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Disruptions in sleep–wake cycles in community-dwelling cancer patients receiving palliative care and their correlates

Marie Solange Bernatchez, Josée Savard, and Hans Ivers

School of Psychology, Université Laval, Quebec City, Quebec, Canada; CHU de Québec-Université Laval Research Center, Quebec City, Quebec, Canada; Laval University Cancer Research Center, Quebec City, Quebec, Canada

ABSTRACT
Significant disruptions in sleep–wake cycles have been found in advanced cancer patients in prior research. However, much remains to be known about specific sleep–wake cycle variables that are impaired in patients with a significantly altered performance status. More studies are also needed to explore the extent to which disrupted sleep–wake cycles are related to physical and psychological symptoms, time to death, maladaptive sleep behaviors, quality of life and 24-h light exposure. This study conducted in palliative cancer patients was aimed at characterizing patients’ sleep–wake cycles using various circadian parameters (i.e. amplitude, acrophase, mesor, up-mesor, down-mesor, rhythmicity coefficient). It also aimed to compare rest–activity rhythm variables of participants with a performance status of 2 vs. 3 on the Eastern Cooperative Oncology Group scale (ECOG) and to evaluate the relationships of sleep–wake cycle parameters with several possible correlates. The sample was composed of 55 community-dwelling cancer patients receiving palliative care with an ECOG of 2 or 3. Circadian parameters were assessed using an actigraphic device for seven consecutive 24-h periods. A light recording and a daily pain diary were completed for the same period. A battery of self-report scales was also administered. A dampened circadian rhythm, a low mean activity level, an early mean time of peak activity during the day, a late starting time of activity during the morning and an early time of decline of activity during the evening were observed. In addition, a less rhythmic sleep–wake cycle was associated with a shorter time to death (from the first home visit) and with a lower 24-h light exposure. Sleep–wake cycles are markedly disrupted in palliative cancer patients, especially, near the end of life. Effective non-pharmacological interventions are needed to improve patients’ circadian rhythms, including perhaps bright light therapy.

KEYWORDS
Sleep–wake cycle; circadian rhythms; palliative cancer patients; poor performance status; cosinor model; 24-h light exposure

Introduction
Sleep difficulties have been found to affect up to 96% of advanced cancer patients (George et al. 2016; Mercadante et al. 2015; Mystakidou et al. 2009). A recent study conducted by our research team in 51 community-dwelling cancer patients receiving palliative care revealed that sleep–wake difficulties may take several forms in this population (Bernatchez, Savard et al., in revision). Indeed, 22% of our participants had an insomnia disorder (+10% with subsyndromal symptoms) as their main sleep–wake complaint, while 22% had a hypersonolence disorder (+8% with subsyndromal symptoms). These diagnoses were based on data collected with the Duke Structured Interview for Sleep Disorders (Carney et al. 2008) and on criteria from the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (American Psychiatric Association, 2013). Thus, compared to cancer patients at an earlier stage of the disease who mainly report insomnia (Savard et al. 2011), those at an advanced phase are also struggling with significant daytime difficulties.

The sleep–wake cycle is one of many circadian rhythms, which are biological cycles that repeat every 24 h. It is related to other circadian rhythms such as core body temperature and melatonin secretion, as well as to environmental factors such as light exposure (Kryger et al. 2011). Marler et al. (2006) developed a cosinor model to characterize the sleep–wake rhythms using three standard circadian activity rhythm parameters, including the amplitude (i.e. the height of the rhythm = maximum activity – median activity), the mesor (i.e. the average activity over the
24-h period) and the acrophase (i.e. the time of daily peak activity). These circadian variables are commonly computed on 24-h data collected with an actigraphic device.

Only a few studies have assessed the sleep–wake cycles of patients with advanced cancer (Chang and Lin 2014; Du-Quiton et al. 2010; Focan et al. 2003; Grutsch et al. 2011a; Innominato et al. 2009; Lévi et al. 2014; Levin et al. 2005; Mormont et al. 2000). These previous findings have consistently shown significant disruptions in the sleep–wake cycles of this population. Using a cosinor model, Grutsch et al. (2011a) compared the rest–activity rhythms of patients with an advanced lung cancer (out- and inpatients) and who mostly had an ECOG of 0 or 1 (Oken et al. 1982) to those of healthy participants. They found that lung cancer patients showed a significantly flatter rhythm than healthy individuals as measured using the mesor. In another study, Lévi et al. (2014) used the dichotomy index (I < O) to assess the reduction in physical activity of colorectal cancer patients when they were in-bed (I) compared to their time out of bed (O). A normal I < O index approaches 100%. The I < O index varied as a function of performance status, with a median value of 98.2% for patients with an ECOG of 0, 96.5% for those with an ECOG of 1 and 91.5% for those with an ECOG of 2. These between-groups differences were statistically significant.

