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ORIGINAL ARTICLE

Associating sleep problems with advanced cancer diagnosis, and immune checkpoint treatment outcomes: a pilot study

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Abstract

Background Sleep problems (SP) are common in cancer patients but have not been previously assessed in patients receiving immune checkpoint inhibitors (ICI).

Methods We collected questionnaire data on sleep apnea risk, insomnia, and general sleep patterns. We used an adjusted multivariate Poisson regression to calculate prevalence ratios (PRs) and associated 95% confidence intervals (CIs) for associations between these SP and metastatic versus localized cancer stage (M1 vs. M0), and adjusted logistic regression models to calculate ORs for associations between SP with the number of ICI infusions completed (6 + vs. < 6).

Results Among 32 patients who received ICI treatment, the prevalence of low, intermediate, and high-risk OSA risk was 36%, 42%, and 21%, respectively. Overall, 58% of participants reported clinically significant insomnia. We did not find a significant association between intermediate or high risk OSA (vs. low risk) and metastatic cancer status (*PR* = 1.01 (95% *CI*: 0.28, 3.67)). Patients in the cohort who reported taking > 15 min to fall asleep were 3.6 times more likely to be diagnosed with metastatic cancer compared to those reporting shorter sleep latency (95% *CI* (1.74, 7.35)). We did not find a significant association between SP and number of ICI infusions completed.

Conclusion Our data associating sleep apnea risk, insomnia, and sleep patterns with more advanced cancer encourages further exploration in larger-scale observational studies and suggests interventional clinical trials focused on sleep quality improvement that could result in better outcomes for these patients.

Keywords Obstructive sleep apnea risk · Immune checkpoint inhibitors · Metastatic cancer · Circadian rhythm

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Introduction

Sleep problems are a prominent concern of cancer patients. Disturbed sleep is reported by 45–80% of cancer patients, compared to 29–32% of the general population [1]. Sleep problems result from sleep disorders (e.g., sleep-disordered breathing (obstructive sleep apnea (OSA), central sleep apnea, upper airway resistance syndrome), insomnia, narcolepsy), poor sleep quality (e.g., non-restorative sleep, sleep fragmentation), improper sleep timing, irregularity (e.g., constant variation in bedtimes and wake times, frequent random nap episodes), or a non-ideal sleep duration. [2]

Cancer therapy and cancer-related anxiety/stress can cause sleep problems [3, 4] and/or reflect previously established carcinogenic roles of sleep problems themselves [5–7] (Fig. 1). The carcinogenic effects of sleep problems could be due to induced intermittent hypoxia (IH, a hallmark of

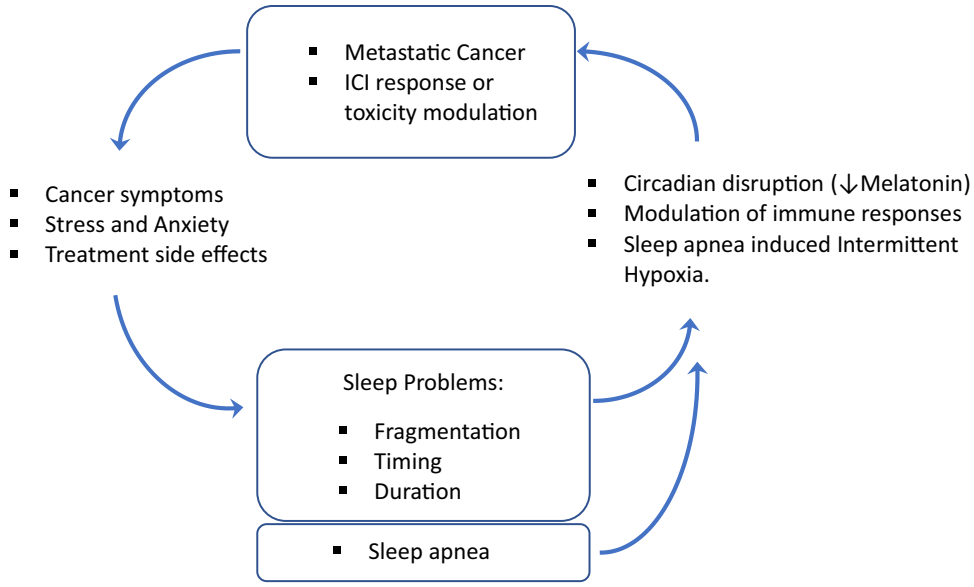

Fig. 1 Conceptual model linking sleep problems to tumor aggressiveness, cancer symptoms, and side effects, and Immune Checkpoint Inhibitor (ICI) outcomes

