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# Sleep characteristics and recurrence in platinum-sensitive ovarian cancer survivors: A prospective cohort study

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ABSTRACT

*Objective:* To describe characteristics of sleep (quality, duration, efficiency, and insomnia) in a cohort of high-grade epithelial ovarian cancer (EOC) survivors who have completed and responded to first-line chemotherapy, and to explore their relationships with disease recurrence.

*Methods:* In this cohort of 97 women, sleep and other factors were assessed at baseline and 4 months later. The distribution of participants by categories of sleep characteristics were calculated. Hazard ratios (HRs) and 95 % confidence intervals (95 % CI) for the association between each sleep characteristic and recurrence were estimated using the Cox proportional hazards model, and adjusted for confounding using propensity scores. Associations were estimated for all women and among those defined as fully platinum-sensitive.

*Results:* At baseline, just over half of participants (52.6 % to 56.7 %) had poor sleep quality, efficiency and duration, while most (62.9 %) did not experience insomnia. Distributions remained similar 4 months later. During follow-up, 47 recurrences occurred. Among all participants, HRs (95 % CIs) of recurrence were close to the value of 1, indicating no association, for sleep quality and efficiency, 1.22 (0.66–2.23) for not meeting vs. meeting sleep duration guidelines and 0.68 (0.34–1.39) for the presence vs. absence of insomnia. In fully platinum-sensitive women, the HRs (95 % CIs) were 1.50 (0.64–3.53) for not meeting duration guidelines, 1.25 (0.56–2.79) for poor sleep efficiency, 1.44 (0.55–3.72) for the presence of insomnia, and remained null for sleep quality.

*Conclusion:* Most EOC survivors have poor sleep quality, duration, and efficiency. Research with larger sample sizes is required to better understand the relationship between these sleep characteristics and the risk of recurrence.

## 1. Introduction

Ovarian cancer stands as the most lethal gynecological cancer globally, with a 5-year survival rate of less than 50 % (Stewart et al., 2019; Siegel et al., 2023). Given the absence of specific early symptoms and limitations in population screening methods, 75 % of cases are diagnosed at an advanced stage (Stewart et al., 2019; Gupta et al., 2019). Nonetheless, the majority of ovarian cancer patients achieve remission after primary treatment, but unfortunately, up to 80 % then face disease recurrence, and median survival for these patients ranges between 12 and 29 months (Corrado et al., 2017; Parmar et al., 2003; Pfisterer et al., 2006).

Factors that are currently established to influence prognosis among ovarian cancer survivors include age at diagnosis, cancer stage, histological type, tumor grade, and residual disease following debulking surgery – all of which are not modifiable (Ezzati et al., 2014). Improving

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prognosis is essential and can be achieved with knowledge of modifiable prognostic factors, among which sleep is particularly promising. The role of sleep in promoting overall health and well-being is widely recognized (Ramar et al., 2021). With regard to cancer, sleep may influence initiation, progression, and survival through multiple mechanisms involving immune function, inflammatory responses, endocrine factors, and DNA damage and repair (Zhou et al., 2022). Poor sleep quality is highly prevalent among gynecological cancer survivors, affecting them twice as much as the general population (Zhao et al., 2022; Wang et al., 2022). Sleep can be improved after cancer treatment through a variety of interventions, including exercise therapy, sleep hygiene modifications, cognitive-behavioral therapy, and pharmacological treatments (Zhao et al., 2022).

Only one previous study has investigated sleep in relation to prognosis among women diagnosed with ovarian cancer (Li et al., 2022). The results suggested a 2.4-fold increased mortality among those with poor vs. good sleep quality. Sleep duration was another parameter that was examined, where a 60 % lower mortality was observed among those sleeping ≥7.5 h/night, compared with 7 to 7.5 h/night. Of note, participants were asked to report their sleep characteristics for the period one month prior to their ovarian cancer diagnosis. The period before diagnosis, as well as during treatment, is a time when sleep may be highly disturbed (Clevenger et al., 2013). Indeed, as women approach an ovarian cancer diagnosis, they may face psychological distress related to the diagnosis, upcoming treatment, and/or waiting periods, all of which can impact their sleep (Zhao et al., 2022; Clevenger et al., 2013). Abdominal discomfort is another frequently reported source of sleep disruption before treatment (Zhao et al., 2022). Treatment itself impacts sleep through side effects such as fatigue, pain, anxiety, and depression (Zhao et al., 2022). While improving sleep during treatment may aid in recovery, it would also be important to understand the prognostic influence of sleep once a patient is in remission, when interventions to improve prognosis may be most relevant and feasible for this goal (Zhao et al., 2022).

The Lifestyle Habits and the Prognosis of Ovarian Cancer in Quebec Study (HPROQ) is a prospective cohort study of women who had completed and responded to first-line treatment for a high-grade ovarian cancer. Using this data, we described sleep characteristics in the population, in particular sleep quality, sleep duration, sleep efficiency and insomnia. In addition, we explored their relationship with cancer recurrence to observe potential directions of association.