Although previous studies have provided some evidence of altered sleep–wake cycles in patients with advanced cancer, only one or two parameters were used to characterize them. Using various circadian parameters like those derived from the cosinor model will provide important information regarding the active period of this specific population (e.g. starting time of activity during the morning, time of activity decline during the evening, time of peak activity during the day). This will lead to a more comprehensive understanding of patients’ rest–activity rhythms. It is also important to highlight that the samples of previous research were mainly composed of participants with a good performance status (i.e. ECOG of 0 or 1). Hence, additional studies are needed to gather a more exhaustive description of the sleep–wake patterns of palliative cancer patients, especially in those having a poorer performance status and who are more likely to display significant disruptions.

Disruptions of sleep–wake cycles have been found to be associated with some physical and psychological symptoms, as well as quality of life in advanced cancer patients. A study conducted in patients with various cancer sites revealed that those experiencing severe pain had a less regular rest–activity rhythm than those with mild pain (Ma et al. 2014). Less robust sleep–wake cycles have also been found to be correlated with more fatigue and depressive symptoms, less appetite, and a poorer quality of life in patients with advanced lung and colorectal cancer (Du-Quiton et al. 2010; Grutsch et al. 2011a; Innominato et al. 2009; Mormont et al. 2000). Moreover, there is some data suggesting that a disrupted rest–activity rhythm is associated with a shorter survival in the context of advanced cancer (Chang and Lin 2014; Innominato et al. 2009; Lévi et al. 2014; Mormont et al. 2000). For instance, a study conducted in 68 patients with various cancer sites (stages II–IV) and who were experiencing pain found a risk of death 4.6 times greater in the disrupted sleep–wake pattern group (I < O index ≥ 89.4%) as compared to those with a regular rhythm, I < O index ≥ 89.5% (Chang and Lin 2014). The authors statistically controlled for many possible confounders (e.g. cancer stage and performance status). However, these cross-sectional findings need to be interpreted carefully, as a poorer prognosis could also lead to worse sleep–wake cycles.

Although some correlates of disrupted rest–activity rhythms have been identified in cancer patients receiving palliative care, there is a need to investigate associations with other variables. For instance, it would be interesting to know to what extent sleep–wake cycle variables are associated with 24-h light exposure, given the widely recognized role of this environmental factor in maintaining robust circadian rhythms (Kryger et al. 2011). Besides, no study has investigated the relationships between disrupted rest–activity rhythm and maladaptive sleep behaviors in advanced cancer patients. This factor has been found to perpetuate insomnia over time in non-metastatic cancer patients (Savard et al. 2009b) and could also result in desynchronizing circadian rhythms.

The goals of this study, conducted in community-dwelling cancer patients with an ECOG of 2 or 3 and receiving palliative care, were to: (1) characterize patients’ sleep–wake cycles using various parameters (i.e. amplitude, acrophase, mesor,
up-mesor, down-mesor, rhythmicity coefficient); (2) compare rest–activity rhythm variables of participants with an ECOG of 2 vs. 3; and (3) evaluate the relationships of sleep–wake cycles parameters with several physical and psychological symptoms, time to death, maladaptive sleep behaviors, quality of life and 24-h light exposure. We decided to study patients still living in their homes because, in the Quebec province where the study was conducted, the average length of stay in a palliative care hospice is only 17.3 days (Alliance des maisons de soins palliatifs du Québec 2013). Hence, studying community-dwelling patients was likely to lead to more generalizable findings.

Patients and methods

Participants

Recruitment

The inclusion criteria were: (a) a diagnosis of advanced cancer (i.e. only palliative treatments possible); (b) significant alterations in daytime functioning as defined by a performance status of 2 or 3 on the ECOG Scale (Oken et al. 1982); (c) ≥ 18 years of age; (d) to be able to read and understand French; (e) to be able to give an informed and free consent; and (f) to live within 90 minutes from L’Hôpital-Dieu de Québec (L’HDQ; CHU de Québec-Université Laval). The exclusion criteria were: (a) to have current delirium, dementia, or severe cognitive impairments as noted by the palliative care team; (b) a score ≤ 23 on the Mini-Mental State Examination (MMSE; Folstein et al. 1975); and (c) presence of suicidal thoughts with a risk of acting out as defined by a score ≥ 1 on items 4 or 5 of the Scale for Suicide Ideation (Beck et al. 1979; Beck and Steer 1991) or a suicide attempt in the last 5 years. Initially, patients older than 75 years old were excluded to decrease the likelihood of including those with significant cognitive impairments. Because the MMSE was also used, a more sensitive screening method, this exclusion criterion was quickly removed at the beginning of the study to recruit a sample more representative of advanced cancer patients receiving palliative care.