OSA) [8, 9] and adverse downstream consequences of sleep fragmentation and disruption to the 24-h circadian rhythm [10, 11]. Mouse models of melanoma and kidney cancers show enhanced tumor growth, invasiveness, and metastasis associated with IH [8, 9]. In addition, disruption to normal circadian rhythms increases inflammation and reduces melatonin hormone production, which in both instances promotes cellular damage [10, 11].

Increasing evidence shows higher tumor-related T-cell levels improve prognosis for many types of cancer [12, 13]. Existing and emerging immunotherapies are harnessing this T-cell response to successfully treat several forms of cancer (e.g., melanoma, renal cell carcinoma (RCC), and non-small cell lung cancer (NSCLC)) by inhibiting immune-suppressive proteins such as programmed cell death-1 receptor (PD-1), its ligand PD-L1 (PD-1/PD-L1), and cytotoxic T lymphocyte antigen 4 (CTLA-4) [14, 15]. As a result, the US Food and Drug Administration (FDA) has approved seven immune checkpoint inhibitors (ICI) that target CTLA-4 (ipilimumab), PD-1 (nivolumab, pembrolizumab, and cemiplimab), or PD-L1 (atezolizumab, avelumab, and durvalumab) for the treatment of cancer [16]. Despite the promise of ICI, patient response is not uniformly favorable. Thus, a better understanding of factors predictive of ICI response is needed. [17].

ICIs are increasingly prescribed for late-stage cancer patients. In this context, the oncology field may benefit from new insights into the impact of circadian rhythms (and/or "circadian rhythm disruption") and sleep problems on immune response and cancer aggressiveness in this patient population. Despite the numerous studies of sleep problems in the context of other cancer treatments (e.g., chemotherapy) [18, 19], to date, there have been no studies correlating sleep problems with metastatic versus localized disease or outcomes in cancer patients receiving ICI therapy [17]. We report here outcomes from The Lifestyle Attributes and Sleep in Immunotherapy Response (LASIR) study describing the burden of sleep problems, its relation to the presence of metastases at diagnosis, and its impact on ICI tolerability in cancer patients previously unexposed to ICI therapy.

Methods

Setting

The LASIR study was conducted at the Seattle Cancer Care Alliance (SCCA). The SCCA is the clinical practice site for the Cancer Consortium formed by partnership of the Fred Hutchinson Cancer Research Center, the University of Washington, and Seattle Children's Hospital. The SCCA is the only national cancer institute–designated comprehensive cancer center serving the five states Washington, Wyoming, Alaska, Montana, and Idaho region [20]. Based on current clinical practice, which stipulates ICI use for first or second line therapies for advanced kidney cancer [21] and for some with metastatic melanoma and lung cancers [22], the vast majority of study participants had advanced-stage disease (stage III/IV) at ICI initiation.

Participant recruitment

Patients were study eligible if they were (1) an adult initiating outpatient treatment with a commercial ICI agent for the first time at the SCCA renal cell carcinoma/melanoma (Ren/Mel) or thoracic/head and neck cancer (THN) clinics, (2) aged between 18 and 84 years, (3) able to provide informed consent, and (4) able to complete the questionnaire

in English. Patient recruitment began in April 2019 and was discontinued due to the COVID-19 global pandemic in mid-March 2020. Of the 63 eligible patients approached for participation, 33 (52%) enrolled in the study (Fig. 2). Patients received ICI treatment in either the adjuvant (melanoma) or metastatic setting (melanoma, RCC or NSCLC).

Data collection and definitions

Data was collected from study participants via three sources. A patient questionnaire was self-administered at the time of enrollment; for majority (85%) of participants, this questionnaire was completed on the day of ICI treatment initiation (min–max time was 0–28 days before initiation). The SleepScore Max device was activated within 5 days of ICI treatment initiation for participants who engaged in this optional component of the data collection. Electronic medical record abstraction occurred at 6 months post ICI treatment initiation.