## 2. Methods

### 2.1. Study population

The HPROQ Study was conducted in Montreal, Canada in three hospitals with specialized units in gynecologic oncology. Women with borderline and low-grade ovarian cancers, whose survival experience differs from the majority of epithelial ovarian cancers, were not included. To be eligible to participate, women had to (1) be between ages 18 and 75 years, (2) have been diagnosed with a high-grade epithelial ovarian cancer (i.e., high grade serous, grade 3 endometrioid, clear cell and high grade carcinosarcoma), and (3) have remained responsive to platinum-based chemotherapy 6 months after the end of treatment. Seventy-eight percent had a high-grade serous cancer. Those who had not responded to treatment for 6 months were considered resistant to platinum-based chemotherapy, and thus were not eligible (Wilson et al., 2017). Thus, baseline was defined as 6 months post-treatment. Finally, women participating in a clinical trial were also not eligible.

Among the 136 eligible women identified from January 2016 to February 2018, 111 (82 %) agreed to participate. After a subsequent review of medical records, 14 women were further excluded, as five did not have high-grade epithelial ovarian cancer, and nine were found to be platinum-resistant. The final cohort for the analysis thus included 97 ovarian cancer survivors. Written informed consent was obtained from participants. The study was approved by the Research Ethics Committee of the Université de Montréal Hospital Centre (CHUM).

### 2.2. Data collection and follow-up

Data were collected by telephone interview at baseline and 4 months later using questionnaires assessing sociodemographic factors, quality of life, and lifestyle behaviours, including sleep characteristics. The Pittsburgh Sleep Quality Index (PSQI) was used to assess sleep quality over the past month (Buysse et al., 1989). The PSQI is a standardized 19-item questionnaire comprising seven sleep components, including subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction (Buysse et al., 1989). Each component is weighted on a 0–3 scale, yielding a global score that ranges from 0 to 21 (Buysse et al., 1989). A higher score indicates poorer sleep quality, and a threshold of 5 has been validated to differentiate good (≤5) vs. poor (>5) sleep quality (Buysse et al., 1989).

The Insomnia Severity Index (ISI) was also administered during interviews. The ISI is a validated 7-item questionnaire assessing the nature and severity of insomnia over the past month (Chen et al., 2018). The seven components evaluated are: severity of sleep onset, sleep maintenance, early morning awakening problems, sleep dissatisfaction, interference of sleep difficulties with daytime functioning, noticeability of sleep problems by others, and distress caused by sleep difficulties (Chen et al., 2018). Each component is weighted on a Likert scale of 5 points (from 0 to 4), yielding a global score range between 0 and 28, where a higher score indicates more severe insomnia (Chen et al., 2018). A cut-off score of 8 has been validated in clinical populations, but other thresholds have also been suggested (Savard et al., 2005; Morin et al., 2011).

Quality of life was measured with the Functional Assessment of Cancer Therapy-Ovarian (FACT-O) questionnaire (Basen-Engquist et al., 2001). Physical activity was measured with the International Physical Activity Questionnaire (IPAQ) long form (Craig et al., 2003). Diet quality was represented by the Canadian Healthy Eating Index (C-HEI) 2005 (Garriguet, 2009), which was calculated from the diet data collected using the Canadian Diet History Questionnaire (C-DHQ) II (Csizmadi et al., 2016). Clinical characteristics, including International Federation of Gynecology and Obstetrics (FIGO) stage, tumor grade, histological type, and type of treatment received (adjuvant vs. neo-adjuvant) were obtained through review of medical records.

The prognostic outcome of interest in this study was recurrence. It was defined according to the presence of symptoms, such as abdominal discomfort and ascites, and the elevation of cancer antigen-125 (CA-125) levels, and confirmed with imaging results (Rustin et al., 2004). Follow-up was performed through medical record review until February 2021 (study end date). The date of recurrence was the date of the CA-125 result that defined recurrence. Person-time of follow-up was calculated from baseline until date of recurrence, censoring due to loss to follow up, enrollment into a clinical trial, or end of study. Women were classified as partially platinum-sensitive if they had a recurrence between six and 12 months after the end of chemotherapy, and fully platinum-sensitive if they were recurrence-free for >12 months after the end of chemotherapy (Wilson et al., 2017).

### 2.3. Definition of sleep characteristic variables

Sleep quality, based on the PSQI global score, was dichotomized according to the validated cut-off score of 5 (Buysse et al., 1989). Sleep duration and sleep efficiency, components of the PSQI, were also investigated separately, as they are important indicators of sleep health (Buysse, 2014). Duration was categorized according to the Canadian 24-Hour Movement Guidelines, which recommends 7 to 9 h for adults aged 18 to 64, and 7 to 8 h for adults aged 65 and older (Wang et al., 2022).

Since our study population covered both age groups, and few women reported duration >9 h/night, we defined a reference category of meeting guidelines as 7 to 8.5 h/night, while not meeting guidelines included sleep durations of either <7 h/night or >8.5 h/night grouped together; both these shorter and longer durations have been associated with an increased risk of cancer incidence, mortality, and adverse health outcomes (Wilunda et al., 2022; Chaput et al., 2020). Sleep efficiency was calculated by dividing the amount of time spent asleep in bed by the total amount of time spent in bed (Buysse et al., 1989). It was then dichotomized according to a threshold of 85 %, proposed by the PSQI, in order to differentiate good (≥85 %) vs. poor (<85 %) sleep efficiency (Buysse et al., 1989). Finally, insomnia, based on the ISI global score, was dichotomized according to the validated cut-off score of 8, to differentiate the absence (ISI<8) vs. presence (ISI≥8) of insomnia (Savard et al., 2005).

