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Sleep Characteristics and Risk of Ovarian Cancer Among Postmenopausal Women

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ABSTRACT

Several studies have assessed the relationship between sleep duration and ovarian cancer risk, but the results are conflicting. Importantly, no studies addressed the relationship between sleep disturbance or sleep quality and ovarian cancer incidence. Moreover, few studies have examined the relationships between sleep measures and subtypes of ovarian cancer. This study included 109,024 postmenopausal women ages 50–79 from the Women's Health Initiative during 1993–1998 and followed through 2018. The Cox proportional hazards model was used to estimate adjusted HRs for the associations between sleep habits and the incidence of ovarian cancer and its subtypes. No association was observed between sleep duration, sleep quality, sleep disturbance, or insomnia and risk of overall ovarian cancer, serous/nonserous, or type I/type II ovarian cancer subtype. However, compared with women with average sleep quality, women with restful or very restful sleep quality had a significantly lower risk of invasive serous subtype [HR: 0.73, 95% confidence interval (CI): 0.60–0.90] while insomnia was associated with a higher risk of invasive serous subtype (HR: 1.36, 95% CI: 1.12–1.66). Associations with insomnia differed significantly by serous and nonserous subtypes, and type I and type II subtypes ($P_{\text{heterogeneity}} = 0.001$ and $P_{\text{heterogeneity}} < 0.001$, respectively). This study provides no evidence on association between sleep habits and overall ovarian cancer risk among postmenopausal women. However, restful or very restful sleep quality was associated with a lower risk of invasive serous ovarian cancer, and insomnia was associated with a higher risk of invasive serous ovarian cancer. Associations with insomnia differed by subtypes.

Prevention Relevance: This study shows no association between sleep duration, sleep quality, or insomnia with the risk of overall ovarian cancer among postmenopausal women. However, restful sleep quality was associated with a lower risk of invasive serous ovarian cancer, and insomnia was associated with a higher risk of invasive serous ovarian cancer.

Introduction

In 2020, it is estimated that 21,750 U.S. women will be diagnosed with ovarian cancer and 13,940 will die from it with ovarian cancer being the leading cause of gynecologic cancer death (1). Established risk factors for ovarian cancer overall or for specific histotypes include genetic factors (e.g., BRCA mutations, Lynch syndrome), family history of breast or ovarian cancer, lifestyle factors (e.g., obesity, tobacco smoking), and health conditions (e.g., endometriosis, pelvic inflammatory disease). Protective factors include fallopian tube ligation or removal, use of oral contraceptives and pregnancy (1).

Sleep plays an important role in promoting health (2). However, more than one-third of the adults in the United States do not get the recommended 7 to 8 hours of sleep per day (3). Several studies have assessed the relationship between sleep duration and ovarian cancer risk with conflicting results (4–6). Importantly, none of these studies addressed the relationship between sleep disturbance or sleep quality and ovarian cancer incidence.

There are five major histotypes of ovarian cancer (high-grade serous, low-grade serous, endometrioid, clear cell, and mucinous; ref. 7), of which the high-grade serous histotype is the most common ovarian cancer; no other single type accounts for more than 10% of cases (1, 8). Each histotype differs with respect to risk factors (9), high-grade serous cancer has the fewest established risk factors (1), while most established risk factors are more strongly associated with nonserous cancer, particularly the endometrioid and clear cell histotypes (10). However, few studies have had adequate sample size to assess

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Note: Supplementary data for this article are available at Cancer Prevention Research Online (http://cancerprevres.aacrjournals.org/).

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the relationship between sleep measures and subtypes of ovarian cancer.

One potential pathway between insufficient and poor sleep and cancer risk is through the disruption of neuroendocrine and immune circadian rhythms (11). Sleep disturbances also can result in immune suppression and a shift to a predominance in cancer-stimulatory cytokines (12).

The Women's Health Initiative (WHI) is a large prospective cohort study with extensive data on risk factors and over 20 years of follow-up. Here, we leveraged the rich WHI dataset to assess the associations between sleep duration, sleep quality, and sleep disturbance and incidence of ovarian cancer and its subtypes among postmenopausal women.

Materials and Methods

Participants

Detailed description about study design of the WHI was published previously (13). A total of 161,808 postmenopausal women between 50 and 79 years of age were recruited from 1993 to 1998 into an Observational Study (OS) or one or more of three Clinical Trials (CT) in 40 U.S. clinical centers. Participants completed screening and enrollment questionnaires by self-report, interview, and physical examination. The study was conducted in accordance with the ethical guidelines of the U.S. Common Rule which is based on the Belmont Report. Approval of the study was obtained from institutional review boards at the WHI Clinical Coordinating Center and 40 clinical centers. All study subjects gave written informed consent.

For this analysis, women were excluded if they had a history of cancer other than nonmelanoma skin cancer at baseline (n = 12,655), had bilateral oophorectomy at baseline (n = 27,627), or provided no follow-up data (n = 515). Women with missing data on sleep duration, sleep quality, or sleep disturbance (n = 2,775) or missing covariate data, that is, body mass index (BMI), physical activity, smoking, alcohol consumption, age at menarche, number of term pregnancies, use of oral contraceptives, and postmenopausal hormone therapy (n = 9,212), were also excluded. For family history of breast or ovarian cancer, menopausal symptoms and depressive symptoms with larger numbers of missing data, we created indicator variables and included them in the multivariable model. A flowchart showing derivation of the included study population is presented as **Fig. 1**.

