderator-analyses showed a significantly weaker association between poor self-reported sleep and reduced overall survival in studies with a higher percentage of women. Furthermore, when adjusting for the percentage of women in the studies, a weaker association between poor self-reported sleep and reduced survival was found in samples of patients with more advanced cancer. One explanation for the moderating effect of female sex in the context of breast cancer could be that while anti-hormonal treatments improve prognosis, they at the same time induce menopausal symptoms that may interfere with sleep, e.g., hot flashes (Desai et al., 2013), thus weakening the association between sleep disturbance and poor prognosis. No studies reporting associations between sleep and response to treatment were eligible for meta-analysis, due to heterogeneity in reported sleep parameter, outcome, and analytic strategy.

Strengths, Limitations, and Future Perspectives

Several strengths of this review should be noted. First, previous reviews have primarily focused on the association between sleep duration and cancer-mortality in the general

TABLE 2 | Meta-analysis of associations between poorer self-reported sleep and overall survival and time to progression, and between poorer objective sleep and overall survival.

				Heterogeneity[c]				Pooled results			
Predictor	**Outcome**	**K[a]**	**N[b]**	**Q**	***p***	***I*²**	**Tau²**	**HR[d]**	**95%CI**	***p***	**95%PI[e]**
Self-reported sleep	Overall survival	11	3050	80.7	<0.001	87.6	0.083	1.33	1.09–1.62	**0.005**	0.67–2.65
	Adj. for publication bias[f]	*(16)*	–	–	–	–	–	*1.02*	*0.85–1.23*	*NS*	–
	Overall survival (sensitivity analysis)[g]	8	2,787	11.4	0.121	38.8	0.012	1.37	1.21–1.56	**<0.001**	1.01–1.87
	Time to progression	3	1,489	0.53	0.766	0.0	0.0	1.40	1.23–1.59	**<0.001**	–
Objective sleep	Overall survival	4	216	13.4	0.004	77.6	0.176	1.74	1.05–2.88	**0.032**	0.20–14.45
	Overall survival (sensitivity analysis)[h]	3	183	9.3	0.010	78.5	0.131	1.54	0.96–2.46	0.071	–

[a]K = number of studies in the analysis; One study reported data for two independent samples (Robinson et al., 2012). [b]N = total number of participants in the analysis. [c]Q-statistic: p-values < 0.10 taken to suggest heterogeneity; I^2 indicates the proportion of the variance in effect sizes explained systematic (non-random) between-study differences. [d]HR = hazard ratio with a value > 1 indicating an association between worse sleep and negative prognosis. [e]PI = 95% prediction interval: The interval in which 95% of future observations will fall, given the observed data, calculated for heterogeneous ESs (I^2 > 0). [f]In case of statistically significant ESs and possible publication bias (Egger's test statistically significant (p < 0.05), "missing studies" are imputed and an adjusted pooled ES calculated (Duval and Tweedie, 2000). [g]Sensitivity analysis, including only studies based on the EORTC QLQ-C30 questionnaire. [h]Sensitivity analysis omitting Kuo et al. (2020), an outlier with a HR (5.57) approaching (93%) two standard deviations from the pooled HR.

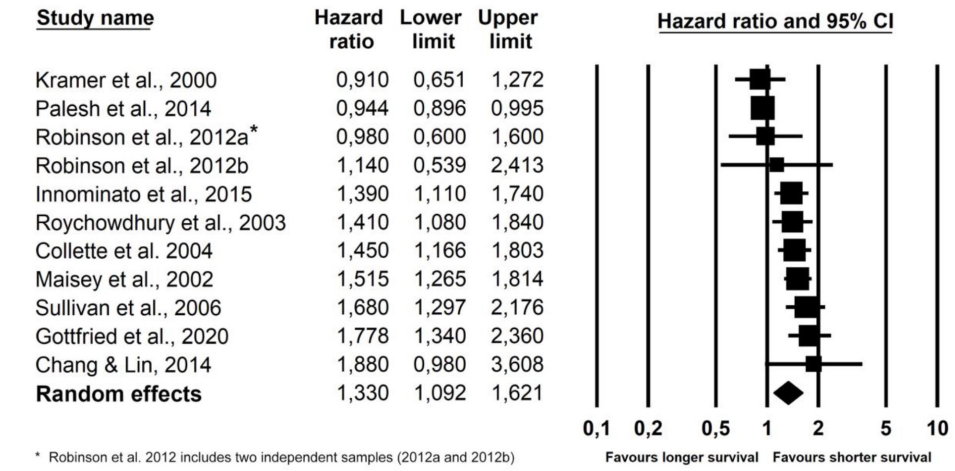

FIGURE 2 | Forest plot of poorer self-reported sleep and overall survival.

TABLE 3 | Exploring moderators of the association between poorer self-reported sleep and overall survival.

Moderator	**K[a]**	**Slope[b]**	**95%CI**	***p***
Percent women	11	−0.006	−0.007 to −0.005	**<0.001**
Percent women (adjusting for stage)	11	−0.006	−0.007 to −0.004	**<0.001**
Follow-up (months)	6	−0.003	−0.011 to 0.006	0.545
Sample mean age	5	0.032	−0.011 to 0.076	0.142
Advanced stage vs. mixed (ref.)	11	−0.117	−0.467 to 0.234	0.514
Advanced stage vs. mixed (ref.) (adjusting for percent women)	11	−0.24	−0.474 to 0.021	**0.032**

[a]Analyses conducted when K ≥ 5. [b]Mixed effects regression (unrestricted ML).

population (Gallicchio and Kalesan, 2009; Ma et al., 2016) and in cancer survivors (Stone et al., 2019). The present review of the role of disrupted sleep and sleep-wake activity, thus, provides a more nuanced picture of sleep assessed during a critical period in the cancer trajectory and its associations with prognostic outcomes. Second, the present review and meta-analysis included both self-reported and objective sleep parameters, providing a broader scope on sleep. Although related and to some extent inter-dependent (Choilek et al., 2021), self-reported and objective parameters represent qualitatively different aspects of sleep (Acker et al., 2021). Actigraphy is typically used to objectively examine sleep-wake-activity and sometimes external light conditions and temperature as proxies for determining sleep and wake periods (Acker et al., 2021), whereas self-reported evaluations of sleep capture the experienced sleep and sleep disturbance

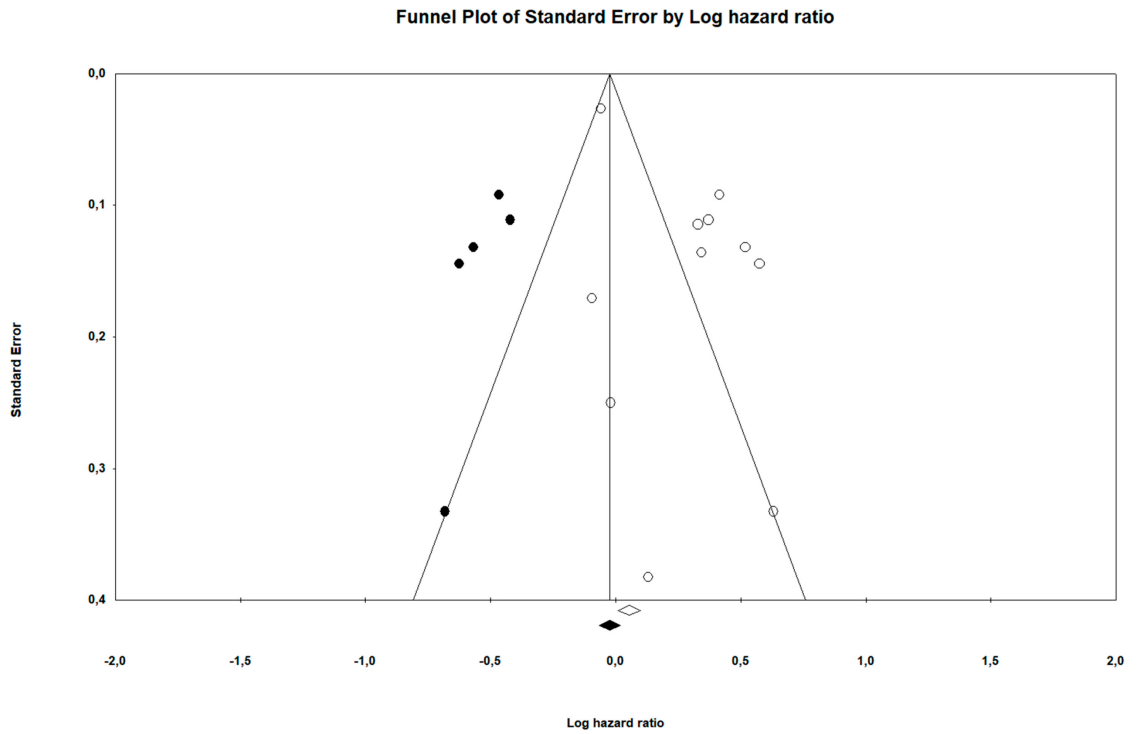

FIGURE 3 | Funnel plot of suggested publication bias.

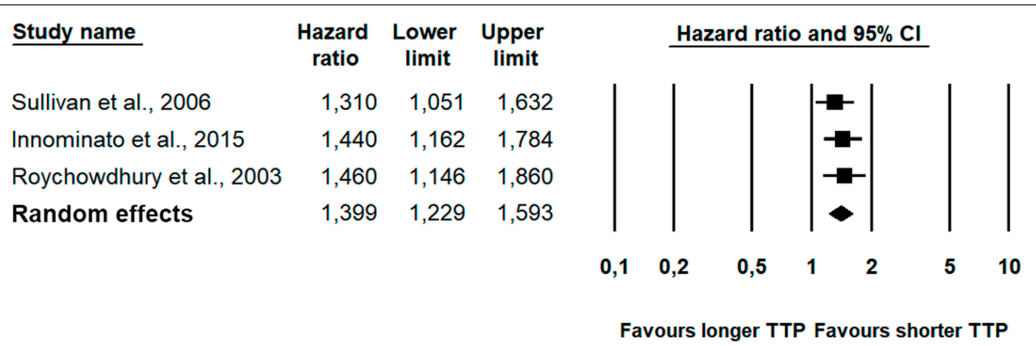

FIGURE 4 | Forest plot of poorer self-reported sleep and time to progression (TTP).

and related effects/side-effects (Bastien et al., 2001; Choilek et al., 2021), and have been shown to be influenced by mood to a larger degree than objective evaluations (Baillet et al., 2016). One type of measure is not necessarily better than the other, but merely highlights the multi-modality of the sleep construct. Both aspects should be taken into account to obtain the most accurate picture of a persons' sleep. Third, our comprehensive search strategy highlighted the fact that the majority of studies (k = 20) were not primarily designed to examine sleep or sleep disturbances in these patients. Our review thereby provides evidence of the need for rigorous longitudinal studies focusing on sleep and sleep-wake activity across the course of treatment and the relationship with prognostic outcomes.

A number of limitations highlighted by the present review should be mentioned. First, although a variety of measures of sleep disturbance were examined in this manuscript, which provided a more nuanced picture of sleep during the cancer trajectory (including self-reported and actigraphy-based measurements of sleep disturbances), their diversity also weakens comparability across studies. Second, a majority of the reviewed studies (19 out of 26) were based on self-reported sleep outcomes, with more than half of these relying on only a single item from the EORTC QLQ-C30. While self-report measures of sleep using multi-item scales such as the Insomnia Severity Index and Pittsburgh Sleep Quality Index have been shown to have good psychometric properties (Beck et al., 2004; Morin et al., 2011), it is unclear whether

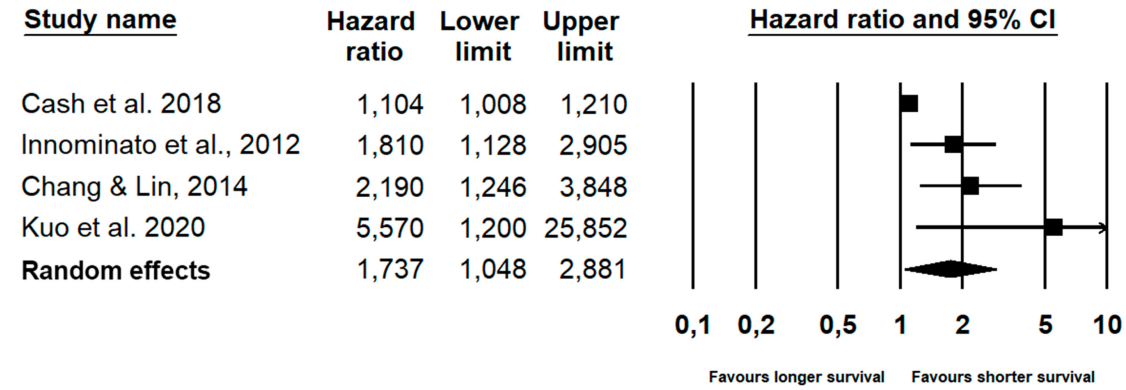

FIGURE 5 | Forest plot of poorer objective sleep and survival.

single-item assessments such as the sleep item from the EORTC QLQ-C30 exhibits the same level of sensitivity and reliability in detecting sleep disturbance, which could compromise the validity of the results. Nevertheless, a sensitivity analysis that only included studies using the single sleep item from the EORTC QLQ-C30, revealed a similar hazard ratio. Third, of the more objective sleep measures included, none consisted of polysomnography, which could have provided important details about underlying sleep architecture. Fourth, we could not include studies of sleep duration in the meta-analysis highlighting the need for further work in that area (Palesh et al., 2014; Collins et al., 2017). Fifth, we were not able to conduct a meta-analysis on the association between sleep and response to treatment due to heterogeneity in study methodology. However, it is worth noting that recent lines of evidence suggest that treatment response may be modulated by therapies affecting sleep and circadian rhythms. For example, administration of melatonin, as an adjuvant cancer therapy, may improve the effectiveness and reduce the side-effects of radio- and chemotherapies through several mechanisms, including stimulation of apoptosis and inhibition on angiogenesis (Li et al., 2017; Farhood et al., 2019; Mortezaee et al., 2019). Moreover, chronotherapies that take advantage of the control of the circadian system may modulate the pharmacokinetic properties of antitumoral agents, thus optimizing their efficacy and reduce toxicity (Ozturk et al., 2017). Sixth, only overall survival was reported in the available studies. Hence, whether these studies reflect associations between sleep and cancer-specific mortality is not clear. Seventh, only half of the studies were eligible for meta-analysis, due to heterogeneity in the analytic strategies, sleep measures and outcome parameters used, thereby limiting our interpretability of our findings. Finally, 80% of studies reported associations based on a single time-point measurement collected immediately prior to or during treatment. However, sleep disturbances have been found to fluctuate both during and after treatment, and may, for some groups, improve over time (Thomas et al., 2010; Savard et al., 2011). Moreover, when compared to inconsistent sleep patterns, more regular sleep behavior has been shown to be associated with lower risk of cancer-specific mortality (Marinac et al., 2017). Thus, single-time point sleep measures may be limited in their ability to predict survival, treatment response and time to progression. This also limits our ability to infer any causal relationship, leaving the question of causality unanswered: Do sleep disturbances reflect disease and symptom burden, or are sleep disturbances disrupting otherwise protective biological mechanisms and compromising treatment efficacy? Our results thus highlight the importance of continuing to investigate the effect of sleep on prognostic outcomes. Finally, future research should also examine sleep in a broader range of cancer populations, as cancer treatment varies according to cancer type.

CONCLUSION

In sum, this review and meta-analysis points to disturbances in sleep and sleep-wake activity as potential predictive markers of reduced survival, poorer response to treatment and shorter time to progression in cancer patients undergoing oncological treatment, though findings ought to be interpreted with caution due to issues with heterogeneity and methodology. Prospective longitudinal studies investigating fluctuations in sleep across the course of treatment and its relationship with prognostics are warranted.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

All authors contributed to the protocol of this systematic review. The literature search and data exportation were performed by LS and librarian Gina Bay, and titles and abstracts

were screened by LS and JTD. LS and JTD performed full text review and quality assessments, validated by RZ, LW and AA. Data extraction was performed by LS and ALCG, and RZ and LS were responsible for the analyses. LS and RZ wrote the manuscript, and all authors critically revised the manuscript and approved the final version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2022.817837/full#supplementary-material

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REVIEW
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Sleep Disruption and Cancer: Chicken or the Egg?

*Adrian Berisha[1], Kyle Shutkind[2] and Jeremy C. Borniger[1]**

[1] Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, United States, [2] Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY, United States

Sleep is a nearly ubiquitous phenomenon across the phylogenetic tree, highlighting its essential role in ensuring fitness across evolutionary time. Consequently, chronic disruption of the duration, timing, or structure of sleep can cause widespread problems in multiple physiological systems, including those that regulate energy balance, immune function, and cognitive capacity, among others. Many, if not all these systems, become altered throughout the course of cancer initiation, growth, metastatic spread, treatment, and recurrence. Recent work has demonstrated how changes in sleep influence the development of chronic diseases, including cancer, in both humans and animal models. A common finding is that for some cancers (e.g., breast), chronic disruption of sleep/wake states prior to disease onset is associated with an increased risk for cancer development. Additionally, sleep disruption after cancer initiation is often associated with worse outcomes. Recently, evidence suggesting that cancer itself can affect neuronal circuits controlling sleep and wakefulness has accumulated. Patients with cancer often report difficulty falling asleep, difficulty staying asleep, and severe fatigue, during and even years after treatment. In addition to the psychological stress associated with cancer, cancer itself may alter sleep homeostasis through changes to host physiology and *via* currently undefined mechanisms. Moreover, cancer treatments (e.g., chemotherapy, radiation, hormonal, and surgical) may further worsen sleep problems through complex biological processes yet to be fully understood. This results in a "chicken or the egg" phenomenon, where it is unclear whether sleep disruption promotes cancer or cancer reciprocally disrupts sleep. This review will discuss existing evidence for both hypotheses and present a framework through which the interactions between sleep and cancer can be dissociated and causally investigated.

Keywords: sleep disruption, cancer, anti-tumor immunity, stress, inflammation, HPA axis, sympathetic nervous system, hypocretin/orexin

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****Correspondence:***
Jeremy C. Borniger
bornige@cshl.edu

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INTRODUCTION

The importance of sleep has been recognized throughout history by the likes of the ancient Egyptians, the Greeks and the Romans-as demonstrated by the names of the gods they worshiped. Sleep is an essential component for maintaining normal physiology and re-establishing homeostasis. Sleep presents a period of vulnerability whereby the brain resides in a relative state of rest and displays reduced sensitivity to external stimuli (e.g., light, sound). Despite this period of vulnerability, sleep remains a highly conserved process whereby humans (and other primates)

spend a significant portion of their lives asleep-about one-third of their total lives. Additionally, the amount of time spent asleep varies greatly in mammals, varying between 3 h and more than 20 h of sleep per day (Siegel, 2008). Indeed, long sleep is not a unique feature of primates as large animals also experience long sleep (Nicolau et al., 2000; Lesku et al., 2008). The functions of sleep remain to be fully elucidated, however, there are several prominent theories that have been postulated attempting to identify ultimate and proximate reasons for why we sleep (Benington and Craig Heller, 1995; Berger and Phillips, 1995; Walker and Stickgold, 2006; Siegel, 2009). In the last few decades, dozens of neuronal circuits have been mapped each contributing to the initiation, maintenance, and transition of sleep/wake states. Among these, subcortical neurons in the hypothalamus and brainstem are the most well-described. For example, hypocretin/orexin (HO) neurons are located within the lateral hypothalamus, a brain region that is essential for critical behaviors such as sleep, feeding, stress, and energy balance.

Normal human sleep consists of two major stages- non-rapid eye movement (NREM) and rapid-eye movement (REM) sleep. Most importantly, these different sleep stages can be easily distinguished using the electroencephalogram (EEG)-measured in microvolts (μV)-to detect changes in electric charge in the brain, in the form of neuronal oscillations or "brain waves." EEG can be used to report the collective activity of many neurons recorded by electrodes placed on the surface of the scalp. These brain waves serve various physiological functions and correlate with the different behavioral states and physiological processes that occur during different sleep stages. In addition, electromyogram (EMG) biopotential signals can be used–in tandem with EEG–as an objective measurement for sleep characterization. Interestingly, scientists have discovered that these brain waves oscillate within specific frequency bands, ranging from very slow (<0.01 Hz) to ultra-fast (>1,000 Hz) oscillations (Penttonen et al., 1998). However, the raw EEG is usually described in terms of conventional frequency bands, including delta (δ; 0.5–4 Hz), theta (θ; 6–9 Hz), alpha (α; 9–12 Hz), sigma (ς; spindle band; 12–15 Hz), beta (β; 12–30 Hz), low (30–60 Hz), and high gamma (γ; 60–100 Hz) (Berger and Phillips, 1995). Consequently, the conventional bandwidth of clinical EEG focuses on the analysis of waveforms ranging from 0.5 to 70 Hz.

Non-rapid eye movement sleep, also known as slow wave sleep (SWS), is the first stage of sleep following the transition from wakefulness. NREM sleep constitutes about 75–80% of total time spent in sleep and is typically associated with reduced cortical neuronal activity. Hence, the most prominent brain waves in the EEG during NREM sleep are low frequency, high amplitude delta (δ) waves. These delta waves reflect synchronization between thalamocortical (TC) neurons-characterized by prolonged periods of hyperpolarization and increased membrane conductance. These changes at the cellular level are reflected at the circuit level as these periods of prolonged hyperpolarization result in a reduction in the encoding of afferent signals, thus temporarily depriving the cerebral cortex of external stimuli (Steriade, 2003). In humans, NREM sleep is subdivided into several stages numbered 1–3, each of which offers the relative depth of sleep and includes unique characteristics and changes in brain activity and physiology. The physiological changes that occur during NREM sleep include decreased blood pressure and heart rate as a result of decreased sympathetic-nerve activity, decreased ventilation and respiratory flow, decreased movements of the eyes under the closed eyelids, and significant changes in blood flow and metabolism (Nowak et al., 2021).

In contrast, REM sleep, also known as "paradoxical" or "active" sleep (as the EEG waveform closely resembles that of wakefulness) is the stage of sleep following the transition from NREM sleep. REM sleep constitutes the remaining 20–25% of total time spent in sleep and is typically associated with increased heart rate and respiration, fluctuations in brain/body temperature, increased brain activity, and active suppression of skeletal muscle activity apart from those controlling eye movement and inflation/contraction of the diaphragm. REM sleep is predominantly characterized by lower amplitude, higher frequency theta (θ) waves that reflect desynchronization of cortical neurons (Vertes, 1984; Frauscher et al., 2016). Theta oscillations are generated in the hippocampus where a combination of cellular characteristics and network interactions facilitate in the generation of rhythms that can be detected in the overlying cortex (O'Keefe, 1993; Colgin, 2013). Several studies have highlighted the role of pyramidal neurons and more recently, parvalbumin interneurons of the hippocampus in mediating theta frequency (Pike et al., 2000; Amilhon et al., 2015). REM sleep is the phase of sleep thought to be responsible for dreaming, although evidence suggests dreams may also occur during NREM sleep (Siclari et al., 2018). During REM sleep, there is total body voluntary muscle paralysis which is believed to be a mechanism that prevents us from acting out our dreams. This temporary paralysis of muscles is achieved through the inhibition of spinal motor neurons *via* brainstem GABA/glycinergic signaling (Carskadon and Dement, 2005; Brooks and Peever, 2012).

Our understanding of the interaction between sleep and circadian rhythms can be partially attributed to the two-process model of sleep regulation which has served as a major conceptual framework in sleep research for the last four decades. Today, we understand that sleep is regulated by a homeostatic, sleep-dependent process (Process S) that interacts with a sleep-independent circadian process (Process C) (Borbély et al., 2016). The two-process model of sleep regulation was organized based on the initial observation that variations in the sleep stages (i.e., sleep propensity) mirror the rhythm of our body temperature (Kleitman, 1933; Murray et al., 1958). Process S represents the sleep propensity, or sleep debt, which increases during wakefulness and declines during sleep. Process C, the circadian component of sleep is closely related to the circadian rhythms of metabolic and endocrine processes, indicating an important role of sleep in maintaining proper energy homeostasis, growth and development (Huang et al., 2011; Depner et al., 2014). Desynchronization of normal circadian rhythms impairs physiological functions in disease processes including metabolic diseases, cardiovascular diseases, and cancer (Fu and Lee, 2003; Sahar and Sassone-Corsi, 2009; Arble et al., 2010; Savvidis and Koutsilieris, 2012; Chaves et al., 2019). In

fact, in 2007, the International Agency for Research on Cancer (IARC) classified "shift work that involves circadian disruption" as a probable human carcinogen (Group 2A in the IARC classification of *Known and Probable Human Carcinogens*). The synchronization of circadian rhythms is an essential component to sleep homeostasis, as the regulation of sleep/wake cycles are mainly controlled by daily circadian rhythms. In this review, we will discuss how sleep disruption may promote tumorigenesis through alterations in a variety of physiological processes such as energy balance and immunity. Reciprocally, we will discuss how cancer-mediated alterations in our physiological processes may lead to aberrant neural activity, affecting a myriad of behavioral changes including disruption of sleep/wake cycles.

SLEEP DISRUPTION-INDUCED CHANGES TO SYSTEMIC PHYSIOLOGY

The prevalence of sleep disorders in modern societies is increasing, affecting 20–40% of the general population (Chattu et al., 2019), likely in part due to increased shift work and exposure to artificial light at night. Sleep disturbances and disruptions in circadian synchronization are associated with the development of several disease states including cancer (Fu and Lee, 2003; Savvidis and Koutsilieris, 2012). Sleep disruption is common across different types of cancers, with the highest prevalence experienced by patients with breast cancer (Davidson et al., 2002; Budhrani et al., 2015). Although a consensus definition of "sleep disruption" does not exist, approximately 30–70% of cancer patients report sleep problems before and during treatment, which is about two times higher than in the general population (Savard et al., 2001; Ancoli-Israel et al., 2006; Palesh et al., 2010; Fiorentino et al., 2011). The most common problems related to sleep in breast cancer are insufficient sleep, hypersomnia, sleep fragmentation, poor sleep efficiency (i.e., time spent asleep/time in bed), hot flashes, and circadian misalignment. To examine the relationship between sleep and cancer risk, studies have largely focused on sleep duration, presence of sleep disorders, and night shift work as risk factors driving cancer.

A growing body of research links sleep disruption and circadian misalignment to subsequent tumor initiation and growth (Hansen, 2001; Schernhammer et al., 2006; Van Dycke et al., 2015). Given that the overall prevalence of sleep disorders is on the rise (Ferrie et al., 2011; Chattu et al., 2019), it is necessary to assess its contribution to tumorigenesis. Notably, a prospective study of approximately 24,000 women by Kakizaki et al. (2008) demonstrated an inverse association between sleep duration and risk of breast cancer, where shorter sleep duration (i.e., 6 h or less) was associated with an increased risk of breast cancer. The hazard ratio (HR) of women who slept less than 6 h was 1.62, of those who slept 8 h was 1.14 and of those who slept 9 h or more was 0.72. In addition, the deleterious effects of sleep disruption on systemic physiology has also been explored in animal models, where several studies implicate sleep disruption in both tumor progression and cancer-related mortality (Maragno-Correa et al., 2013; Hakim et al., 2014). In this section, we will delve into inflammation, altered metabolism, anti-tumor immunity, stress, and sympathetic nervous system activity in driving tumor initiation, growth, and subsequent metastasis as potential mechanisms linking disrupted sleep to cancer outcomes.

Sleep Disruption and Anti-Tumor Immunity

Sleep and the immune system engage in a form of bi-directional communication, and comprise two essential components in health and disease (Lorton et al., 2006). As we will discuss in later sections of this review, activation of the immune system (e.g., *via* immune-cell-derived cytokines) alters sleep, and reciprocally, sleep affects both the innate and adaptive arms of the immune system. Several human studies have demonstrated sleep disruption-induced elevations in circulating immune cells, including granulocytes (e.g., neutrophils) T cells, and B cells (Born et al., 1997; Faraut et al., 2011; Besedovsky et al., 2016), indicative of an inflammatory state. In addition, studies in mice have recently illuminated the role of sleep deprivation in promoting tumor progression as a result of impaired anti-tumor immunity (De Lorenzo et al., 2018; Huang et al., 2021). A study by De Lorenzo et al. (2018) demonstrated the deleterious effects of 18-h sleep deprivation on antitumor immunity in a murine model of melanoma. The results demonstrated that sleep deprivation reduced the number of cytotoxic cells (i.e., NK and CD8+ T cells), concurrent with increased numbers of pro-tumor regulatory T cells, in the tumor microenvironment (TME). In addition, similar effects were observed systemically as the number of CD4+ and CD8+ T cells were reduced in the blood of sleep-deprived mice along with a decreased population of dendritic cells (antigen-presenting), indicative of an immunosuppressive phenotype. The effects of this immunosuppressive phenotype were exemplified by an earlier onset of lung metastasis in sleep-deprived animals, leading to increased metastatic burden. Previous work by De Lorenzo et al. (2015) demonstrates a role of the sympathetic nervous system (SNS) in sleep disruption-induced reductions in the number and cytotoxic activity of NK cells, as treatment with the beta-2 adrenergic receptor (β_2-AR) antagonist propranolol reversed the effects of sleep disruption on NK cell phenotypes. However, the causality of sleep disruption-induced alterations to the immune landscape and subsequent tumor growth remains unclear.