The study questionnaire was self-administered at the time of study enrollment and included an assessment of OSA risk, insomnia, and general sleep patterns. In particular, the sleep data for the primary analysis was a self-reported 8-item–validated *STOP-BANG* questionnaire for the assessment of OSA risk with scores ranging from 0 to 8; scores were categorized into low risk (0–2), intermediate risk (3–4), and high risk (5–8) of OSA according to the questionnaire guidelines. Details of the *STOP-BANG* questionnaire content are described elsewhere [23]. Sleep data for secondary analyses included the 5-item Women's Health Initiative Insomnia Rating scale (*WHIIRS*), which addresses sleep onset and sleep maintenance insomnia, early morning awakenings, and sleep quality [24]. Although the questionnaire was initially developed and validated in women, it has widespread use in sleep research in populations of men and women [25]. The *WHIIRS* requires individuals to rate the quality of their sleep and the frequency with which they experience certain sleep problems in the last month with scores ranging from 0 to 20 in increasing order of insomnia symptoms; a score > 9 was considered clinically significant. Details of the WHIIRS are described elsewhere [26]. Other self-reported sleep data included history of OSA diagnosis and chronotype. Chronotype was classified according to a participant's subjective rating of when they perform best in a 24-h day [26]. A person's chronotype should align with their circadian rhythm under natural circumstances, but because of our societal expectations (such as work and school schedules), sometimes this is not the case. In order to limit the participation burden of cancer patients enrolled in our study, we restricted our questioning on chronotype to a single item from the MEQ questionnaire: [27].

> One often hears about "morning" and "evening" types of people. Which one of these types do you consider yourself to be? Options: 1) Definitely a morning type 2) More a morning than an evening type 3) More an evening than a morning type 4) Definitely an evening type.

We also collected data on sleep latency categorized into 15 + min vs. < 15 min based on the distribution of the responses. Finally, we assessed typical sleep duration and categorized into < 6 or > 9 vs. 7–8 h [28].

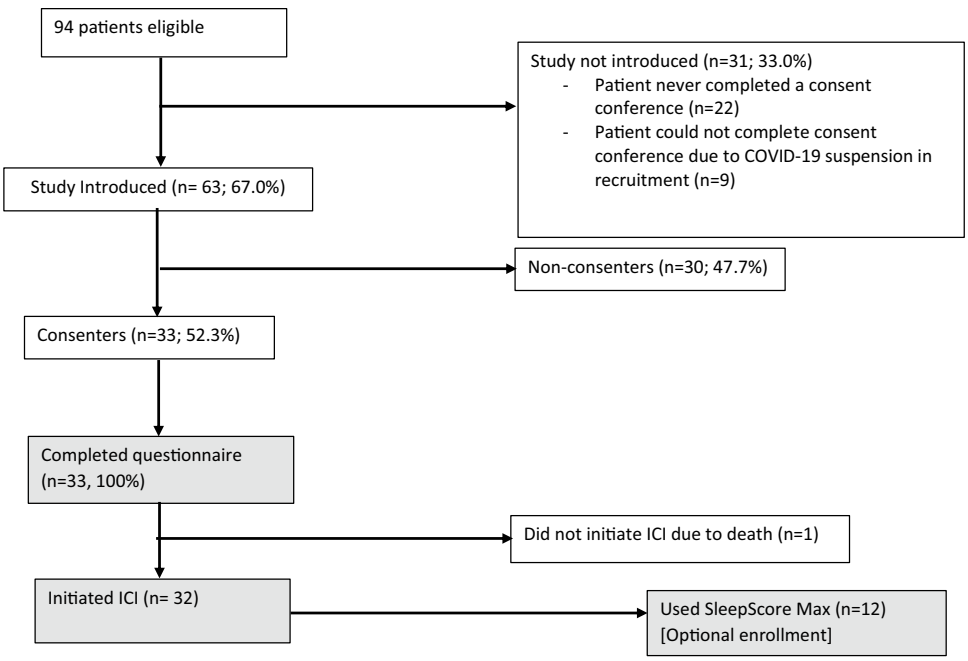

Fig. 2 LASIR study recruitment and retention

With regard to additional relevant lifestyle and patient attribute data collected in the questionnaire, we collected information on smoking status (current, former, or never smoking), marital status (married or domestic partnered vs. single, separated, divorced, or widowed), and education level (less than college (including < 8th grade, some high school, high school diploma/GED, some college or technical degree or certificate), college degree, graduate/professional degree). Participants also reported perceived stress based on 4-item perceived stress scale (PSS) indicating the magnitude of lifestyle challenges and stress management abilities during the previous months (scored as high (8–16) or low (0–7)) [29]. Participants also reported previous diagnoses of hypertension, diabetes, and high cholesterol and treatment status for these conditions to describe their baseline comorbidities.