Patients were recruited by a research assistant prior to their follow-up appointment at the Outpatient Palliative Care Clinic of L’Hôtel-Dieu de Québec (L’HDQ; CHU de Québec-Université Laval) or during activities of the Day Care Center of Maison Michel-Sarrazin (MMS), a palliative care hospice in Quebec City. This study was approved by the research ethics committees of both institutions.

Of the 433 patients approached, 236 accepted the screening procedure. Of those, 143 were excluded, and 36 refused to participate in the study, thus giving a participation rate of 61.3% (N = 57; Figure 1). There were no significant differences between participants and non-participants on sex, age, cancer site and stage, presence of distant metastases, and performance status (all ps > .22). Six participants dropped out before the end of the data collection (see Figure 1). Nevertheless, valid actigraphic data were available for 55 participants (96.5% of patients who accepted to participate).

Measures

Main dependent variable

Actigraphy. Sleep-wake patterns were computed from data recorded using the Actiwatch-64® (Philips Respironics, Andover, MA). The Actiwatch is a small, nonintrusive actigraphy device that is worn on the wrist. By calculating the orientation and movement, the Actiwatch records activity throughout 24-hour periods. Data were recorded using 30-sec epochs. Then, each trace was scored manually on screen using 30-second epochs. Data from daily sleep diaries completed during the same period as the actigraphic recordings were used to help score naps, lights out/lights on periods, and periods when the actigraph was removed. Periods of rest (sleep), nap, and activity, as well as artifacts, were scored independently by the first author (MSB) and a trained research assistant. Inter-rater agreement analyses on rest and activity periods revealed excellent intraclass rates (varying between 86.2–96.3%). Thus, no change was made to the traces and only those scored by the first rater (MSB) were used given her greater experience scoring this type of data. According to the American Academy of Sleep Medicine, actigraphy is a validated and recommended tool to assess circadian activity parameters in the elderly (Morgenthaler, Alessi et al., 2007). Actigraphy was also validated in 68 patients with advanced lung cancer (in- and outpatients; ECOG
0–2) to assess sleep-wake cycles using the cosinor model (Grutsch et al. 2011b). In outpatients, strong correlations (rs = .45 to .58) were obtained between circadian activity rhythm parameters (i.e. mesor, amplitude, rhythmicity coefficient) and daytime functioning as assessed with two items from the Pittsburgh Sleep Quality Index (PSQI). The mesor was also associated with the global PSQI score in these patients (r = −.48).

**Secondary variables**

**Physical symptoms.** Pain diary (PD). A PD was used to provide daily subjective estimates of the worst pain during the previous 24 h (0–10). This single item was taken from the Brief Pain Inventory (short form), a questionnaire that was specifically designed to assess pain in cancer patients (Cleeland 1994). The French version of this item was found to be highly correlated with the pain interference items from the same questionnaire (α = .84) in metastatic cancer patients (Serlin et al. 1995). This specific item has also previously been used to study the relationship between disrupted rest-activity rhythms and pain in advanced cancer patients (Ma et al. 2014).

Physical Symptoms Questionnaire (PSQ). The PSQ is an adaptation of the Memorial Symptom Assessment Scale (Portenoy et al. 1994). In the current study 14 physical symptoms (e.g. headaches,
constipation, breathing difficulties) commonly reported by palliative cancer patients were assessed for the previous seven days. When patients reported having the symptom, its frequency was rated on a 4-point Likert scale ranging from “1” (rarely) to “4” (very much) and the distress associated with it was scored on a 5-point Likert scale ranging from “0” (not at all) to “4” (extremely).

Functional Assessment of Chronologic Illness Therapy Fatigue Scale (FACIT-FS). The FACIT-FS was specifically developed to assess fatigue among cancer patients. It is composed of 13 items that are rated on a 5-point Likert scale ranging from ‘0’ (not at all) to ‘4’ (very much) for a total score varying between 0 and 52. A lower score indicates more severe fatigue and a score of less than 43 suggests a clinical level of fatigue (Cella 1997; Cella et al. 1993).

Psychological symptoms and quality of life. Hospital Anxiety and Depression Scale (HADS). The HADS is a 14-item questionnaire rated on a scale from 0 to 3 that was designed to assess anxiety and depression symptoms in populations with a medical condition such as cancer. It is divided into two subscales: depression symptoms (HADS-D: seven items) and anxiety symptoms (HADS-A: seven items). It evaluates symptoms experienced in the past seven days. The HADS has the advantage of not containing any somatic item that may be confounded with symptoms of the medical condition. Scores for each subscale range from 0 to 21 (Savard et al. 1998; Zigmond and Snith 1983).