Until recently, most studies investigating the immune landscape in the context of sleep deprivation used flow cytometric analysis with little-to-no use of high-dimensional single-cell techniques. These approaches are required to garner critical information on the molecular and cellular interactions underpinning sleep disruption associated malignancies. A study by Liu et al. (2021) provide unique insight into the dynamic single-cell alterations underlying sleep disruption-induced rewiring of the immune cell landscape. Blood was collected from six healthy individuals before and after 24-h sleep deprivation (preSU and postSU, respectively) and then subsequently analyzed using mass cytometry by time of flight (CyTOF) and single-cell RNA sequencing (scRNA-seq). Coincident with the aforementioned studies, Liu et al. (2021) found increases in circulating T cells (TC) as well as decreases in

myeloid cells (MYE) postSU as assessed by classical lineage markers using scRNA-seq. Next, the five major immune cell lineages (TC, NK, BC, MC, and DC) were further sub-clustered into transcriptionally distinct subsets. Following 24-h sleep deprivation, single-cell clustering identified the onset of lymphocythemia (i.e., increased number of lymphocytes) as demonstrated by increases in $CD8^+$ effector memory TCs (CD8 T_{EM}), proliferating TCs (mitotic TC, T-mito), and exhausted TCs (Tex) (as a percent of CD45+). Next, Liu et al. (2021) sought to identify the molecular events associated with 24-h sleep deprivation which was achieved through the analysis of differentially expressed genes from blood immune cells in the postSU group compared with the preSU group. All six participants in the study showed an increase in several inflammatory genes including markers of DNA damage, AP-1 family genes (*JUN*, *FOS*), IFNG and interferon-related developmental regulator 1 (*IFRD1*). In addition, gene ontology (GO) identified the upregulated genes across participants postSU were enriched in the AP-1 pathway, leukocyte activation, and cellular responses to stress (i.e., cellular senescence). The most prominent downregulated genes postSU were those involved in metal ion homeostasis and detoxification. These findings indicate that sleep deprivation induces general oxidative stress and an inflammatory state in circulating immune cells. Importantly, TCs, BCs, and DCs were the cell types most strongly affected by sleep deprivation among individuals according to their upregulated genes. Within $CD4^+$ TCs, Liu et al. (2021) demonstrated that sleep-deprivation resulted in an increase Th17 differentiation markers CCR6, CXCR3, the cell proliferating marker Ki67, and apoptotic marker CD279. In addition, increased levels of CXCR3, CCR6, and the autoimmune-related BC (ABC) marker T-bet were identified in B cells after sleep-deprivation, indicative of autoimmune-associated changes in effector lymphocytes postSU.

Importantly, Liu et al. (2021) revealed that functional marker expression of cytotoxic cells (i.e., NK and $CD8^+$ TCs) were altered postSU, including decreased expression of transcription factors (e.g., T-bet) that normally promote differentiation and functional polarization of cytotoxic cells. In addition, sleep-deprivation upregulated levels of *PFN1*, a negative regulator of cytotoxic cell killing and migratory functions. Thus, the cytotoxic cells present in postSU blood show transcriptional alterations that favor an increase in an inflammatory phenotype and coincident decrease in cytotoxic activity. Lastly, Liu et al. (2021) demonstrated that the particular cell-cell interactions in the blood after sleep-deprivation were those mainly involved in inflammatory activation of lymphocytes to other cells and chemotaxis of MYEs to other cells. In addition, unique intercellular interactions between TCs, NKs, and BCs were identified with upregulated expression of the ephrin family and their receptor EPH family in the postSU group which are implicated in the onset of inflammation and disease pathogenesis. Thus, sleep deprivation promotes an inflammatory environment in peripheral tissues with reduced differentiation and immune activity of cytotoxic cells, likely increasing susceptibility to tumorigenesis. The findings by Liu et al. (2021) can be used to inform the cellular and molecular mechanisms underlying sleep disruption-induced pathogenesis, including its potential contribution to development and progression of cancer (**Figure 1**).

Sleep Disruption-Induced Inflammation

Inflammation is an evolutionarily ancient process wherein cells of the innate and adaptive arms of the immune system are activated and recruited to sites of host insult or pathogen invasion. Equally important to host defense is inflammation's role in tissue repair and regeneration. Although vital for normal health, several decades of research have firmly implicated inflammation in the development and progression of cancer. Site specific chronic inflammation and subsequent cancer development is a common theme for many organ systems. Prominent examples highlighting this relationship include cigarette smoking and chronic viral hepatitis increasing the risk of lung cancer and liver cancer, respectively. Epidemiologic evidence also demonstrates that inhibition of inflammation with NSAIDs reduces incidence and mortality of many cancers following long term use (Rothwell et al., 2011).

Substantial experimental evidence demonstrates that sleep disruption promotes inflammation in both animal models and in human studies. In one study, rats that were selectively sleep deprived of REM sleep for 72 h showed significant increases in proinflammatory cytokines compared to controls. The elevated markers include IL-1 alpha, IL-1 beta, IL-6, IL-17, TNF-alpha, corticosterone, and homocysteine. The shift to a pro-inflammatory state persisted for at least 1 week, as levels of IL-17, TNF-alpha, corticosterone, and homocysteine remained elevated despite having the opportunity for normal sleep and sleep rebound (Yehuda et al., 2009). Even just one night of sleep loss in healthy adults induces an inflammatory response. In a study where volunteers underwent partial sleep deprivation (awake from 11 p.m. to 3 a.m.), morning monocyte production of IL-6 and TNF-alpha was significantly elevated compared to prior mornings following uninterrupted sleep (Irwin et al., 2006). The rise in proinflammatory signaling following sleep loss is largely mediated through the transcription factor NF-kB. Following a single night of partial sleep deprivation, mononuclear cell NF-kB was significantly elevated compared to uninterrupted or recovery sleep. NF-kB is intimately tied to chronic inflammation and tumorigenesis where it provides cells with resistance to apoptotic insults and leads to the production of growth factors (Karin and Greten, 2005). In another study, 24 healthy adults undergoing one night of partial sleep deprivation similarly showed greater expression of IL-6 and TNF-alpha relative to baseline. These inflammatory cytokines were accompanied by increased monocytic expression of activated (phosphorylated) STAT1 and STAT5 (Irwin et al., 2015). STAT proteins transduce signals to the nucleus where they function as transcription factors, with certain STAT proteins (STAT1) acting to increase anti-tumor immunity and others (namely STAT3) facilitating cancer-promoting inflammation (Yu et al., 2009). Interestingly, there appears to be sex differences in sleep disruption driven inflammation. In the morning after sleep loss, LPS-stimulated IL-6, and TNF-alpha concentrations were equally elevated in both females and males. However, production of these cytokines remained elevated in females into the evening whereas it decreased in males (Irwin et al., 2010). These findings suggest

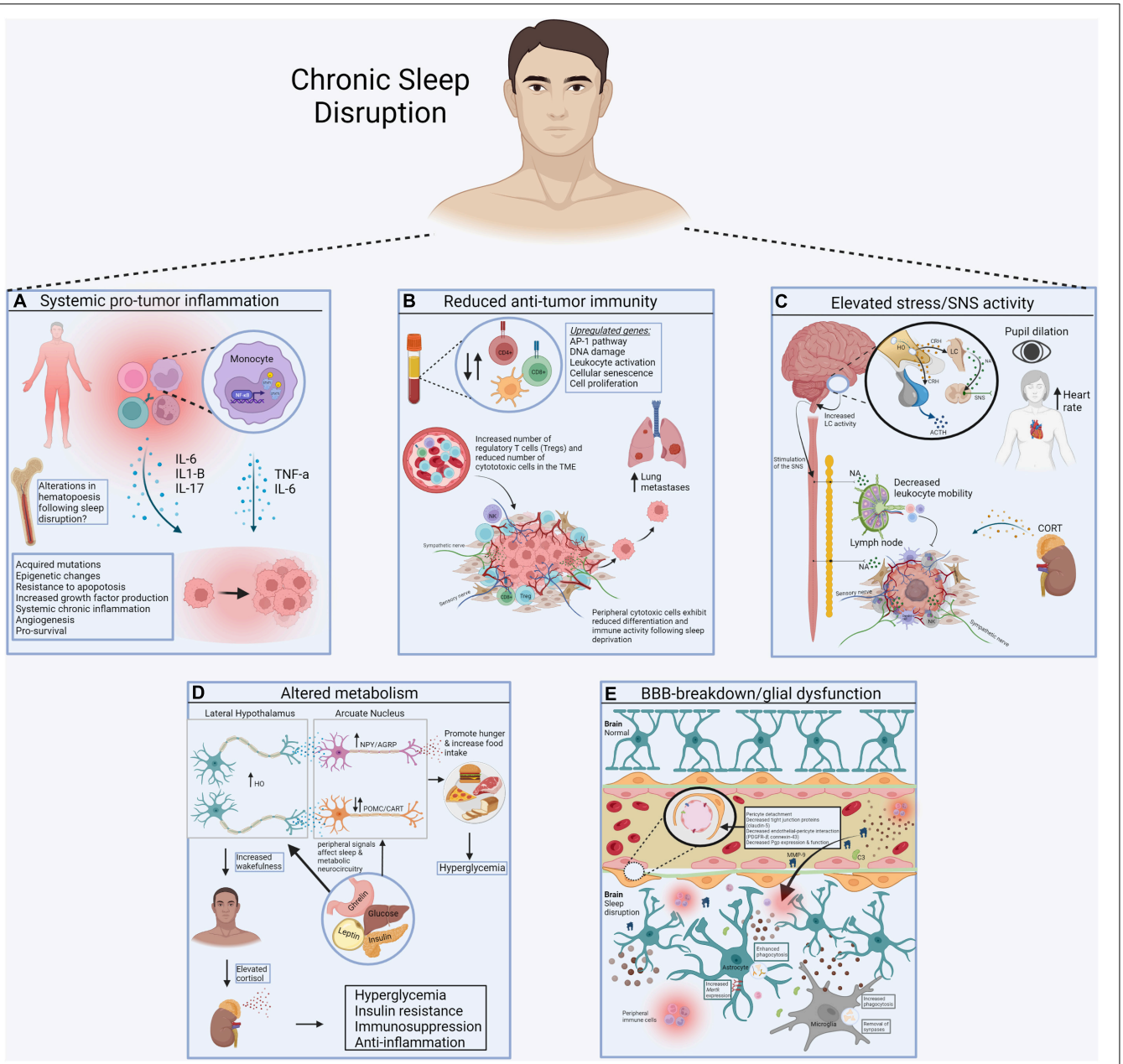

FIGURE 1 | Systemic consequences of sleep disruption. **(A)** Sleep disruption-induced inflammation establishes a pro-tumor inflammatory environment in peripheral tissues, including the increase in proinflammatory cytokines like IL-6, IL1-b, and IL-17, mediated by the transcription factor NF-kB. **(B)** Sleep disruption reduces anti-tumor immunity. Alterations in the number of circulating and intra-tumor lymphocytes and myeloid cells contributes to immunosuppression in cancer. Reduced differentiation of cytotoxic cells further prevents cancer elimination. **(C)** Sleep disruption engages the HPA axis and autonomic nervous system. Glucocorticoids and catecholamines have widespread effects on the immune system and energy balance important for tumor progression. **(D)** Sleep disruption alters systemic metabolism. Wake-promoting neurons (e.g., hypocretin/orexin) regulate the activity of others that control food intake and metabolic health (e.g., POMC, AgRP, NPY neurons). **(E)** Sleep disruption promotes the breakdown of the blood brain barrier (BBB). Disrupted sleep results in vascular endothelial cell dysfunction and inflammation, further contributing to BBB impairment. This allows inflammatory molecules in blood to reach the brain, where they alter the function of sleep/wake regulatory systems (Made with BioRender.com).

sleep loss may exert a differential risk for inflammatory driven disorders across sexes.

The evidence linking sleep disruption and induction of a pro-inflammatory state is vast, however, the underlying mechanisms remain to be fully studied. Sleep induced inflammation is driven by complex neuro-immune interactions, likely mediated through neuroendocrine axes (e.g., HPA axis) and the autonomic nervous system, as previously discussed. As discussed above, sleep disturbance activates the HPA axis. In turn, a chronically active HPA axis can lead to glucocorticoid resistance of

immune cells, wherein immune cells lose sensitivity to the anti-inflammatory effects of glucocorticoids (Webster et al., 2001). A natural decrease in sympathetic nervous system (SNS) activity that occurs during the night is also prevented when sleep loss occurs. This increased sympathetic outflow is carried forward into the day and influences inflammation. Noradrenergic signaling through beta receptors can activate NF-kB and induce the production of inflammatory cytokines (Irwin and Cole, 2011). In a study examining sleep and cardiovascular disease, mice undergoing chronic sleep fragmentation developed larger atherosclerotic plaques and produced less hypocretin in the lateral hypothalamus compared to controls. Additionally, the aortas and blood of sleep deprived mice contained higher levels of monocytes, neutrophils, and macrophages. Hypothalamic hypocretin reduced gradually and was inversely correlated with leukocytosis throughout the sleep disruption paradigm. It was determined that the link between reduced hypocretin and leukocytosis is mediated through hypocretin sensitive pre-neutrophils, whose production of colony stimulating factor-1 is decreased in response to hypocretin. Taken altogether, hypocretin dysfunction alters the immune landscape, leading to a relative leukocytosis that favors atherosclerosis. Whether alterations in hematopoiesis in response to sleep disruption similarly increases tumorigenesis is yet to be determined.

Inflammation's role in tumor initiation is multifactorial. Sleep induced inflammation is systemic and differs from the traditional model of "site specific" chronic inflammation leading to organ-specific tumors. Cytokine and immune cell alterations following sleep disruption may create an environment favoring cancer development and progression. For example, mice that constitutively produce IL-15, a proinflammatory cytokine and growth factor, developed fatal lymphocytic leukemia (Fehniger et al., 2001). Macrophage-migration inhibitory factor, another proinflammatory cytokine, suppresses the activity of p53 (Hudson et al., 1999). IL-1 is required for angiogenesis and invasiveness as mice deficient in IL-1alpha or IL-1beta exhibit impaired tumor development and blood vessel growth in melanoma, mammary adenocarcinoma, and prostate cancer (Voronov et al., 2003). CSF-1 serves as a regulator of mammary tumor metastasis as its overexpression accelerated the progression and invasion of the primary tumor to other sites (Lin et al., 2001). Inflammation can trigger mutagenesis through ROS formation by macrophages and neutrophils (Canli et al., 2017). Inflammatory cytokines such as IL-1, IL-6, and TNF-alpha can activate epigenetic machinery in epithelial cells, altering expression of oncogenes and tumor suppressor genes (Grivennikov, 2013). Inflammation has also been shown to induce tumor initiating stem-cell like cells from normal epithelium (Schwitalla et al., 2013). Further, cytokine receptor signaling through NF-kB, JAK/STAT, and other cascades may induce pro-survival pathways, increasing the likelihood for a cancerous cell to survive and produce successful clones (Grivennikov et al., 2009). Thus, unresolved inflammation that arises due to sleep disruption sustains a proinflammatory environment, both locally within tissues and systemically. This favors tumorigenesis through aberrant cytokine signaling and subsequent cell growth, increased cell turnover, and immune evasion.

Sleep Disruption, Stress, and the Sympathetic Nervous System

Psychological or psychosocial stress has been implicated in the etiology of several prominent diseases in humans including clinical depression, cardiovascular disease (CVD), human immunodeficiency virus (HIV/AIDS), and cancer (Cohen et al., 2007). Moreover, chronic stress has emerged as a key factor associated with cancer initiation, progression, and subsequent metastasis in animal models and humans (Sklar and Anisman, 1981; Kim-Fuchs et al., 2014; Le et al., 2016). A combination of retrospective, prospective, and observational studies have explored the effects of psychological stress on tumorigenesis, revealing that stressful life events (e.g., death of a family member, divorce, etc.) frequently precede the appearance of several forms of malignancies including breast cancer (Cooper et al., 1989; Geyer, 1991; Ginsberg et al., 1996). Several behavioral changes that occur as adaptations or coping responses to stressful life events such as loss of sleep and exercise, increased smoking or alcohol consumption, and reduced adherence to medical regimens constitute several pathways by which stressors increase susceptibility to developing a chronic disease. In addition, two stressor-induced endocrine responses provide additional pathways influencing disease risk; namely the hypothalamic-pituitary-adrenocortical (HPA) axis and the sympathetic-adrenal-medullary (SAM) system. Glucocorticoids, the primary output of the HPA axis, regulate a multitude of physiological processes (e.g., glucose mobilization, immunosuppression) and are also involved in resetting the circadian clock in peripheral tissues (Balsalobre et al., 2000; Dibner et al., 2010). The prolonged activation of these endocrine responses can interfere with their control of normal physiological systems including immune, metabolic, and neurological functions, resulting in increased susceptibility to the development of physiological and psychological disorders.

Sleep disruption triggers a stress response, which in turn increases concentrations of adrenal glucocorticoids and epinephrine (i.e., adrenaline). Research findings have firmly established that our own life-experiences, such as stressful events, have an impact on the quality, duration and physiology of sleep. Reciprocally, sleep influences stress, resulting in an overlap between stress and sleep disruption-induced physiological changes. Thus, it is difficult to disentangle the independent effects of sleep disruption alone, as sleep disruption results in emotional and physiological stress with large implications for subsequent health and disease. The connection between sleep and stress has recently been described as Li et al. (2020) demonstrated that hypocretin/orexin (HO) to CRH neuron signaling causes stress-induced insomnia.

Since the reports of the discovery of the HO neuropeptides and their receptors in 1998, research has firmly established the primary role of HO neurons in the maintenance of wakefulness (Sakurai, 2005, 2007; Adamantidis et al., 2007; Inutsuka and Yamanaka, 2013; Tyree et al., 2018). HO neurons are sensitive to circulating peripheral signals such as acyl-ghrelin, leptin, and

glucose (Yamanaka et al., 2003; Adamantidis and De Lecea, 2009) which become deregulated throughout the course of cancer progression. In response, HO neurons alter their firing rates to elicit appropriate physiological responses to putatively re-establish homeostasis. HO neurons are more active during wakefulness (e.g., during sleep deprivation), resulting in an increase in the activity of post synaptic neurons in brain regions that receive their projections. More specifically, there are two critical efferent projections from HO neurons that are likely responsible for changes in peripheral physiology observed in cancer: the HPA axis and autonomic output nuclei [e.g., locus coeruleus (LC), ventrolateral medulla, A5, A1]. HO neurons project to various autonomic output nuclei in the brainstem, namely the locus coeruleus, which projects to the spinal cord to alter peripheral physiology *via* the sympathetic nervous system (SNS) (Geerling et al., 2003; Samuels and Szabadi, 2008a,b). The physiological changes that accompany increased activity of noradrenergic neurons in the locus coeruleus is increased arousal and vigilance and increased activity of sympathetic nerves in the periphery as assessed by dilation of the pupils (Murphy et al., 2014; Costa and Rudebeck, 2016; Joshi et al., 2016; Liu et al., 2017). Importantly, sympathetic nerves are implicated in exacerbating primary tumor growth and subsequent metastasis in animal models of breast cancer and in human patients (Sloan et al., 2010; Monje et al., 2020; Zahalka and Frenette, 2020), providing an anatomical pathway linking stress, sleep disruption, and cancer in the body.

A study by Kamiya et al. (2019) demonstrated that sympathetic innervation of tumors accelerates progression of human breast cancer xenografts in mice. Sympathetic nerves within the TME were constitutively activated, which was achieved using adeno-associated virus (AAV) delivery of a mutant sodium channel that remains open, promoting tonic depolarization of neuronal membranes. Two-photon calcium imaging of sympathetic nerve endings in the TME confirmed stimulation of sympathetic nerves, which was concurrent with increased tumor volume of the primary tumor in the mammary fat pad and increased metastasis to the lungs, a primary site of breast cancer metastasis. However, AAV delivery of diphtheria toxin A subunit (DTA) to ablate innervating sympathetic nerves, resulted in decreased primary tumor growth with no measurable metastasis. The results of the DTA-induced elimination of sympathetic nerves were recapitulated in animal models that experienced increased stimulation of parasympathetic nerves in the TME, thus highlighting the duality between the two divisions of the autonomic nervous system relevant to breast cancer (Kamiya et al., 2019). Importantly, Kamiya et al. (2019) demonstrated a similar phenomenon in human breast tumors of 29 patients who underwent surgical resection of primary breast tumors. Of these 29 patients, 10 patients subsequently experienced recurrence of breast cancer whereas the remaining 19 patients did not. Immunofluorescence staining of surgically resected primary tumors revealed a positive correlation between sympathetic nerve fiber densities and cancer recurrence. Specifically increased sympathetic nerve densities were observed in the primary tumors of patients who subsequently experienced recurrence, which was also associated with a lower recurrence-free survival rate. The opposite correlation was observed for parasympathetic nerve densities. Thus, increased stimulation of sympathetic nerves (or reduced parasympathetic input) within the TME results in enhanced tumor growth, progression, subsequent metastasis, and increased incidence of recurrence in animal models and patients with breast cancer. Mechanistically, this may have to do with the actions of the sympathetic nervous system on local immune cells important for anti-tumor immunity. Kamiya et al. (2019) also demonstrated that genetic sympathetic nerve denervation (and parasympathetic neurostimulation) reduced the expression of immune checkpoint molecules (e.g., PD-1, PD-L1)-exploited by cancer cells in order to evade the host immune-response- in the TME in animal models of breast cancer. Once again, these findings highlight the effects of local sympathetic nerve output on anti-tumor immunity and subsequent cancer progression. In addition, sympathetic nerves were closely associated with PD-1+ and FOXP3+ tumor infiltrating lymphocytes (TILs) with innervation of PD-L1+ tumor tissue in human breast cancer (Kamiya et al., 2019). Activation of the SNS decreases leukocyte (i.e., CD4+ and CD8+ T cells) mobility in peripheral tissues, as systemic administration of the SNS neurotransmitter NA and/or administration of the βAR agonist isoprenaline sequestered leukocytes in lymph nodes (Devi et al., 2021). Devi et al. (2021) demonstrated this impaired immune response was due to SNS-induced vasoconstriction and subsequent hypoxia which resulted in increased calcium signaling within leukocytes, ultimately reducing their mobility. Altogether, these results indicate a critical role for the SNS in driving tumor progression and promoting an immunosuppressive, pro-tumorigenic environment characterized by increased neurotransmitter signaling, hypoxia and reduced leukocyte motility.

In addition to the control HO neurons exert on autonomic nuclei and subsequent SNS activity in the periphery, HO neurons also modulate activity of the HPA axis. Both intracerebroventricular (icv) administration of HO and optogenetic stimulation of HO neurons results in a rapid elevation of circulating glucocorticoids (e.g., corticosterone, cortisol), the primary humoral output of the HPA axis (Kuru et al., 2000; Bonnavion et al., 2015). In agreement with the results from preclinical models, sleep deprivation in humans activates the HPA axis, as sleep deprived individuals demonstrate amplified cortisol levels (Minkel et al., 2014). In addition, sleep deprivation results in a marked increase in corticotrophin-releasing hormone (CRH) expression and release into various brain regions in rats (Fadda and Fratta, 1997). The activation of the HPA axis and subsequent secretion of glucocorticoids by the adrenal cortex is highly relevant to tumorigenesis and tumor progression as glucocorticoids are widely recognized for their anti-inflammatory, immunosuppressive effects that promote tumor initiation and progression (Barnes, 1998; Coutinho and Chapman, 2011). In addition to the systemic effects, stressors elicit activation of the LC through the actions of CRH, a key component of the HPA axis (McCall et al., 2015). The net effect of CRH binding to their receptors (CRHRs) in the LC is increased neuronal discharge resulting in high-tonic activity and increased activation of the SNS in the periphery (Samuels and Szabadi, 2008a,b; Valentino and Van Bockstaele, 2008).

Thus, it is likely that sleep deprivation (partially due to increased hypocretin neuronal activity) has both direct and indirect influences on sympathetic output. Direct (projections to the LC) and indirect (engagement of the HPA-axis) actions of hypocretin neurons on LC activity results in increased stimulation of the sympathetic nervous system.

In addition to the interplay between these two brain regions controlling stress and SNS activity in the central nervous system (CNS), stress and SNS activity are intimately linked in the periphery. Treatment of spleen-derived NK cells with the glucocorticoid receptor agonist dexamethasone upregulates expression of β_2-adrenergic receptors (β_2-AR) on NK cells, suggesting that glucocorticoids are able to induce expression of β_2-AR (De Lorenzo et al., 2015). This results in a decrease in the number and cytotoxic activity of NK cells, further highlighting the dynamic interplay between sleep disruption-induced stress, SNS activity, and immune-suppression relevant to cancer. Thus, the consequence of these CNS interactions extends to the periphery, further promoting the propensity of cancer cells to grow and proliferate in an immunosuppressive environment.

Sleep Disruption-Induced Metabolic Alterations

Mounting evidence relates sleep loss to the development of obesity, diabetes, and other metabolic abnormalities. Metabolic abnormalities because of poor sleep are likely a risk factor for the development of many cancers. Interactions between sleep and metabolic regulation is primarily mediated through the hypothalamus. In a similar fashion to sleep, hypothalamic control over metabolism occurs through two networks that inhibit each other. Neuropeptide Y (NPY) and agouti-related protein (AgRP) neurons promote hunger and actively inhibit pro-opiomelanocortin (POMC) and amphetamine-related transcript (CART) neurons, which suppress appetite. Further, both populations of neurons are sensitive to leptin and ghrelin, which serve as major humoral cues of hunger and energy expenditure. Leptin simultaneously suppresses activity of NPY and AgRP neurons and activates POMC and CART neurons whereas ghrelin has the inverse effect in both sets of neurons (Rolls et al., 2010).

In addition to the actions of peripheral hormones on neurocircuitry, increased risk of metabolic dysfunction may be linked to sleep-induced alterations of HO neurons. Interactions between HO neurons and hypothalamic metabolic centers likely contribute to many of the metabolic abnormalities seen in those who experience chronic sleep disruption. HO neurons can sense and respond to glucose, leptin, and ghrelin, allowing for adaptive augmentation of arousal in response to changes in energy balance (Yamanaka et al., 2003; Tyree et al., 2018; Walker and Borniger, 2019). Further supporting the role of HO neurons in metabolism is the anatomical connectivity between HO neurons and metabolic nuclei of the hypothalamus. HO axons directly contact NPY and POMC neurons in the arcuate nucleus of rats and signaling through these axons has been shown to regulate their activity in a manner reciprocal to leptin (Muroya et al., 2004). Moreover, ghrelin-induced food intake is significantly reduced in mice pretreated with antibodies against HO and HO knockout mice (So et al., 2018). In the context of sleep deprivation, the activity of HO neurons increases to maintain wakefulness against increased pressure to sleep (Wu et al., 2002). Thus, sleep loss resulting in overactivity within HO neurons likely plays a role in the metabolic effects of sleep loss as these same neurons influence the activity of metabolic centers in a way that promotes eating and energy mobilization.

Low-grade systemic inflammation due to obesity and hyperglycemia can increase the risk and progression of many cancers, including malignancy of the breast (Greten and Grivennikov, 2019). Furthermore, liver, pancreatic, colorectal, and breast cancer all show an association with Type II diabetes mellitus (Vigneri et al., 2009; Suh and Kim, 2011). In one study, patients with breast cancer had increased glucose concentrations during the time of their diagnosis when compared to age-matched controls (Ryu et al., 2014, p. 201). Similarly, in a study assessing the effects of multiple nights of partial sleep loss, it was found that the rate of glucose clearance following injection was reduced by 40% after sleep restriction compared to sleep recovery nights in a sample of healthy volunteers aged 18–27 years (Spiegel et al., 1999). Glucose effectiveness, which is the ability of glucose to mobilize itself independent of an insulin response, and acute insulin response to glucose were both found to be 30% lower during mornings after sleep loss compared to mornings after sleep recovery. Sleep loss was also accompanied by an increase in afternoon and evening plasma cortisol levels. The authors proposed that the raised cortisol concentrations later in the day reflect impaired negative-feedback control of the HPA axis, which is a component of age-related insulin resistance. This study was one of the first to show that just several days of sleep disruption in healthy people is linked to drastic alterations in metabolic function, and sleep loss induced changes that mimic characteristics of aging (Spiegel et al., 1999)-which is the greatest risk factor for almost all cancers.

It is well-known that chronic hyperglycemia has profound negative health consequences, in part mediated through the formation of advanced glycation end products (AGEs). AGEs form throughout life *via* non-enzymatic glycation of various proteins and lipids, a process that is accelerated by hyperglycemia and inflammation. Interactions between AGEs and its receptor, receptor for advanced glycation end products (RAGEs), alters vascular homeostasis and contributes to the development and progression of cardiovascular disease (Senatus and Schmidt, 2017). AGE-RAGE interactions and downstream signaling may also be involved in tumorigenesis. The actions of AGEs associated with cancer development include activation of RAGE leading to signaling cascades favoring proliferation, inflammation, and increased levels of ROS (Lin et al., 2016). AGEs have been implicated in the promotion of several tumor types *in vitro*, including breast, colon, and lung cancer, among others (Takino et al., 2010; Ishibashi et al., 2013; Chen et al., 2014). Epidemiologic and animal studies support these findings with high-AGE diets increasing the risk of many cancer types (Shimomoto et al., 2012; Foster et al., 2014; Jiao et al., 2015). In summary, sleep disruption alters systemic metabolism in a way that favors tumor initiation and growth.

SLEEP DISRUPTION-INDUCED CHANGES TO THE CNS

The blood brain barrier (BBB) is a complex organization of cerebral endothelial cells, pericytes, and supporting astrocytes which serves to provide a stable environment for neural function through regulation of peripheral neurotransmitter infiltration, hormones, macromolecules, and the ionic microenvironment around synapses and axons. Moreover, the BBB allows for stringent control of CNS homeostasis by monitoring and detecting circulating toxins, pathogens, and inflammation. Hence, the BBB limits paracellular permeability due to the presence of tight junctions between the continuous monolayer of endothelium in the brain vasculature. However, the presence of nutrient transporters (e.g., glucose, amino acids, ketones) and receptors (e.g., for insulin, leptin) on endothelial cells lining the cerebral vasculature enables the delivery (*via* passive diffusion, active transport or receptor-mediated endocytosis) of essential molecules required for neural development and proper neural function. Thus, the unique structure, function, and location of the BBB enables this structure to serve as key regulator of entry into the CNS- serving a crucial role in the protection of the brain parenchyma from injury and disease.