The optional SleepScore Max [30] (SleepScore Labs, Carlsbad, CA) bedside sleep monitoring device was used to measure nighttime sleep patterns for a maximum of 30 days post ICI initiation in a subset of consented participants ($n = 12$). The Sleepscore Max is a non-contact sleep sensor which uses a smartphone app and web-based app to record sleep patterns [30]. Specifically, it uses smartphone speaker capabilities to track and measure breathing rate and body movement, to provide an in-depth analysis of sleep, including chest and abdominal respiratory movement, and to measure key sleep attributes [30]. The non-contact device has been validated in several studies: it combines high sensitivity to wake (73.1%) with high sensitivity to sleep (93.8%) making it a highly accurate non-contact, non-polysomnography (PSG) sleep measurements device [31–33]. The device recorded data on total night sleep time, sleep onset latency, wake after sleep onset, number of awakenings, sleep architecture (deep, light, and rapid eye-movement (REM) sleep), and overall sleep quality (sleep score ranging from 0 to 100, with a higher score indicating better sleep quality).

Electronic health records (EHR) data was collected 6 months post ICI initiation. Extracted EHR data included age, gender, weight, and height on the date corresponding to the patient's last visit at SCCA prior to or at ICI initiation. Body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared and grouped into three categories: < 25 kg/m^2, 25–29 kg/m^2, and ≥ 30 kg/m^2. We extracted information pertaining to cancer diagnosis date, tumor attributes at diagnosis, and prior cancer treatments (chemotherapy, radiotherapy, surgery, and other treatment regimens). Tumor attributes included M-stage and summary stage (I–IV) at diagnosis. We extracted dates of the first six, and last ICI infusions along with the type of each ICI initiated, and ICI adverse event incidence within the first 6 months of ICI initiation. We extracted participant vital status (death status, cause of death, and date of death) within the first 6 months of ICI initiation.

Main outcome definitions

Metastatic cancer status was defined by M-stage (M0 vs. M1). ICI tolerance was defined in close consultation with experienced SCCA oncologists. Six or more infusions of the same immunotherapy treatment regimen were considered to represent both ICI tolerability and treatment benefit within the 6-month assessment period. Within the included clinics at the SCCA, most immunotherapy treatments for advanced disease are given for 3–4 infusions (depending on the exact medication, dose, and schedule) prior to imaging-based disease response assessment (typically CT or PET scans). Thus, receipt of the same medication for 6 + cycles suggests some clinical benefit (typically either stable or decreasing cancer burden) as, in the absence of benefit, patients would likely have switched to a different treatment regimen.

Statistical analysis

All analytical procedures were conducted using Stata 14.0 (College Station, Texas) [34], with statistical significance considered at a 2-sided alpha value of 0.05. In descriptive analyses, we examined the distribution of participants' overall baseline characteristics and stratified by OSA risk (low vs. intermediate/high). We ran a multivariate Poisson regression with robust standard errors (SEs) to assess the association between sleep problems and metastatic tumor status at diagnosis (M-stage (M0 vs. M1)), adjusting for age, gender, and BMI. We opted to use a Poisson model instead of a logistic model due to sleep problems being common in cancer populations and the high prevalence of advanced disease in cancer patients initiating ICI. We used robust SEs in the Poisson model to account for any violation of the distribution assumption that the variance equals the mean. We reported the prevalence ratio (PR) and associated 95% *CI* for associations.

We used logistic regression models to calculate odds ratios (ORs) to assess the associations of OSA and insomnia risk, chronotype, and sleep latency with the number of ICI infusions (6 + vs. < 6), adjusting for the following selected attributes: male gender, age at ICI treatment, and prior cancer treatment.

We analyzed the supplementary SleepScore Max data by averaging the sleep attributes measured over a max of 30 days to report a single summary estimate across the 12 participants (Supplemental Table 1). We also plotted the daily average of the sleep attribute values (Supplemental Fig. 1).