Missoula-VITAS® Quality of Life Index (MVQOLI). This tool was designed to assess various dimensions of quality of life specifically in patients with a terminal illness. In this study, we used subscales assessing quality of life related to symptoms (5 items) and functioning quality of life (5 items). The respondents indicate the extent to which they agree or disagree with the statement. Scores for each subscale range from −30 to +30, a higher score indicating a better quality of life. We also used the MVQOLI global item to assess patients’ global quality of life on a scale ranging from ‘1’ (worst possible) to ‘5’ (best possible) (Byock and Merriman 1998). A translation from English to French was made by our research team with the help of a professional translator, but this version of the MVQOLI has not been validated.

Sleep habits. Sleep Behaviors Questionnaire (SBQ). The SBQ is a 24-item questionnaire adapted from the Sleep Behavior Self-Rating Scale (Kazarian et al. 1979) that assesses maladaptive sleep habits on a Likert scale ranging from “0” (never) to “4” (very often).

Environmental factors. Actilight® (Cambridge Neurotechnology, Cambridge, United Kingdom). The Actilight® is an ultra light-weight device which detects and logs light intensity in lux. This device detects light intensity ranging from 0.5 to 40,000 lux with the following resolutions: (a) 0–200 lux = 0.1 lux; (b) 200–2000 lux = 2 lux; (c) 2000–8000 lux = 4 lux; (d) 8000–20,000 lux = 50 lux; (e) 20,000–40,000 lux = 200 lux. Data were recorded using 30-sec epochs and stored in a 128 kB internal memory. The beginning time of the Actilight® and the Actiwatch® recorders were synchronized for each participant by a member of the research team.

Demographics, health behaviors and cancer characteristics. Demographics and medication use were collected using a questionnaire. Cancer-related data (e.g. cancer site and stage, palliative treatments received during study, date of death) were extracted from the patient’s medical record.

Procedure

MSB or another trained graduate student in clinical psychology went to the participant’s home to administer the MMSE, the battery of self-report scales and to hand them the PD, the Actiwatch® and Actilight® recorders (home visit #1). The battery of self-report scales was completed on two different home visits, about half on that day and the other half one week later, to reduce the burden on the participants. When needed, questionnaires were completed with the assistance of the patient’s caregiver (7 participants).

Participants wore the actigraphic and light recorders 24-h per day for 7 consecutive days and completed the PD (and sleep diary) every morning for the same period. Participants were instructed to wear the light recorder on their clothes when out of bed and place it on their nightstand when in bed (to prevent the recorder
being covered by the bed sheets). At the end of the week, the material was retrieved at the participant’s home (home visit #2) and the remaining self-report scales were completed.

**Statistical analyses**

Raw data were entered by two independent assistants and were compared to ensure maximal integrity. Data from actigraphic and light recordings with 30-sec epochs were transformed into 60-sec epochs by computing the mean of the data available for each 60-sec epoch. This linear extrapolation minimized the impact of outlier data and led to an exponential smoothing of time series data. Analyses were conducted using SPSS (version 13.0; SPSS Institute Inc., Chicago, IL, 2000). Sleep-wake rhythms were analyzed by fitting each participant’s actigraphic data to a five-parameter extended cosinor model (Marler et al. 2006) using a SAS statistical software macro (version 9.3; SAS Institute Inc, Cary, NC, 2011). Table 1 shows the five circadian activity rhythms parameters used in this study, a brief description of them and their meaning.

Independent sample T tests (2-tailed) were computed to assess differences on rest-activity rhythm parameters between patients with an ECOG of 2 and those with an ECOG of 3 and Hedges’ gs were calculated to determine effect sizes. The Hedges’ g provided a measure of effect size weighted according to the relative size of each sample (Hedges 1981). Finally, Spearman correlations were conducted to determine associations of sleep-wake cycle parameters with physical and psychological symptoms, time to death, maladaptive sleep behaviors, quality of life, and 24-h light exposure. To reduce the number of variables, a principal component analysis was conducted to create a single composite score (Z-score) encompassing the three dimensions assessed by the PSQ (i.e. total number of symptoms, frequency, distress). The alpha level was fixed at 5%, 1-tailed, because the direction of correlations was highly predictable. Spearman’s correlations were used because of their greater robustness when analyzing small samples and data not normally distributed (Howell 1998). All the analyses were computed using only participants who had an R-squared (rhythmicity coefficient of the sleep-wake cycle) >5% to avoid an impact on results of outliers’ data. Therefore 4 participants were excluded, thus giving a final sample of 51 participants. Excluded patients were significantly more likely to have a stage 3 cancer ($\chi^2 = (1, n = 44) = 7.69$, $p = .01$) and to have no metastasis ($\chi^2 = (1, n = 52) = 6.59$, $p = .01$) as compared to those retained in the analyses. No significant difference was found on any of the other sociodemographic and medical variables (all $p$s ≥ .09).