Sleep Disruption-Induced Blood Brain Barrier Disruption

Studies have illuminated the role of sleep in providing a "restorative function" in that sleep promotes removal of neurotoxic waste products that accumulate in the interstitial space during wakefulness *via* a "garbage collector" system termed the glymphatic system (i.e., cerebrospinal fluid transport) (Xie et al., 2013; Ding et al., 2016; Hauglund et al., 2020). In addition, recent studies have demonstrated the role of both endogenous circadian rhythms and sleep in promoting the clearance of metabolites along the BBB at night (Cuddapah et al., 2019). This is mainly achieved *via* regulation of BBB permeability through the activity of permeability-glycoprotein multidrug transporters [also known as Pgp, multidrug resistance protein 1, or ATP-binding cassette sub-family B member 1(ABCB1)] which are less active at night (i.e., reduced function), thus increasing permeability of the brain overnight. The presence and activity of Pgp on brain capillary endothelial cells serves as an efflux pump to expel substrates back into the circulation after they initially diffuse into the endothelial cells, restricting entry into the brain parenchyma. Additional studies have demonstrated the role of sleep loss in impairment of BBB function and subsequent increase in BBB permeability to proinflammatory cytokines (e.g., TNF-a) and immune cells (He et al., 2014a,b; Opp et al., 2015; Hurtado-Alvarado et al., 2017; Medina-Flores et al., 2020). A study by He et al. (2014b) investigated whether chronic sleep restriction (CSR) contributed to pathophysiological processes in the brain. Indeed, they demonstrated that CSR affects genes involved in vascular endothelial function and inflammation. In addition, they demonstrated that CSR increased the uptake of sodium fluorescein 10 min after intravenous injection in the brainstem, cerebellum, and subcortical regions, demonstrating a functional breakdown in the barrier. Similarly, Medina-Flores et al. (2020) described the interactions between brain endothelial cells and pericytes that promote BBB disruption after sleep loss in rats. They demonstrated that daily 20-h sleep restriction for 10 days [i.e., chronic sleep restriction (CSR)] reduces pericyte-brain endothelial cell interactions as assessed by decreased expression of the pericyte-endothelial cell interaction markers connexin 43 and platelet-derived growth factor receptor-B (PDGFR-B) in the cerebral cortex and hippocampus. In addition, CSR promotes brain pericyte detachment–which was not concurrent with apoptosis of pericytes–from the capillary wall in both the cerebral cortex and hippocampus, resulting in impairment of blood brain barrier function as assessed by subsequent increase in permeability to sodium fluorescein and Evans Blue.

In alignment with these findings, previous studies in rats have demonstrated that co-culture of endothelial cells and pericytes are more effective in increasing transendothelial electrical resistance (TEER) and lowering permeability to both low and large molecular weight tracers as compared to monocultures of endothelial cells alone (Nakagawa et al., 2009). In addition, Medina-Flores et al. (2020) demonstrated that disruption of endothelial cell-pericyte interactions (i.e., BBB impairment) was also associated with decreased expression of the tight junction protein claudin-5 in both the cerebral cortex and hippocampus which was associated with overexpression of matrix metalloproteinase-9 (MMP-9). Lastly, Medina-Flores et al. (2020) demonstrated that the BBB disruption in CSR rats was concurrent with an increased blood-brain barrier permeability to the chemical compound rhodamine 123, which is often used as a functional reporter of PGP activity. Thus, these findings highlight the contribution of sleep loss, independent of tumor burden, on BBB disfunction. Given the contribution of various disease states (e.g., cardiovascular disease, kidney disease, diabetes, cancer) in promoting sleep disruption, it is becoming increasingly necessary to further characterize the relationship between sleep and pathological conditions. In addition, further studies need to assess the potential contribution of sleep loss-induced BBB disruption in promoting an additional, unregulated route by which peripheral signals enter the brain parenchyma in various pathologies, exacerbating aberrant neural circuitry in a vicious cycle.

Sleep Disruption and Glial Cells

Glial cells are present in both the central and peripheral nervous systems and serve many vital functions (e.g., myelin production) and are essential regulators in the formation, maintenance, and function of synapses. The major type of glial cells in the central nervous system (i.e., brain and spinal cord) are astrocytes, oligodendrocytes, microglia, and ependymal cells–each of which contain their respective function and molecular/cellular characteristics. Neurons and glial cells occupy a comparable amount of space in nervous tissue; however, the number of glial cells outnumber that of neurons. Thus, a comprehensive review of the effects of sleep disruption on tumorigenesis–and reciprocally, the effects of peripheral tumors in promoting sleep disruption–must encompass the potential contributions of glial cells. Recently, a role of glial cells in the regulation

of sleep-wake cycles is emerging, highlighting the dynamic interactions present within neural circuits that influence sleep in both health and disease (Garofalo et al., 2020; Ingiosi et al., 2020). For example, a study by Bellesi et al. (2017) demonstrated that sleep loss enhances astrocyte phagocytosis as observed by an increase in the number of synaptic elements (e.g., spine head, axon, dendrite) surrounded by peripheral astrocytic processes (PAPs) in mice that underwent sleep deprivation (SD) or chronic sleep restriction (CSR). In addition, translating ribosome affinity purification technology and microarrays identified increased astrocytic *Mertk* expression- a "wake" gene upregulated in both spontaneous wake and sleep deprivation. In addition, Bellesi et al. (2017) demonstrated that only CSR is associated with microglia activation in the mouse cerebral cortex, assessed by analyzing the morphology (i.e., branching) of microglial cells since it correlates closely with their state of activation. Subsequently, the group demonstrated that there was higher expression of C3, a major component of the innate immune complement cascade required for microglial phagocytosis, in SD and CSR mice. Thus, CSR is associated with microglial activation and increased phagocytosis without a notable increase of inflammatory mediators in the CSF. The observed glial phagocytosis may serve different functions such as the removal of abundant synapses that become established during extended wake periods. In addition, studies have demonstrated that microglial activation can occur in response to systemic inflammation and, in turn, can communicate systemic inflammation to the brain [91]. Thus, systemic inflammation induced by sleep deprivation, cancer, or chemotherapy treatment can result in glial-mediated synaptic elimination which may contribute to the cognitive impairment observed in cancer patients and/or represent a mechanism by which sleep deprivation affects cognitive function. In addition, aberrations in neuronal circuitry during sleep deprivation that promote systemic inflammation and subsequent tumorigenesis may be attributed to synaptic remodeling by activated glial cells (**Figure 2**).

NON-CNS TUMOR EFFECTS ON SLEEP NEUROCIRCUITRY

Poor sleep experienced by cancer patients and survivors could be attributed to the presence of one or more underlying sleep disorders. Thus, one of the most prominent concerns in cancer patients is the onset of sleep disorders including difficulty falling asleep, problems maintaining sleep, poor sleep efficiency and early awakening. Early immunologists treated the nervous and immune systems as largely separate entities. However, today there is consensus that there is bi-directional communication between the nervous and immune systems in both health and disease states. To date, there are several pathways that have been proposed in the field of neuroimmunology as being important for the communication between the immune system and central nervous system: the neural route (e.g., vagal afferent signaling), BBB active transport of cytokines and secretions from BBB cells, passive diffusion at circumventricular organs which lack a BBB (e.g., median eminence), infiltration of peripheral immune cells, as well as interactions with meningeal lymphatics (Quan and Banks, 2007; Kipnis, 2016; Prinz and Priller, 2017). Thus, peripheral cues can signal to the CNS whereby the CNS coordinates appropriate responses (i.e., sickness behavior) as an adaptive strategy to an immune challenge. For example, intravenous (IV) administration of inflammatory cytokines interleukin-1 (IL-1), tumor necrosis factor alpha (TNF-alpha), and interleukin-6 (IL-6)- all of which are upregulated during cancer progression- has been shown to induce sickness behavior (including sleep disruption) similar to those observed during infection in both mice and humans (Focà et al., 1983; Lesnikov et al., 1991; Ching et al., 2007). Interestingly, two additional reflex responses to systemic LPS have been well-studied, including both fever and the activation of the HPA axis (Hosoi et al., 2000; Romanovsky, 2005). Given the role of peripheral signals in influencing the CNS, it is unsurprising that LPS as well as additional proinflammatory cytokines (e.g., IL1-B and TNFa) exert somnogenic effects, in that they are involved in the regulation of sleep (Opp, 2005). In addition, studies have demonstrated that LPS-induced lethargy is mediated by alterations to HO activity (Grossberg et al., 2011). In this section we will discuss additional routes (e.g., humoral, neural) that are critical for relaying information to inform the brain about the peripheral environment.

Humoral Route

Tumors in the periphery present a systemic challenge, altering metabolic, immune, and (likely) cognitive capacity. The nervous system and peripheral tumors (i.e., non-CNS tumors) engage in bidirectional communication as well. A growing body of literature illuminates the role of nerves in cancer initiation, progression, and subsequent metastasis through direct interactions with cancer cells or through interactions with stromal cells in the TME (Faulkner et al., 2019; Monje et al., 2020; Zahalka and Frenette, 2020). Just as normal, healthy tissues recruit and maintain innervation of the peripheral nervous system (PNS) (e.g., autonomic nervous system) to promote regeneration and repair of tissue, peripheral tumors co-opt these pathways to aid in the recruitment of nerves into the tumor microenvironment through the release of neurotrophic factors (e.g., NGF, BDNF, NT-3). Subsequent outgrowth of nerves into the TME results in enhanced cholinergic or adrenergic signaling in the TME, resulting in tumorigenesis and increased aggressiveness of gastric and breast cancer, respectively (Sloan et al., 2010; Hayakawa et al., 2017). In addition, innervation of sensory nerves in the TME mediates pain responses relevant to cancer progression. Consequently, increasing tumor burden in peripheral tissues has been shown to affect neural activity in the brain, with significant consequences on sleep-controlling neurocircuitry in the hypothalamus (Walker and Borniger, 2019). The hypothalamus is sensitive to peripheral signals and is able to sense these signals (*via* humoral and neural routes) and subsequently alter neural activity (Francis and Borniger, 2021). Consequently, the hypothalamus is able to generate physiological and behavioral responses through its influence on both the autonomic nervous system (i.e., sympathetic and parasympathetic divisions) and the

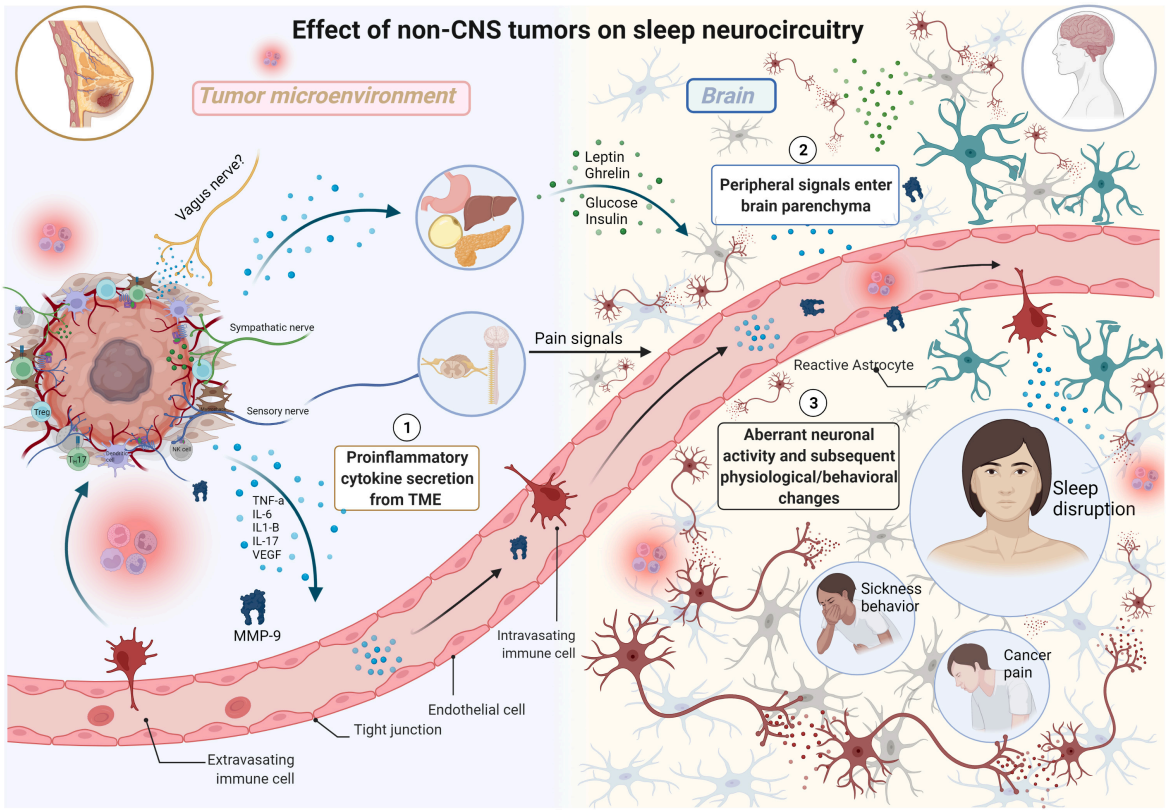

FIGURE 2 | The effects of non-CNS tumors on sleep neurocircuitry. TME-derived proinflammatory signals (e.g., TNFa, IL-6, IL1-B, IL-17) enter systemic circulation, eventually moving into the brain parenchyma impacting neurocircuitry including sleep. TME-derived proinflammatory signals also exert effects on distant organs including stomach, liver, pancreas, and adipose tissue resulting in elevated secretion of satiety/hunger hormones (e.g., leptin, ghrelin) and glucose and insulin which all exert differential effects on sleep neurocircuitry in the CNS. Sensory nerves in the TME relay information from the TME, resulting in the production of severe pain in various malignancies including breast cancer. This results in neurochemical changes in the spinal cord and forebrain, including elevated levels of noradrenaline (NA), in the brain parenchyma with negative consequences on both quality of life and survival. Aberrant neuronal activity results in subsequent physiological/behavioral changes including sleep disruption, sickness behavior, and cancer pain (Made with BioRender.com).

hypothalamus-pituitary-adrenal (HPA) axis. A more thorough review on the role of the hypothalamus as a systemic integrator in both homeostasis and in response to homeostatic challenges (e.g., cancer) can be found here (Francis and Borniger, 2021).

Borniger et al. (2018) demonstrated tumor-induced sleep and metabolic abnormalities in a mouse model of non-metastatic breast cancer, independent of behavioral deficits or cachexia. The metabolic abnormalities were reflected in alterations to satiety hormone signaling (i.e., leptin and ghrelin) and hepatic glucose processing which was found to coincide with peripheral IL-6-driven inflammation. IL-6 levels were elevated both in the tumors and serum of tumor-bearing mice which was also associated with increased protein concentrations of the IL-6 regulated transcription factor pSTAT3 and increased expression of downstream targets of IL-6 signaling in the liver (e.g., *Stat3*). In addition, brain and muscle activity were detected using EEG and EMG, respectively, to assess changes to sleep-wake states throughout cancer progression. Interestingly, the presence of the peripheral tumor was found to disrupt sleep-wake states in the later course of tumor progression as evidenced by reduced time spent awake and an increase and fragmentation of NREM but not REM sleep. These observed sleep-wake aberrations were mainly attributed to enhanced activity of HO neurons as evidenced by increased cFos immunoreactivity during the active phase in tumor-bearing mice. Importantly, the altered sleep patterns were not due to altered immune activation in the brain, as there were no indications of increased pro-inflammatory cytokines (IL-6, TNF-a, IL1-B) in several brain regions. Borniger et al. (2018) also demonstrated that the use of a HO-receptor antagonist (Almorexant) and not neutralizing antibodies against IL-6, attenuated tumor-induced impairments in glucose metabolism and improved sleep quality–indicative of active sensing of HO neurons to peripheral signals on metabolic and immune status, as previously reported (Adamantidis and De Lecea, 2009). In addition, the reported alterations in metabolism (i.e., impaired glucose tolerance, spontaneous hyperglycemia) were attributed to HO-mediated control of the sympathetic nervous system. Chemical sympathectomy (*via* the neurotoxin 6-OHDA) attenuated metabolic abnormalities in tumor-bearing mice as evidenced by restoration of blood glucose concentrations and normalization of several hepatic genes involved in gluconeogenesis/glycolysis (ldha, gck, pklr).

These findings provide mechanistic insight into tumor-driven alterations in sleep-wake neurocircuitry that may be coupled to changes in metabolism or immune signaling in the periphery. These findings warrant further discussion on reprogramming the use of current clinically approved hypocretin receptor antagonists (e.g., Suvorexant) for improving metabolic and sleep aberrations in cancer patients (Walker and Borniger, 2019).

Neural Route (*via* Sensory Neurons)

Sensory neurons form the afferent division of the peripheral nervous system and are primarily responsible for conveying various signals arising from the viscera and the skin to the central nervous system, in turn activating neuroendocrine and visceromotor reflexes. The cell bodies of sensory neurons reside in the dorsal root ganglia (DRG) of the spinal cord or along cranial nerves. Sensory neurons are subdivided into visceral and somatic sensory neurons, which transmit sensory information primarily from internal organs and skin and skeletal muscles, respectively. In addition, sensory neurons contain different receptors for different stimuli (e.g., thermoreceptors, mechanoreceptors, nociceptors, photoreceptors, and chemoreceptors) which in turn allow for the perception of various sensations including pain, temperature, and touch.

Recent studies highlight the role of sensory neurons in the initiation, migration, progression and metastasis of pancreatic and breast cancer (Demir et al., 2015; Saloman et al., 2016; Le et al., 2021). In addition, sensory neurons are implicated in the production of severe pain in breast, prostate, colon, pancreatic, and bone cancer, which is in part due to perineural invasion of cancer cells (Cain et al., 2001; Liebig et al., 2009; Andersen and Kehlet, 2011; Mantyh, 2013). Cancer pain does not only influence quality of life but also affects the survival of cancer patients (Mantyh, 2006). Nociceptors (i.e., pain receptors) are densely packed on afferent fibers of sensory neurons where they primarily relay noxious stimuli to the spinal cord that are then, *via* ascending pathways, conveyed to various brain regions to elicit pain sensations. Nociceptors are capable of detecting different forms of noxious stimuli (ATP, IL1, IL6, NGF, VEGF, TNFa, protons) that are secreted by cancer cells and other components of the TME (Mantyh et al., 2002). Consequently, sensory neurons alter their pattern of expression of various signaling molecules which partly underlies increased sensitization and subsequent hyperalgesia/allodynia. In addition to the changes in sensory neurons, the spinal cord and forebrain both undergo neurochemical and structural changes as chronic pain develops during cancer progression which alters neuronal activity (Honore et al., 2000a,b). A key brain region that has been extensively studied in several pain conditions and is involved in the modulation of pain is the locus coeruleus (LC), through the release of NA and subsequent action on adrenergic receptors (Brightwell and Taylor, 2009; Llorca-Torralba et al., 2016; Taylor and Westlund, 2017). Importantly, the LC has direct relevance to sleep as the LC is important for promoting arousal (Foote et al., 1983; Berridge and Waterhouse, 2003; Aston-Jones and Cohen, 2005). Neurons in the LC fire tonically at 1–3 Hz during wakefulness, fire less during NREM sleep and are essentially silent during REM sleep (G. Aston-Jones and Bloom, 1981a,b). When a painful stimulus is applied at the periphery, both ascending and descending pain pathways are activated, in which the LC is a key structure in both pathways (Hwang et al., 2001; Howorth et al., 2009). In the ascending pathway, the pain information is first transmitted to the spinal cord and subsequently along ascending axons to supraspinal structures, including the paragigantocellular nucleus (PGi), which exerts excitatory effects on the LC (Ennis et al., 1992). After reaching the LC, pain information is transmitted to other brain regions such as the amygdala, hypothalamus, thalamus, and cortex engaging more complex behaviors in response to pain (e.g., sleep and stress-related responses). Additionally, given the critical role of LC-noradrenergic neurons in the transition between sleep and wakefulness, studies have shed some insight into the possible involvement of the LC in pain-related sleep disruption (Koh et al., 2015). Since the hypocretin-mediated sleep-wake transition is heavily dependent on its projections to LC noradrenergic neurons, there may also be an important functional role of HO neurons in nociceptive perception and subsequent sleep-wake regulation in response to pain (Hagan et al., 1999; Mohammad Ahmadi Soleimani et al., 2015; Mohammad-Pour Kargar et al., 2015; Ahmadi-Soleimani et al., 2020). Thus, sensory neurons play a critical role in relaying pain information (e.g., tumor-induced inflammation) arising from the periphery to the CNS with impacts on sleep-controlling brain regions such as the lateral hypothalamus and LC (i.e., increased wakefulness). In addition, sleep disruption can increase pain sensitivity, and pain can in turn disrupt sleep physiology (Alexandre et al., 2017).

On the other hand, the descending noradrenergic pathway involves those mainly projecting to the spinal cord (Howorth et al., 2009). Interestingly, the descending noradrenergic pathway from the LC to the spinal cord is mainly ipsilateral, although there is also crossing over of the information at the midline to innervate the opposite side of the dorsal horn. However, these studies demonstrate the projections of the pain-responsive noradrenergic neurons originating in the LC to the lumbar dorsal horn. Whether or not a subset of pain-responsive noradrenergic neurons originating in the LC and projecting to other divisions of the spinal cord has not been assessed. The lateral horn of the spinal cord contains the neuronal cell bodies of the sympathetic division. Thus, it is possible that pain-induced stimulation of the LC results in the activation of descending pathways that project to the lateral horn of the spinal cord, resulting in the activation of the SNS and further promoting tumor progression. Consequently, growing tumor burden in the periphery increases pain perception *via* ascending pathways that project to the LC. As a result, noradrenergic neurons in the LC increase their firing rates, resulting in downstream effects on peripheral tissues–establishing a vicious cycle.

Active Surveillance of the Periphery by the Vagus Nerve Cranial Nerve X (CNX)

The discovery of the cholinergic anti-inflammatory pathway provides another example of the important function of peripheral nerves in sensing, encoding, and relaying inputs to the CNS

regarding our body's internal state (e.g., fluctuations in peripheral cytokines and toxins, tissue injury) (Tracey, 2002). Since the characterization of the cholinergic anti-inflammatory pathway, a plethora of studies have established the role of local and systemic inflammation in the activation of vagal efferent fibers, resulting in suppression of cytokine release from macrophages (Tracey, 2007). Most of the evidence for the action of the anti-inflammatory pathway have been demonstrated in a model of LPS administration in rodents (Borovikova et al., 2000a,b; Wang et al., 2003). Unsurprisingly, the vagus nerve may have a critical role in informing the brain about the tumor microenvironment with subsequent consequences on neuronal activity (Gidron et al., 2005).

Interestingly, several studies highlight a contribution of the vagus nerve in the sleep-promoting effects of IL1-B. A study by Hansen and Krueger (1997) demonstrated that subdiaphragmatic vagotomy blocks the sleep and fever-promoting effects of IL1-B in rats. Rodents were separated into two groups, those that received a vagotomy (Vx) or sham surgery (i.e., vagus nerve remained intact). Subsequently, both Vx and sham groups were given an intraperitoneal (IP) injection of low-dose (0.1 μg/kg) IL-1B and the amount of time spent in sleep was analyzed. Hansen et al. observed that administration of low-dose IL1-B in sham rats increased NREM sleep, whereas administration of low-dose IL1-B in Vx rats failed to induce significant changes in NREM sleep compared to controls. In addition, Hansen et al. demonstrated that the administration of low-dose IL1-B in sham rats induced a significant increase in body temperature (i.e., fever response), whereas the increase in body temperature was completely blocked in Vx animals. One important aspect of this study is that vagotomy did not block the sleep and fever responses when rats were subject to high-dose (2.5 μg/kg) IL1-B. Thus, subdiaphragmatic vagotomy completely abolishes low-dose IL1-B-induced NREM sleep and fever responses. However, the inability of the vagotomy to block the sleep and fever responses in rats subjected to high-dose of IL-1B can be attributed to mechanisms that are not dependent on intact subdiaphragmal vagi. These findings indicate that in addition to the subdiaphragmatic vagus control of sleep and fever in response to acute inflammation, alternative pathways exist that influence the CNS at more severe levels of inflammation (i.e., chronic inflammation or sepsis). Thus, elevation of IL1-B in the systemic circulation (induced by sleep disruption, cancer, chemotherapy, etc.) effect sleep neurocircuitry *via* vagal input and likely enter the brain parenchyma *via* aforementioned mechanisms (i.e., BBB-mediated transport and/or passive diffusion at circumventricular organs) resulting in aberrant neuronal activity.

Systemic Inflammation and Blood Brain Barrier Breakdown

Sleep is regulated by both humoral and neuronal mechanisms that are dependent on each other. Several studies have demonstrated that proinflammatory cytokines (e.g., IL-1B and TNF-a) have a somnogenic effect, increasing both sleep (e.g., NREM) and lethargy following peripheral immune activation (Opp, 2005). Interestingly, the concentrations of TNF-a and IL-1B in the CNS display circadian oscillations, with IL-1B and TNF-a mRNA expression and protein content in the brain coinciding with the amount of NREM sleep (Bredow et al., 1997; Taishi et al., 1997). In addition, many immunomodulators of sleep-wake behaviors including cytokines, chemokines, and growth factors, all of which may become deregulated in cancer patients (Dranoff, 2004). Alterations in the levels of these signaling molecules have dynamic effects on many biological processes including release of neurotransmitters, peptides, and hormone secretions which have profound effects on sleep-wake neurocircuitry.

In addition to the established somnogenic effects of proinflammatory cytokines and chemokines (Opp, 2005), *via* vagal afferents (Hansen and Krueger, 1997) and additional mechanisms, proinflammatory cytokines have also been implicated in disruption and impairment of the BBB. A key component of the BBB architecture is the presence of tight junction proteins between brain capillary endothelial cells that serve to limit the movement of substances into the brain. Numerous studies have demonstrated a role of systemic inflammation (e.g., cancer) and cancer therapies (e.g., chemotherapy) in cytokine-mediated breakdown of the BBB [reviewed in Wardill et al. (2016)]. In addition, more recent studies have demonstrated that the exposure of the endothelium to immune cell-derived proinflammatory cytokines (e.g., TNF-alpha, IL-1b, IFN-g) results in disruption of BBB integrity and enhanced leukocyte endothelial adhesion and migration. Thus, it is becoming increasingly important to recognize the contribution of BBB disruption as an additional route by which aberrant neuronal activity arises during cancer progression. In addition, tumor-induced disruption of the BBB promotes host death in preclinical models (Kim et al., 2021). A study by Kebir et al. (2007) demonstrated a role of human T_H17 lymphocytes in promoting blood-brain barrier disruption and central nervous system inflammation. Interestingly, T_H17 lymphocytes were able to migrate across the BBB both *in vitro* (using human BBB-EC's) and *in vivo* as analyzed by human CNS postmortem tissues from individuals with multiple sclerosis, a disease with well-characterized BBB disruption. Kebir et al. also demonstrated that the binding of both IL-17 and IL-22, two identified cytokine products of T_H17 lymphocytes, to their receptors (IL-17R and IL-22R, respectively) on human brain endothelium was critical for the increased permeability of the BBB. IL-17 consists of a family of proinflammatory cytokines secreted primarily by activated T-helper type 17 (T_H17) lymphocytes. IL-17 plays an important role in the homeostasis of tissues in health but also contributes to autoimmunity, chronic inflammation and invasion in various inflammatory diseases such as multiple sclerosis, rheumatoid arthritis, inflammatory bowel diseases and type I diabetes (Jin and Dong, 2013). A role for IL-17 in promoting breast cancer progression and metastasis has been described, which is associated with a worse prognosis (Du et al., 2012; Chen et al., 2013; Jin and Dong, 2013, p. 1; Coffelt et al., 2015). Within the tumor microenvironment, IL-17 is primarily secreted by tumor-infiltrating lymphocytes in two murine models of breast cancer (Du et al., 2012). Thus, IL-17 production by immune cells in the TME both promotes breast cancer progression and results

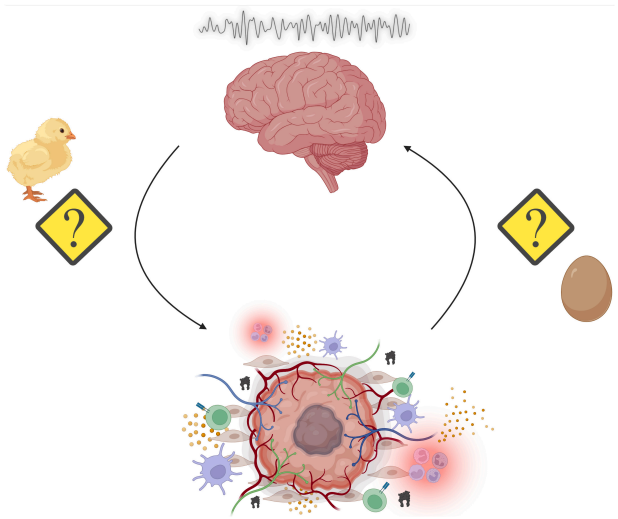

FIGURE 3 | Summary of the overarching principles highlighted in this review. Sleep disruption may promote tumorigenesis through alterations in a variety of physiological processes such as energy balance, immunity, and stress. Reciprocally, the genesis of peripheral tumors and the subsequent assembly of the tumor microenvironment (TME) results in cancer-mediated alterations to our physiological processes. The consequences include aberrant neural activity, which affect a multitude of behavioral outputs including disruption of sleep/wake cycles. This results in a "chicken or the egg" phenomenon, where it is unclear whether sleep disruption promotes cancer or cancer reciprocally disrupts sleep (Made with BioRender.com).

in disruption of the BBB. The consequences of BBB disruption are increased entry of proinflammatory cytokines into the brain parenchyma, resulting in an additional route of entry by which somnogenic cytokines alter sleep neurocircuitry. This, in turn, alters the activity of the HPA axis and SNS signaling in the periphery, further promoting cancer progression (**Figure 3**).

CLINICAL IMPLICATIONS

Clinical Data-Sleep Disruption and Breast Cancer

Although sleep disruption because of cancer is a well-established symptom of malignancy, its significance has been largely overlooked in traditional oncology treatment regimens. In one study, about 50% of women with non-metastatic breast cancer reported symptoms of insomnia prior to surgery, whereas rates on insomnia in men diagnosed with prostate cancer was about 30% prior to surgery (Savard et al., 2011). Clinical studies suggest that sleep disruption is particularly relevant in breast cancer. In addition to being highly prevalent, sleep problems are independently associated with a higher risk of earlier death and poor treatment response (Palesh et al., 2014; Innominato et al., 2015). Disrupted sleep patterns in breast cancer are also evidenced by alterations in the rhythmic secretion of cortisol, which is regulated by the central circadian clock in the suprachiasmatic nuclei (SCN) (Buijs et al., 2003; Abercrombie et al., 2004; Kiessling et al., 2017). VIP (vasoactive intestinal peptide) neurons within the SCN rely on tightly coordinated clock gene and neuronal rhythms to control their input to PVN corticotrophin-releasing hormone producing neurons (Jones et al., 2021). Normally, cortisol levels build up throughout the night, reach peak levels around the time of waking, and then steadily decline through the day (Weitzman et al., 1971). Studies have found that aberrant cortisol rhythms can even serve as a predictor of breast, lung, and ovarian cancer mortality, where patients with "flat" or abnormal rhythms show earlier mortality (Sephton et al., 2000, 2013; Schrepf et al., 2015). Experimental studies exploring the mechanistic link between circadian and cortisol rhythm disruption and cancer outcomes may be able to transform this relationship from a prognostic factor to the focus of treatments.