### 2.4. Statistical analysis

Baseline characteristics of the study population were described as means and standard deviations (SD) for continuous variables, and frequencies and percentages for categorical variables. Similarly, means, standard deviations, frequencies and percentages were calculated to describe the sleep characteristics of the population at baseline and 4 months post-baseline. The association between sleep characteristics and recurrence was explored in the full study population and the sub-sample defined as fully platinum-sensitive. We estimated Kaplan-Meier survival curves of the probability of remaining recurrence-free during follow-up according to categories of each of the sleep characteristics. For the subset of women who were fully platinum-sensitive, i.e., who responded to chemotherapy for 12 months, baseline was defined as 12 months after the end of chemotherapy, and we used their reported sleep characteristics from the second interview, which was closest to this baseline.

We then calculated hazard ratios (HR) and the corresponding 95 % confidence intervals (CI) for the association between each sleep characteristic and ovarian cancer recurrence using Cox proportional hazards models. For the analysis of the overall study population, participants had up to two exposure measurements (i.e., baseline and 4 months later), so we used time-dependent Cox regression models. For the subgroup analysis of fully platinum-sensitive women, only the 4-month post-baseline exposure measurement was considered. The proportional hazards assumption was assessed with Schoenfeld residuals and the Grambsch-Therneau test; for each sleep characteristic, the assumption seemed satisfied ($p>0.05$ for each sleep characteristic). Graphics of Schoenfeld residuals were consistent with the Grambsch-Therneau test.

Potential confounding in the Cox models was addressed using a propensity score approach with inverse probability weighting (IPW), in order to minimize the degrees of freedom in our models given the limited sample size (Austin and Stuart, 2015). The propensity scores, defined as the probability of exposure, for each binary sleep characteristic were estimated using logistic regression. Covariates included in the propensity score models were the minimally sufficient set of confounders identified with a directed acyclic graph (DAG; Figure S1), based on a literature review (Austin and Stuart, 2015), and included: age at diagnosis (continuous), FIGO stage at diagnosis (I-II, III-IV), smoking status (never, ever), quality of life (continuous), physical activity (meeting guidelines, not meeting guidelines) and diet quality (continuous). Time-varying covariates, i.e., covariates whose values could change during follow-up, included smoking status, quality of life, physical activity, and diet quality. Time-fixed covariates were age at diagnosis and FIGO stage at diagnosis. Given the low proportion of missing values among covariates (≤3%), we used simple imputation of the mode for categorical variables and the median for continuous variables.

Each participant had up to two propensity scores, the first estimated with baseline covariates and sleep characteristics and the second with covariates and sleep characteristics at 4 months post-baseline. For continuous covariates, the assumption of linearity between the variable and the logit of the probability of exposure was visually checked with graphs and tested using a multivariable fractional polynomials (MFP) approach (Zhang, 2016). Based on a likelihood ratio test, the model with the best-fitting second-degree fractional polynomial function was compared to the model with linear terms (Zhang, 2016). All tests were non-significant at an α alpha level of 0.05. Based on both approaches, linear terms were adopted.

Based on the estimated model parameters, we calculated propensity scores for each participant, the inverse of which was then used as weights in the Cox regression models. We used stabilized weights to avoid extreme weights and for appropriate variance estimates (Austin and Stuart, 2015; Xu et al., 2010). We assessed the balance of covariates before and after IPW using standardized mean differences (SMD) (Austin and Stuart, 2015). A variable with an absolute SMD value of less than 0.1 was considered well-balanced (Austin and Stuart, 2015). After weighting, all covariates showed acceptable balance between exposure groups. All statistical analyses were performed using R statistical software, version 4.3.0.

## 3. Results

The 97 women included in this study were recruited and interviewed an average of 6 months (5th and 95th percentile: 5.3 and 7.4 months, respectively) following the end of first-line chemotherapy. During follow-up (median, 18.5 months; interquartile range, 24.0 months), 47 recurrences occurred. Observations on six participants were censored at the date they were randomized into a clinical trial. Three participants were lost to follow-up, with the corresponding observations censored at

**Table 1**
Characteristics of HPROQ study participants at baseline.

| | Total (n = 97) |
|---|---|
| **Continuous variables, mean (SD)** | |
| Age at diagnosis | 60.1 (8.8) |
| Diet quality[1] | 69.0 (9.6) |
| Quality of life[2] | 116.7 (16.4) |
| **Categorical variables, n (%)** | |
| FIGO stage at diagnosis | |
| I-II | 28 (28.9) |
| III-IV | 69 (71.1) |
| Treatment | |
| Adjuvant | 51 (52.6) |
| Neoadjuvant | 46 (47.4) |
| Ancestry | |
| French-Canadian | 68 (70.1) |
| Other European | 17 (17.5) |
| Other/mixed | 12 (12.4) |
| Education level | |
| ≤High school | 38 (39.2) |
| College/technical | 22 (22.7) |
| ≥University | 37 (38.1) |
| Smoking status | |
| Never | 44 (45.4) |
| Ever | 53 (54.6) |
| Body mass index | |
| Normal (<25 kg/m$^2$) | 46 (47.4) |
| Overweight (25–29.9 kg/m$^2$) | 27 (27.8) |
| Obese (>29.9 kg/m$^2$) | 24 (24.7) |
| Physical activity | |
| Meeting guidelines[3] | 66 (68.0) |
| Not meeting guidelines | 31 (32.0) |

SD: Standard deviation. FIGO: International Federation of Gynecology and Obstetrics.