**Results**

**Demographic and medical characteristics**

The sample was composed of 55 white French-Canadian patients receiving palliative care for advanced cancer and still living in their homes (Table 2). Participants were 66 years of age on average, 52.7% of them were males, and 63.6% were married or cohabitating. Mean time to death from the date of the first home visit was 254.9 days ($SD = 250.0$, range 28–1082; $n = 46$).

**Descriptive statistics on sleep-wake rhythms**

On average, the sample had severely disrupted sleep-wake activity cycles (R-squared = .27; range .09–.51). The mean time of the peak activity rhythm (acrophase) was 13:35 (range 10:34–20:10). The mean activity level (mesor) was 45.4 (range 3.6–167.8) and the mean height of the rhythm (amplitude) was 47.0 (range 5.4–178.8). Finally, the mean time from low to high activity (up-mesor) was 8:18 (range 2:00–14:00) and the mean time from high to low activity (down-mesor) was 19:23 (range 16:20–22:00).

Table 3 compares sleep-wake cycle variables obtained by performance status. There were no significant between-groups differences on any circadian rest-activity rhythm variable between patients with an ECOG of 2 vs. 3. However, moderate effect sizes were observed for differences on the mean activity level (mesor; $g = .59$), the height of the rhythm (amplitude; $g = .44$) and on the starting time of activity during the morning (up-mesor; $g = .53$).
Figure 2 shows the raw actigraphic data of a female participant (68 years old) with an ECOG of 2 (F.B.) for 7 consecutive 24-h periods, while Figure 3 illustrates those of a female participant (69 years old) with an ECOG of 3 (M.F.). These participants were selected to illustrate possible differences across different levels of functioning despite similarities on other demographic and clinical aspects. Indeed, these two patients were in the same age bracket (i.e. 60–70), were not receiving any cancer treatment at the time of the study, were both taking pain medications (i.e. opioids) and corticosteroids (i.e. dexaméthasone), and both had hypersomnolence as their main sleep-wake disorder. They also had a similar caffeine intake during the study, but their alcohol and cigarette consumption was different (i.e. F.B: 14 glasses of wine/week and no cigarettes; M.F.:15 cigarettes/day and no alcohol consumption).

Although F.B. showed some disruptions of her sleep-wake patterns, there is a clear contrast between her daytime and night-time activity with minimal body movements during the night. Her bedtime and wake time were fairly regular across the 7 nights and her daytime activity was fairly stable across the 7 days. In comparison, M.F. showed a marked disruption of rest-activity cycles with little contrast between daytime and night-time activity. An irregular bed and wake time, a high level of body movements during the night and a variable daytime activity level were observed in this patient.

Correlations between sleep-wake rhythm parameters and other variables

Table 4 shows Spearman’s correlations obtained between sleep-wake rhythm parameters and other variables. Specifically, significant correlations were observed between a dampened circadian rhythm (lower amplitude and mesor, a later acrophase) and a poorer global quality of life. In addition, a later time of decline of activity in the evening (higher down-mesor) was significantly associated with a poorer global and functioning quality of life. A less rhythmic sleep-wake cycle (lower amplitude, lower mesor, lower R-squared) was also significantly related to a shorter time to death (from the first home visit). On the other hand, significant correlations were found between a more robust rest-activity rhythm (higher amplitude, higher mesor, higher R-squared) and a greater 24-h exposure to a light intensity >1000 lux. None of the circadian activity rhythm variables was significantly correlated with pain, fatigue, depression symptoms and maladaptive sleep behaviors.

Discussion

This study, conducted in community-dwelling cancer patients (ECOG of 2 or 3) receiving palliative care, aimed to characterize their rest-activity rhythms. The study also compared the rest-activity rhythm variables of patients with an ECOG of 2 to those with an ECOG of 3, and evaluated the relationships of sleep-wake cycle parameters with several possible correlates. Overall, a low mean
activity level, a dampened circadian rest-activity rhythm, an early mean time of peak activity rhythm during the day, a late starting time of activity during the morning and an early time of activity decline in the evening were observed in the sample. Although no significant differences were found between patients with an ECOG of 2 vs. 3, between-groups effect sizes of a moderate magnitude were obtained for three circadian rest-activity rhythm parameters (i.e. amplitude, mesor, up-mesor). A less rhythmic sleep-wake cycle (i.e. lower amplitude, lower mesor, lower R-squared) was associated with a shorter time to death (from the first home visit), while a more robust one was related to a greater 24-h light exposure.