Epidemiological Data and Controversy in the Field

As with many emerging fields, the current epidemiological evidence relating sleep quality, sleep duration, and shift work to subsequent cancer development is controversial. Several epidemiological studies have found that women working night shifts have a significantly elevated risk of breast cancer (Manouchehri et al., 2021). Similar relationships were observed for prostate and gastrointestinal tract cancer (Schernhammer et al., 2003; Kubo et al., 2006). However, several recent systematic reviews and meta-analyses have reported no associations between altered sleep and cancer initiation (Fritschi et al., 2013; Li et al., 2015; Chen et al., 2018). In addition, a recent paper by Titova et al. (2021) employed the use of mendelian randomization (MR), an epidemiologic technique used to determine the causal role of genetic variants for disease risk, to assess the effect of sleep duration on cancer risk. Titova et al. (2021) concluded that the MR study showed a casual association between both short and long sleep duration and risk of some site-specific cancers but not overall cancer. Titova et al. (2021) concluded that there is a lack of robust evidence to support causal associations of sleep duration with risk of overall and site-specific cancers. However, recent prospective studies demonstrate an increased risk of cancer in men who reported sleep duration of 5–6 h per night compared with those who slept 7–8 h (Gu et al., 2016). Given that the current evidence is unclear, additional, well-designed, longitudinal cohort studies examining sleep and cancer are warranted. Future work could uncover the types of cancer that are most closely associated with sleep disturbances, as well as the dose-response relationship for a given sleep-related risk factor. Epidemiological studies are uniquely positioned to evaluate population level relationships that may otherwise go undetected in the laboratory.

Management of Sleep Disruption in Patients

The current approach to managing sleep disturbances in patients with cancer initially focuses on non-pharmacologic treatments, such as sleep hygiene modifications, cognitive behavioral therapy for insomnia (CBTI), and relaxation techniques. CBTI is an evidence-based, structured program that is used to combat insomnia in the general population. Recent trials have found

that CBT-I can significantly improve sleep measures in breast cancer survivors and patients undergoing treatment (Savard et al., 2005; Espie et al., 2008; Berger et al., 2009). Results from these studies suggest that cancer patients may benefit from psychological interventions. If these are not available or successful, pharmacologic treatments that have not been thoroughly studied in cancer populations are usually prescribed, such as benzodiazepine receptor agonists (e.g., zolpidem) and benzodiazepines (lorazepam). In a recent survey of cancer patients, 22.6% were taking medication for sleep problems, with half of these patients using the medication every day for longer than 6 months. Long term use of hypnotic medications appears to be widely used by patients with cancer despite limited data regarding long-term efficacy and possible adverse effects, such as daytime sedation and cognitive impairments. Furthermore, chronic use is associated with dependence and offers no real evidence of benefit (Kripke, 2000). The current approach to sleep problems in patients with cancer is not sufficient given the impact sleep disruption has on both quality of life and cancer outcomes. The etiology of cancer induced sleep disruption is likely different than that of the general population, so standard sleep treatments may not offer the same benefit to patients with cancer. Recent advances in fMRI technology and analysis have allowed researchers to accurately screen for vulnerability to sleep deprivation using resting-state network measures coupled with machine learning (Xu et al., 2021). This type of novel screening tool may have useful applications in the context of cancer wherein patients could be assessed for their risk of cancer-induced sleep disruption during the initial stages of their diagnosis and treatment.

Melatonin as a Treatment

Melatonin is a physiological signal of darkness that is associated with sleep in humans. The role of melatonin suppression has been causally investigated as a contributor to increased cancer risk. Thus, considerable research has focused on the role of artificial light exposure during the night and melatonin suppression, which appears to be related to an increased cancer risk (Yang et al., 2014; Jardim-Perassi et al., 2014). *In vivo* studies have demonstrated that melatonin treatment reduced tumor size and cell proliferation, as well as a decrease in VEGF receptor 2 density, in mice with breast cancer xenografts (Jardim-Perassi et al., 2014). Moreover, important to tumor suppression, melatonin has gained increased notoriety over the last several decades for its antioxidant properties as melatonin influences both antioxidant enzyme activity and cellular mRNA levels for these enzymes (Tan et al., 1993; Steinhilber et al., 1995; Reiter, 1998; Reiter and Maestroni, 1999).

Experimental models and epidemiological studies indicate that melatonin may have an onco-protective role. These studies have shown that melatonin improves the sensitivity of cancers to chemotherapy and has the potential to reverse drug resistance in tumors (Uguz et al., 2012; Dauchy et al., 2014; Xiang et al., 2015). Moreover, melatonin has been shown to inhibit molecular processes associated with metastasis (Su et al., 2017). Prior to cancer initiation, melatonin also serves as a free radical scavenger (Tan et al., 2002), preventing DNA damage that could lead to oncogenic mutations. Given these findings, a more complete understanding of melatonin in homeostasis and malignancy would be of immediate clinical utility. Melatonin is synthesized by the pineal gland and represents a biological timing signal that is driven by the activity of the SCN of the anterior hypothalamus and synchronized to the light/dark cycle (Claustrat et al., 2005). Experimental studies examining how changes in this neurocircuitry affect oncogenesis, cancer progression, and cancer treatment would be highly valuable to the clinic. For example, bilateral electrolytic lesion of the SCN results in disruption of circadian rhythms and subsequent acceleration of tumor growth (Filipski et al., 2002). Treatment modalities targeting this neurocircuitry or melatonin itself could prove useful in cancer prevention or as an adjuvant of current cancer therapies. The information gathered from these studies should be translated to the clinic, granting providers the knowledge to deliver evidence-based cancer prevention recommendations.

In clinical trials where melatonin was used as an adjuvant therapy with other chemotherapeutic drugs there was enhanced therapeutic efficacy, higher survival rate, and increases sleep and quality of life (Cerea et al., 2003; Lissoni et al., 2003). Support for the anti-cancer properties of melatonin supplementation is less consistent in epidemiological studies. Several studies report a protective role of melatonin in cancer (Basler et al., 2014), while other studies find no significant relationship (Travis et al., 2004; Sturgeon et al., 2014). Thus, melatonin treatment may help resolve the sleep disturbances experienced by patients with cancer while also decreasing tumor progression. However, melatonin is "messy" in that it signals through two distinct receptors on majority of cells and has many receptor-independent effects which could decrease the efficacy of melatonin as a therapeutic strategy in cancer patients.

UNANSWERED QUESTIONS AND FORWARD DIRECTIONS FOR THE FIELD

Employing Modern Neuroscience Techniques to Address These Questions

We are just beginning to appreciate the bi-directional communication between cancer and the nervous system. The last decade has seen an explosion in discoveries regarding the role of nerves in the tumor microenvironment. Recent advances in modern neuroscience techniques have allowed us to expand upon these findings and trace their influence on the central nervous system. These modern techniques (e.g., optogenetics, calcium imaging) should be leveraged to dissect the neural circuits disrupted by cancer, leading to a more complete understanding of the pathophysiology of malignancy. Uncovering the neural correlates of cancer-related sleep disruption has the potential to inform novel treatment approaches and screening tools that will improve patient care and oncology outcomes. Despite recent progress, many questions remain regarding sleep in the context of cancer.

A potential focus for preclinical discovery will be to localize specific sleep-associated brain nuclei deregulated by cancer and

then employ targeted stimulation or inhibition of these circuits to see what their role is in the development of cancer-associated sleep disruption. Advances in neuroimaging, such as serial two photon tomography (STPT), are already allowing researchers to examine how an entire brain responds to selective perturbations (e.g., drug administration, social interaction) (Kim et al., 2015; Ueda et al., 2020). Unbiased screens of cancer-induced changes in neuronal activity will allow for identification and subsequent manipulation of specific neuronal circuits. Neuroendocrine and metabolic changes must also be elucidated as they are closely tied to sleep physiology. Central nervous system sensitivity to immune related changes is another area that will inform many unanswered questions.

A detailed understanding of how cytokines and metabolic factors affect the central nervous system will become increasingly more important as future cancer treatments targeting or harnessing the immune system become more widely used. Immune checkpoint inhibitors, such as antibodies targeting PD-1/PD1 or CLTA-4, and cellular therapy utilizing chimeric antigen receptor (CAR) T cells are all likely to alter the cancer-induced cytokine and metabolic milieu. Developing a neuroimmune effector map now will translate into the ability to predict the effects targeted immunotherapies may have on the CNS.

Computational approaches will be key in handling the large amounts of data generated by EEG/polysomnography and pulling out important cancer-related changes in brain function. These include machine learning/artificial intelligence techniques, which can (in certain situations) identify small but important changes in data structure that may be missed by classic sleep scoring techniques. This will promote a research cycle where computational approaches allow us to generate hypotheses from large datasets that can then be tested and refined *in vivo*. Finally, we need additional input from oncologists, as not all cancers influence sleep in the same way, and the amelioration of these problems will likely require close collaboration with those who know the details of specific cancer-secreted molecules, propensity for neural invasion, and treatment resistance.

AUTHOR CONTRIBUTIONS

AB prepared figures and figure legends. JB supervised the work. All authors designed, wrote, and edited the manuscript.

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Sleep Disturbance and Its Association With Sluggish Cognitive Tempo and Attention in Pediatric Brain Tumor Survivors

*Ineke M. Olsthoorn[1], Alice Ann Holland[2,3], Raymond C. Hawkins II[4], Allen E. Cornelius[4], Muhammad Usman Baig[5†], Grace Yang[5], Daniel C. Holland[4], Wafik Zaky[5] and Peter L. Stavinoha[5]**

[1] Department of Neurology, McGovern Medical School, University of Texas Health Science Center at Houston (UT Health), Houston, TX, United States, [2] Department of Psychiatry, University of Texas Southwestern Medical School, Dallas, TX, United States, [3] Department of Psychiatry, Children's Medical Center of Dallas, Dallas, TX, United States, [4] School of Psychology, Fielding Graduate University, Santa Barbara, CA, United States, [5] Department of Pediatrics, University of Texas MD Anderson Cancer Center, Houston, TX, United States

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Joy Perrier,
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Milenna Van Dijk,
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Elizabeth Begyn,
Indiana University Bloomington, United States

***Correspondence:**
Peter L. Stavinoha
PStavinoha@mdanderson.org

†Present address:
Muhammad Usman Baig,
Department of Pediatrics, Loma Linda University School of Medicine, Loma Linda, CA, United States

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Background: Pediatric brain tumor (PBT) survivors are at risk for developing sleep disturbances. While in other pediatric populations sleep disturbance has been associated with worse cognitive functioning, it is unclear to what extent this relationship generalizes to PBT survivors. The aim of the current study was to assess the relationship between sleep disturbance and aspects of cognition, including sluggish cognitive tempo (SCT) as well as attention and working memory.

Materials and Methods: Eighty-three PBT survivors 6–18 years of age who were at least 3 months post-treatment were included in the present cross-sectional study. Level of sleep disturbance was measured as a composite score reflecting various sleep problems as rated by caregivers. Cognitive measures included caregiver-ratings of sluggish cognitive tempo and attention problems, as well as performance-based cognitive measures assessing attention and executive functioning. Hierarchical regression analysis was used to assess associations between sleep and cognition.

Results: Of all caregivers, 32.5% reported one or more sleep disturbances as "very/often true" and over 68% of caregivers rated at least one sleep-related item as "somewhat true." Of all cognitive variables, scores were most frequently impaired for SCT (30%). A higher level of sleep disturbance was associated with worse SCT and parent-rated attention problems. Associations between sleep and performance-based cognitive measures assessing attention and working memory were not statistically significant.

Conclusion: Findings of the current study highlight the importance of further investigation into the relationship between sleep and cognition in PBT survivors, which may assist efforts to maximize cognitive outcome and health-related quality of life in PBT

survivors. The current study additionally suggests further investigation of SCT in this population is warranted, as it may be more sensitive to detecting possible associations with sleep disturbance relative to discrete measures that assess cognitive performance under ideal circumstances.

Keywords: sleep, sluggish cognitive tempo, attention, executive functioning, pediatric, brain tumor survivor, cancer

INTRODUCTION

As survival rates for children and adolescents diagnosed with a brain tumor have improved, the importance of maximizing health-related quality of life (HRQOL) in pediatric brain tumor (PBT) survivors has been increasingly recognized (Burns et al., 2016; Netson et al., 2016). Cognitive dysfunction has been related to worse quality of life in PBT survivors, and understanding risk factors for cognitive dysfunction may inform prevention and treatment recommendations to maximize cognitive outcomes. Many factors have been found to be associated with cognitive impairments in PBT survivors, including—both collectively and individually—the tumor, secondary neurological complications, and treatment-related factors such as radiation therapy, chemotherapy, and surgery (Hardy et al., 2008; Tonning Olsson et al., 2014; Taiwo et al., 2017; Ikonomidou, 2018).

A less extensively researched factor that may impact cognitive functioning and HRQOL in PBT survivors is suboptimal sleep (Daniel et al., 2016; Merz and Tomfohr-Madsen, 2016), especially since sleep disruption has been associated with reduced HRQOL in broad samples of pediatric cancer patients and survivors (Kaleyias et al., 2012; Steur et al., 2016). In healthy pediatric populations, it has been shown that suboptimal sleep may negatively affect brain maturation and the associated development of cognitive functions (Peirano and Algarín, 2007; Astill et al., 2012). Sleep disturbances have been associated with changes in networks related to working memory and attention, including the frontal-parietal and default mode networks (de Havas et al., 2012; Nie et al., 2015; Yeo et al., 2015; Krause et al., 2017; Tashjian et al., 2018). Additionally, disrupted sleep may result in changes in motivation and effort perception which, in turn, may affect performance (Robert and Hockey, 1997; Hockey, 2011, 2013; Monk, 2012; Massar et al., 2019).

Relevant to PBT survivors, it is noteworthy that in healthy children and adolescents, shorter sleep duration has been particularly associated with worse performance on cognitive tests assessing working memory, processing speed, and sustained attention (Astill et al., 2012; Vriend et al., 2013; Louca and Short, 2014)—functions which are commonly compromised in PBT survivors (Ullrich and Embry, 2012; Wolfe et al., 2012; Hoang et al., 2014). Furthermore, it is known that PBT survivors have an elevated risk for sleep difficulties (Gapstur et al., 2009; Rosen and Brand, 2011; Nolan et al., 2013; Brimeyer et al., 2016; Desaulniers et al., 2018). Estimates of the prevalence of sleep problems in PBT survivors have ranged from 20 to 82% (Brimeyer et al., 2016; Pilotto et al., 2018; van Kooten et al., 2019), as compared to rates of 12–25% in healthy populations (Melendres et al., 2004; van Litsenburg et al., 2010). The wide range of estimates for PBT survivors reflects that sleep disturbances are often described as general symptoms rather than specific to criteria for a sleep disorder (Otte et al., 2015; Daniel et al., 2020). Sleep disturbances can persist into adulthood for pediatric cancer survivors (Zhou and Recklitis, 2014; Daniel et al., 2020). In fact, excessive daytime sleepiness has been found to be more common in survivors of pediatric brain tumors as compared to survivors of other pediatric cancers (Verberne et al., 2012).

A range of sleep disturbances have been observed in pediatric cancer patients and survivors, including insomnia, excessive daytime sleepiness, poor sleep quality, circadian rhythm disorders, parasomnias, and sleep-disordered breathing (van Someren et al., 2004; Rosen and Brand, 2011; Nolan et al., 2013; Zhou and Recklitis, 2014; Sheikh et al., 2021). Various mechanisms have been proposed to explain elevated rates of sleep disturbances in children diagnosed with cancer (Daniel et al., 2016; Merz and Tomfohr-Madsen, 2016). Potential contributing factors are those specific to the disease and its treatment (e.g., damage to brain areas involved in sleep; Mandrell et al., 2020; Klages et al., 2021; Sheikh et al., 2021), environmental factors (e.g., sleep disruption due to hospitalizations or spending excessive time in bed; Hinds et al., 2007; Linder and Christian, 2012; Lee et al., 2017), family factors (e.g., increased distress or conflict due to altered family dynamics; Pai et al., 2007; El-Sheikh et al., 2012; Marcus, 2012; Pollock et al., 2013; Wiener et al., 2017), psychological factors specific to the child (e.g., traumatic stress, anxiety or depression; Shah et al., 2015; McDonnell et al., 2017; Kim et al., 2020), and reduced physical activity (Orsey et al., 2013; Antwi et al., 2019).

One construct that has been associated with sleep disturbances in both healthy adolescents as well as children and adolescents with neurodevelopmental conditions (such as ADHD) is sluggish cognitive tempo (SCT; e.g., Mayes et al., 2021; Fredrick et al., 2022), which refers to a set of symptoms that includes mental fogginess and confusion, slowed behavior/thinking, daydreaming, feelings of confusion, and low motivation (Becker et al., 2016). However, SCT does not merely reflect a cluster of individually measurable cognitive functions (Becker, 2021), and its empirical differentiation from constructs such as internalizing emotional disorders (e.g., anxiety, depression) and ADHD-related symptoms (e.g., inattention and hyperactivity) suggests it should be seen as a distinct entity (Smith et al., 2019). SCT has

Abbreviations: CBCL, Child Behavior Checklist; CPT-II, Conners Continuous Performance Test, Second Edition; DSF, Digit Span Forward; DSB, Digit Span Backward; PBT, pediatric brain tumor; GAI, general ability index; HRQOL, health-related quality of life; Hit RT, Hit Reaction Time; NPS, Neurological Predictor Scale; SES, socioeconomic status; SCT, sluggish cognitive tempo; WAIS-IV, Wechsler Adult Intelligence Scale–Fourth Edition; WISC-IV/V, Wechsler Intelligence Scale for Children–Fourth Edition/Fifth Edition.

also been found to be distinct from excessive daytime sleepiness (Langberg et al., 2014; Smith et al., 2019), and in fact has been shown to mediate the relationship between sleep disturbance and academic performance in a sample of healthy children (O'Hare et al., 2021). In recent years, SCT has been associated with deficits in various cognitive functions that are commonly observed in the PBT population—namely, working memory, cognitive speed, attention, and executive function (Becker et al., 2016; Stavinoha et al., 2018; Kofler et al., 2019; Rey-Casserly and Diver, 2019). Researchers have additionally noted that the concept of SCT offers a unique framework for understanding the neurocognitive challenges faced by PBT survivors (Kahalley et al., 2011; Willard et al., 2013; Peterson et al., 2021). However, to our knowledge, SCT has not explicitly been studied in relation to sleep disturbances in PBT survivors.

Regarding cognitive functions commonly associated with SCT in PBT survivors, studies of children with mixed neurological conditions have demonstrated that worse sleep quality relates to worse performance on measures of attention, working memory, and cognitive efficiency (McCann et al., 2018a,b). In adult oncology populations, researchers have also observed associations between sleep and self-rated cognitive impairment, memory, and attention (Chen et al., 2012; Jean-Pierre et al., 2015; Myers et al., 2015; von Ah and Tallman, 2015; Janelsins et al., 2016), as well as associations between sleep and performance on measures of verbal and executive functioning (Caplette-Gingras et al., 2013; Hartman et al., 2015). Furthermore, in adult survivors of pediatric cancer, insomnia has been related to worse performance on measures of executive functioning, attention, processing speed, and other cognitive functions (Tonning Olsson et al., 2020).

Nonetheless, scant research has investigated sleep and cognition in survivors of pediatric cancer who have not yet reached adulthood. Associations between sleep disturbance and performance on executive functioning and processing speed measures have been observed in female survivors of acute lymphoblastic leukemia (Cheung et al., 2017), and sleep disturbances have been associated with worse executive functioning in mixed PBT samples (van Kooten et al., 2019). Conversely, studies of small samples of children and adolescents with craniopharyngioma have not demonstrated a relationship between excessive daytime sleepiness and cognitive outcomes such as attention and executive functions (Jacola et al., 2016). A recent study identified a relationship between cognitive speed and fatigue among pediatric survivors of posterior fossa tumors (Levitch et al., 2022), but this investigation did not isolate sleep disturbances as separate from fatigue. Sleep and fatigue are distinct concepts in pediatric oncology, with fatigue defined more as a lack of energy and feeling of exhaustion not necessarily associated with sleepiness (Walter et al., 2015).

The need for more sleep research in pediatric cancer populations, including investigations of the role of sleep in neurocognitive outcomes, has been highlighted in a recent position paper by the International Psycho-Oncology Society Pediatrics Special Interest Group (Daniel et al., 2020). Sleep represents a potentially modifiable target for intervention to possibly improve aspects of HRQOL and related cognitive performance in domains that are particularly vulnerable after treatment for PBT. Given the relationships that have been identified between sleep and cognition in healthy children and adolescents, adult cancer survivors, and pediatric samples with various neurologic conditions, the purpose of the current study was to first examine the association between sleep disturbance and sluggish cognitive tempo (SCT) in a clinical sample of PBT survivors. Because SCT is associated with cognitive vulnerabilities that commonly occur in PBT survivors, a secondary aim was to examine the association between sleep disturbance and the specific cognitive functions of working memory, reaction speed, and attention. We hypothesized that sleep disturbance would be associated with greater SCT, and that performance on individual cognitive domains of attention, working memory, and reaction time would be poorer as sleep disturbance increased.

MATERIALS AND METHODS

Participants and Procedure

The data for the current cross-sectional, retrospective study were obtained from a referred sample of PBT survivors seen for neuropsychological evaluation between January 1, 2005, and July 24, 2019, at the University of Texas MD Anderson Cancer Center, Department of Pediatrics, in Houston, TX, United States. The study was approved by Institutional Review Board (IRB) of the University of Texas MD Anderson Cancer Center. In addition to the administration of cognitive tests to PBT survivors as part of clinical evaluations, caregivers completed standardized questionnaires regarding their child. All included participants had a history of a brain tumor and had completed treatment. PBT survivors were defined as having completed all tumor-directed active treatment (i.e., surgery, chemotherapy, radiation) at least 3 months prior to evaluation, a cutoff that has been used previously (Barrera et al., 2018). Other inclusion criteria included an age range between 6:0 and 18:11 years (to align with the measures of interest) and completion of neuropsychological testing in either English or Spanish. Although participants were not systematically screened for other neurological or neurodevelopmental conditions during the clinical assessment, children who were determined to have a developmental delay not explained by their brain tumor (e.g., predating tumor diagnosis) based on a review of medical records by a neuropsychologist were excluded from analysis. Of 90 identified potential participants, a total of 83 met inclusion criteria. Demographic and medical characteristics of the sample are summarized in **Table 1**. The age of the participants at the time of neuropsychological evaluation ranged from 6 years, 4 months to 18 years, 9 months ($M = 12.48$ years, $SD = 3.12$ years).

Measures

Child Behavior Checklist Sleep Composite

The Child Behavior Checklist [CBCL/6-18; (Achenbach and Rescorla, 2001)] was used to measure parent-reported sleep disturbance. The CBCL is a rating scale of behavioral functioning with well-established psychometric properties in clinical,

TABLE 1 | Demographic and medical characteristics of participants.

	Min.	Max.	*M*	*SD*
Age at evaluation	6.33	18.75	12.48	3.11
Age at diagnosis	0.16	16.75	7.56	4.44
Years of treatment	0.42	15.17	3.53	2.96
General cognitive ability	42	127	96.24	15.46
Disease burden (Neurological Predictor Scale)	1	11	4.76	2.22
			n	**%**
Gender				
Male			35	42.2
Female			48	57.8
Ethnicity				
Caucasian			48	57.8
Black			6	7.2
Hispanic/Latino			22	26.5
Asian/Asian American			5	6.0
Hawaiian			1	1.2
Unknown			1	1.2
Socioeconomic status				
I–High			15	18.1
II			19	22.9
III			25	30.1
IV			10	12.0
V–Low			9	10.8
Unknown			5	6.0
Tumor type				
Medulloblastoma			10	12.0
Juvenile pilocytic astrocytoma/other astrocytoma			24	28.9
Ependymoma			7	8.4
Glioma			7	8.4
Germ cell tumor			7	8.4
Craniopharyngioma			5	6.0
Retinoblastoma			4	4.8
Optic glioma			3	3.6
Primitive neuro-ectodermal tumor (PNET)			2	2.4
Mixed or other tumor			14	16.9
Treatment[a]				
Radiation therapy			59	71.1
Chemotherapy			47	56.6
Surgery			70	84.3

N = 83.
[a]*Reflects the number and percentage of participants who received specific cancer treatments per medical record.*

non-clinical, cross-cultural, and Spanish speaking populations (e.g., Achenbach and Rescorla, 2001; Ivanova et al., 2007; Rescorla et al., 2007; Lubke et al., 2009). Although this measure was not originally designed with a specific scale measuring sleep functioning, a number of items describe aspects of sleep, reflecting the disturbances "nightmare" (item 47), "tired" (item 54), "sleeps less" (item 76), "sleeps more" (item 77), "sleep walk" (item 92), "sleep problem" (item 100), and "wets bed" (item 108). A summed CBCL sleep composite score has been previously utilized to measure sleep in pediatric samples (Gregory et al., 2011; Beebe et al., 2014; Becker et al., 2015b), which will be referred to in the current study as the CBCL Sleep Composite. All items are rated on a 3-point scale ("not true," "somewhat/sometimes true," and "very true/often true") as occurring "now or in the past 6 months," with higher scores reflecting a higher level of sleep disturbance (Achenbach and Rescorla, 2001; Becker et al., 2015b).

Several validation studies of the CBCL Sleep Composite provide support for the convergent and discriminant validity of the CBCL Sleep Composite as a screening measure for sleep disturbance in archival studies (e.g., Gregory et al., 2011; Becker et al., 2015b; Murray et al., 2016; Rondon et al., 2020). The CBCL Sleep Composite has been used in a range of studies investigating the relationship between sleep disturbance and clinical variables, including cognition (e.g., Murray et al., 2016; Hambrick et al., 2018; Rondon et al., 2020).

The present study used the CBCL Sleep Composite with six items—in the current investigation referred to as the CBCL Sleep Composite-6—based on an assessment of the internal consistency of the full scale seven-item scale (i.e., CBCL Sleep Composite-7) as compared to the internal consistency of the CBCL Sleep Composite-6. First, a reliability analysis was performed to determine the internal consistency of the CBCL Sleep Composite-7, as used in prior research (e.g., Beebe et al., 2014). The overall scale's internal consistency, Cronbach's $\alpha = 0.58$, was below the recommended minimum cutoff value of $\alpha = 0.60$ (Nunnally and Bernstein, 1994). The correlation between the item "wets bed" and the total CBCL Sleep Composite-7 score was inverse ($r = -0.03$) and substantially lower than the recommended 0.30 (Field, 2009). The extent to which bed wetting stems from sleep disturbance is not well understood (Al-Omar et al., 2014), and in the present study, the greatest increase in alpha came from deleting this item.

A second reliability analysis was conducted to determine the internal consistency of the CBCL Sleep Composite-6, which revealed fair internal consistency for the CBCL Sleep Composite-6, with Cronbach's $\alpha = 0.62$, similar to the internal consistency observed in several prior studies using this 6-item scale (Becker et al., 2015b; Rondon et al., 2018). None of the remaining items were indicated to increase Cronbach's α further if deleted. While the items "sleeps less," "sleeps more," and "sleep walk" remained relatively weakly correlated with the overall CBCL Sleep Composite-6 score (i.e., *r*'s = 0.250–0.291), this was unsurprising as the CBCL Sleep Composite-6 scale includes various sleep difficulties that are not necessarily expected to co-exist (Gregory and O'Connor, 2002). Based on these results, the CBCL Sleep Composite-6 scale was selected as the primary measure of sleep disturbance in the current study.

Child Behavior Checklist Sluggish Cognitive Tempo and Attention Problems Subscales

The CBCL for ages 6–18 years was used to assess sluggish cognitive tempo and attention (Achenbach and Rescorla, 2001). The CBCL includes a specific Sluggish Cognitive Tempo subscale that has been previously used to assess SCT in PBT survivors (e.g., Willard et al., 2013) and was the primary measure of

interest. The CBCL SCT subscale yields an age/gender normed T-score ($M = 50$, $SD = 10$), with higher scores representative of poorer functioning.

The CBCL Attention Problems subscale also yields an age/gender normed T-score ($M = 50$, $SD = 10$), with higher scores representative of poorer functioning. As compared to clinic-based discrete measures of cognitive functions such as attention, the CBCL Attention Problems subscale provides information based on caregiver/parent observation over a long period of time in the child's everyday environment.

The combination of the CBCL SCT and Attention Problems subscales has been utilized previously investigating aspects of attention and SCT in mixed cancers, including PBT survivors (Willard et al., 2013).

Wechsler Digit Span Forward and Backward

Clinical assessment of attention and working memory included the Digit Span subtest of the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV; Wechsler, 2003), either the English or the Spanish version of the Wechsler Intelligence Scale for Children, Fifth Edition (WISC-V; Wechsler, 2003, 2014), or the Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV; Wechsler, 2008), based on each participant's age. The WISC-IV, WISC-V, and WAIS-IV have been combined in previous research investigating the relationship between sleep and cognition (e.g., McCurdy et al., 2016; Sali et al., 2018; Calhoun et al., 2019). The subtests Digit Span Forward (DSF) and Digit Span Backward (DSB) were included. While DSF involves listening to and repeating sequences of numbers in the same order, DSB requires listening to and repeating sequences of numbers in the reverse order, with comparable instructions between the WISC-IV, WISC-V, and WAIS-IV versions (Wechsler, 2003, 2014; Calhoun et al., 2019). Norm-referenced scaled scores ($M = 10$, $SD = 3$) for the total number of correctly repeated sequences were used as an outcome measure, with higher scores reflecting a better performance. The WISC-V DSF and DSB split-half reliabilities are good (i.e., $r = 0.81$ and $r = 0.80$, respectively). WISC-IV, WISC-V, and WAIS-IV DSF and DSB test-retest reliabilities are adequate to good (i.e., corrected $r = 0.74$–0.82; Wechsler, 2003, 2008, 2014). The DSF and DSB subtests have been used previously in studies investigating the relationship between sleep and cognition (McCann et al., 2018a,b).

Conners Continuous Performance Test, Second Edition

The Conners Continuous Performance Test, Second Edition (CPT-II; Conners, 2000) is a computer-administered task measuring aspects of attention and reaction time. The test takes approximately 14 min to complete and requires the test-taker to press a key as quickly as possible after a letter appears on the screen, while refraining from pressing the key when the letter is an "X." Split-half reliabilities are adequate, ranging between $r = 0.66$ and 0.95, and test-retest reliabilities are excellent for individuals in a neurological assessment setting. The test can differentiate between clinical and non-clinical groups (Homack and Riccio, 2006) and has been used before in studies investigating the relationship between cognition and sleep (Kuula et al., 2015). Omissions (i.e., missed targets), Hit Reaction Time (Hit RT), and Commissions were used to measure visual sustained attention and response speed.