[1] Based on the Canadian Healthy Eating Index 2005 (score range: 0 to 100).

[2] Measured with the Functional Assessment of Cancer Therapy-Ovarian (score range: 0 to 152).

[3] Defined as ≥360 MET-minutes/week, as recommended for cancer survivors.

the participant's last follow-up visit. Table 1 presents sociodemographic, clinical, and lifestyle characteristics of the HPROQ study population at baseline (6 months post-treatment). The mean (SD) age at diagnosis was 60 (8.8) years. The majority of women were of French-Canadian ancestry (70 %), had been diagnosed with advanced stage (III-IV) ovarian cancer (71 %), and just over half had received adjuvant therapy (53 %). Regarding lifestyle habits, around half of the study participants had a normal BMI (47 %) and had never smoked (45 %). The majority of women met physical activity targets for cancer survivors (68 %) at baseline (Campbell et al., 2019). The mean (SD) diet quality score based on the C-HEI 2005 was 69 (9.6). The global score of this questionnaire ranges from 0 to 100, with higher scores indicating better diet quality. The mean (SD) quality of life score based on the FACT-O was 117 (16.4). The global score of this questionnaire ranges between 0 and 152, with higher scores indicating better quality of life.

Sleep characteristics at baseline and 4 months later remained similar across the study population (Table 2). The median PSQI score was 7, with most women having poor sleep quality (PSQI>5). Over 50 % of the study population had poor sleep efficiency (<85 %), with a median sleep efficiency of around 83 %. Moreover, the median sleep duration was 7 h, with around half of the women not meeting sleep duration guidelines. Of the women who did not meet sleep duration guidelines, shorter and longer durations were experienced by 36 % and 16 % at baseline, respectively, and 40 % and 12 % 4 months later. The median ISI score was 5 at baseline and 6 at 4 months post-baseline, with the majority not having insomnia (ISI<8). In addition, the median sleep latency was 15 min, with most women falling within the normal range (i.e., 30 min or less) (Buysse et al., 1989). Finally, 60 % of women had not used sleep medication in the previous month, while approximately a quarter reported using sleep medication three or more times weekly.

Table 2 presented sleep characteristics at the two time points at the population level. At the individual participant level, from baseline to 4 months later, there were 20 women who changed categories for overall sleep quality, 17 for sleep duration guidelines, 22 for sleep efficiency, 18 for insomnia, and 13 for sleep latency. Among those women, just over half went from not meeting to meeting sleep duration guidelines (53 %), from poor to good sleep efficiency (55 %), from presence to absence of insomnia (61 %), from good to poor sleep latency (54 %), and from good to poor overall sleep quality (55 %).

**Table 2**
Sleep characteristics of ovarian cancer survivors at baseline and 4 months later.

| | Baseline (n = 97) | 4 months (n = 77) |
|---|---|---|
| **Sleep quality** | | |
| Good (PSQI ≤ 5) | 42 (43.3) | 30 (39.0) |
| Poor (PSQI>5) | 55 (56.7) | 47 (61.0) |
| Median PSQI score, IQR | 7.0 [4.0–10.0] | 7.0 [4.0–10.0] |
| **Sleep duration, *hours*** | | |
| Meeting guidelines (7–8.5) | 46 (47.4) | 37 (48.1) |
| Not meeting (<7 or >8.5) | 51 (52.6) | 40 (51.9) |
| Median sleep duration, IQR | 7.0 [6.0–8.0] | 7.0 [6.0–8.0] |
| **Sleep efficiency, *%*** | | |
| Good (≥85) | 44 (45.4) | 35 (45.5) |
| Poor (<85) | 53 (54.6) | 42 (54.5) |
| Median sleep efficiency, IQR | 82.4 [70.0–91.4] | 83.3 [75.0–90.0] |
| **Insomnia** | | |
| Absence (ISI<8) | 61 (62.9) | 50 (64.9) |
| Presence (ISI≥8) | 36 (37.1) | 27 (35.1) |
| Median ISI score, IQR | 5.0 [2.0–11.0] | 6.0 [3.0–9.0] |
| **Sleep latency, *minutes*** | | |
| Good (≤30) | 76 (78.4) | 59 (76.6) |
| Poor (>30) | 21 (21.6) | 18 (23.4) |
| Median sleep latency, IQR | 15 [5.0–30.0] | 15 [10.0–30.0] |
| **Use of sleep medication** | | |
| None | 59 (60.8) | 45 (58.4) |
| <1/week | 8 (8.2) | 6 (7.8) |
| 1–2 times/week | 2 (2.1) | 6 (7.8) |
| ≥3 times/week | 28 (28.9) | 20 (26.0) |

IQR: Interquartile range. Data are presented as n (%) for categorical variables and median (IQR) for continuous variables.