The markedly disrupted sleep-wake cycles observed in our sample are in line with previous research in advanced cancer patients with a better performance status in general and using other methods to characterize circadian rhythms (Chang and Lin 2014; Grutsch et al. 2011a; Innominato et al. 2009; Lévi et al. 2014; Levin et al. 2005; Mormont et al. 2000). The cosinor model used in this study (Marler et al. 2006) was previously employed in women with non-metastatic breast cancer prior to chemotherapy. In that study, actigraphic data were collected in 65 patients and showed strong and synchronized sleep-wake patterns. Indeed, the mean time of the peak activity rhythm (acrophase) was 14:40 (range 11:43–19:41), the mean time from low to high activity (up-mesor) was 7:13 (range 4:54–11:36), and the mean time from high to low activity (down-mesor) was 22:20 (range 16:50–3:45; Ancoli-Israel et al. 2006). Overall, this suggests that our participants had a shorter active period during the day than non-metastatic breast cancer patients, with an up-mesor approximately one hour later (8:18 vs 7:13) and a down-mesor three hours earlier (19:23 vs 22:20). Moreover, this study’s participants reached their peak activity during the day one hour earlier (mean acrophase at 13:35 vs 14:40) and had less rhythmic rest-activity patterns than non-metastatic breast cancer patients (R-squared .27 vs .47; Ancoli-Israel et al. 2014).

The lack of significant differences found on rest-activity rhythm variables between patients with an ECOG of 2 and those with an ECOG of 3 is surprising. Indeed, Lévi et al. (2014) reported significant between-groups differences on a rhythmicity index (I < O) in colorectal cancer patients having and ECOG of 0 vs. 1 and vs. 2. Our findings may be interpreted as suggesting that patients with an ECOG of 2 or 3 have more similar sleep-wake cycles. However, the absence of significant between-groups differences is more likely to be due to a lack of statistical power (and a small
number of patients with an ECOG of 3; \( n = 8 \). Indeed, moderate effect sizes were obtained for three circadian rest-activity rhythm parameters (i.e. amplitude, mesor, up-mesor).

Some findings obtained on correlates of sleep-wake rhythm parameters also deserve comment. Similarly, to previous research (Chang and Lin 2014; Innominato et al. 2009; Lévi et al. 2014; Mormont et al. 2000), a less rhythmic sleep-wake cycle (i.e. lower amplitude, lower mesor, lower R-squared) was associated with a shorter time to death (from the first home visit). This finding has typically been

Table 3. Mean sleep–wake rhythm variables by performance status (\( N = 51 \)).

<table>
<thead>
<tr>
<th></th>
<th>ECOG 2 (( n = 43 ))</th>
<th>ECOG 3 (( n = 8 ))</th>
<th>( t, p ) value (( df = 49 ))</th>
<th>( g )</th>
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<tbody>
<tr>
<td>Amplitude (activity count)</td>
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<tr>
<td>M</td>
<td>49.1</td>
<td>35.8</td>
<td>1.15, ( p = .26 )</td>
<td>.44</td>
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<tr>
<td>SD</td>
<td>31.2</td>
<td>20.3</td>
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<td>Range</td>
<td>5.4–178.8</td>
<td>10.3–60.7</td>
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<td>Acrophase (h)</td>
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<tr>
<td>M</td>
<td>13:33</td>
<td>13:43</td>
<td>−0.29, ( p = .78 )</td>
<td>.11</td>
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<tr>
<td>SD</td>
<td>1:33</td>
<td>1:36</td>
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<td>Mesor (activity count)</td>
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<tr>
<td>M</td>
<td>48.1</td>
<td>30.7</td>
<td>1.54, ( p = .13 )</td>
<td>.59</td>
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<tr>
<td>SD</td>
<td>30.8</td>
<td>17.7</td>
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<tr>
<td>Range</td>
<td>3.6–167.8</td>
<td>10.4–53.1</td>
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<td>Up-mesor (h)</td>
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<tr>
<td>M</td>
<td>8:08</td>
<td>9:10</td>
<td>−1.38, ( p = .17 )</td>
<td>.53</td>
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<td>SD</td>
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<td>1:40</td>
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<td>Range</td>
<td>2:00–14:00</td>
<td>7:00–11:10</td>
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<td>Down-mesor (h)</td>
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<tr>
<td>M</td>
<td>19:20</td>
<td>19:39</td>
<td>−0.60, ( p = .55 )</td>
<td>.23</td>
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<tr>
<td>SD</td>
<td>1:17</td>
<td>1:31</td>
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<tr>
<td>Range</td>
<td>16:20–22:00</td>
<td>16:50–21:30</td>
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<tr>
<td>R-squared</td>
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<tr>
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<td>.25</td>
<td>0.48, ( p = .63 )</td>
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</tr>
<tr>
<td>SD</td>
<td>.13</td>
<td>.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>.09–.51</td>
<td>.09–.40</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 2. 7-day actigraphic data for a patient with an ECOG of 2 (F.B.). This patient showed some disruptions of sleep-wake patterns despite the clear contrast between daytime and night-time activity and minimal body movements during the night. Her bedtime and her wake time were fairly regular across the 7 nights and her daytime activity level was pretty stable across the 7 days. Of note, this is a double-plot figure in which actigraphic data are shown from 12:00 pm on a given day to 12:00 pm on the next day.
interpreted as indicating a negative effect of disrupted sleep-wake rhythms on cancer survival. However, we think that this cross-sectional finding needs to be interpreted cautiously as the relationship can also go the other way around. More precisely, a poorer prognosis predicting more sleep-wake cycle impairments rather than impaired sleep-wake cycles predicting a poorer prognosis. At the end of life, patients have important alterations in their functioning with a wide range of symptoms (e.g. pain, fatigue, nausea, constipation, loss of appetite, drowsiness; Hayduk et al. 2010) that may lead to increased time in bed and daytime sleep. Indeed, a study found that pain and fatigue were associated with a greater risk to nap during the day in elderly individuals (Goldman et al. 2008). As a consequence, patients with a poorer prognosis are likely to be less exposed to environmental and social time cues, such as natural daylight, regular meal times, as well as social schedules and exchanges. These factors normally play a crucial role in synchronizing circadian rhythms on a 24-h period, including the sleep-wake cycle (Schulz and Steimer 2009).