Demographic and Control Variables

Disease Burden

In all analyses investigating the association between sleep disturbance and cognitive functioning, disease burden was included as a control variable, as a higher impact of disease and treatment factors has been related to lower cognitive functioning in PBT survivors (e.g., Taiwo et al., 2017), and is hypothesized to negatively affect sleep (Merz and Tomfohr-Madsen, 2016). Thus, when not controlled for disease burden, a relationship between sleep disturbance and cognition could merely reflect the impact of the disease and treatment. The Neurological Predictor Scale (Micklewright et al., 2008) was used to quantify neuro-oncological risk factors, as this measure provides a single, cumulative estimate of the exposure to tumor- and treatment-related risk factors (Micklewright et al., 2008). The NPS consists of four items, which represent various sources of neuro-oncological risk including tumor-related complications (e.g., the presence of a hormone deficiency, hydrocephalus, or antiepileptic medication), surgical events, radiation therapy, and chemotherapy. Total raw scores have been analyzed as a continuous variable in prior studies (Micklewright et al., 2008; Taiwo et al., 2017) and range from 0 to 16, with higher values reflecting a higher level of disease burden. In the present study, the scores were calculated by a physician based on information obtained from the medical records. The reliability and concurrent validity of the NPS has been demonstrated in both children and adults surviving pediatric brain tumors (Micklewright et al., 2008; Papazoglou et al., 2008; Taiwo et al., 2017).

Demographic Variables

Demographic variables examined in the current study were age, gender, age at diagnosis, months off treatment, socioeconomic status (SES), and general cognitive ability. SES was measured with the Hollingshead Two Factor Index of Social Position (Hollingshead, 1957), which has been used in recent studies (Allen et al., 2016; Hirakawa et al., 2019) and yields a numeric rating based on the occupation and educational attainment of caregivers. The Wechsler General Ability Index (GAI) was used to measure general cognitive ability. The GAI generally subsumes the verbal and perceptual indexes from the WISC-IV, WISC-V, and WAIS-IV, while excluding measures of working memory and cognitive efficiency. Scores are expressed in standard scores ($M = 100$, $SD = 15$), with higher scores reflective of greater cognitive ability (Wechsler, 2003, 2014).

Statistical Analyses

Data were analyzed using SPSS Statistics Version 26. Descriptive statistical analyses were conducted to determine the characteristics of the sample, and zero-order correlations between all variables were computed in order to evaluate the relationship between all combinations of two variables. One-sample *z*-tests were performed to compare cognitive functioning scores with normative data. Data were analyzed to identify

potential influential cases and violations of assumptions prior to hypothesis testing. *P*-values of <0.05 were considered to be statistically significant. Six general linear model hierarchical multiple linear regression analyses were conducted to assess the relationships between sleep disturbance and cognitive functions of interest. Disease burden (NPS score) was entered in Model I as a control variable, with the CBCL Sleep Composite-6 entered as a continuous predictor variable in Model 2. Separate regressions were conducted for each dependent measure (i.e., CBCL Sluggish Cognitive Tempo, CBCL Attention Problems, DSF, DSB, CPT-II Omissions, CPT-II Hit RT, and CPT-II Commissions). Prior to hypothesis testing, it was decided to report the results of the regression analyses without correcting for multiple testing. Given the paucity of research on the relationship between cognition and sleep in PBT survivors, missing an existing relationship between sleep and cognition (i.e., Type II error) was considered to be more harmful than reporting a false-positive (i.e., Type I error). All variables and measures used in the study are summarized in **Table 2**.

RESULTS

Participants

Details regarding the demographic and medical characteristics of the 83 participants are presented in **Table 1**. Age at evaluation ranged between 6.33 and 18.75 years ($M = 12.48$, $SD = 3.11$), and age at tumor diagnosis was 0.16–16.75 years ($M = 7.56$, $SD = 4.44$). Participants had completed treatment 0.42–15.17 years ($M = 3.53$, $SD = 2.96$) prior to evaluation. In total, 42.2% of the sample identified as male and 57.8% as female. Zero-order Pearson correlations were computed between demographic variables, disease burden, sleep disturbance, and the cognitive variables in the regression analyses. Only disease burden was significantly associated with both sleep disturbance (i.e., $r = -0.23$, $p < 0.05$) as well as cognition (i.e., DSB $r = -0.23$, $p < 0.05$; CPT-II Hit RT $r = -0.25$, $p < 0.05$; CBCL Attention Problems $r = -0.31$, $p < 0.01$). Therefore, only disease burden was included as potential confounding factor in the regression analyses in order to maximize power.

Characteristics of Sleep Disturbance and Cognition

Details regarding CBCL Sleep Composite-6 scores and endorsement of specific items are presented in **Table 2**. Of all sleep-related disturbances rated to be very true, "tired" and "sleeps more" were most frequently endorsed. A total of 27 (32.5%) parents rated at least one sleep symptom as "very true" or "often true" for their child, while 26 caregivers (31.3%) rated no sleep-related symptoms. Thus, nearly two-thirds of the sample endorsed at least one sleep-related symptom.

Neuropsychological characteristics of the participants are presented in **Table 3**. The percentage of participants with impaired scores was highest for CBCL Sluggish Cognitive Tempo (30%), followed by CBCL Attention Problems (20.48%), DSF (17.5%), CPT-II Hit RT (16.05%), DSB (8.75%), CPT-II Omissions (7.32%), and CPT-II Commissions (4.88%). On average, participants' scores were significantly different than the normative mean on DSF, DSB, CPT-II Hit RT, CBCL Attention Problems, and CBCL Sluggish Cognitive Tempo and all in the expected (pathological) direction for a PBT sample. Only CPT-II Omissions and CPT Commissions were not statistically significantly different from the population mean. Thus, this sample of PBT survivors on the whole appears to exhibit difficulties relative to the general population on cognitive dimensions known to be vulnerable to PBT and treatment.

Association Between Sleep Disturbance and Cognition

Prior to conducting the regression analyses, it was determined that assumptions were satisfactorily met, and no concerns were identified regarding influential cases. Notably, the percentage of missing data for each variable included in the analyses was 3.6% ($n = 3$) at most. Results of separate hierarchical multiple regression analyses examining relationships between sleep disturbance and measures of cognitive functioning after controlling for NPS score are shown in **Table 4**. For the primary regression analysis with CBCL Sluggish Cognitive Tempo as the dependent variable, Model 1 indicated that the variance accounted for (R^2) by the control variable (i.e., disease burden)

TABLE 2 | Descriptive statistics for CBCL sleep items and composite.

			Frequency of item endorsement		
Item	***M* ± *SD***	**Range[a]**	**Not true (0)**	**Somewhat/sometimes true (1)**	**Very/often true (2)**
Nightmare		0–2	66 (79.5%)	14 (16.9%)	3 (3.6%)
Tired		0–2	56 (67.5%)	14 (16.9%)	13 (15.7%)
Sleeps less		0–2	69 (83.1%)	11 (13.3%)	3 (3.6%)
Sleeps more		0–2	55 (66.3%)	15 (18.1%)	13 (15.7%)
Sleep walk		0–1	75 (90.4%)	8 (9.6%)	0 (0.0%)
Sleep problem		0–2	60 (72.3%)	15 (18.1%)	8 (9.6%)
	M* ± *SD	**Range**	**Total score of 0**	**At least one item rated as very/often true**	
CBCL Sleep Composite-6	1.89 ± 2.11	0–8	31.3%	32.5%	

N = 83.

[a]*Range reflects the range of observed scores. Range of possible values is 0–2 for specific items and 0–12 for CBCL Sleep Composite-6.*

TABLE 3 | Neuropsychological characteristics.

Variable	*n*	*M*	*SD*	Min.	Max.	*z*	Cohen's *d**	*p*	% impaired**
CBCL									
SCT	80	58.19	8.39	50	75	7.33	0.82	<0.001	30.00
Attention problems	83	58.37	8.72	50	86	7.63	0.84	<0.001	20.48
Wechsler									
DSF	80	8.35	2.84	3	15	−4.92	−0.55	<0.001	17.50
DSB	80	8.97	2.78	1	16	−3.07	−0.34	<0.01	8.75
CPT-II									
Omissions	82	51.52	13.01	40.06	122.38	1.38	0.15	0.17	7.32
Hit RT	81	53.09	14.15	27.10	93.30	2.78	0.31	<0.01	16.05
Commissions	82	49.70	10.99	21.04	70.77	−0.91	−0.10	0.36	4.88

*As compared to the normative sample.
**Percentage of individuals with scores 1.5 standard deviation from the mean.

equaled 0.04, which was not significantly different from zero, $F(1,78) = 3.49$, $p = 0.07$. In Model 2, the change accounted for by the CBCL Sleep Composite-6 (ΔR^2) was equal to 0.28, which was significantly different from zero, $F(1,77) = 32.47$, $p < 0.001$. Thus, 28% of the variance in Sluggish Cognitive Tempo was accounted for by the CBCL Sleep Composite-6 score.

Subsequently, secondary regression analyses were performed on cognitive dimensions that are vulnerable to sleep difficulties. For the regression analysis with CBCL Attention Problems as the dependent variable, Model 1 indicated that the variance accounted for (R^2) by the control variable (disease burden) equaled 0.09, which was significantly different from zero, $F(1,81) = 8.41$, $p < 0.01$. In Model 2, the change accounted for by the CBCL Sleep Composite-6 (ΔR^2) was equal to 0.19, which was significantly different from zero, $F(1,80) = 20.53$, $p < 0.001$. Thus, 19% of the variance in CBCL Attention Problems was accounted for by the CBCL Sleep Composite-6 score. None of the performance-based measures of cognition was significantly associated with sleep disturbance after adjusting for overall disease burden [i.e., DSF: $\Delta R^2 = 0.00$, $F(1,77) = 0.06$, $p = 0.81$; DSB: $\Delta R^2 = 0.01$, $F(1,77) = 0.52$, $p = 0.47$; CPT-II Omissions: $\Delta R^2 = 0.04$, $F(1,79) = 3.46$, $p = 0.07$; CPT-II Hit RT: $\Delta R^2 = 0.00$, $F(1,78) = 0.07$, $p = 0.80$; CPT-II Commissions: $\Delta R^2 = 0.00$, $F(1,79) = 0.00$, $p = 0.99$]. Notably, results of all regression analyses were comparable when performed without inclusion of a control variable. Furthermore, exploratory interaction effects were not observed for gender, disease burden, and months off treatment, except for a significant interaction for months off treatment and CBCL Sluggish Cognitive Tempo and CBCL Attention Problems. Specifically, for both variables, the association with the CBCL Sleep Composite was strongest for participants who completed treatment most recently (CBCL Sluggish Cognitive Tempo: $R^2 = 0.45$; CBCL Attention Problems: $R^2 = 0.37$), and weakest for children with the longest time since completion of treatment (CBCL Sluggish Cognitive Tempo: $R2 = 0.12$; CBCL Attention Problems: $R^2 = 0.13$).

DISCUSSION

The primary aim of the current study was to investigate whether a higher level of sleep disturbance was associated with worse sluggish cognitive tempo (SCT) and/or cognitive functions associated with SCT—including attention and working memory—in a clinical sample of PBT survivors. To our knowledge, this is the first study to investigate the relationship between SCT and sleep in the PBT survivor population. The analysis investigating the primary aim provided support for the hypothesized relationship between a higher level of sleep disturbance and worse SCT. The secondary analyses focusing on aspects of attention and working memory were partially supported. Specifically, while no significant association was observed for Digit Span Forward, Digit Span Backward, CPT-II Omissions, CPT-II Hit RT, or CPT-II Commissions higher levels of sleep disturbance were related to worse CBCL Attention Problems.

In terms of overall frequency of sleep difficulties, nearly a third of caregivers reported at least one significant sleep disturbance in their child, and over two-thirds of caregivers reported at least occasional occurrence of sleep disturbances. These results align with what is known for PBT survivors, with estimates of sleep problems ranging between 20 and 82% (Brimeyer et al., 2016; Pilotto et al., 2018; van Kooten et al., 2019), as compared to rates of 12–25% in healthy populations (Melendres et al., 2004; van Litsenburg et al., 2010). Somnolence and increased sleep duration were the most frequently endorsed individual sleep-related symptoms, which parallels prior literature suggesting that excessive daytime sleepiness is the most common sleep-related disturbance in children diagnosed with cancer (Rosen and Brand, 2011; Walter et al., 2015).

Comparison of sample performance to normative means indicated that our sample performed significantly worse than the normative mean for all variables except CPT-II Omissions and CPT-II Commissions, which largely validates that our sample conformed to known neurocognitive vulnerabilities in PBT survivors. Among all included cognitive variables, caregiver ratings of SCT were most frequently impaired (30%; <1.5 *SD* relative to the mean); in contrast, attention problems were rated as impaired by 20.48% of caregivers. The relatively high endorsement of SCT in the current study adds to mounting evidence that SCT is common in the PBT population in a manner that is distinct from other neurocognitive deficits (Kahalley et al., 2011; Willard et al., 2013; Peterson et al., 2021).

TABLE 4 | Hierarchical regression results for cognitive variables.

Variable	*B*	95% CI for *B*		*SE B*	β	R^2	ΔR^2
		LL	*UL*				
Dependent variable: CBCL Sluggish Cognitive Tempo							
Step 1						0.04	0.04
Constant	61.90	57.54	66.25	2.19			
Neurological Predictor Scale	−0.77	−1.60	0.05	0.41	−0.21		
Step 2						0.33	0.28***
Constant	55.54	51.24	59.84	2.16			
Neurological Predictor Scale	−0.30	−1.01	0.42	0.36	−0.08		
CBCL Sleep Composite-6	2.16	1.40	2.91	0.38	0.55		
Dependent variable: CBCL Attention Problems							
Step 1						0.09	0.09**
Constant	64.12	59.78	68.46	2.18			
Neurological Predictor Scale	−1.21	−2.03	−0.38	0.42	−0.31		
Step 2						0.28	0.19***
Constant	58.78	54.23	63.33	2.29			
Neurological Predictor Scale	−0.81	−1.58	−0.05	0.38	−0.21		
CBCL Sleep Composite-6	1.83	1.03	2.63	0.40	0.44		
Dependent variable: Digit Span Forward							
Step 1						0.01	0.01
Constant	8.83	7.33	10.34	0.75			
Neurological Predictor Scale	−0.10	−0.39	0.19	0.15	−0.08		
Step 2						0.01	0.00
Constant	8.95	7.17	10.72	0.89			
Neurological Predictor Scale	−0.11	−0.41	−0.19	0.15	−0.09		
CBCL Sleep Composite-6	−0.04	−0.36	0.28	0.16	−0.03		
Dependent variable: Digit Span Backward							
Step 1						0.05*	0.05*
Constant	10.31	8.88	11.75	0.72			
Neurological Predictor Scale	−0.29	−0.56	−0.01	0.14	−0.23		
Step 2						0.06*	0.01
Constant	9.99	8.30	11.68	0.85			
Neurological Predictor Scale	−0.26	−0.55	0.03	0.14	−0.21		
CBCL Sleep Composite-6	0.11	−0.19	0.41	0.15	0.08		
Dependent variable: CPT-II Omissions							
Step 1						0.02	0.02
Constant	47.71	40.76	54.66	3.50			
Neurological Predictor Scale	0.81	−0.54	2.17	0.68	0.13		
Step 2						0.06	0.04
Constant	43.93	35.98	51.89	4.00			
Neurological Predictor Scale	1.10	−0.27	2.47	0.69	0.18		
CBCL Sleep Composite-6	1.28	−0.09	2.65	0.69	0.21		
Dependent variable: CPT-II Hit RT							
Step 1						0.06	0.06
Constant	45.33	37.82	52.84	3.77			
Neurological Predictor Scale	1.65	0.19	3.10	0.73	0.25		
Step 2						0.04	0.00
Constant	45.93	37.07	54.78	4.44			
Neurological Predictor Scale	1.60	0.09	3.11	0.76	0.24		
CBCL Sleep Composite-6	−0.19	−1.70	1.31	0.76	−0.03		
Dependent variable: CPT-II Commissions							
Step 1						0.00	0.00
Constant	51.25	45.34	57.16	2.97			
Neurological Predictor Scale	−0.33	−1.48	0.82	0.58	−0.06		
Step 2							
Constant	51.22	44.31	58.13	3.47		0.00	0.00
Neurological Predictor Scale	−0.33	−1.52	0.86	0.60	−0.06		
CBCL Sleep Composite-6	0.01	−1.18	1.12	0.60	0.00		

CI, confidence interval; LL, lower limit; UL, upper limit.
*$p < 0.05$; **$p < 0.01$; ***$p \leq 0.001$.*

Our findings suggest that the relationship between SCT and sleep disturbance observed in pediatric populations with neurodevelopmental conditions such as ADHD and autism (e.g., Mayes et al., 2021; Fredrick et al., 2022) appears applicable to PBT survivors as well, and this has implications for screening and assessment. Recognition of this association underscores the importance of differential assessment of SCT and sleep to improve identification of core difficulties experienced by PBT survivors with the goal of maximizing HRQOL. For example, recent evidence suggests that SCT is associated with social difficulties such as low social engagement and initiation, along with withdrawal and isolation (Becker et al., 2019), and interestingly the nature of these social difficulties is similar to that of the social competence difficulties commonly experienced by PBT survivors (Hocking et al., 2015). Similarly, there is overlap between SCT and anxiety/depression symptoms, excessive daytime sleepiness, and low motivation (Smith et al., 2019), which also may be within the scope of HRQOL surveillance for PBT survivors. Findings of the current study suggest that when only focusing on clinic-based measures of cognition administered one-on-one with a patient, the relationship between sleep and cognitive functioning may be missed despite being potentially meaningful for daily functioning.

Thus, incorporating assessment of both sleep and SCT into existing psychological and neuropsychological monitoring of PBT survivors might contribute to clearer differentiation of symptoms and thereby improve linkage to targeted intervention. Indeed, interventions for varied difficulties ranging from sleep to apathy to attention problems to SCT would likely involve markedly different treatment approaches. For example, there may be medication options that could be researched in PBT survivors demonstrating SCT, such as modafinil (Kumar, 2008), which has demonstrated efficacy for symptoms including attention, speed, and drowsiness in adult cancer patients (Lundorff et al., 2009). Sleep interventions might look quite different, as parents tend to be more receptive to behavioral sleep interventions compared to medication options (Daniel et al., 2016). There is also the possibility that improvement of sleep and/or SCT symptoms could enhance response to other supports—ranging from social to academic interventions—by reducing the impact of an overarching problem that is not specific to any neurocognitive domain. For example, directing intervention efforts at sleep and/or SCT could possibly enhance cognitive training interventions, which have thus far provided limited generalizable relief to PBT survivors experiencing significant neurocognitive late effects (Hocking et al., 2021). To illustrate, in a sample of healthy adolescents, treatment of sleep disturbance has been shown to result in improved executive functioning (de Bruin et al., 2015), though the extent to which such findings generalize to PBT survivors is unknown, given the impact of the tumor, complications, and treatment on the cognitive developmental trajectory in this population (Mahajan et al., 2021). Results of our archival study do not address whether there is a causal relationship between sleep and SCT, so further research will be necessary to identify optimal treatment paradigms to target core problems that may manifest as overlapping symptoms and difficulties.

The fact that parent-reported sleep was associated with SCT and parent-rated attention problems, but not with individually administered clinic-based measures of attention of working memory, is important to consider. One possible explanation for the discrepant findings between parent-rated and performance-based measures of cognition is that these modalities may tap into different aspects of cognitive performance. Specifically, Toplak et al. (2013) suggested that a performance-based measure assesses whether someone is able to successfully complete an executive functioning task in isolation, while not measuring the extent to which that individual is able to regulate their behavior in the absence of continuing direction by an examiner and/or in the presence of multiple competing stimuli and distractions. Thus, it may be that sleep disturbances—at least with respect to the relatively mild levels reported in the present study—impact cognitive functioning in everyday life more than performance on discrete tests. When combined with performance-based measures, collateral (e.g., parent, teacher) ratings may provide a more complete picture of a PBT survivor's capacity for cognitive functioning as well as their efficacy at implementing those cognitive functions in everyday life (Toplak et al., 2013). Therefore, including ratings of SCT and attention problems in neuropsychological evaluations may enhance detection of subtle cognitive difficulties associated with sleep disturbance.

The idea that relatively mild sleep disturbances are related more to the execution of cognitive tasks in less structured settings than to test performance in an evaluation setting is in keeping with the model proposed by Monk (2012), which suggests that chronic sleep disruption can lead to a progressive loss of alertness and motivation as time progresses. Supporting this idea, several studies have demonstrated associations between various types of sleep disruption and lower engagement in tasks that are perceived as more cognitively demanding (Engle-Friedman et al., 2010, 2018; Libedinsky et al., 2013). Further, the impact of motivation on performance in PBT survivors was illustrated by Holland et al. (2016), who demonstrated that external incentive improves effort on discrete timed academic tasks, indicating that motivation is a fluctuating variable that can substantively alter the situational performance of PBT survivors. Considering these findings, it may be that PBT survivors who experience sleep difficulties may choose less effortful activities when possible, and this choice may be available to a lesser extent during a neuropsychological evaluation as compared to daily life. This conceptualization would align with the known and persistent difficulty with the execution of cognitive tasks in daily life experienced by PBT survivors in everyday life, even when corresponding aspects of clinic-based assessment reflect average overall performance relative to the general population (Holland et al., 2015). Notably, our findings align with the notion that the construct of SCT—among other concepts—taps into a motivational component of cognitive functioning in daily life (Becker et al., 2016; Smith et al., 2019).

LIMITATIONS AND FUTURE DIRECTIONS

The findings of this study should be considered in light of a number of limitations, foremost of which being the method of assessing sleep disturbances, which did not include objective measures such activity tracking or polysomnography. While the CBCL Sleep Composite has been validated against accepted sleep measures and has been deemed appropriate for archival studies (Gregory et al., 2011; Becker et al., 2015a,b; Murray et al., 2016) objective characterization and differentiation of specific types of sleep disturbances may help to clarify the nature of the relationship between sleep and cognition in PBT survivors. In other words, the present study provides evidence for an association between sleep and cognition in this population, but the specific elements of sleep disturbance that may have relatively more or less impact on cognitive performance require further elucidation.

Another limitation of the CBCL Composite is a lack of clarity regarding the timeframe during which parents are rating sleep disturbances. Parents are instructed to rate their child's behavior over the past 6 months, and this leaves unclear the extent to which the presence or absence of sleep disruptions directly prior to the time of their ratings may have affected their reports as well as association with cognitive tests completed at the same time as the ratings. Thus, our study neglects the important consideration of whether there is a differential effect on cognition for longer-term chronic sleep disturbances as compared to more acute sleep problems. In addition to caregiver ratings, when feasible, self-reports of sleep may provide valuable information. For instance, Short et al. (2013) observed a tendency for parents to underreport sleep problems in their adolescent children. Thus, the level of sleep disturbance experienced by at least some of our study participants may have been higher than suggested by caregiver ratings. Finally, the possibility that the association between parent-rated sleep and parent-rated cognition partially reflects rater bias cannot be excluded. Specifically, while a suggested advantage of ratings relative to objective cognitive measures is that they may tap more directly into real-word circumstances, it has also been stressed that ratings may be impacted by a halo-effect, central tendency bias, social desirability bias, or a general propensity to under- or over-report (Toplak et al., 2013; Dekker et al., 2017; Emser et al., 2018; Brandt et al., 2021). For instance, parental anxiety may increase attention for the child's symptoms, which, in turn, may affect their ratings (Smith et al., 2020).

Characterization of risks for sleep disturbances in PBT survivors remains incomplete. Thus, it is important to further investigate biological [e.g., tumor-related factors such as tumor type and location (Helligsoe et al., 2022) or treatment modalities], environmental, family-related, psychological, and behavioral factors that are most strongly associated with the onset and perpetuation of sleep problems in PBT survivors. The construct and measurement of SCT is evolving (Becker et al., 2019), and as measurement methods advance future researchers can incorporate more refined metrics to assess SCT in PBT survivors. Additionally, future researchers may use prospective designs at each stage of the trajectory from diagnosis to active treatment to long term PBT survivorship to determine whether sleep is causally related to cognitive performance, as appears to be the case in other types of cancer. More comprehensive understanding of the nature of the association between sleep and cognitive performance in PBT survivors may yield insights into important targets for prevention and intervention that could have a significant positive impact on aspects of health-related quality of life.

CONCLUSION

In the present sample of PBT survivors, higher levels of parent-rated sleep disturbances were associated with higher levels of sluggish cognitive tempo (SCT) and worse parent-reported attention functioning. There were no significant correlations with performance-based measures of attention and working memory. Findings of the current study highlight the importance of further investigation into the relationship between sleep and cognition in this vulnerable population, as greater knowledge in this regard may assist efforts to maximize cognitive outcome and HRQOL in PBT survivors. The current study additionally suggests further investigation of SCT in this population is warranted, as it may be more sensitive to detecting possible associations with sleep disturbance relative to discrete measures that assess cognitive performance under ideal circumstances.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board, University of Texas MD Anderson Cancer Center. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

IO: review and editing, original draft, conceptualization, formal analysis, and visualization. AH, RH, and DH: review and editing and supervision. AC: review and editing, formal analysis, and supervision. WZ, MB, and GY: review and editing and investigation. PS: review and editing, original draft, supervision, conceptualization, resources, data curation, and visualization. All authors approved the submitted version.

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EDITED BY
Belinda Pletzer,
University of Salzburg, Austria

REVIEWED BY
Robin Yuan,
Brigham and Women's Hospital and Harvard Medical School, United States
Dan Denis,
University of York, United Kingdom

*CORRESPONDENCE
Bénédicte Giffard
benedicte.giffard@unicaen.fr

†These authors have contributed equally to this work

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Sleep-dependent memory consolidation in breast cancer: Use of a virtual reality prospective memory task

Mylène Duivon[1], Joy Perrier[1], Carine Segura-Djezzar[2,3], Florence Joly[2,3,4,5], Stéphane Rehel[1], Christian Berthomier[6], Jean-Michel Grellard[2], Bénédicte Clarisse[2], Julien Geffrelot[2,3], George Emile[2,3], Christelle Lévy[2,3], Fausto Viader[1], Francis Eustache[1], Béatrice Desgranges[1†], Géraldine Rauchs[1†] and Bénédicte Giffard[1,5*]

[1]Neuropsychologie et Imagerie de la Mémoire Humaine, U1077, Normandie University, UNICAEN, PSL Université, EPHE, INSERM, CHU de Caen, GIP Cyceron, Caen, France, [2]Department of Clinical Research Unit and Medical Oncology, Caen, France, [3]Institut Normand du Sein, Centre François Baclesse, Caen, France, [4]U1086 ANTICIPE, INSERM, Normandie University, UNICAEN, Caen, France, [5]Cancer and Cognition Platform, Ligue Nationale Contre le Cancer, Caen, France, [6]Physip, Paris, France

Background: Previous studies have revealed both sleep alterations and prospective memory (PM) impairments in breast cancer (BC) patients. PM refers to memory of intended actions and is crucial for daily living tasks and treatment compliance. As sleep is known to favor memory consolidation, one may expect that changes in sleep quality related to BC would have an impact on PM performance. This study aimed at assessing sleep-dependent consolidation of intentions using an ecological, virtual reality-based PM task in BC patients not treated with chemotherapy.

Materials and methods: Thirty-seven early stages BC patients and 21 healthy controls (HC) participated in this study. PM was assessed using a virtual reality task, during which participants learnt a list of intentions and recalled them after a retention interval filled with a day awake or a night of sleep monitored by polysomnography. Sleep spindles and slow waves, brain oscillations involved in sleep-dependent memory consolidation, were quantified automatically using the Aseega software (Physip). Subjective sleep disturbances and markers of quality of life (psychological distress, fatigue, and well-being) were assessed by questionnaires.

Results: Greater PM performance was observed after sleep than after an equivalent period of daytime wakefulness for both groups (HC and BC). PM performance after sleep did not differ significantly between groups. Yet, BC patients reported greater sleep disturbances than HC which were related with poorer intentions retrieval, greater psychological distress, fatigue and poorer well-being. The frequency of spindles was higher and the amplitude of slow waves lower in BC patients compared to HC. However, no significant

association was observed between polysomnography parameters and PM scores in the whole sample of participants.

Conclusion: Although subtle changes in brain oscillations involved in sleep-dependent memory consolidation were observed, these changes did not significantly impair overnight PM consolidation in BC patients. Nevertheless, poorer PM performance was associated with greater sleep complaints which in turn were related to poorer quality of life. Overall, these data suggest that sleep-dependent PM consolidation mechanisms are not altered in early stages BC patients not treated with chemotherapy. Further investigations are needed to understand the association between markers of quality of life and sleep-dependent memory consolidation.

KEYWORDS

breast cancer, cognition, sleep, polysomnography, prospective memory, memory consolidation, virtual reality

Introduction

Sleep disturbances and memory impairments are one of the most frequent complaints from breast cancer (BC) patients (Lange et al., 2019; Leysen et al., 2019; Perrier et al., 2021). Sleep complaints are related to greater fatigue and poorer quality of life in cancer survivors (Nishiura et al., 2013; Xu et al., 2018). Previous studies, although scarce and conducted on small samples, suggested that both cancer and chemotherapy treatment might lead to subtle changes in sleep architecture measured by polysomnography (PSG; Roscoe et al., 2011; Tag Eldin et al., 2019). The studies reporting significant changes revealed a decrease in total sleep time with shorter time spent in REM (Rapid-Eye Movement) sleep and longer time spent in lighter sleep stages, i.e., N1 and N2 (Parker et al., 2008; Tag Eldin et al., 2019). A recent study has shown changes in cortical activity during sleep in BC patients not treated with chemotherapy, with notably lower delta power during non-REM sleep in patients compared to healthy controls (HC; Perrier et al., 2022). Delta power is the EEG activity related to slow waves which are, together with sleep spindles, one of the electrophysiological signatures of sleep-dependent memory consolidation (Holz et al., 2012; Klinzing et al., 2019).