Overall, the median recurrence-free survival time in the cohort was 27.1 months (i.e., 2.3 years). Kaplan-Meier survival curves for the overall study population suggested that recurrence probabilities over follow-up were higher in those with baseline characteristics of good sleep quality, good sleep efficiency, absence of insomnia, and not meeting sleep duration guidelines (Fig. 1). For the results from the Cox regression models, given the limited sample size and exploratory nature of our analysis, we highlight the direction and magnitude of the estimated HRs, accounting for the width of the 95 % CI (i.e., the precision of the HR estimates) and whether the null value (i.e., HR = 1) was included in the CI, indicating that the HR was not statistically significant. In the overall study population, crude HR estimates were consistent with the Kaplan-Meier curves, suggesting a lower recurrence risk for poor vs. good sleep quality, poor vs. good sleep efficiency, and the presence vs. absence of insomnia, although the 95 % CIs were very wide (Table 3). However, in the IPW models, which took into account a number of potential confounders, these HRs were attenuated and for sleep quality and sleep efficiency, the IP-weighted HRs were virtually null. For sleep duration, both the crude and IP-weighted HRs suggested an increased risk of recurrence associated with not meeting guidelines, but again, the 95 % CIs were very wide.

Among women who were fully sensitive to platinum-based chemotherapy, where baseline was defined as 12 months post-treatment, 24 recurrences occurred over a median follow-up of 19.3 months (interquartile range: 19.4 months). Kaplan-Meier survival curves suggested that recurrence probabilities over follow-up were higher in those with good sleep quality and not meeting sleep duration guidelines (Fig. 2), while recurrence probabilities were similar between groups for sleep efficiency and insomnia. In Cox proportional hazards models (Table 4), 95 % CIs were wide and included the null value, but the crude HRs were in the direction of a lower recurrence risk for poor vs. good sleep quality and the presence vs. absence of insomnia. However, in the IPW models, the HR was null for poor sleep quality, and above the null for the presence of insomnia. Both the crude and IP-weighted HRs suggested an increased risk of recurrence for not meeting vs. meeting sleep duration guidelines, and poor vs. good sleep efficiency.

In sensitivity analyses, the results remained similar in the overall study population (**Table S1**) when using a PSQI threshold of 8, which has been proposed for cancer patients (Chen et al., 2018). For insomnia, the HR was weaker when using an ISI threshold of 11, indicating more severe insomnia (IP-weighted HR, 0.82; 95 % CI, 0.56–1.97) (Morin et al., 2011). In fully platinum-sensitive women (**Table S2**), the HR suggested an increased recurrence risk for poor vs. good sleep quality when using a threshold of 8 (IP-weighted HR, 1.29; 95 % CI, 0.53–3.14), but was weaker (null) for the presence vs. absence of insomnia when using a threshold of 11 (IP-weighted HR, 1.04; 95 % CI, 0.35–3.12).

## 4. Discussion

In this study population of women entering remission after treatment for high-grade ovarian cancer, we observed that the majority experienced poor sleep quality, with over half having poor sleep efficiency and not meeting sleep duration guidelines, though most did not experience insomnia symptoms. The distribution of the population according to these sleep characteristics did not appreciably change when measured 4 months later. In our analysis of associations with ovarian cancer recurrence, confidence intervals were wide as expected, but the adjusted HRs in the overall study population suggested an increased recurrence risk with not meeting sleep duration recommendations, while associations were virtually null for sleep quality and sleep efficiency, and inverse for insomnia. Among fully platinum-sensitive women, the adjusted HRs similarly suggested a greater recurrence risk for those who did not meet sleep duration guidelines, as well as for those who had poor sleep efficiency and experienced insomnia, while the association remained null for overall sleep quality.