Figure 3. 7-day actigraphic data for a patient with an ECOG of 3 (M.F.). This patient showed marked disruptions of rest-activity cycles with little contrast between daytime and night-time activity, irregular bed and wake times, a high level of body movements during the night and a variable daytime activity level. Of note, this is a double-plot figure in which actigraphic data are shown from 12:00 pm on a given day to 12:00 pm on the next day.

Table 4. Spearman’s correlations between circadian rhythm parameters and other variables (N = 51; $r^2 > 5\%$).

<table>
<thead>
<tr>
<th></th>
<th>Amplitude (activity count)</th>
<th>Acrophase (h)</th>
<th>Mesor (activity count)</th>
<th>Up-mesor (h)</th>
<th>Down-mesor (h)</th>
<th>R-squared</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain (0–10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PSQ composite score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FACIT-FS (0–52)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time between 1st home visit and death (days)</td>
<td>242.9</td>
<td>.32*</td>
<td>.07</td>
<td>.27*</td>
<td>.01</td>
<td>.09</td>
</tr>
<tr>
<td>HADS-A (0–21)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HADS-D (0–21)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>SHQ (0–4)</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>MVQOLI_global (1–5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MVQOLI_symptoms (−30 to +30)</td>
<td>8.2</td>
<td>.25**</td>
<td>.23*</td>
<td>.27*</td>
<td>.14</td>
<td>.31*</td>
</tr>
<tr>
<td>MVQOLI_functioning (−30 to +30)</td>
<td>7.7</td>
<td>.17</td>
<td>.00</td>
<td>.27*</td>
<td>.11</td>
<td>.04</td>
</tr>
<tr>
<td>Total 24-h light exposure (lux)</td>
<td>1 097 719.4</td>
<td>.17</td>
<td>.00</td>
<td>.27*</td>
<td>.11</td>
<td>.04</td>
</tr>
<tr>
<td>Light exposure &gt; 1000 lux (min)</td>
<td>75.0</td>
<td>.33*</td>
<td>.08</td>
<td>.42**</td>
<td>.17</td>
<td>.15</td>
</tr>
</tbody>
</table>

Note. *≤ .05 **≤ .01; small ($r = ± .10$); moderate ($r = ± .30$); large ($r = ± .50$) correlation. a) A lower score on the FACIT-FS indicates a more severe fatigue and a score lower than 43 suggests a clinical level of fatigue. Forty-seven participants (92.2%) had a clinical level of fatigue.
Besides, our study was not designed to assess survival rates and a small sample was available. Nevertheless, our findings at least indicate that patients’ sleep-wake rhythms are increasingly disrupted as they approach the end of life.

Besides, in line with a previous study conducted among advanced lung cancer patients with a better performance status (i.e. mostly ECOG of 0 or 1; Grutsch et al. 2011a), a more disrupted rest-activity rhythm (i.e. lower amplitude and mesor and a later acrophase) was associated with a poorer global quality of life. Moreover, a later time of activity decline in the evening (higher down-mesor) was related to a poorer global and functioning quality of life. Together, these findings suggest that patients with a worse quality of life were less active and had a phase delay of their active period over 24 hours.