Results

Patient characteristics

The mean age of the cohort was 61 years, 61% were male, 85% were white, 64% were partnered, 70% had a college

degree, 49% had BMI greater than 30 kg/m^2, and 3% were current smokers. Patients with intermediate or high risk OSA were, on average, older and had (1) fewer years of education, (2) high stress levels, and (3) higher prevalence of diabetes, high cholesterol, and high blood pressure (Table 1).

Tumor attributes

The most common cancer site was melanoma (52%). Seventy three percent were diagnosed with a late-stage disease (III/IV), and 42% with a metastatic disease. The majority of patients had had cancer treatment prior to ICI initiation (64%), of whom 66.7% had surgery, 23.8% were treated with chemotherapy, and 19% with radiotherapy (Table 2).

ICI treatment attributes

The majority of patients initiated a PD-1 blockade (94%), 16% initiated ICI with chemotherapy, and 72% had six or more ICI infusions within a 6-month period. Median time (IQR) from cancer diagnosis to ICI treatment initiation was 0.4 (0.2, 2.3) years. Participants reported, on average, three adverse events post ICI initiation. The most common incident adverse events were rash and vitiligo (47%), general body pain (39%), hypothyroidism (25%), and severe diarrhea (22%). Thirteen percent of enrolled participants died within the 6-month follow-up period. The average time from cancer diagnosis to death and from ICI initiation to death was 13 months and 2 months, respectively (Table 3).

Prevalence of sleep problems

The prevalence of OSA symptoms was 21% for daytime sleepiness, 33% for observed apnea, and 21% for snoring; 51% reported none of these three symptoms. Among those with sleep apnea symptoms, the prevalence of low, intermediate, and high OSA risk was 36%, 42%, and 21%, respectively. The prevalence of a self-reported OSA diagnosis at

Table 1 Selected baseline characteristics overall and according to OSA risk in the LASIR cohort, $n=33$

	Total ($n=33$)	Sleep apnea risk	
		Low ($n=12$)	Intermediate/high ($n=21$)
Mean age at enrollment (SD)	61.1 (13.4)	58.4 (13.9)	62.5 (13.1)
Males	60.6	16.7	85.7
Married, domestic partnered	63.6	50.0	71.4
Education			
< college	30.3	25.0	33.3
College degree	45.5	66.7	33.3
Grad or professional deg	24.2	8.3	33.3
White	84.8	83.3	84.7
Hispanic	3.3	0	4.8
Smoking at cancer diagnosis			
Current	3.3	0	4.8
Former	45.5	33.3	52.4
Never	51.5	66.7	42.9
BMI at cancer dx kg/m2 mean (SD)	30.9 (8.1)	29.8 (11.4)	31.4 (5.7)
< 25	21.2	41.7	9.5
25–29	30.3	16.7	38.1
30 +	48.5	41.7	52.4
Perceived stress			
Median (IQR)	5.0 (3.0, 6.0)	5.0 (2.5, 6.0)	6.0 (3.0, 7.0)
Low stress (< 8)	81.8	83.3	81
High stress (8–16)	18.2	16.7	19.1
Self-reported disease history/ medication			
High blood pressure/ hypertension medications	48.5	25.0	61.9
High cholesterol/cholesterol medications	39.4	25.0	47.6
Diabetes/treated diabetes	9.1	0.0	14.3

Categorical variables are in percentages, continuous measures in mean (*SD* standard deviation) or median (*IQR* inter quartile range), *% may not sum to 100% due to missing data or rounding

Table 2 Selected baseline cancer attributes in the LASIR cohort, $n=33$

	Total ($n=33$)
Cancer site	
Melanoma	51.5
Squamous cell carcinoma	6.1
Renal cell carcinoma	21.2
Lung	21.2
Cancer summary stage at diagnosis	
I	9.1
II	9.1
III	33.3
IV	39.4
Cancer treatment prior to ICI	63.6
Chemotherapy	23.8
Radiotherapy	19.1
Surgery	66.7
Gene therapy	15.3

*% may not sum to 100% due to missing data or rounding. *SD* standard deviation

enrollment was 18%. The prevalence of low, intermediate, and high OSA risk among those who self-reported an OSA diagnosis was 33%, 17%, and 50%, respectively.