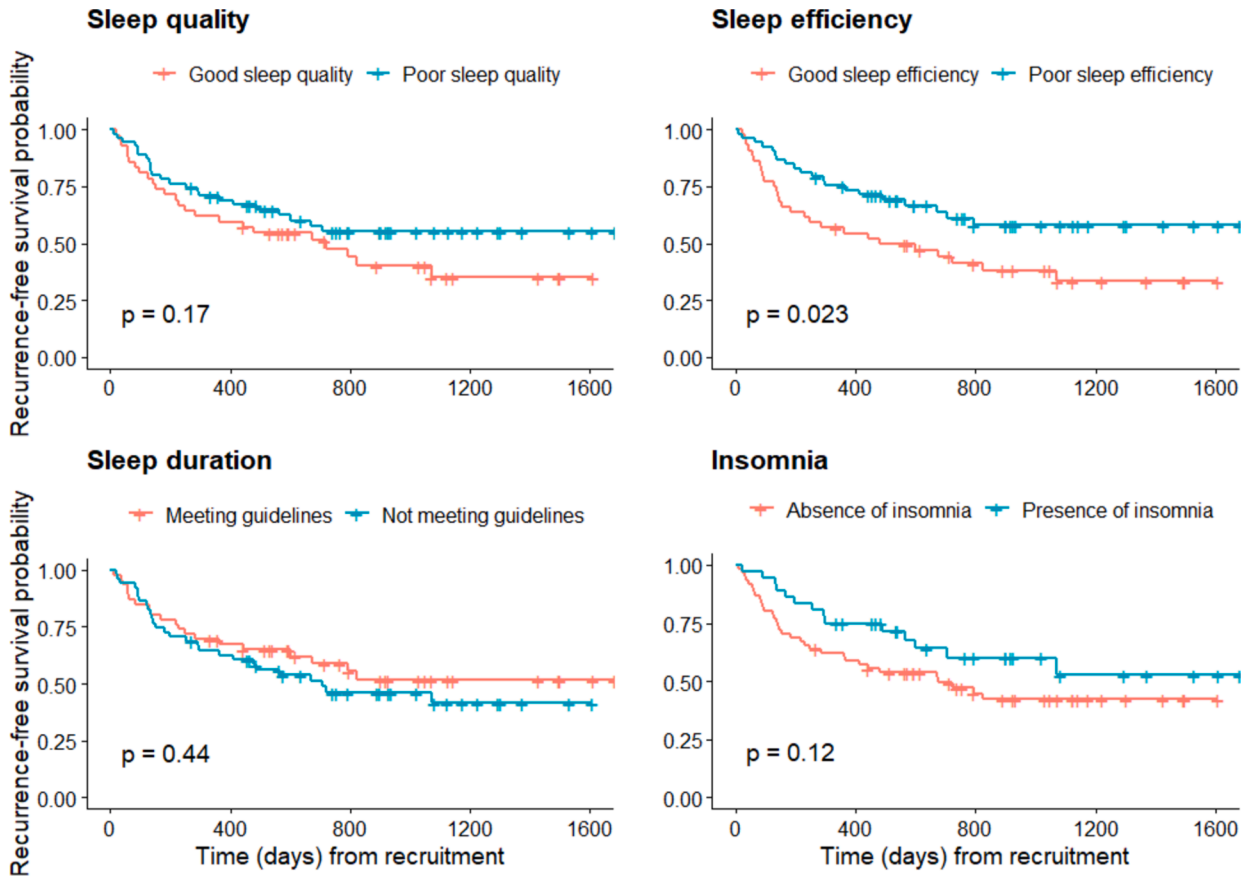


**Fig. 1.** Kaplan-Meier recurrence-free survival curves and p-values from log-rank tests for each sleep characteristic in the overall study population.

**Table 3**
Hazard ratios and 95% confidence intervals for sleep characteristics in relation to ovarian cancer recurrence, in the overall study population.

| | Person-months of observation | Events, n | Crude HR (95 % CI) | IP-weighted HR[1] (95 % CI) |
|---|---|---|---|---|
| **Sleep quality** | | | | |
| Good (PSQI≤5) | 787.7 | 22 | 1.00 (ref.) | 1.00 (ref.) |
| Poor (PSQI>5) | 1183.0 | 25 | 0.76 (0.43–1.35) | 1.03 (0.56–1.89) |
| **Sleep duration** | | | | |
| Meeting guidelines (7–8.5 h) | 1064.3 | 20 | 1.00 (ref.) | 1.00 (ref.) |
| Not meeting (<7h or >8.5 h) | 906.4 | 27 | 1.39 (0.78–2.49) | 1.22 (0.66–2.23) |
| **Sleep efficiency** | | | | |
| Good (≥85 %) | 906.9 | 23 | 1.00 (ref.) | 1.00 (ref.) |
| Poor (<85 %) | 1063.8 | 24 | 0.83 (0.47–1.47) | 0.94 (0.52–1.69) |
| **Insomnia** | | | | |
| Absence (ISI<8) | 1277.7 | 35 | 1.00 (ref.) | 1.00 (ref.) |
| Presence (ISI 8) | 692.9 | 12 | 0.57 (0.30–1.10) | 0.68 (0.34–1.39) |

[1] Model IP-weighted for age at diagnosis, stage at diagnosis, quality of life, physical activity, diet quality, and smoking status.

Consistent with our research, prior studies evaluating sleep quality in women diagnosed with ovarian cancer reported a prevalence of poor sleep quality of 58–67 % after treatment (Clevenger et al., 2013; Sandadi et al., 2011). For insomnia, the prevalence was 33 % two years after diagnosis in one study and 60 % in a population undergoing treatment for recurrent ovarian cancer (Ross et al., 2020; Webber et al., 2019). One previous study using the PSQI reported a prevalence of 51 % and 43 % of poor sleep efficiency and sleep medication use, respectively, among ovarian cancer survivors two years after diagnosis, consistent with our research (Sandadi et al., 2011). This study also reported that 59 % of ovarian cancer survivors slept <7 h/night, which is higher than the 36–40 % prevalence we observed. However, 81 % of their study population was receiving chemotherapy at the time of sleep measurement, which may explain the observed difference. Finally, the same study reported a 28 % prevalence of good sleep latency (<15 min), whereas we observed a much higher 78 % prevalence (Sandadi et al., 2011). However, their category of poor sleep latency (≥15 min) was included within our category of good sleep latency (<30 min), thereby affecting comparisons./

With regard to the relation between sleep characteristics and prognosis among ovarian cancer survivors, only one previous study has been published (Li et al., 2022). In this Chinese cohort study, where sleep was measured during the month prior to diagnosis, longer sleep duration (>7.5 h vs. 7–7.5 h) was associated with a lower risk of all-cause mortality, whereas a null association was observed for shorter sleep durations (<7h vs. 7–7.5 h) (Li et al., 2022). This contrasts our observed HRs that suggested that not meeting sleep duration guidelines may contribute to an increased risk of recurrence. Given our limited sample size, we could not separately examine longer and shorter durations. Moreover, the category for long sleep duration in the Chinese study of >7.5 h was included within our reference category of meeting guidelines (7–8.5 h), thus affecting comparisons between studies.