According to the "Hippocampo-Neocortical Dialog" hypothesis, both slow waves and spindles are involved in the reorganization of newly acquired information into long-term memory stores (Buzsaki, 1996). The modifications in cortical activity observed in BC patients raise the question of the impact of such sleep changes on memory consolidation. Previous studies revealed an association between sleep complaint and cognitive impairment in BC patients, including memory performance (Caplette-Gingras et al., 2013; Duivon et al., 2021). A recent study also revealed that worse cognitive functioning was predicted by poorer subjective sleep quality, less robust circadian rhythms, and longer naps but not by sleep parameters (e.g., total sleep time and wake after sleep onset) assessed by actigraphy (Ancoli-Israel et al., 2022). However, none of them evaluated specifically sleep-dependent memory consolidation in BC patients.

Among other types of memory, prospective memory (PM) is of particular interest in BC because it is essential for daily living tasks, medical adherence, and autonomy. Moreover, PM difficulties have been highlighted in this population (Cheng et al., 2017; Paquet et al., 2018; Li et al., 2020). The few studies conducted mostly focused on the impact of chemotherapy and hormone receptor (Cheng et al., 2017; Li et al., 2017, 2020) and revealed difficulties in remembering *event-based* (EB) intentions. Two kinds of intentions are classically distinguished in laboratory tasks: EB intentions when the action has to be performed in response to an external event, and *time-based* (TB) ones when the action has to be executed at a specific time (Einstein and McDaniel, 1990). In addition, two components (prospective and retrospective) are fundamental to correctly execute delayed intentions (Einstein and McDaniel, 1990). The prospective component involves remembering that something has to be done at the appropriate time. The retrospective component refers to the content of the intention (i.e., remembering what has to be done).

Previous studies revealed that sleep facilitates the spontaneous remembering of intentions at the appropriate time (Scullin and McDaniel, 2010; Diekelmann et al., 2013a). Especially, sleep reinforces the association between prospective and retrospective components, whatever the type of intentions

Abbreviations: AHI, Apnea-Hypopnea Index; BC, Breast cancer; EB, Event-based; ET, Endocrine therapy; HC, Healthy control; PM, Prospective memory; REM, Rapid eye movement; TB, Time-based; TST, Total sleep Time; WASO, Wake after sleep onset.

(i.e., TB or EB; Diekelmann et al., 2013b; Esposito et al., 2015). The beneficial effect of sleep on PM depends on several factors and a recent meta-analysis revealed that age and study type (i.e., experimental or observational) moderated this effect (Leong et al., 2019a). The effect size of sleep benefits is small in observational studies or studies including older adults, whereas it is generally moderate in experimental studies or studies including younger adults. Thus, one study reported that frontal slow wave activity was associated with PM in healthy adults, but this association was no longer significant when adjusted for age (Scullin et al., 2019). In return, this study revealed that REM sleep stage mediated the effect of age on sleep-dependent consolidation of PM.

In this context, this study aimed at assessing sleep-dependent consolidation of intentions in PM in BC patients. To do so, we recruited BC patients not treated with chemotherapy and HC who completed sleep questionnaires and underwent ambulatory PSG. PM was assessed using an original virtual reality based task adapted from Rehel et al. (2019). Virtual reality recreates naturalistic situations from daily life while maintaining experimental rigor and was therefore used to improve the ecological validity of the PM task. Fatigue, well-being, and psychological distress were also assessed using validated questionnaires. We hypothesized that sleep-dependent consolidation of intentions would be impaired in BC patients, and associated with changes in slow waves and sleep spindles. We also expected that poorer subjective sleep quality in patients would be associated with poorer PM performance, and that these two parameters would also be associated with greater fatigue, psychological distress and poorer well-being.

Materials and methods

Participants

All participants were recruited between January 2018 and March 2020 and provided written informed consent after detailed information about the study. The study was approved by the ethics committee (CPP Ile de France III; n°ID-RCB: 2017-A02778-45).

Patients' inclusion criteria were: (i) be less than 70 years old, (ii) no metastatic BC, (iii) already undergone surgical or radiotherapy treatment, (iv) radiotherapy finished since at least 6 months and no chemotherapy treatment, (v) menopausal status since at least 1 year at the time of inclusion, (vi) no personality disorder and progressive psychiatric disorder (vii) no neurological sequelae, (viii) no drug use or alcohol abuse, (ix) be a native French speaker, (x) have at least 7 years of education.

Inclusion criteria for HC were the same as for patients, including no history of cancer and a score superior to 25 at the Montreal Cognitive Assessment (Nasreddine et al., 2005); see Duivon et al. (2018) for further details on study protocol and neuropsychological tests used.

Fifty patients, i.e., 25 patients treated with endocrine therapy (ET) and 25 patients not treated with ET approached in the French regional cancer center François Baclesse (Caen, Normandy) agreed to participate. The rationale for the target sample size was calculated according to the literature on cognitive decline in BC patients under ET (detailed in Duivon et al., 2018). Thirteen patients did not complete the entire protocol: nine withdrew, three presented symptoms similar to motion sickness during the virtual reality task, and one did not perform a session due to a technical problem with the virtual reality task. Five PSG recordings of patients were not exploitable and thus excluded from analyses. Among the twenty-five HC recruited, three withdrew and one could not stand virtual reality. Finally, 21 HC and 32 patients completed the entire protocol and were included in the analyses.

Procedure

The experimental procedure has been fully described in Duivon et al. (2018). Only the main points are presented here. The study included three sessions with a 1-week delay in-between to minimize the risk of interference. The first session consisted of a familiarization of participants with the virtual environment and the PM task. During this session, participants were asked to memorize nine intentions and recall them 10 min after their encoding. During the second and third sessions, intentions were encoded in the morning and retrieved in the evening for the wake session, and encoded in the evening and retrieved the next morning for the sleep session. The order of sleep and wake sessions was counterbalanced between participants. During the wake session, participants performed their usual activities, with the instruction not to nap. During the sleep session, participants went back home or spent the night in a hotel. Sleep was monitored using ambulatory PSG.

Polysomnography

Participants underwent a PSG using a portable device (Siesta, Compumedics, Victoria, Australia). The PSG consisted in recording the electroencephalogram (EEG), electrooculogram (EOG), electrocardiogram (ECG), chin electromyogram (EMG), respiratory movements using thoracic and abdominal belts, respiratory airflow using nasal and oral thermistors, and oxygen saturation using a finger pulse oximeter. For the EEG recording, twenty electrodes were placed over the scalp according to the international 10–20 system (Fp1, Fp2, F3, F4, F7, F8, Fz, C3, C4, Cz, T3, T4, P3, P4, Pz, O1, O2, vertex ground, and a bi-mastoid reference), with impedances kept below 5 kΩ. The EEG signal was digitalized at a sampling

rate of 256 Hz, high-pass (0.3 Hz) and low-pass (35 Hz) filters were applied for the visual scoring. Sleep stages (N1, N2, N3, and REM) were visually scored by an electrophysiology technician (S.R.) in epochs of 30 s according to the AASM rules (Berry et al., 2017). Standard sleep parameters, including the percentage of each sleep stage, as well as respiratory parameters, such as the apnea-hypopnea index (AHI), were computed. Artifacts (eye movements, ECG, EMG, or movement-related artifacts) were detected visually and rejected (J.P.), and analyses were conducted on artifact-free epochs. Automatic quantification of sleep spindles and slow waves from the Cz-Pz derivation was performed during N2-N3 and N3 stages respectively, using the ASEEGA software (PHYSIP, Paris, France). The validation of the original algorithm is fully described elsewhere (Berthomier et al., 2007). An adapted amplitude slow wave's criterion (Rosinvil et al., 2021) instead of the 75°microVolts standard criterion was used to detect slow waves. More specifically, the detection method for spindles and slow waves was based on data-driven criteria using multiple iterations in order to cope with inter-subject and inter-recording variability. The first iteration determined the recording-specific thresholds on the basis of EEG amplitude and EEG power ratios in frequency bands. The second iteration determined the precise temporal localization of each event. The final iteration validated the pre-detected events according to frequency and duration criteria (> 0.5 s) for spindles (Dang-Vu et al., 2017), amplitude and duration criteria (0.25 s $<$ duration < 2 s) for slow waves. For spindles, iteration 1 and 3 dealt with raw EEG data, while iteration 2 was applied on the EEG filtered in the spindle (sigma) frequency range. For the slow waves, iteration 1 dealt with raw EEG data, while iterations 2 and 3 were applied on the EEG filtered in the slow waves (delta) frequency range. Finally, the density of spindles (i.e., number of spindles during stages N2-N3 divided by the time spent in N2-N3) and slow waves (i.e., number of slow waves during stage N3 divided by the time spent in N3) was computed.

Questionnaires

Subjective sleep disturbances were assessed using the Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989) a 19-item questionnaire measuring sleep habits and disturbances over the previous month (total score ranging from 0 to 21). In cancer population, a PSQI score above 8 is considered to reflect poor sleep (Carpenter and Andrykowski, 1998), instead of five in healthy population (Buysse et al., 1989). Insomnia symptoms were measured with the Insomnia Severity Index (ISI; Morin et al., 2011) a seven-item questionnaire (score ranging from 0 to 28). The cut-off score of eight indicating a subthreshold insomnia has been validated in cancer patients (Savard et al., 2005; Michaud et al., 2021). For both questionnaires, higher scores indicate higher sleep disturbances and insomnia related symptoms.

The level of alertness/sleepiness was measured with the Karolinska Sleepiness Score (KSS, Akerstedt and Gillberg, 1990) before every encoding and retrieval phases of the PM task. KSS is a nine-item questionnaire (total score ranging from 1 to 9) with higher scores indicating greater sleepiness.

Depressive symptoms were assessed with the Beck Depression Inventory (BDI), a validated 13-item questionnaire with a total score ranging from 0 to 39 (Beck et al., 1961). Anxiety was assessed with the State Trait Anxiety Inventory (Spielberger et al., 1970). The first 20 items assess state anxiety (STAI-A), i.e., how the participant feels at the moment of the assessment; the remaining 20 items assess trait anxiety (STAI-B), i.e., how the participant usually feels; each range from 20 to 80. The STAI questionnaire was fulfilled during the first session of familiarization, thus the STAI-A score was not representative of the anxiety state at the time of sleep session and only the STAI-B score was reported here. For both questionnaires, i.e., BDI and STAI-B, higher values indicate higher depression and trait-anxiety symptoms.

Fatigue and well-being were assessed in BC patients only, using the Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F; Yellen et al., 1997), a 13-item questionnaire (score ranging from 0 to 52) and the Functional Assessment of Cancer Therapy–General (FACT-G; Cella et al., 1993), a 27-item questionnaire (score ranging from 0 to 108). For both questionnaires, higher scores indicate lower fatigue and greater well-being, respectively.

Prospective memory task

The PM task was adapted from Rehel et al. (2019).

During the encoding phase, participants were asked to learn nine intentions that they had to remember after a certain amount of time (recall time specified by the session). The nine intentions included three TB intentions (e.g., "at 12:11, go to the restaurant for lunch"), and six EB intentions (e.g., "at the cafeteria, buy a black coffee" or "at the child-care center, ask for a map of the Memorial"). A new set of nine intentions was learnt in every session. Each intention was presented on a computer screen, then a cued-recall test was performed and repeated until each intention was correctly learnt. Finally, to ensure that all intentions were correctly encoded, they were retrieved in a last global cued-recall test.

During the retrieval phase, participants were immersed in the virtual environment for a maximum of 20 min. The environment featured a reproduction of the Memorial museum dedicated to World War II and located in Caen (Normandy, France). Participants were placed in an immersive room composed of four wide screens for 3D stereoscopic projections, wore stereoscopic glasses with position sensors and freely

navigated in the museum using a joystick. Participants were asked to visit the museum while memorizing pictures displayed in the environment (ongoing task) and recalling intentions at the appropriate place or time. EB intentions had to be recalled in response to a specific cue in the environment, and TB intentions at the appropriate time. For this purpose, a button on the joystick was available to check time.

Each intention was rated according to three components, i.e., the prospective component, the retrospective component, and the associative one (correct action recalled at the appropriate time or place). A maximum of two points was awarded to every component for a correct recall i.e., if every detail of the retrospective component was recalled at the appropriate time. If the intention was recalled during the second passage or within 1 min of the target time, only one point was attributed to the prospective score. If the intention was recalled at a later passage or within 2 min of the target time, only 0.5 points were awarded to the prospective component [see Duivon et al. (2018) for scoring details]. Each intention had therefore a maximum score of six points corresponding to the sum of the three components scores. Thus, each type of intention had a maximum score of 36 for EB intentions (6*6 EB intentions) and 18 for TB intentions (6*3 TB intentions). Every component had a maximum score of 18 corresponding to the sum of component scores for each intention (2*9 intentions).

Statistical analyses

Analyses were performed using the R software (version 4.0.3), with statistical significance set at $p < 0.05$. Normality hypothesis was assessed using the Shapiro test. When the normality hypothesis was rejected, data were analyzed using non-parametric tests.

Wilcoxon tests were performed to compare demographic characteristics, scores of depression (BDI), scores of sleep questionnaires (ISI, PSQI), score of alertness/sleepiness (KSS), and encoding performance (i.e., number of intentions retrieved during the last global cued recall test). The STAI-B scores were compared using student *t* test.

Analyses of covariance (ANCOVA) were conducted with sleep architecture parameters (i.e., general sleep parameters and sleep stages) as dependent variables, group as independent variable, and the Apnea-Hypopnea index (AHI) as covariate. As no significant effect of AHI was observed on quantification of slow waves and sleep spindles, comparisons between groups were realized with Wilcoxon tests.

An analysis of variance (ANOVA) was performed to evaluate the time-of-day effect on PM performance with PM scores at session 1 as the dependent variable, group and session-time (morning or evening) as independent variables. A paired ANOVA was performed to evaluate group and session effect on PM retrieval using PM scores as the dependent variable, group and session (wake and sleep) as independent variables. Furthermore, in order to evaluate PM consolidation during sleep (PM scores at the sleep session) accounting for performance obtained during the day (PM scores at the wake session), we performed an ANCOVA for each PM score. PM performance during the sleep session was the dependent variable, group the independent variable, and PM performance during the wake session the covariate. As the normality hypothesis was rejected for the retrospective PM score, this latter was log transformed.

In order to control for the effect of ET received by some patients, the analyses of sleep questionnaires, PSG parameters (architecture, slow waves, and spindles characteristics) and PM scores detailed above were conducted with ET status (i.e., with three groups: the patients treated with ET, the patients not treated with ET and HC) as covariate. When the normality hypothesis was rejected, the score was log transformed.

Then, Spearman correlation analyses were performed in the whole sample of participants (HC and BC patients), to assess the associations between subjective sleep assessments (PSQI and ISI scores), PM scores (each intention and component) during the sleep session, psychological distress (BDI and STAI-B scores) and well-being and fatigue (FACT-G and FACIT-F, in BC patients only). Finally, Spearman correlation analyses were performed to test the associations between PSG parameters (i.e., % of N3 and REM sleep, number of awakenings > 1 min, spindles and slow waves parameters) and PM scores (each intention and component) during the sleep session.

Results

Participants characteristics

Demographic characteristics of participants and clinical characteristics of patients are reported **Table 1**. No significant difference on demographic characteristics and levels of anxiety and depression was observed between groups (all *ps* > 0.40).

Sleep

The analyses of sleep questionnaires revealed a significant difference between groups on subjective sleep disturbances (PSQI, $p = 0.020$) and insomnia severity (ISI, $p = 0.004$), indicating that BC patients had greater sleep complaints and more severe insomnia symptoms than HC (**Table 2**). This difference between BC and HC remained significant when ET status (i.e., the three groups: patients receiving ET, patients not receiving ET and HC) was added as covariate for the ISI but not the PSQI (see **Supplementary Table 1**).

Subjective sleep disturbances and insomnia severity were positively associated with trait anxiety assessed using the STAI-B

(PSQI: $r = 0.28$, $p = 0.043$; ISI: $r = 0.31$, $p = 0.027$) in the whole sample of participants. The insomnia severity was positively associated with depression assessed using the BDI (ISI: $r = 0.35$, $p = 0.01$). Thus, higher sleep complaints were related with greater psychological distress in the whole group of participants. PSQI and ISI scores were also negatively associated with FACIT-F (PSQI: $r = -0.59$, $p < 0.001$; ISI: $r = -0.51$, $p = 0.003$) and FACT-G scores (PSQI: $r = -0.65$, $p < 0.001$; ISI: $r = -0.57$, $p < 0.001$) in BC patients. Thus, higher sleep complaints were related to greater fatigue and poorer well-being in BC patients (see **Supplementary Table 5**).

Standard PSG parameters of the two groups are reported in **Table 2**. A significant effect of group [$F(1,50) = 7.10$, $p = 0.010$] was observed only for the number of awakenings longer than 1 min, with patients having significantly more awakenings than HC.

Sleep spindles frequency differed between groups ($p = 0.025$) with patients having a faster frequency than HC (**Table 3**). The peak-to-peak amplitude of slow waves also differed between groups ($p = 0.040$), with lower amplitude in BC patients compared with HC.

For the sake of completeness, we conducted all the analyses on PSG parameters detailed above adding the ET status as covariate. These analyses revealed that the effect of group on the number of awakenings longer than 1 min, the spindle frequency and slow waves amplitude was no longer significant (see **Supplementary Table 1**). On the contrary, a difference on slow waves density became significant [$F(1,50) = 4.91$, $p = 0.031$].

Prospective memory performance

Effect of time-of-day on prospective memory performance

In each group, half of the participants performed the session 1 in the morning and the other half in the evening in order to control for an effect of time-of-day on PM performance. The ANOVA revealed no significant effect of time-of-day [$F(1,49) = 0.11$, $p = 0.74$] and group [$F(1,49) = 0.20$, $p = 0.66$], and no significant interaction between these factors [$F(1,49) = 0.35$, $p = 0.56$] on encoding performance. No significant effect of time-of-day [$F(1,49) = 0.05$, $p = 0.82$] and group [$F(1,49) = 0.50$, $p = 0.48$], and no significant interaction between these factors [$F(1,49) = 0.12$, $p = 0.74$] on global PM performance (i.e., sum of three components scores) was observed. Moreover, no significant effect of group, time-of-day and interaction were observed whatever the type of intention and component (all *p values* > 0.05, results not shown).

A comparison of the level of alertness/sleepiness (KSS) was performed between groups. Whether at the wake session or the sleep session, or before encoding or retrieval, no significant difference was observed between the groups (all *p values* > 0.2, results not shown).

These results indicate that there was no different effect of time-of-day on encoding and recall performance between groups.

Encoding

The number of intentions retrieved during the last cued-recall test of the encoding phase did not differ significantly between groups (mean for the sleep session HC = 8.2; BC = 7.7; $p = 0.25$; mean for the wake session HC = 8.1; BC = 7.9; $p = 0.75$). This effect became significant when ET status was added as covariate for both sessions (all *p values* < 0.02).

Effect of group and session (sleep vs. wake) on prospective memory performance

An analysis of variance revealed better global PM performance during the sleep session compared to the wake session [$F(1,51) = 21.5$, $p < 0.001$]. Neither a significant effect of group [$F(1,51) = 1.48$, $p = 0.23$], nor a significant interaction between group and session [$F(1,51) = 0.09$, $p = 0.76$] was observed. Similar results were observed for each intention and component (all *p values* > 0.15, see **Table 4** for further details). Thus, better PM retrieval performance was observed after a night of sleep rather than after an equivalent period of daytime wakefulness, in both groups of participants.

Sleep-dependent prospective memory retrieval

Table 4 summarizes PM performance in BC patients and HC during the wake and sleep sessions. Analyses of co-variance were conducted on PM scores obtained during the sleep session, accounting for PM scores obtained during the wake session. PM performance did not differ between groups whatever the type of intention (EB or TB; all *p values* > 0.55) or the component (Prospective, Retrospective, and Associative; all *p values* > 0.39). When ET status was added as covariate, a significant difference between BC and HC was observed for the prospective [$F(1,49) = 5.3$, $p = 0.025$] and the associative components [$F(1,49) = 4.50$, $p = 0.039$], with patients having lower scores than HC.

Prospective memory performance was not significantly related with psychological distress, i.e., STAI-B and BDI scores in the whole sample of participants (see **Supplementary Table 5**). A significant correlation was observed between the retrieval of the retrospective component and the FACIT-F score ($r = 0.38$, $p = 0{,}030$). Thus, higher fatigue is related with lower retrieval of the retrospective component in BC patients. No other significant correlation was observed.

Associations between sleep and prospective memory performance

No significant correlation was observed during both sessions between encoding performance (i.e.,

number of intentions retrieved during the last cued-recall test of the encoding phase), scores on sleep questionnaires (PSQI, ISI, all *p values* > 0.1, results not shown) and fatigue (FACIT-F only in BC patients, all *p values* > 0.1).

The PSQI total score was significantly associated with the retrieval of EB intentions ($r = -0.36$, $p = 0.010$) and retrospective components of the whole intentions ($r = -0.29$, $p = 0.038$). The ISI score was significantly associated with the retrieval of EB intentions ($r = -0.41$, $p = 0.003$) and retrospective components of the whole intentions ($r = -0.42$, $p = 0.002$). Thus, higher sleep disturbances and insomnia complaints were associated with poorer recall of EB intentions and retrospective components after a night of sleep in the whole sample of participants. Furthermore, FACIT-F score was significantly related with the retrospective component score ($r = 0.38$, $p = 0.03$), indicating that greater fatigue was related with poorer recall of the retrospective component of intentions in BC patients.

No significant correlation was observed between PSG parameters (% of N3 and REM sleep, number of awakenings longer than 1 min and all spindles and slow

TABLE 1 Demographic and clinical characteristics of participants (mean ± SD).

Demographic characteristics	**HC (*n* = 21)**	**BC (*n* = 32)**	***P*-values**
Age (years)	62.6 ± 4.4	61.8 ± 5.2	0.63
Education (years)	11.8 ± 1.7	11.8 ± 3.5	0.44
Anxiety (STAI-B)	42.3 ± 9.3	40.8 ± 10.5	0.60
Depression (BDI)	4.1 ± 3.2	3.6 ± 3.2	0.44
Clinical characteristics	**HC (*n* = 21)**	**BC (*n* = 32)**	
Stage of the cancer, n (%): 0 I IIA	NA	17 (53%) 12 (38%) 3 (9%)	
Tumorectomy, n (%) Mastectomy, n (%)	NA	29 (91%) 4 (13%)*	
Time since radiotherapy (months)	NA	8 ± 2.4	
Treated with endocrine therapy, Not treated with endocrine therapy	NA	16 (50%) 16 (50%)	
Fatigue (FACIT-F)	NA	36.6 ± 10	
Well-being (FACT-G)	NA	84.6 ± 17	

*One patient receiving tumorectomy and mastectomy.
HC, healthy controls; BC, breast cancer; STAI-B, State Trait Anxiety Inventory–Trait; BDI, Beck depression inventory; FACIT-F, Functional Assessment of Chronic Illness Therapy–Fatigue; FACT-G, Functional Assessment of Cancer Therapy–General.
Age, Education, and Depression were compared with Wilcoxon tests and Anxiety with the student's *t*.test.

TABLE 2 Sleep characteristics, i.e., subjective sleep quality and sleep architecture (mean ± SD).

Sleep questionnaires	**HC (*n* = 21)**	**BC (*n* = 32)**	***P*-values**		
Sleep disturbances (PSQI total score)	5.48 ± 2.8	8.29 ± 4.5	**0.020**		
Insomnia severity index (ISI score)	7.19 ± 4.5	11.9 ± 6.6	**0.004**		
Sleep architecture (AHI as co-variate)	**HC (*n* = 21)**	**BC (*n* = 32)**	***F (1,50)***	***P*-values**	**η^2**
Total sleep time (min)	356 ± 68	355 ± 68	0.001	0.97	< 0.01
Sleep efficiency (%)	76.9 ± 11	74.1 ± 11	0.75	0.39	0.01
Number of awakenings > 1 min	6.76 ± 2.8	9.59 ± 4.4	7.10	**0.010**	0.12
WASO%	16.5 ± 12	19.9 ± 11	1.22	0.28	0.02
N1 (% TST)	8.6 ± 3.7	8.86 ± 5.2	0.059	0.81	< 0.01
N2 (% TST)	50.3 ± 7.2	52.0 ± 6.0	0.91	0.35	0.02
N3 (% TST)	22.9 ± 6.1	22.6 ± 7.3	0.024	0.88	< 0.01
REM (% TST)	18.3 ± 4.8	16.6 ± 3.9	1.95	0.17	0.04
Apnea-hypopnea index (AHI)	19.6 ± 13	19.8 ± 12	NA	0.83	NA

HC, Healthy Controls; BC, breast cancer patients; PSQI, Pittsburgh Sleep Quality Index; ISI, Insomnia Severity Index; WASO, Wake After Sleep Onset; TST, Total sleep time; REM, Rapid-Eye-Movement sleep. *P*-values < 0.05 are in bold. Effects size: Small ($\eta^2 \geq 0.01$), medium ($\eta^2 \geq 0.06$), and large ($\eta^2 \geq 0.14$). Comparison of the PSQI and the AHI scores were realized with Wilcoxon tests and ISI score with the student's *t*.test. Comparison of the sleep architecture was realized with analyses of co-variance with AHI as covariate.

TABLE 3 Sleep spindles features during N2 + N3, and slow waves features during N3 (mean ± SD).

Parameters		**HC (*n* = 21)**	**BC (*n* = 32)**	***P*-values**
Spindles (N2 + N3)	Frequency (Hz)	13.6 ± 0.6	13.9 ± 0.5	**0.025**
	Maximum amplitude (μV)	10.0 ± 2.5	9.57 ± 2.7	0.41
	Density (number per epoch)	2.81 ± 0.9	2.79 ± 1.4	0.55
Slow waves (N3)	Peak to peak amplitude (μV)	80.4 ± 17	72.6 ± 20	**0.040**
	Density (number per epoch)	9.01 ± 3.6	7.95 ± 3.9	0.13

HC, Healthy Controls; BC, breast cancer patients. *P*-values < 0.05 are in bold. Analyses were realized with Wilcoxon tests.

TABLE 4 Prospective memory (PM) performances during the wake and sleep sessions (mean ± SD) and analyses of the group and session effects.

	HC (n = 21)		BC (n = 32)		Group effect		Session effect		Group effect (accounting for wake session performance)		
	Wake	Sleep	Wake	Sleep	F (1,51)	P-values	F (1,51)	P-values	F (1,49)	P-values	η^2
Total (/54)	30.0 ± 7.7	34.8 ± 8.0	26.6 ± 10	32.2 ± 11	1.48	0.23	21.5	< **0.001**	0.05	0.83	< 0.01
Intentions											
EB (/36)	22.4 ± 6.2	25.5 ± 6.3	20.2 ± 7.8	24.3 ± 7.1	1.07	0.31	14.0	< **0.001**	0.02	0.89	< 0.01
TB (/18)	7.52 ± 3.0	9.24 ± 4.6	6.45 ± 4.6	7.88 ± 5.0	1.27	0.27	6.21	**0.016**	0.36	0.55	< 0.01
Components (/18)											
Prospective	8.86 ± 3.2	10.7 ± 3.6	8.36 ± 3.5	9.56 ± 3.6	0.96	0.33	9.37	**0.004**	1.03	0.32	< 0.01
Retrospective	12.81 ± 2.7	13.8 ± 3.1	11.3 ± 4.1	13.5 ± 3.5	1.04	0.31	15.1	< **0.001**	0.30	0.59	< 0.01
Associative	8.29 ± 3.4	10.3 ± 2.8	7.00 ± 3.9	9.06 ± 4.3	1.77	0.19	19.1	< **0.001**	0.25	0.62	< 0.01

HC, healthy controls; EB, event-based; P-values < 0.05 are in bold. TB, time-based. Analyses of variance were used for the group and session effect. Analyses of co-variance were used with performance during the wake session as co-variate for the group effect (accounting for wake session performance).

waves parameters) and PM performance (all p *values* > 0.05, see **Supplementary Table 4**).

Discussion

The aim of this study was to assess, sleep-dependent consolidation of intentions in PM in BC patients not receiving chemotherapy. First, BC patients reported greater sleep disturbances and insomnia symptoms than HC. Greater sleep complaints were related with poorer PM performance and markers of quality of life, i.e., fatigue, well-being and psychological distress. An objective assessment of sleep using PSG revealed more awakenings longer than 1 min, decreased amplitude of slow waves and increased frequency of sleep spindles in BC patients compared to HC. These subtle sleep modifications were not related to sleep-dependent consolidation of intentions whose remembering did not differ between groups.

Greater subjective sleep disturbances and insomnia severity were related to greater difficulty remembering EB intentions and retrospective components in the whole group of participants. These results are in line with previous studies in BC patients revealing a significant correlation between sleep complaint and cognitive performance (Duivon et al., 2021) including memory performance (Caplette-Gingras et al., 2013). In the present study, both groups had greater PM performance during the sleep session than during the wake session, highlighting the significant benefit of sleep on consolidation of intentions. BC patients had no encoding difficulties as evidenced by the equivalent number of intentions recalled at the end of the encoding phase, except when controlling for ET. Moreover, encoding performance was not related to subjective sleep assessment and fatigue, meaning that self-reported sleep disturbances and fatigue could have a specific impact on retrieval process but not on memory encoding. According to the Multiprocess framework (McDaniel and Einstein, 2000), PM retrieval relies on a continuum from strategic processes to relatively spontaneous processes depending on several characteristics such as the distinctiveness of the cue and the strength of the association between the prospective and retrospective components. Previous studies conducted in healthy subjects, revealed that sleep benefits spontaneous retrieval processes, by strengthening the association between the two components, rather than strategic monitoring processes (Diekelmann et al., 2013b; Esposito et al., 2015). In our study, no significant correlation was found with the associative component to confirm this hypothesis. Nevertheless, the correlation with the recall of EB intentions and the retrospective component suggests a benefit of sleep on the episodic memory dimension, i.e., the spontaneous processes of remembering the corresponding action when the cue is detected, rather than on the strategic processes needed to check the environment and estimate time. However, contrary to our hypotheses, sleep-dependent consolidation of intentions in PM was not impaired in BC patients. In the present study, the mean score of PSQI of BC patients was equal to the cutoff score proposed in this pathology (Carpenter and Andrykowski, 1998). Moreover, the mean ISI score in BC patients was considered to reflect subthreshold insomnia (Morin et al., 2011). Thus, although BC patients had greater sleep complaints than HC related to poorer PM performance, the level of subjective sleep disturbances in this group of patients was relatively low. This may explain the lack of sleep-related impairment of PM consolidation in BC patients.