Table 3 Distribution of ICI attributes in the LASIR cohort, $N=32$*

	Total ($n=32$)
ICI initiated	
Cemiplimab (PD-1)	6.3
Ipilimumab (CTLA-4)	6.3
Nivolumab (PD-1)	43.8
Pembrolizumab (PD-1)	43.8
ICI initiated with chemo	16.1
Years from cancer dx to ICI, median (IQR)	0.4 (0.2, 2.3)
Total ICI initiation mean (SD)	6.8 (3.6)
% < 6 infusions	28.2
% 6 + infusions	71.9
Time between 1st and last infusion, months (SD)	4.00 (2.08)
% Incidence of common adverse events	
Rash and Vitiligo	46.9
General body pain	39.3
Hypothyroidism	25.0
Severe diarrhea	22.0
Total events, mean (SD)	3.3 (2.5)
Vital status	
% Death *	12.5
Time from cancer dx to death, months mean (SD)	13.2 (7.7, 39.8)
Time from ICI to death, months mean (SD)	2.1 (1.32, 5.2)

SD standard deviation; *1 patient died without getting immune checkpoint inhibitor (ICI)

Of the secondary sleep problems considered, 58% of participants reported clinically significant insomnia, 72% experienced average or restless sleep, 30% reported taking 15 min or longer to fall asleep, 44% had non-ideal night sleep. Thirty six percent of participants reported an evening chronotype (Table 4).

The SleepScore Max data is summarized in Supplemental Fig. 1 and Supplemental Table 1. In this small sample, there was little evidence of changes in within-person sleep patterns over the 30-day period post ICI initiation. Overall, the mean nighttime total sleep duration was 6 h, mean latency was 19 min, and mean number of wake times was five. Participants had an average of 4 h of light and 1 h of deep and REM sleep. The overall sleep quality measured by the Sleepscore Max devices was 80%.

Association between sleep problems and metastatic cancer

Table 4 presents PRs and 95% *CI*s for associations between sleep problems and metastatic cancer at diagnosis. We did not find a significant association between intermediate or high risk OSA and metastatic cancer compared to low risk OSA (1.01 (0.28, 3.67)); similarly, metastatic status was not associated with continuous STOP-BANG scores for OSA risk (1.15 (0.74, 1.77)).

Of the secondary sleep attributes considered, patients reporting 15 min or more to fall asleep were 3.6 times more likely to have been diagnosed with metastatic cancer compared to those reporting shorter sleep latency (95% *CI* (1.74, 7.35)). Additionally, patients reporting an evening chronotype were more likely to have been diagnosed with metastatic cancer compared to those reporting morning chronotypes (4.36 (1.73, 11.00)).

Association between sleep problems and ICI treatment tolerance

Table 5 presents HRs and 95% *CI*s for associations between sleep problems and the number of ICI infusions as a measurement of ICI treatment tolerance. We did not find any significant association between intermediate or high risk OSA and six or more infusions compared to low risk OSA (0.27 (0.02, 3.41)) and between continuous OSA risk scores and six or more infusions (0.72 (0.37, 1.40)). Similarly, we found no significant association between insomnia and six or more infusions (0.23 (0.03, 1.60)) and between insomnia total scores and six or more infusions (0.77 (0.59, 1.02)). Additionally, we did not find any significant association between evening chronotype and six or more infusions compared to morning chronotype (0.57 (0.11, 2.97)) and patients reporting 15 min or more to fall asleep compared to those reporting shorter sleep latency (0.51 (0.07, 3.53)).

Table 4 Prevalence ratios (PRs) for tumor aggressiveness comparing across sleep problem groups in the LASIR cohort, $N=33$

	Summary*	Diagnosis M-stage [M0 ($n=19$) vs M1 ($n=14$)]	
		PR (95% *CI*)	*p*-values
Primary sleep problems			
Sleep apnea risk (0–8)			
Total score (1-unit increment)	3.2 (1.7)	1.15 (0.74, 1.77)	0.533
Intermediate risk (3–4)/high risk (5–8)	42.4/21.2	1.01 (0.28, 3.67)	0.990
Low risk (0–2) (ref)	36.4	1	
Secondary sleep problems			
Insomnia risk (0–20)			
Total score (1-unit increment)	9.5 (4.3)	1.08 (0.97, 1.20)	0.147
Clinically significant insomnia (9 +)	57.6	1.24 (0.49, 3.14)	0.649
Not clinically significant (< 9) (ref)	42.4	1	
Sleep latency, min			
15 +	30.3	3.58 (1.74, 7.35)	0.001
0–14 (ref)	69.7	1	
Total sleep duration, *h*			
< = 6 or 9 +	54.6	0.70 (0.25, 1.93)	0.489
7–8 (ref)	45.5	1	
Chronotype			
Evening	36.4	4.36 (1.73, 11.00)	0.002
Morning (ref)	63.6	1	
Overall sleep quality			
Restless	33.3	2.25 (0.51, 9.91)	0.285
Average	39.4	1.31 (0.40, 4.28)	0.659
Sound (ref)	27.3	1	