An innovative aspect of this study is the assessment of the relationship between sleep-wake cycles in cancer patients receiving palliative care and 24-h light exposure. Our results indicated that a lower exposure was significantly associated with greater disruptions in several sleep-wake cycle parameters (i.e. lower amplitude, lower mesor, lower R-squared). This may have important clinical implications. While no causality can be inferred from this cross-sectional study, it still suggests that bright light therapy (BLT) could be helpful in improving rest-activity rhythms in this population. Such an approach was tested in non-metastatic breast cancer patients and was found to be beneficial. More specifically, in women undergoing chemotherapy for breast cancer, BLT was found to prevent rest-activity rhythm desynchronization, fatigue from worsening and quality of life deterioration that are typically observed during chemotherapy (Ancoli-Israel et al. 2012; Jeste et al. 2013; Nekrug et al. 2012). Besides, a significantly greater improvement of fatigue was also obtained in breast and gynecological cancer survivors receiving BLT as compared to those in a dim red light condition (Redd et al. 2014). Moreover, this treatment was found to strengthen sleep-wake cycles in Alzheimer’s patients, a population with significant impairments in daytime functioning (Brown et al. 2013). Studies should be conducted to test whether BLT could also have these effects in cancer patients receiving palliative care.

Surprisingly, rest-activity patterns were not significantly associated with pain, nor with depressive symptoms. However, our participants experienced a lower intensity of these symptoms as compared to patients in prior studies, which found such relationships. Indeed, Ma et al. (2014) showed that a less rhythmic sleep-wake cycle (i.e. lower I < O index) was related to greater levels of worst pain in the previous 24-h, but mean pain levels reported were more severe ($M = 5.5/10$) than in our sample ($M = 3.9/10$). Similarly, a prior study showed significant associations between circadian rest-activity rhythm parameters derived from a cosinor model and depression symptoms. In that study 15.6% of the sample had a HADS-D score ≥ 11 (Du-Quiton et al. 2010), while these scores were reported only by 8% of our participants.

The absence of significant correlations between disrupted sleep-wake cycle variables and fatigue was also unexpected given the prior literature showing such relationships (Grutsch et al. 2011a; Innominato et al. 2009; Mormont et al. 2000). This inconsistency could be due to a lack of variability. Indeed, the majority of our participants had a clinical level of fatigue. Finally, the absence of significant relationships between maladaptive sleep behaviors and sleep-wake cycles seems to suggest that behavioral therapy would not be sufficient as a stand-alone treatment to resynchronize sleep-wake cycles of these patients. However, it could be offered in combination with other treatments, such as BLT. More research is needed on this issue before firm conclusions are drawn.

This study is characterized by several strengths, including an assessment of sleep-wake cycles during 7 consecutive 24-h periods and the use of a validated model to characterize circadian rhythms with a wide range of parameters. Moreover, the objective assessment of light exposure and the use of validated tools to evaluate possible correlates are clear assets of this study. On the other hand, the fact that only a small proportion of all patients approached participated in the study and the relatively small sample, which comprised only a few patients with an ECOG of 3, limits the generalization of our findings. In fact, recruiting patients with significant alterations in daily functioning was a major challenge in this study. Nevertheless, our sample size is appreciable given the typical recruitment difficulties that are encountered in this population (Hanson et al. 2014). It also compares advantageously to those of many of the previous studies conducted in advanced cancer patients with better performance status (range
between 25–68 participants; Chang and Lin 2014; Focan et al. 2003; Grutsch et al. 2011a; Levin et al. 2005). We also reached an acceptable participation rate of 61.3%. The use of a cross-sectional design does not allow inferring causality. Finally, while it increases the generalization of the findings, the heterogeneity of our sample may have blurred some differences across cancer sites.

In summary, this study confirms that sleep-wake cycles are markedly disrupted in community-dwelling cancer patients receiving palliative care, and particularly, near the end of life. Pharmacotherapy, including hypnotic medications for insomnia and psychostimulants for hypersomnolence, is the most frequently used treatment option to manage sleep-wake cycle disruptions in palliative care. However, such medications have numerous side effects and their efficacy and innocuity remain to be substantiated in this population (Bernatchez et al. 2015; Kuriya et al. 2015). For instance, a common side effect of hypnotic medication is residual daytime sleepiness (Kvale and Shuster 2006). Thus, resolving the insomnia problem by using such a medication is likely to lead to or aggravate excessive daytime sleepiness, and therefore impair the sleep-wake cycles. Clinical studies are needed to develop appropriate non-pharmacological interventions to improve sleep-wake cycles in palliative cancer patients, and this study suggests that bright light therapy could constitute an interesting alternative.

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**Declaration of interest**

The authors declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article. The authors alone are responsible for the content and writing of the article.

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