Subtle sleep changes were observed when analyzing PSG data. BC patients had more awakenings longer than 1 min than HC, but neither sleep efficiency nor the time awake after sleep onset differed between groups. Thus, these awakenings did not modify sleep architecture of BC patients. Concerning PM, SWS appears to be involved in the consolidation of intentions in young adults (Diekelmann et al., 2013a; Leong et al., 2019b, 2021). However, these results are not consistently reported since Cunningham et al. (2021) found a negative association between SWS and PM performance in young adults. In the study by Leong et al. (2021), while older adults had lower PM performance and spent less time in SWS than young adults, no significant relation was found between SWS and PM in the older group. The authors suggested that the role of SWS on

PM consolidation may be disrupted and thus ineffective in older adults. Meanwhile, Scullin et al. (2019), in a study conducted in adults aged 18–84 years, revealed that REM sleep duration explained the variance in PM consolidation when controlling for age. In the present study, in which we included older participants, neither time spent in SWS (N3 sleep) nor time spent in REM sleep were related to PM performance. Further analyses on REM sleep, which would rather be involved in intentions consolidation in older adults, should be conducted. Distinguishing for instance between phasic and tonic phases (Simor et al., 2020), which might play distinct roles in memory consolidation, would be interesting.

Aging is characterized by a decrease in the amplitude and density of slow waves and density and duration of sleep spindles (Mander et al., 2017). In a study assessing sleep-dependent consolidation of intentions in young and older adults, Scullin et al. (2019) reported a correlation between slow wave activity and the recall of EB intentions, which was no longer significant when adjusted for age. As suggested for time spent in SWS, the role of slow waves on sleep-dependent memory consolidation must be less effective in older adults. This hypothesis could explain the lack of relationship between slow waves characteristics and PM performance, and the lack of PM difficulties despite lower slow wave's amplitude in BC patients. In the present study, only a change in slow wave's amplitude was observed. Thus, we could surmise that the density of slow waves, rather than their amplitude, is relevant for memory consolidation but this hypothesis requires further investigations. A significant increase in spindle frequency was also observed in BC patients but this change was not related to PM performance. The lack of significant association could be explained by the low variability of this spindle feature. However, this result is consistent with previous studies conducted in healthy adults and revealing no significant association between sleep spindles and retrieval of intentions (Scullin et al., 2019; Leong et al., 2021).

Prospective memory remembering was related to subjective sleep disturbances but not to objective sleep changes. These results are in line with a recent study in BC revealing a relationship between neuropsychological performance and subjective sleep quality but not with objective sleep parameters measured with actigraphy (Ancoli-Israel et al., 2022). The discrepancy between subjective and objective sleep measures frequently observed in healthy subjects (Rezaie et al., 2018) is also observed in BC patients. Reinsel et al. (2015) showed no difference in sleep architecture between patients with and without insomnia complaints. In the same way, a discrepancy is frequently observed between subjective and objective measures of cognitive functioning in BC patients (Ganz et al., 2013; Bray et al., 2018). Some studies suggest that this discrepancy could be due to the nature of the assessment. PSG and neuropsychological tests have a poor ecological validity which may underestimate difficulties measured with questionnaires (Savard and Ganz, 2016). In the present study, we used a virtual reality-based task to reproduce as finely as possible situations of everyday life. This type of paradigm is supposed to be more sensitive to measure cognitive difficulties experienced in everyday life (Lecouvey et al., 2017; Rehel et al., 2019). Nevertheless, PM impairment in the group of BC patients might be too subtle to be detected even by an ecological task but still related with worse subjective sleep quality and fatigue. This result is reminiscent of the study by Mihuta et al. (2016) who reported no PM deficit in BC patients using a virtual reality task but reported associations between PM scores and cognitive complaints. The laboratory context encourages participants to muster all their abilities to succeed in the task and the ongoing task is not as demanding as in real-world situations. These limitations, compared to an assessment with a naturalistic task, seem difficult to overcome. However, our PM task could be made even more ecological. We could take the example of the Virtual Reality Everyday Assessment lab (VR-EAL) where realistic intentions were used such as "Take the chocolate pie out of the oven" and "Collect the carrot cake from the bakery at 12 pm" (Kourtesis et al., 2020).

Fatigue, psychological distress, sleep disturbances, and cognitive impairment are the most common side effects reported by BC patients (Bower, 2008). In the study by Xu et al. (2018), using a Bayesian network method to represent multivariate relationships between sets of variables, cognitive performance was directly related to sleep complaints, and also indirectly related to fatigue (through sleep) and depression (through sleep and fatigue). Higher fatigue has been previously related with PM impairment in BC patients (Paquet et al., 2013). In our study, worse PM performance was related to poorer sleep quality and greater fatigue and in turn sleep disturbances were associated with worse psychological distress, fatigue, and well-being. Thus, we can surmise that PM impairment usually reported in BC patients (not treated with chemotherapy) would rather be related to several factors affecting their quality of life such as greater sleep disturbances, fatigue, and psychological distress, rather than to a specific alteration of physiological mechanisms involved in sleep-dependent memory consolidation. As the patients included in this study had no major psychological distress in comparison to HC, and no major sleep disturbances, fatigue or poorer well-being (according to the normative data of the questionnaires), this could explain the lack of PM impairment in BC patients. Further studies with larger samples are needed to better understand the role of factors related to quality of life on sleep-dependent memory consolidation in BC patients not treated with chemotherapy.

The patients included in this study were in the early stages of BC (0, I, and II), not treated with chemotherapy and assessed at least 6 months after radiation therapy. These criteria were chosen to minimize as much as possible the negative effect of the treatments, particularly the well-known effects of chemotherapy on sleep and memory. However, half of BC patients were under ET at the time of assessment and ET has been associated

with higher sleep complaints (Dhruva et al., 2012) and lower episodic memory performance (Underwood et al., 2018, 2019). Thus, in order to control for the impact of ET on sleep-dependent PM consolidation, complementary analyses were performed, adding the ET status as covariate. These analyses revealed that there was no longer a significant difference for the numbers of awakenings longer than one minute, the frequency of spindles and the amplitude of slow waves between BC and HC. Nevertheless, a significant difference was revealed for the density of slow waves, the encoding of new intentions and the retrieval of prospective and associative components. Thus, it appears that ET had subtle effect on objective sleep parameters and PM functioning. Further investigations with larger sample size should be conducted to precisely address this issue.

Conclusion

This study reveals greater sleep complaints and subtle sleep changes in BC patients compared to HC. Despite the role of slow waves and spindles in sleep-dependent memory consolidation, the modifications observed in BC patients had no significant impact on sleep-dependent PM consolidation. Our results suggest that PM impairment reported in previous studies would be due more to an altered quality of life reflected by several factors such as poorer sleep quality and fatigue, rather than to a slight alteration of sleep-dependent memory consolidation mechanisms. Thus, in this study focusing on patients at early stages of BC, not treated with chemotherapy and without psychological distress and severe sleep disturbances, sleep-dependent consolidation of intentions was not impaired.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by CPP Ile de France III (n°ID-RCB: 2017-A02778-45). The patients/participants provided their written informed consent to participate in this study.

Author contributions

MD collected and analyzed the data and wrote the first draft of the manuscript. SR, CB, and JP realized sleep analyses. CS-D, JG, GE, CL, and FV participated in the investigation. J-MG, BC, BG, and JP participated in the project administration. BG, JP, BD, FE, and FJ participated in the funding acquisition and design of the study. BG, BD, GR, and JP participated to the rewriting and editing of the study. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

CB has ownership/directorship and was employed by Physip, who owns Aseega.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2022.908268/full#supplementary-material

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EDITED BY
Bénédicte Giffard,
INSERM U1077 Neuropsychologie et Imagerie de la Mémoire Humaine, France

REVIEWED BY
David Kiesl,
Kepler University Hospital GmbH, Austria
Charlotte Sleurs,
Leuven Brain Institute, KU Leuven, Belgium

*CORRESPONDENCE
Delmy Oliva
Delmy.Oliva@rjl.se
Lasse D. Jensen
lasse.jensen@liu.se

†These authors have contributed equally to this work

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Opposing inflammatory biomarker responses to sleep disruption in cancer patients before and during oncological therapy

Delmy Oliva[1,2*†], Bengt-Åke Andersson[3†], Freddi Lewin[1,2] and Lasse D. Jensen[4*]

[1]Department of Oncology, Ryhov County Hospital, Jönköping, Sweden, [2]Department of Biomedical and Clinical Sciences, Linköping University, Linköping, Sweden, [3]Department of Natural Science and Biomedicine, School of Welfare, Jönköping University, Jönköping, Sweden, [4]Division of Diagnostics and Specialist Medicine, Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden

Background: Sleep disruption is known to be highly prevalent in cancer patients, aggravated during oncological treatment and closely associated with reduced quality of life, therapeutic outcome and survival. Inflammatory factors are associated with sleep disruption in healthy individuals and cancer patients, but heterogeneity and robustness of inflammatory factors associated with sleep disruption and how these are affected by oncological therapy remain poorly understood. Furthermore, due to the complex crosstalk between sleep-, and therapy-associated factors, including inflammatory factors, there are currently no established biomarkers for predicting sleep disruption in patients undergoing oncological therapy.

Methods: We performed a broad screen of circulating biomarkers with immune-modulating or endocrine functions and coupled these to self-reported sleep quality using the Medical Outcomes Study (MOS) sleep scale. Ninety cancer patients with gastrointestinal, urothelial, breast, brain and tonsillar cancers, aged between 32 and 86 years, and scheduled for adjuvant or palliative oncological therapy were included. Of these, 71 patients were evaluable. Data was collected immediately before and again 3 months after onset of oncological therapy.

Results: Seventeen among a total of 45 investigated plasma proteins were found to be suppressed in cancer patients exhibiting sleep disruption prior to treatment onset, but this association was lost following the first treatment cycle. Patients whose sleep quality was reduced during the treatment period exhibited significantly increased plasma levels of six pro-inflammatory biomarkers (IL-2, IL-6, IL-12, TNF-a, IFN-g, and GM-CSF) 3 months after the start of treatment, whereas biomarkers with anti-inflammatory, growth factor, immune-modulatory, or chemokine functions were unchanged.

Conclusion: Our work suggests that biomarkers of sleep quality are not valid for cancer patients undergoing oncological therapy if analyzed only at a single timepoint. On the other hand, therapy-associated increases in circulating inflammatory biomarkers are closely coupled to reduced sleep quality in cancer patients. These findings indicate a need for testing of inflammatory and other biomarkers as well as sleep quality at multiple times during the patient treatment and care process.

KEYWORDS

cancer, sleep, inflammation, oncological therapy, biomarkers

Introduction

Cancer patients are at higher risk of developing sleep disruption pathologies such as insomnia and excessive daytime sleepiness (Fiorentino and Ancoli-Israel, 2007; Savard et al., 2015). It is estimated that sleep disruption is 3–5 times more prevalent among cancer patients compared to the general population, exceeding 50% of the entire patient group in some studies (Divani et al., 2022). As sleep disruption in cancer patients is closely linked to reduced quality of life and survival (Innominato et al., 2012), timely diagnosis and treatment is of critical importance to extend high quality life expectancy in this patient group. A clear example of the impact sleep disruption may have on cancer patients was reported by Innominato et al. (2012) who discovered that survival was extended by almost 8 months in colorectal cancer patients with robust daily (circadian) sleep patterns (49% of the population) compared to patients with disrupted sleep patterns (Innominato et al., 2012). As such, being able to rapidly and routinely identify patients at risk of suffering from poor sleep quality may have enormous prognostic value in oncological practice.

Clinical diagnosis of sleep disruption in cancer patients

There are currently no instruments implemented into routine clinical practise for diagnosing or quantifying the quality of sleep or extent of sleep disruption in cancer patients. Oncology guidelines such as the Pan-Canadian guidelines, however, raise the importance of assessing, preventing and treating sleep disruption in adult cancer patients (Howell et al., 2013). These guidelines propose an algorithm that starts with the diagnosis of a "sleep problem" based on the patient responding "yes" to a question if he/she suffers from "sleep problems," followed by asking whether this has persisted for more than three nights and is influencing the patients daytime function (Howell et al., 2013). While this is a somewhat crude assessment of sleep disruption, these guidelines represent the first attempt to include this important issue in routine cancer care. Within clinical research, however, numerous questionnaires and other instruments have been developed to investigate sleep disruption in cancer patients [recently reviewed by Jensen et al. (2021)]. The most commonly used is the extensive 19-item Pittsburgh Sleep Quality Index (Divani et al., 2022), which however is time-consuming to both fill and analyze. A shorter and more intuitive form is the 12-item Medical Outcomes Study (MOS) Sleep Scale which, in spite of the condensed format, evaluates multiple aspects of sleep quality including sleep duration, somnolence, and sleep-related daily function (Bower et al., 2000). The methodology applied to analyze the responses to the MOS Sleep Scale has, however, differed within the research community, and has in the past only included fragments of the scale. Currently an intuitive and unified readout from the MOS scale that take all the answers into account in a clinically meaningful manner, is lacking. The development of such a readout would greatly facilitate the use of this instrument, and indeed the routine and standardized evaluation of sleep quality in cancer patients in general.

Sleep and inflammation

Cytokines and chemokines are small proteins that control local and systemic immune and inflammatory reactions in the organism and are thought to play a significant role in sleep (Irwin et al., 2008: Kapsimalis et al., 2008). Pro-inflammatory cytokines such as tumor necrosis factor (TNF)-a, interferon (IFN)-gamma, interleukin (IL)-2, 6 and 12, and granulocyte-macrophage colony stimulating factor (GM-CSF) are known to induce daytime sleepiness (Mantovani et al., 2008). On the other hand, sleep disruption is also linked to augmented inflammatory processes through their cytokine- and chemokine-mediated control mechanisms (Irwin et al., 2013; Wright et al., 2015). As such, pro-inflammatory cytokines are often found at elevated levels in both cancer patients and people suffering from poor sleep [reviewed in Jensen et al. (2021)], and are associated with

nausea, depression and a generalized feeling of illness (Vgontzas et al., 2007; Kapsimalis et al., 2008; Vumma et al., 2017). In addition to inflammatory cytokines and chemokines, C-reactive protein (CRP) is a commonly used biomarker of inflammation (Sproston and Ashworth, 2018). CRP is commonly used to monitor potential infection during oncological treatment (Howren et al., 2009; Bribriesco, 2020), but has also been suggested as a biomarker of sleep disruption (Jensen et al., 2021). The associations between deregulated circulating levels of inflammatory biomarkers including CRP and sleep disruption are however still poorly understood, and to what extent these are influenced by oncological treatment is not known.

The complexity of sleep disturbance and inflammation in cancer patients

Diagnosing cancer-associated inflammation and sleep disruption is complicated by the high incidence of low-grade inflammation and sleep disruption in the elderly population to which cancer patients often belong, even in the absence of malignancy (da Silva et al., 2016; Abd El-Kader and Al-Jiffri, 2019). Other factors that are often co-existing with malignant disease such as menopausal symptoms and circadian rhythm disturbances related to for example steroid treatments could also lead to sleep disturbances and changes in systemic inflammatory profiles in cancer patients (Fox et al., 2020). Some malignancies such as CNS cancers may also disrupt the central circadian organizers (located in the suprachiasmatic nucleus) or sleep organizers in other areas of the brain, which further adds to the risk of developing sleep disruptions in this patient group (Gapstur et al., 2009), Furthermore, toxicities linked to oncological treatments including off-target tissue damage, bone marrow suppression, fatigue, anxiety, pain, and depression to mention a few, are associated with increased risk of *de novo* or deterioration of existing sleep disturbances (Oliva et al., 2019), and an upregulation of pro-inflammatory cytokines (Mills et al., 2008; Wang et al., 2010), which in both cases could persist long after the conclusion of the treatment cycle. As these cytokines might trigger loss of REM sleep (Irwin, 2015; Irwin and Opp, 2017), cancer patients that experience toxic side-effects from such oncological treatment may suffer (further) reduced sleep quality and therefore sleep disruption-associated treatment resistance, progression, reduced quality of life (Oliva et al., 2014) and survival (Innominato et al., 2012; Balachandran et al., 2021). Cancer patients, however, exhibit highly diverse toxic phenotypes and to varying degrees (Oliva et al., 2017), and it is not currently possible to predict which patients will suffer from treatment-associated sleep disruption, or how this can be prevented. Combined, characterizing, and understanding the landscape of sleep disruption and its effect on systemic inflammation in cancer patients undergoing oncological treatment is highly challenging and complex, which complicates the understanding the underlying etiology and prevent the development of effective diagnostic tools.

Here we sought to develop a general view on how oncological therapies may affect sleep and circulating levels of inflammatory and various other plasma proteins across different malignancies and therapies. We further aimed to identify specific biomarkers, or biomarker families, coupled to treatment-associated sleep disruption.

Materials and methods

Participants

Ninety patients undergoing systemic oncological treatment for different types of cancer: gastrointestinal cancer, urothelial cancer, breast cancer, brain tumor and tonsillar cancer were included in this study at the Oncology clinic, Ryhov County Hospital, Jönköping, Sweden between 2017 and 2018. The inclusion criteria were patients planned to receive adjuvant or palliative treatment, having an ECOG performance status of 0 or 1, and having sufficient understanding of the Swedish language to understand the information given. The patients were informed about the study orally and on paper by an oncology nurse and were given 30 min or until the next appointment to consider their participation.

The included patients answered the 12-point MOS sleep scale and provided a blood sample (10 ml) both before starting treatment and 3 months after treatment started. Other demographic data were also obtained through a structured anamnesis.

Ethical permission was obtained from the Regional Ethical Review Board in Linköping, Sweden (Dnr 2016/379-31).

Medical Outcomes Study sleep scale

The MOS – Sleep Scale is a commonly used instrument for subjective evaluation of sleep disturbances in patients with chronic illness or malignant diseases (Naughton et al., 2002; Manas et al., 2011; Hsiao et al., 2013; Sharp et al., 2013). The MOS sleep scale is based on 12 items and takes no more than 5 min to complete. It measures important origins and parameters of sleep, which are significant for cancer patients as well as other patient groups. It includes questions related to sleep initiation, maintenance, adequacy, somnolence, and respiratory impairments (Allen et al., 2009). In this study, the answers to each of the 12 questions were aggregated to a single "aggregated MOS score" by adding the scores given to questions 1, 3b, and 3j (answered on a 1–5 Likert scale where 5 indicate the worst possible sleep quality) to the inverted scores (i.e., six minus the score value) given to questions 3a and 3c-i (also answered

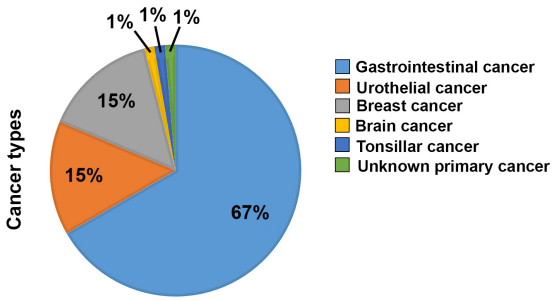

FIGURE 1
Overview of the diagnoses of the patients included in the study. Percentages of the 90 patients included having either a Gastrointestinal (60), Urothelial (13), Breast (14), Brain (1), Tonsilar (1), or Unknown Primary (1) cancer diagnosis.

on a 1–5 Likert scale where 5 indicate the best possible sleep quality). A value of eight was subtracted from the answer to question 2 (the average number of hours slept per night), and negative values were divided by –1 to result in the (positive) number of additional or fewer hours of sleep compared what is recommended, and this value was added to the other scores. The resulting aggregated MOS score had a minimum value of eleven and a maximum score of 71.

Laboratory assessments for serum biomarkers

Levels of plasma CRP were analyzed using a high-sensitivity CRP test based on the Advia 1800 instrument and reagents from Siemens (Siemens Healthcare, Erlangen, Germany) allowing detection of CRP levels in the range of 0.16–10 mg/L. When higher levels than 10 mg/L were detected, a standard CRP test with a range of 4–300 mg/L was done on the same instrument and with the same reagents.

Analyses of plasma biomarkers was first done on 17 patients with established good (n = 9) or poor (n = 8) sleep quality respectively, using Human Cytokine/Chemokine/Growth Factor 45-Plex ProcartaPlex Panel 1 (Thermo Fisher Scientific, Austria). Out of this panel of 45 biomarkers, 17 (BDNF, Eotaxin, GM-CSF, GRO-a, HGF, IFN-g, IL-10, IL-12p40, IL-2, IL-5, IL-6, IL-7, LIF, MCP-1, PIGF-1, RANTES, and TNF-a) were selected based statistical significance of $p < 0.10$ when comparing groups of "good" versus "poor" sleeping cancer patients at baseline and when comparing patients before and after 3 months of oncological treatment. Analyses of the 17 biomarkes were done with a custom procartaplex 17-plex (Thermo Fisher Scientific, Austria) using multiplex fluorochrome technique, (Luminex xMAP^{TM} Technology, Austin, TX, USA) according to the manufacture's recommendations. A Bio-Plex 200 system with Bio-Plex Manager Software 5.0 were used to collect the fluorescence intensities. A 9-standard concentration set (included in the kit) were used to generate a standard curve for the calculation of the analyte concentration.

The 17 biomarkers were grouped into one of 5 biomarker families based on consensus from the collected scientific literature of their known or best described function. As such, TNF-a, IFN-g, IL-6, IL-2, IL-12, and GM-CSF were classified as "pro-inflammatory cytokines," IL-10 and LIF were classified as "anti-inflammatory cytokines," BDNF, PLGF, and HGF were classified as "growth factors," Eotaxin, Rantes, MCP-1, and GRO were classified as "chemokines" and IL-5, IL-7, and CRP were classified as "modulatory and other" biomarkers. This classification should however not be seen as an exclusive function of a given factor within the family.

Aggregated plasma values for an entire biomarker family was generated by normalizing the concentrations for each biomarker and patient against the average of the patient population (e.g., dividing the concentration of for example BDNF for a given patient by the average for the entire population), followed by averaging such normalized levels of all biomarkers within the family (e.g., averaging normalized levels of BDNF, PLGF, and HGF from a given patient to derive the aggregated plasma value for the "growth factors" biomarker family for that patient).

Statistics

All data was considered to not significantly deviate from binomial distribution and is therefore presented as means ± standard error (Figures 1, 3, 5, 6), alternatively as means with 95% confidence intervals shown as box-plots (Figure 2) or as swarm plots with linear inserted regression graphs (Figures 2, 4). Where means are presented in Figures 2, 3A–C these are means of the entire population of 71 patients. Means presented in Figures 4, 6 represent the means of the patients within the given sleep quality group, where the individual values are shown in the swam plots directly above the histograms. Means in Figure 7 represent values from 8, 55, and 8 patients in the < -9, intermediate and > 9 groups respectively. Changes in biomarker levels or MOS scores in a patient were derived by subtracting the values at baseline from those measured at follow-up. Differences between two groups were evaluated using students t-test as shown using red boxes in Figure 2, black lines connecting the two groups being compared and coupled to statistical indicators (NS: non-significant, $^{*}p < 0.05$, $^{**}p < 0.01$ and $^{***}p < 0.001$), alternatively p-values, placed directly above the lines in Figures 4, 6, 7. Correlation lines shown in swam plots of Figures 3–6 illustrate linear regressions, the significance of which could not be uniformly calculated due to many missing values for a few of the biomarkers, and are therefore omitted.

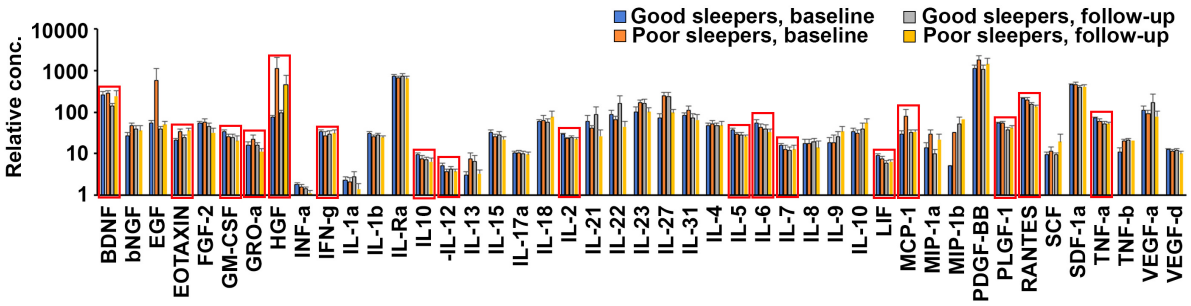

FIGURE 2
Poor and/or deteriorated sleep quality during oncological treatment is coupled to changes in plasma levels of 17 cytokines. Quantification of the average levels of 45 cytokines in the plasma of patients reporting good (aggregated MOS score < 24, $n = 9$) and poor (aggregated MOS score > 25, $n = 8$) sleep at baseline or follow-up, after 3 months of oncological treatment. Significant ($p < 0.1$) differences were observed between good and poor sleepers at baseline for Eotaxin, IFN-g, IL12, IL2, IL5, and MCP-1, between good and poor sleepers at follow-up for GRO-a and IL6 and for those exhibiting good sleep at baseline that deteriorated to poor sleep at follow-up for BDNF, GM-CSF, HGF, IL10, IL5, IL7, LIF, PlGF, RANTES, and TNF-a. These 17 biomarkers are indicated with red boxes in the graph.

Results

A total of 90 patients diagnosed with gastrointestinal (67%), urothelial (15%), breast (15%), brain (1%), tonsillar (1%), or unknown primary (1%) cancer were recruited to the study (Figure 1). Among these, nineteen patients failed to provide the requested follow-up samples or withdrew their consent without disclosing the reason, and could therefore not be fully analyzed. Medical treatment consisted mainly of high-dose cytostatic and/or cytotoxic drugs but varied depending on various clinical factors in accordance with current treatment guidelines. Approximately 2/3 were male at a median age of 68 and 1/3 were female at a median age of 61 years. Additional demographic, diagnostic, and co-morbidity-data from the study population is presented in Table 1.

Plasma levels of 45 biomarkers were analyzed from nine patients who reported high sleep quality (i.e., low aggregated MOS scores) and eight who reported poor sleep quality (i.e., high aggregated MOS scores). We found that Eotaxin and MCP-1 were significantly upregulated, and IFN-g, IL-12, IL-2, and IL-5 were significantly downregulated ($p < 0.1$, using students t-test) in poor sleepers versus good sleepers at baseline. Compared to baseline levels we also found that HGF was significantly upregulated and BDNF, GM-CSF, IL-10, IL-5, IL-7, LIF, PlGF-1, RANTES, and TNF-a were significantly downregulated ($p < 0.1$, using students t-test) at follow-up in good sleepers and IL-6 and GRO-a were significantly downregulated ($p < 0.1$, using students t-test) in poor sleepers (Figure 2). We therefore selected these 17 proteins for further analysis in the entire patient cohort.

The 17 biomarkers exhibited great variation among the patients at baseline (Figure 3A). While the plasma levels measured in most patients were within (broad) 95% confidence intervals, a few patients exhibited levels significantly above or below these "reference" levels. Similarly, the scores given to the 12 MOS scale questions also varied greatly at baseline (Figure 3B) and some of the MOS scale scores exhibited dramatically increased or reduced values for a few of the patients compared to the 95% confidence intervals. This was particularly clear for the answers to question 3c related to having shortness of breath or headache when waking up in the morning. All patients, however, fit within the 95% confidence interval for the aggregated MOS score (Figure 3C). Furthermore, the aggregated MOS score did not differ significantly among different patient subgroups including patients with different cancer diagnoses, age at diagnoses or treatment regimen (Supplemental Figure 1), suggesting that the this is a more robust measure for sleep disruption in cancer patients compared to any of the questions in isolation.