M-stage metastatic cancer stage. Adjusted for age, male, and body mass index. *Summary: categorical variable in %; continuous variables in mean (SD). *% may not sum up to 100% due to missing data or rounding

Discussion

This study is the first to examine sleep patterns in cancer patients receiving ICI therapy. Our study also assessed objective sleep patterns over time in cancer patients post ICI treatment initiation, which, to our knowledge, has not been done before. We found a high burden of sleep problems prior to ICI treatment initiation in this cohort. In particular, two-thirds of enrolled participants had intermediate to high sleep apnea risk and an average/restless night sleep, more than half experienced clinically significant insomnia, and about a third reported taking 15 min or longer to fall asleep and evening chronotype. We also observed that objective sleep patterns remained mostly consistent over time in a subset of participants assessed, suggesting that sleep information collected at study baseline remains indicative of sleep patterns through, at least, early stages of the treatment period. In a multivariable-adjusted regression analysis, we did not find a statistically significant association between intermediate or high risk OSA and metastatic cancer compared to low risk OSA. However, of the secondary sleep problems assessed, patients who reported taking longer to fall asleep were more likely to have been diagnosed with metastatic cancer compared to those reporting shorter sleep latency. Additionally, patients reporting an evening chronotype (patients who are most active and alert in the evening) were more likely to have been diagnosed with metastatic cancer compared to those reporting a morning chronotype (patients who are most active and alert in the morning). Our second goal was to determine the association between sleep problems and ICI treatment tolerance. While we did not find any significant association between OSA risk, insomnia, and six or more infusions during the first 6 months after ICI initiation, the direction of the estimates showed higher odds for poor ICI treatment tolerance in patients with certain sleep problems.

Our study corroborates other studies of sleep problems in more traditional cancer treatment cohorts (e.g., patients receiving radiotherapy and chemotherapy) [18, 19]. In particular, prior studies noted a high burden of sleep problems, including insufficient sleep duration, insomnia symptoms, and poor overall sleep quality [18, 19], that have been, in turn, linked with poor cancer prognosis

Table 5 Association between sleep problems and number of ICI infusions in the LASIR cohort, $N = 32$

Tumor attributes	Number of infusions (6 + vs < 6)	
	OR (95% *CI*)	*p*-values
Sleep apnea risk (STOP-BANG, 0–8)		
Continuous		
Total score (1-unit increment)	0.72 (0.37, 1.39)	0.335
Categorical		
Intermediate risk (3–4)/high risk (5–8)	0.27 (0.02, 3.41)	0.308
Low risk (0–2) (reference)	1	
Insomnia risk (WHIIS, 0–20)		
Continuous		
Total score (1-unit increment)	0.77 (0.59, 1.02)	0.071
Categorical		
Clinically significant insomnia (9 +)	0.23 (0.03, 1.60)	0.138
Not clinically significant < 9 (reference)	1	
Chronotype		
Evening	0.57 (0.11, 2.97)	0.506
Morning (ref)	1	
Sleep latency, min		
15 +	0.51 (0.07, 3.53)	0.493
0–14 (ref)	1	

WHIIS health initiative insomnia scale. *STOP-BANG* snoring, daytime tiredness, observed apnea, blood pressure, body mass index, age, neck circumference, and gender. Treatment tolerability: number of infusions > 6. Adjusted: age, sex, and prior cancer treatment

[1, 35]. For instance, cancer patients with insufficient sleep duration (≤ 6 h sleep/night) and who snore might be experiencing more severe underlying sleep problems and, therefore, subsequent worse cancer outcomes [1, 35]. Furthermore, although our finding of positive association of evening chronotype with metastatic cancer is based on small numbers, other studies have suggested that individuals with an evening chronotype have a higher risk for several forms of cancer [36–39] and greater risk for certain cancer treatment side effects [40, 41]. Evening chronotype has also been associated with elevated levels of c-reactive protein (CRP) [42], which, in turn, has been associated with immunosuppression and poor overall survival in patients with melanoma receiving ICIs [43]. Additionally, other studies have shown prolonged sleep onset latency (an indicator of insomnia) is associated with severe burden of health conditions (including all-cause mortality) and, in particular, cancer severity [36, 44–47].