The study from China also examined sleep quality and observed that a PSQI score >5 was associated with an increased risk of all-cause mortality (Li et al., 2022), whereas the HRs we observed were null,

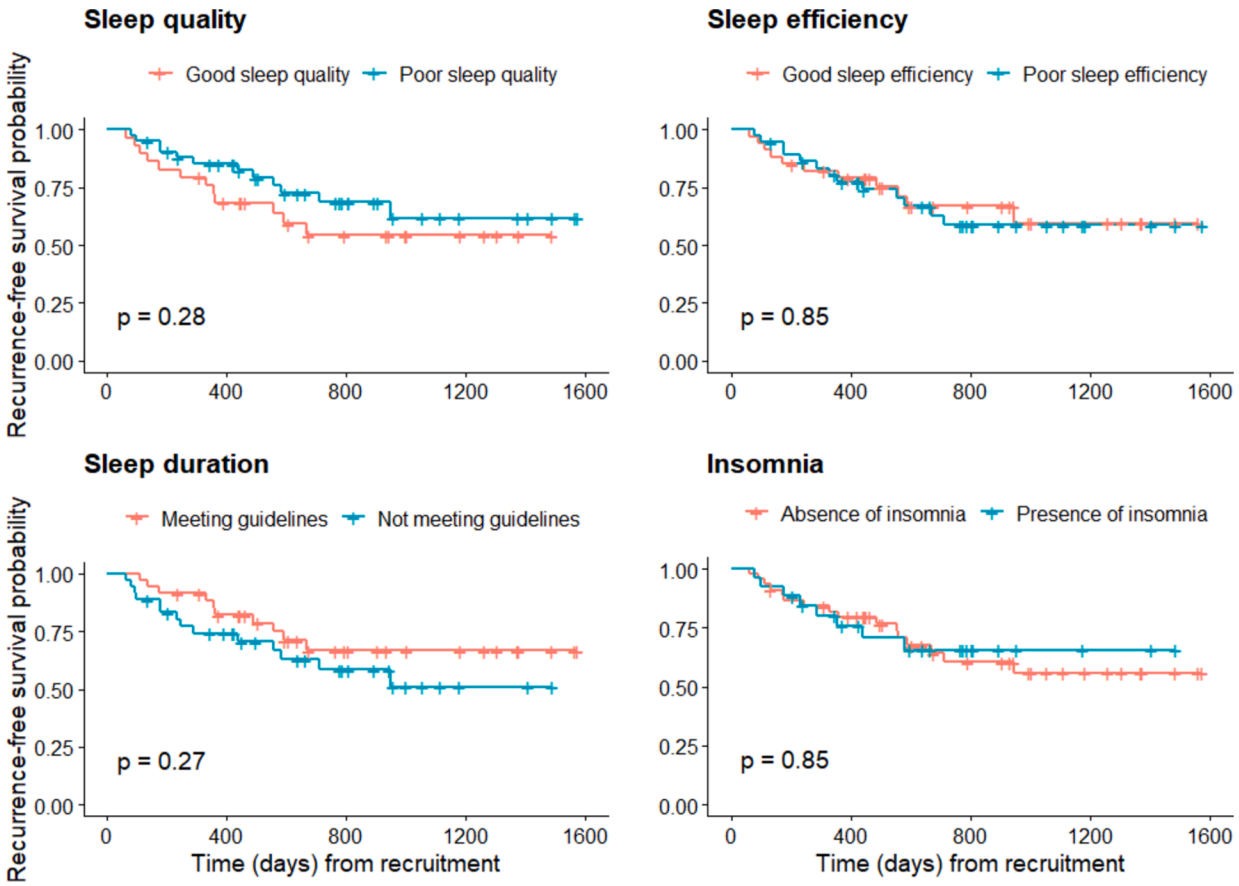


**Fig. 2.** Kaplan-Meier recurrence-free survival curves and p-values from log-rank tests for each sleep characteristic in fully platinum-sensitive women.