We next investigated the relationship between the levels of the 17 investigated biomarkers and sleep quality as measured by the aggregated MOS score (Figures 3D–U). Plasma concentrations of these 17 biomarkers or CRP did not exhibit any obvious correlation to the sleep quality measured by the aggregated MOS score within this cohort, suggesting that both the regulation of these biomarkers as well as sleep physiology is complex in cancer patients and that sleep disruption cannot be accurately predicted by any single biomarker. Grouping the biomarkers into five families, and analyzing changes in aggregated plasma levels for entire families between different sleep quality patient groups using student t-test (Figure 4), we found that the factors within the pro-inflammatory, growth factor and chemokine families were significantly reduced ($p < 0.05$, $p < 0.05$, and $p < 0.01$, respectively) in the lowest sleep quality (aggregated MOS score > 30) compared to the highest sleep quality (aggregated MOS score < 21) groups. Chemokine biomarkers, furthermore, were significantly reduced ($p < 0.05$) in the entire population of poor sleepers (aggregated MOS score > 24) compared to good sleepers (aggregated MOS

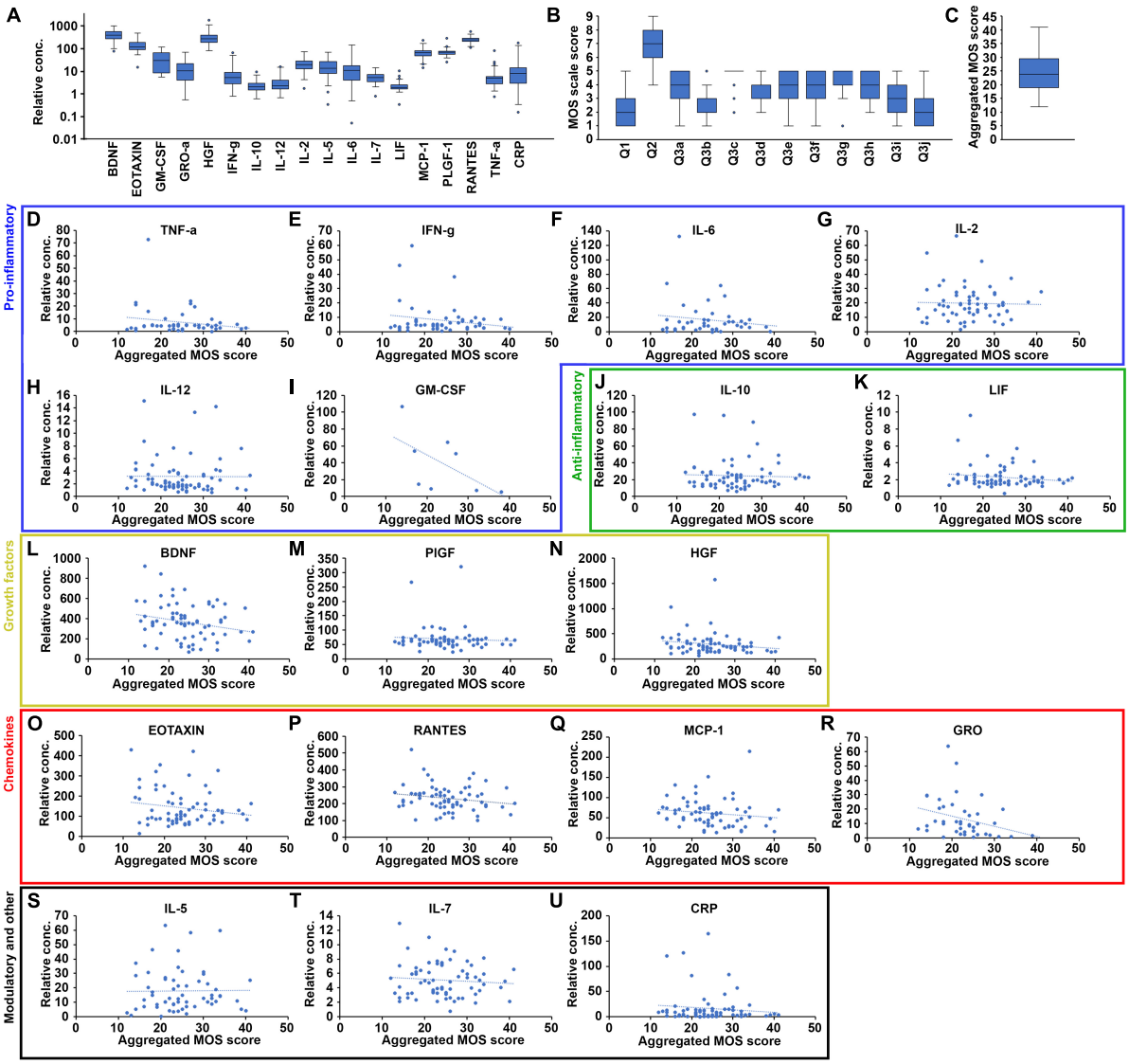

FIGURE 3
Correlation between cytokine biomarker plasma levels and sleep quality at baseline for some but not all of the 17 selected cytokines. **(A)** Quantification of the plasma levels of the 17 biomarkers for the fully evaluated patients at baseline, shown as a box-plot with the median values represented as a black lines, and the 95% confidence intervals contained within the error bars (n = 71). **(B)** Quantification of the range of scores given to each of the 12 questions included in the MOS sleep scale for the fully evaluated patients at baseline, shown as a box-plot with the median values represented as black lines and the 95% confidence intervals contained within the error bars (n = 71). **(C)** The range of aggregated MOS scores calculated form the answers to the 12 individual questions of the MOS sleep scale for the fully evaluated patients at baseline, shown as a box-plot with the median value represented as a black line and the 95% confidence interval contained within the error bars (n = 71). Plasma levels of each of the 17 selected biomarkers plotted against the aggregated MOS score of the same patient, for all fully evaluated patients at baseline. The biomarkers were organized into functional groups including pro-inflammatory (**D–I**, blue box), anti-inflammatory (**J,K**, green box), growth factors (**L–N**, yellow box), chemokines (**O–R**, red box), and immune-modulatory and other (**S–U**, black box) biomarkers. N = 71, blue dashed lines indicate linear regression curves for the sample population.

score < 25, Figures 4A–E). Aggregating all 17 biomarkers and CRP levels into a single value for each patient demonstrated that this panel of biomarkers were robustly reduced both for all poor sleepers (aggregated MOS score > 25) compared to good sleepers ($p < 0.01$) but even more so among those having the worst (aggregated MOS score > 31) compared to the best (aggregated MOS score < 20, $p < 0.001$, Figure 4F) sleep quality.

We next investigated if the biomarker levels in plasma were affected by the 3 months oncological treatment regimen. Interestingly, patients who slept well (aggregated MOS score < 24) after the medical treatment period now exhibited lower aggregated levels of growth factor and chemokine family biomarkers, as well as the global aggregation of all 17 biomarkers and CRP compared to baseline (Figures 4I,J,L). On the other

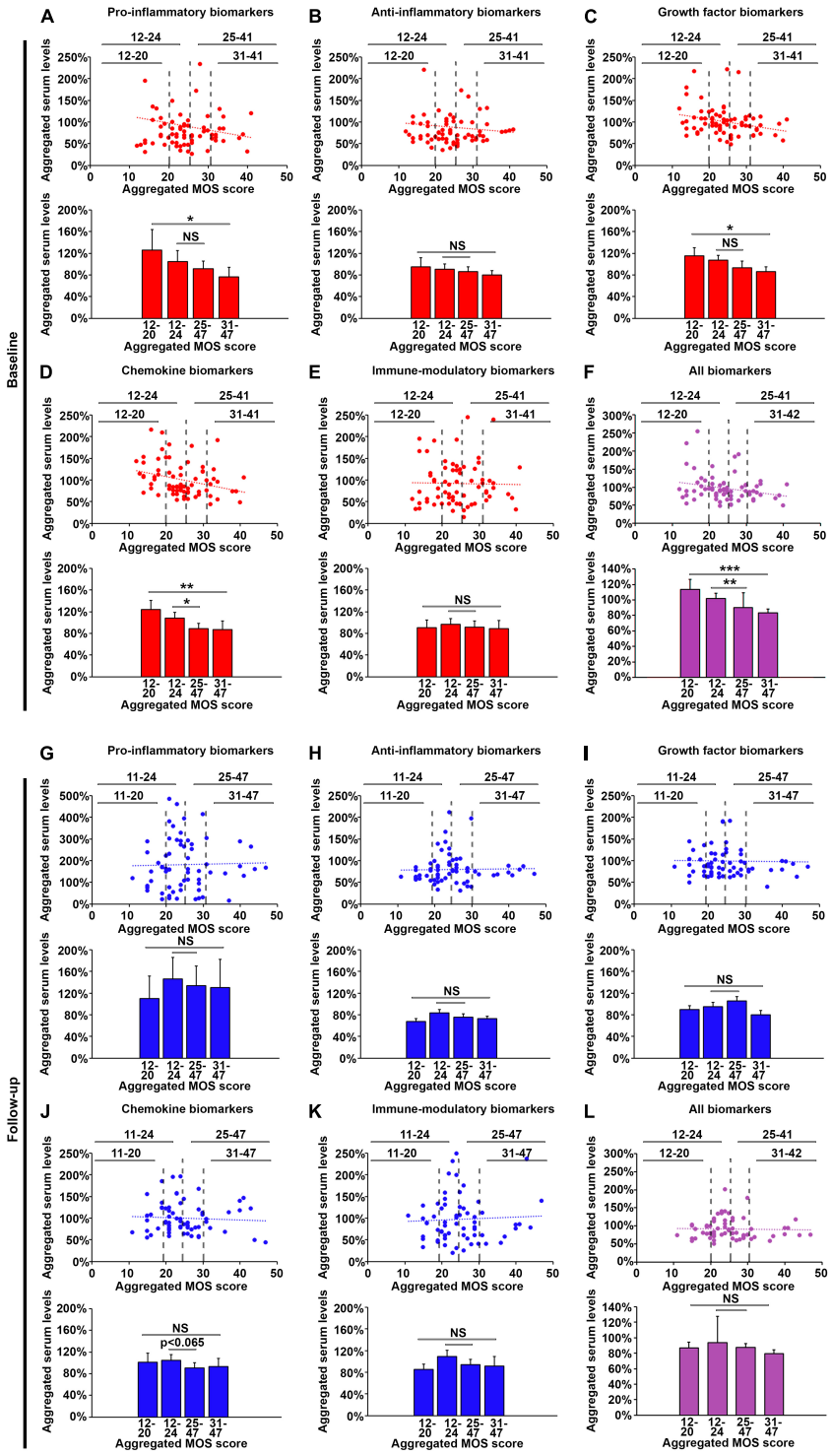

FIGURE 4
Pro-inflammatory, growth factor and chemokine biomarkers in the plasma are lowered in patients exhibiting poor sleep at baseline, but not at follow-up. Average levels of normalized plasma concentrations for biomarkers in each of the five categories pro-inflammatory biomarkers **(A,G)**, anti-inflammatory biomarkers **(B,H)**, growth factor biomarkers **(C,I)**, cytokine biomarkers **(D,J)** and immune-modulatory biomarkers **(E,K)**, as well as for all 17 biomarkers (purple graphs, **F,L**) at baseline (red graphs, **A–F**) and follow-up (blue graphs, **G–L**). The top graphs show the normalized, averaged levels of these biomarkers plotted against the aggregated MOS score for each patient, and the lower histographs show the averaged levels of these biomarkers for patients within four sleep quality groups: very good sleep (aggregated MOS score < 20), good sleep (aggregated MOS score < 24), poor sleep (aggregated MOS score > 25), and very poor sleep (aggregated MOS score > 31). $N = 71$. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, NS: non-significant.

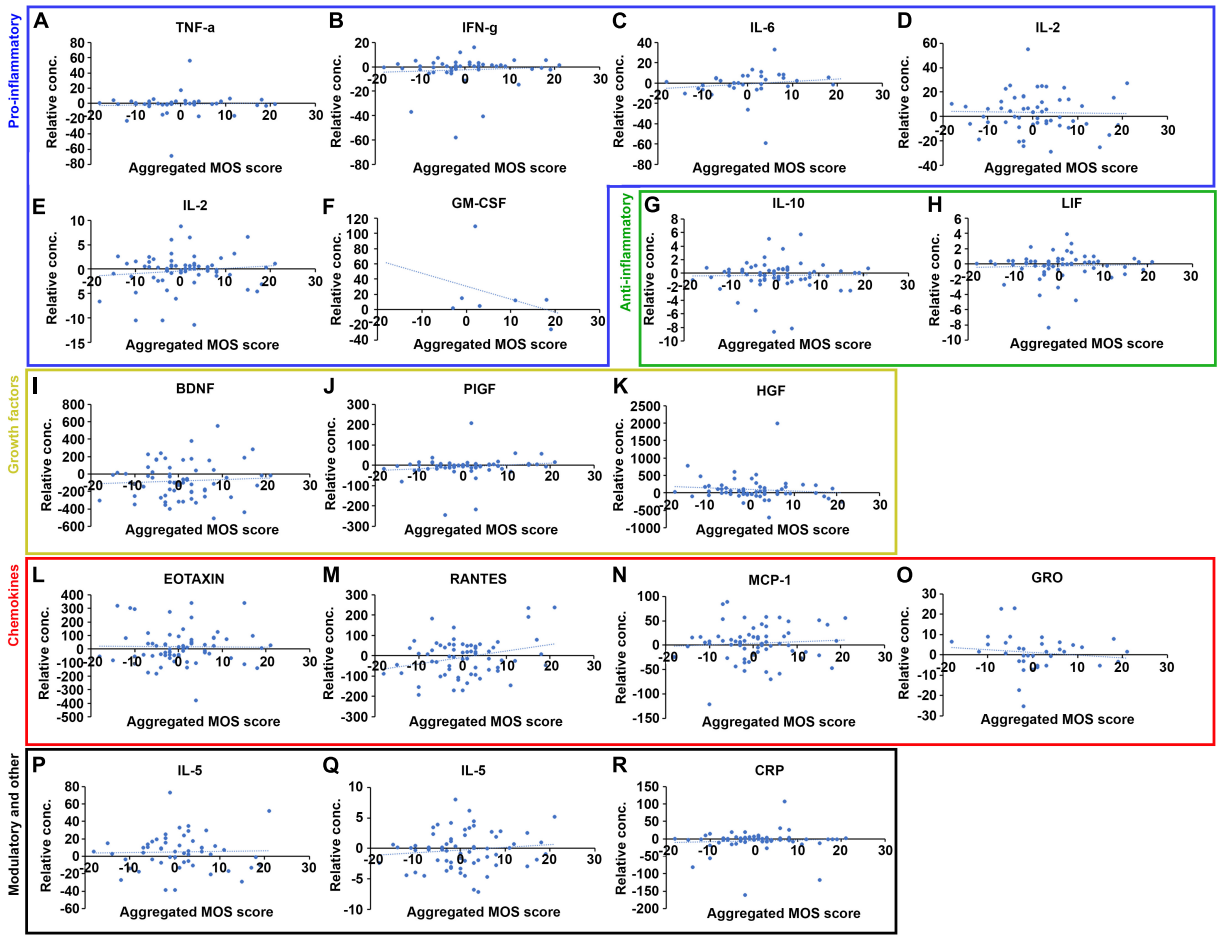

FIGURE 5
Correlation between changes in cytokine biomarker plasma levels and changes in sleep quality between baseline and follow-up for a few of the 17 selected cytokines. Changes in plasma levels plotted against changes in aggregated MOS score, calculated as the plasma level or MOS score at follow-up minus the plasma level/MOS score at baseline, for each of the 17 selected cytokines and organized into functional groups including pro-inflammatory (**A–F**, blue box), anti-inflammatory (**G–H**, green box), growth factors (**I–K**, yellow box), chemokines (**L–O**, red box) and immune-modulatory and other (**P–R**, black box) biomarkers. *N* = 71, blue dashed lines indicate linear regression curves for the sample population.

hand, pro-inflammatory biomarkers were elevated among poor sleepers at follow-up compared to baseline (Figure 4G) leading to none of the biomarker families being predictive of sleep quality in patients after 3 months of oncological treatment ($p > 0.05$ using students *t*-test, Figures 4G–L). These results highlight the complexity and dynamics of circulating biomarkers of sleep disruption during oncological treatment in cancer patients and suggest that commonly studied biomarkers such as sub-pathologically elevated CRP (detected by a high sensitivity test) or pro-inflammatory cytokines are not predictive for evaluating sleep disruption in cancer patients undergoing treatment.

To understand whether the oncological treatment caused the changes in biomarker levels, alternatively to what extent this may be coupled to a concurrent improvement or reduction in sleep quality, we investigated how the aggregated MOS scale values and biomarker plasma levels changed from baseline to follow-up for each individual patient. Whereas some biomarkers including TNF-a, IFN-g, PlGF, HGF, and CRP did not change for almost any of the patients (Figures 5A,B,J,K,R), many biomarkers were found to either increase or decrease dramatically in individual patients (Figures 5C–I,L–Q). The aggregated changes in plasma levels for the biomarker families demonstrated that all 17 biomarkers combined did not correlate to a improvement or deterioration in sleep quality (Figure 6A). However, the levels of pro-inflammatory biomarkers increased significantly ($p > 0.05$ analyzed using students *t*-test) in patients whose sleep quality deteriorated during treatment (change in aggregated MOS score > 0) compared to those whose sleep quality improved (change in aggregated MOS score < 0, Figure 6B). Taken together, these findings suggest that analyzing at the plasma levels of proinflammatory cytokines only after

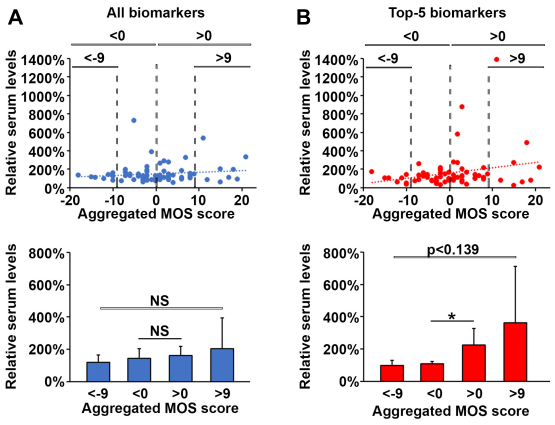

FIGURE 6
An increase in pro-inflammatory biomarkers is associated with loss of sleep quality during oncological treatment. Normalized changes in plasma levels of all 17 selected cytokines **(A)** or pro-inflammatory cytokines **(B)** with values lower than 100% indicating a reduction in cytokine levels at follow-up compared to baseline and plotted against changes in aggregated MOS scores with negative values indicating improved sleep quality whereas positive values indicate deteriorated sleep quality at follow-up compared to baseline. The lower histographs show the average normalized values for these cytokines among patients with very good sleep (aggregated MOS score < 20), good sleep (aggregated MOS score < 24), poor sleep (aggregated MOS score > 25), and very poor sleep (aggregated MOS score > 31). *N* = 71. **p* < 0.05, NS, non-significant.

an oncological treatment cycle will not allow identification of patients with good or poor sleep quality (Figure 4G) but measuring the change in the levels of these factors, however, might be highly indicative of experienced improvement in or deterioration of sleep quality.

Next, we hypothesized that the expression level of some of the investigated plasma proteins at baseline might be associated with increased risk of or protection from losing sleep quality during an oncological treatment cycle. However, only one cytokine, IL-5, exhibited significantly higher plasma concentrations ($p < 0.05$ using students *t*-test) at baseline in patients that dramatically gained sleep quality (change in aggregated MOS score < -9) during the 3 months treatment period (Figure 7). As none of the biomarkers were changed at baseline in the patients whose sleep quality deteriorated during treatment, it was not possible to establish a prognostic principle for predicting this adverse effect. We do, however, suggest that further studies investigate the potential role of IL-5 in protecting against oncological treatment-induced sleep deterioration.

Discussion

In this study we have evaluated the diagnostic value of 45 circulating biomarkers associated with immune function for identifying subjective sleep disruption in cancer patients. First, to improve and standardize the evaluation of sleep quality and -disruption in cancer patients, we developed a new framework for analysis of a popular sleep-instrument, the MOS sleep scale by a new aggregated MOS score, which is the first score based on this instrument that includes all of the 12 questions of the scale. This aggregated MOS score represents a single value related to the sleep quality of the patient which we propose allows a stronger, more robust and intuitive use of the MOS sleep scale compared to the various sub-scale scores that have been used in the past (Agrafiotis et al., 2022). We found that, at baseline, the mean of this aggregated MOS score was 24,4 and that patients with a score of 25 or higher (indicating poor sleep) exhibited significantly lower levels of 17 among the original 45 biomarkers analyzed, compared to those having an aggregated MOS score of 24 or lower (indicating good sleep). The differences were, however, higher for patients with more severe sleep disruption (aggregated MOS score of 31 or higher) compared to those with an aggregated MOS score of 20 or lower. Growth factor-, chemokine- and pro-inflammatory biomarkers were more strongly suppressed in patients with severe sleep disruption compared to anti-inflammatory and immune-modulatory biomarkers. This was, however, only seen at baseline, prior to initiation of oncological therapy. At the first follow-up examination, after 3 months of treatment, the correlation between sleep quality and plasma levels of all biomarkers analyzed were completely abrogated. In the case of the pro-inflammatory biomarkers, this abrogation was mainly due to a dramatic increase in the serum levels of these markers in patients reporting poor sleep quality, suggesting that therapy-induced inflammation is unabated if sleep quality is impaired. Indeed, plasma concentrations of pro-inflammatory biomarkers were found to increase several fold during oncological therapy but only in patients whose sleep quality concurrently deteriorated during this period. These findings are in line with previous studies showing that pro-inflammatory biomarkers such as IL-1b, IL-2, IL-6, IL-12, and TNF-a increase in cancer patients following a period of sleep disruption (Mantovani et al., 2008; Jensen et al., 2021; Tucker et al., 2021). Surprisingly, patients reporting improved sleep quality during oncological therapy exhibited reduced plasma levels of pro-inflammatory cytokines clearly demonstrating that sleep disruption rather than cytostatic or cytotoxic therapy is driving the increased systemic inflammation observed in these patients.

Previous studies aiming to identify biomarkers of sleep disruption in cancer patients have been designed to investigate relatively homogeneous patient cohorts. In such studies, survivors of childhood ALL exhibiting poor sleep were found to have elevated plasma levels of IL-6, IL1b and CRP (Cheung et al., 2017), and elevated IL-6 levels were correlated to poor sleep in non-small cell lung cancer patients receiving chemoradiotherapy (Wang et al., 2010). Tucker et al found that IL-2, IL-1b, and IL-6 were upregulated in cancer

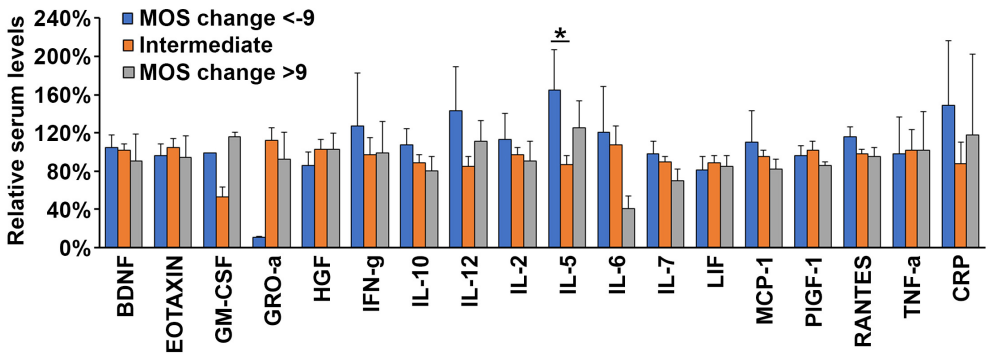

FIGURE 7
High serum levels of IL5 is associated with sleep improvement during oncological therapy. Average levels of normalized plasma concentrations of each of the 17 biomarkers selected for this study and CRP within groups of patients exhibiting a large gain in sleep quality (MOS change < -9, blue bars), an intermediate gain or loss of sleep quality (MOS change < ±9, orange bars) and a large loss of sleep quality (MOS change > 9, gray bars) after a round of oncological therapy. $N = 71$. *$p < 0.05$.

survivors exhibiting reduced sleep duration based on actigraph measurements, but not in patients with self-reported sleep disruption where instead IL-10 were found to be upregulated (Tucker et al., 2021). Here we took a different approach by keeping the inclusion criteria broad: All cancer patients with performance status 0 or 1, scheduled for oncological therapy were invited to participate regardless of age, gender, cancer type, tumor stage, type of planned oncological therapy, pre-treatment status, prior surgery, etc. Looking specifically at adjuvant versus palliative therapy, type of drugs selected for treatment and tumor types, we saw that these parameters did not influence the plasma levels of the biomarkers examined in this study. The heterogeneity of this cohort may, nevertheless, contribute to why no single biomarker was found to significantly correlate with sleep disruption in this study. As such, while other studies have found that IL-6, IL-1b, and CRP is significantly up-regulated in specific groups of cancer patients exhibiting poor sleep (Wang et al., 2010; Cheung et al., 2017), this/these biomarker(s) did not correlate significantly with sleep quality in our broader cohort. Taking an OMICs-like approach, we instead identified functional panels of biomarkers that combined were robustly correlated to sleep disruption even in our broad patient cohort. In particular the pro-inflammatory markers TNF-a, IFN-g, IL-6, IL-12, IL-2, and GM-CSF constituted one such pro-inflammatory panel that could predict both sleep disruption at baseline (in patients expressing below-average levels of these biomarkers) as well as deteriorating sleep quality during treatment. Some of the factors analyzed in this study may have several, context-dependent functions. GM-CSF, for example, in addition to being a pro-inflammatory cytokine, also has both chemokine and growth factor properties as this factor is used to mobilize and expand hematopoietic stem cells from the bone-marrow in cancer patients during chemotherapy (Siena et al., 1989). The chosen classification for the factors analyzed in this study therefore reflects how these factors are described by the bulk of the literature. Some of the factors found in the pro-inflammatory cytokines panel are well known biomarkers of circadian and sleep disruption (TNF-a and IL-6, see above), whereas the others have not previously been coupled to sleep disruption in cancer patients (e.g., GM-CSF).

A cancer diagnosis may, by itself, cause sleep disruptions as the incidence of sleep disruption is on average three times higher among cancer patients compared to the general population, with breast cancer patients being at particularly high risk (Palesh et al., 2010; Yennurajalingam et al., 2018). In our study we found that the subsequent oncological treatment did not further affect the extent of sleep disruption, within the study population in general, with the possible exception of patients treated with taxanes, which seemed to further deteriorate their sleep quality compared to other types of treatment. Furthermore, sleep disruption may persist long into survivorship, even months or years after completed treatment (Otte et al., 2009). While individual patients may improve or further disrupt their sleep quality following treatment, these findings strengthen the view that medical therapy does not impact the sleep quality of cancer patients in general.

A weakness of this study is the relatively small size of the study cohort, especially considering the broad inclusion criteria. As a likely consequence of this, we did not find single factors that correlated with poor sleep quality at baseline or a loss of sleep quality during oncological therapy. The broad inclusion criteria could, however, also be seen as a strength as our finding that (small) panels of inflammatory biomarkers exhibit robust correlation with sleep disruption across diagnoses and treatment regimens, are likely more generalizable within cancer care. While we included patients with a variety of malignancies, it should be noted that colorectal cancer patients were somewhat overrepresented (47%) in this patient cohort. Indeed, among the cancers with high incidence in Sweden, colorectal cancer is commonly treated aggressively using chemotherapeutic agents,

which is not as common in for example prostate or breast cancer patients, which could explain why such patients were favored for inclusion in this study. Furthermore, both the oncology infrastructure at the study site and differences in the motivation and workload among patient-recruiting nurses within different specialities may also play a role in determining the distribution of patients across different diagnoses in this study. Other studies looking at sleep disruption in cancer patients and correlating this to effects of treatments have similar cohort sizes to that of the present study (Innominato et al., 2012; Jensen et al., 2021), but are focusing on more defined patient populations. Innominato et al. (2012), for example, studied circadian disruption using Actigraph accelerometers worn on the wrist for 3 days and found that sleep disruption in 77 patients with metastatic colorectal cancer undergoing medical treatment with 5-FU, Oxaliplatin and/or Leucovorin had significantly shortened survival compared to those with non-disrupted sleep (Innominato et al., 2012). Similarly, Cash et al reported significantly shorter overall survival among patients exhibiting disrupted activity/rest rhythms in a cohort of 55 head and neck cancer patients undergoing chemoradiation therapy (Cash et al., 2018). None of these studies, however, investigated circulating biomarkers or inflammatory profiles in the patients. In a meta-analysis on sleep disruption in patients with different types of CNS cancer, a particularly complex patient group in this context as their sleep physiology may also be directly affected by their disease or treatment, 24 of the 25 studies included between 1 and 115 patients (20 patients per study on average) (Gapstur et al., 2009). While our study should still be seen as a pilot study, it does in this context have a relatively high power. The potential of the suggested panel of six pro-inflammatory biomarkers as a tool for diagnosing sleep disruption in cancer patients both before and after oncological treatment initiation, however, needs to be validated in larger studies in the future.

TABLE 1 Demographic data.

Parameter	*n* = (%)
Age (min–max)	31–82
Female	28 (37)
Male	47 (63)
ECOG Performance Status*	
0	46 (63)
1	29 (37)
Alcohol consumption	
No	23 (30)
Yes	52 (70)
Nausea experience before treatment	
Pregnancy nausea (only female)	8 (11)
Travel nausea	7 (9)
No nausea at all	60 (80)
Occupation	
Retired	49 (65)
Worker	25 (33)
Unemployed	1 (2)
Civil State	
Married/Partner	64 (85)
Single	10 (13)
Widower	1 (2)
Smoking	
No	65 (87)
Yes	10 (13)
BMI	
Min	19
Max	43
Average	26
Tumor classification	
Gastrointestinal cancer (colorectal, pancreas, liver, esophageal)	50
Urotelial cancer (Bladder, prostate)	11
Breast cancer	11
Brain tumor	1
Tonsillar cancer	1
Cancer of unknown primary	1
Comorbidity	
Hypertension	9
Diabetes	8
Hypothyreosis	1
Hypercholesterolemia	1
Rheumatoid arthritis	1
Chronic obstructive pulmonary disease including Asthma	4
Depression	1

*ECOG, Eastern Cooperative Oncology Group.

Conclusion

In conclusion, in this study we found that while 17 of 45 small plasma proteins studied were individually de-regulated in poor compared to good sleepers in a small sub-cohort of 17 cancer patients, this could not be reproduced in a larger cohort of 71 patients. However, combining factors with a similar mode of action into panels of biomarkers and deriving an aggregated measure of how such panels were deregulated allowed identification of a panel of six pro-inflammatory biomarkers exhibiting high accuracy and robustness for predicting sleep disruption following a 3-month oncological therapy cycle in the complete, broad cohort of cancer patients independent of diagnosis, age or therapy. This is the first-time plasma protein biomarkers have found to correlate with sleep disruption during treatment in such a broad cohort of cancer patients. Furthermore, changes in these pro-inflammatory biomarkers could in this study be un-coupled from therapy-induced inflammation and were found to be completely dependent on changes in sleep quality after

3 months of treatment. This interesting finding warrants further mechanistic studies in the future.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethical Review Board in Linköping, Sweden (2016/379-31). The patients/participants provided their written informed consent to participate in this study.

Author contributions

DO, B-ÅA, FL, and LJ designed the study, analyzed data, and wrote the manuscript. DO conducted clinical examinations, recruited patients, and performed follow-up analysis of patient journals. B-ÅA performed laboratory experiments and preliminary data analysis. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2022.945784/full#supplementary-material

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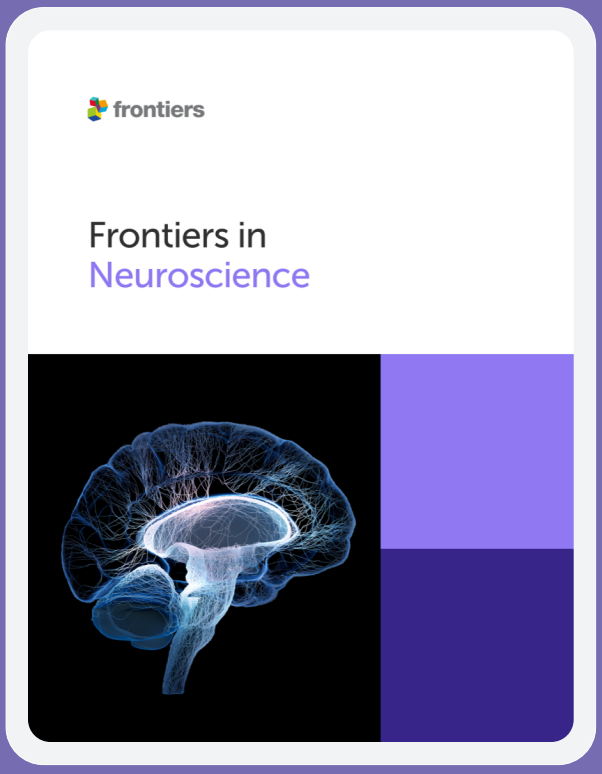

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