Additionally, the longitudinal sleep data collected with the Sleepscore Max may suggest the impact and durableness of the single time point sleep over time.

The results from these analyses have some key limitations. Chief among them is the limited sample size, which could explain the mostly non-statistically significant results. Relatedly, although we limited our study to patients receiving ICI within two clinical units at a single institution, the physiologic insults of sleep problems on cancer prognosis are heterogeneous across cancer sites and possibly molecular types [17, 48, 49]. Thus, by combining data across patients with multiple cancer sites, some cancer site–specific relationships may have been obscured. However, small numbers precluded us from conducting site-specific analyses.

Secondly, study participants self-reported their sleep problems. Given the focus of this study on the patient population initiating ICI for the treatment of their late-stage cancer, several factors might be impacting participant sleep patterns (e.g., stress, side effects from previous lines of therapy as illustrated in Fig. 1); thus, observed sleep patterns may not be reflective of pre-diagnostic sleep patterns. In addition, it is possible that poor cancer prognosis, or side effects of prior cancer treatments, could cause sleep problems instead of the reverse (Fig. 1). However, this is less concerning for the ICI response outcome analysis since it is downstream of reported sleep problems at enrollment. Additionally, our study did not measure immune response biomarkers (e.g., inflammatory markers cytokines, including IL-1, IL-6, and TNF-α) that may be more sensitive to underlying sleep problems [50, 51]. However, our sleep data is based on validated questionnaires and, unlike most studies assessing sleep problems in cancer which have focused on a single sleep dimension (e.g., sleep duration) [52], we evaluated multiple sleep dimensions, including *STOP-BANG* OSA risk levels [23, 53].

Another important study limitation is in the assessment of ICI response. The primary response measure in ICI studies and the clinic settings is based on RECIST 1.1 guidelines [54]. This guideline is based on tumor imaging data incorporating information on changes in lesion size and new lesions to distinguish ICI "responders" from "non-responders" [54]. We were unable to incorporate the guidelines into our study due to lack of obtaining this data at the end of 6-month follow-up.

Finally, there is also an issue of representativeness of the SCCA cancer population to the general ICI cancer treatment population. Specifically, our study population is relatively racially homogenous (mainly of European descent, 85% white) and likely has higher socioeconomic status.

Despite these study limitations, this study is the first, to our knowledge, to examine the biologically plausible and potential impact of sleep problems in cancer patients receiving ICI therapy. In result, given the burden and potential impact of sleep problems on ICI treatment response, we believe the study limitations are outweighed by the importance of this study in setting the stage for larger studies with more comprehensive sleep and ICI response assessments.

Conclusions

This study provides new insights into the burden of sleep problems on cancer patients receiving ICI treatment. We hope these results will motivate larger studies of ICI-treated patients to include sleep problems in their assessment [17] that could potentially inform interventional clinical trials focused on sleep quality improvement in ICI treatment populations.

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Author contribution Arthur Sillah conceptualized codeveloped and implemented the study, data collection, analysis, and writing. Alison Silverman co-implemented the study, data collection, and general study management along with Rachel Malen. Amanda Phipps, Ulrike Peters, and Nathaniel Watson did general work supervision and writing. All other authors contributed content knowledge, writing and extensive edits, and feedback.

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Availability of data and materials Not applicable.

Code availability Not applicable.

Declarations

Ethics approval The study protocol was reviewed and approved by the Fred Hutchinson Cancer Research Center, Seattle WA USA.

Consent to participate All included study participants signed an informed consent.

Consent for publication All authors gave their consent for publication.

Conflict of interest SB: report advisory board participation (with honorarium) from Genentech, EMD-Serono, Bristol-Myers-Squibb (BMS) and Sanofi-Genzyme, and research funding to his institution (University of Washington) from EMD-Serono, Merck, BMS, Novartis, Incyte, Exicure, Nektar, NantKwest, Oncosec, and Immune Design. All other authors declare there is no conflict of interest.

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