**Table 4**
Hazard ratios and 95% confidence intervals for sleep characteristics in relation to ovarian cancer recurrence, in fully platinum-sensitive women.

| | Person-months of observation | Events, n | Crude HR (95 % CI) | IP-weighted HR[1] (95 % CI) |
|---|---|---|---|---|
| **Sleep quality** | | | | |
| Good (PSQI ≤ 5) | 601.5 | 12 | 1.00 (ref.) | 1.00 (ref.) |
| Poor (PSQI>5) | 931.4 | 12 | 0.65 (0.29–1.44) | 0.99 (0.38–2.56) |
| **Sleep duration** | | | | |
| Meeting guidelines (7–8.5 h) | 834.5 | 10 | 1.00 (ref.) | 1.00 (ref.) |
| Not meeting (<7h or >8.5 h) | 698.4 | 14 | 1.57 (0.70–3.54) | 1.50 (0.64–3.53) |
| **Sleep efficiency** | | | | |
| Good (≥85 %) | 750.9 | 11 | 1.00 (ref.) | 1.00 (ref.) |
| Poor (<85 %) | 782.0 | 13 | 1.08 (0.48–2.42) | 1.25 (0.56–2.79) |
| **Insomnia** | | | | |
| Absence (ISI<8) | 1020.5 | 16 | 1.00 (ref.) | 1.00 (ref.) |
| Presence (ISI 8) | 512.4 | 8 | 0.92 (0.39–2.16) | 1.44 (0.55–3.72) |

[1] Model IP-weighted for age at diagnosis, stage at diagnosis, quality of life, physical activity, diet quality, and smoking status.

though very imprecise. Unlike our study population of women with aggressive ovarian cancer types, their study population included all ovarian cancer types and thus was more heterogeneous than our population with respect to likely survival experience, which differs by grade and histology (Ezzati et al., 2014). Furthermore, they examined pre-diagnostic sleep which may not be indicative of sleep after treatment and recovery. Indeed, women tend to adopt a healthier lifestyle after being diagnosed with ovarian cancer, and sleep quality may improve in the six months following treatment (Clevenger et al., 2013; Alimujiang et al., 2019).

A recently published Mendelian randomization study found that genetically predicted insomnia was associated with shorter survival of invasive epithelial ovarian cancer (Wang et al., 2024). Moreover, a recent systematic review on post-diagnostic sleep and breast cancer outcomes suggested that insomnia was associated with an increased risk of all-cause mortality (D'Cunha et al., 2023). This systematic review also suggested that poor sleep efficiency (<85 %) may be associated with an increased risk of breast cancer progression (D'Cunha et al., 2023). These findings are consistent with the direction of the associations in our study, suggesting that poor sleep efficiency and insomnia may contribute to an increased risk of recurrence in women who are fully platinum-sensitive.

A possible limitation of our study is that participants self-reported their sleep, which may have led to errors compared to more objective sleep measurements such as polysomnography and actigraphy (Chen et al., 2018). For the observed associations with recurrence, since sleep was assessed prior to recurrence, any misclassification is expected to be non-differential, which in most cases, would bias HR estimates toward the null value. Furthermore, recall errors were likely minimized as participants were asked to report their sleep from the last month, which is a recent and short period. To ensure the validity of sleep measures, we used standardized questionnaires that have been validated in clinical and research populations (Buysse et al., 1989; Chen et al., 2018; Fabbri et al., 2021). In addition, by measuring sleep characteristics at two different time points during follow-up, we were able to observe sleep

trends over the four-month period and consider changes in sleep variables that may affect the risk of recurrence.

The 3 % loss to follow-up rate suggests that the reported HR estimates were likely not greatly affected by selection bias. We used a DAG to conceptualize the relationships between several variables, including key prognostic factors for ovarian cancer, and we adjusted for these using a propensity score approach, which allowed for parsimony in our statistical models. Nonetheless, the possibility of uncontrolled confounding due to unknown or unmeasured confounders cannot be ruled out, particularly given the limited understanding of the mechanisms involved in ovarian cancer progression.

A strength of our study is that all participants were in the same phase in their trajectory as a cancer survivor, i.e., 6 months post-treatment. In addition, all participants had had a high-grade ovarian cancer type. Thus, the distribution of sleep characteristics may not apply to survivors of less aggressive ovarian cancer types, and their associations with recurrence may also differ, given the differences in survival outcomes by ovarian cancer type (Ezzati et al., 2014).

In summary, our study provides a comprehensive description of sleep characteristics among high-grade epithelial ovarian cancer survivors. Specifically, it is the first study to describe the distribution of specific sleep characteristics in platinum-sensitive ovarian cancer survivors entering remission, and to explore their relation with ovarian cancer recurrence. Our findings provide information on the possible direction of relationships with prognosis that can be followed up in future research with larger cohort sizes. Further longitudinal studies may also consider objective sleep measures, such as that provided by accelerometers, to complement subjective measures of sleep quality and thus offer a better understanding of the relationships (Kreutz et al., 2021; Donzella et al., 2024).

## CRediT authorship contribution statement

**Mélanie Benoit:** Writing – review & editing, Writing – original draft, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Marie-Pierre Sylvestre:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Geetanjali Datta:** Writing – review & editing, Conceptualization. **Lucy Gilbert:** Writing – review & editing, Resources. **Vikki Ho:** Writing – review & editing, Conceptualization. **Igor Karp:** Writing – review & editing, Conceptualization. **Julie Lacaille:** Writing – review & editing, Resources. **Susie Lau:** Writing – review & editing, Resources. **Vanessa Samouëlian:** Writing – review & editing, Resources. **Anita Koushik:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gore.2024.101540.

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