Exposure measurement

Sleep duration, sleep quality, and sleep disturbance were assessed through the baseline questionnaire for CT and OS participants, reassessed after one year for all CT participants and for some randomly selected CT participants every 2 years thereafter, and reassessed 3 years after baseline screening for OS participants. While in the primary analyses, we used sleep measures captured at baseline, in sensitivity analyses we updated the sleep measures over time based on follow-up questionnaires responses.

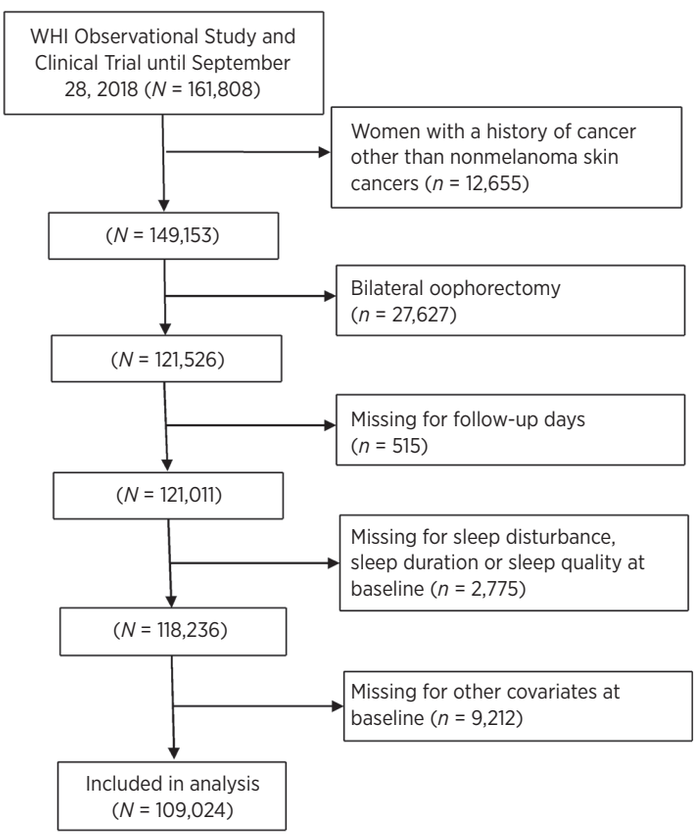

Figure 1.
Flow diagram of participants included in the analysis.

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For sleep duration, the question is "about how many hours of sleep did you get in a typical night during the past 4 weeks?"; women reported 5 hours or less, 6, 7, 8, 9, or 10 hours or more. We collapsed sleep duration categories of 9 and 10 hours or more of sleep to preserve sample size. Sleep quality, sleep disturbance level, and insomnia came from the WHI Insomnia Rating Scale (WHIIRS; ref. 14) which is composed of five sleep-related questions describing the situation in the past 4 weeks: (i) Did you have trouble falling asleep? (ii) Did you wake up several times at night? (iii) Did you wake up earlier than you planned to? (iv) Did you have trouble getting back to sleep after you woke up too early? (v) Overall, was your typical night's sleep: very restless, restless, average quality, sound or restful, or very sound or restful. Sleep quality was derived from the fifth question. There were only a small number of women with very restless sleep quality, which were combined with women who reported restless sleep quality, and restful and very restful were also combined into one category. Each WHIIRS item was measured on a scale of 0–4, and an overall sleep disturbance score was computed on the basis of 5 items ranging from 0 to 20 with a higher score indicating greater sleep disturbance. The sleep disturbance variable (0–4, 5–8, and 9–20) was created with three categories based on the tertile score distribution, and a score of 9 or above was used to measure problematic insomnia (15). Reliability and validity of the WHIIRS have been evaluated previously (15, 16), and test–retest correlations for WHIIRS were 0.96, 0.79, 0.70 for same-day, over-one-month, and over-one-year administration, respectively (15).

Outcome measurement

The primary outcome of interest was incident ovarian cancer. The diagnosis of ovarian cancer was identified through self-administered questionnaires, then confirmed by a review of pathology reports, and subsequently adjudicated by a local Clinical Center and then centrally by the WHI Clinical Coordinating Center (17). In this study, 83.2% (832) of ovarian cancer was centrally adjudicated, 0.1% (1) was locally adjudicated. A total of 16.7% (167) of ovarian cancer were only determined by the cause of death.

Histology, grade, and stage were available for the first ovarian cancer diagnosis (83.3%, 833). To explore the effect of sleep habits on the risk of specific ovarian cancer subtypes, serous (including borderline and invasive; codes 8020, 8021, 8022, 8050, 8120, 8130, 8260, 8441, 8442, 8450, 8460, 8461, 8462, 8463, and 9014) and nonserous ovarian cancer were grouped on the basis of International Classification of Disease on Oncology, Second edition (ICD-O-2). There were 484 serous (448 invasive serous) and 349 nonserous ovarian cancer (70 endometrioid, 48 mucinous, 37 clear cell, and 194 other epithelial subtypes).

Information about histology, grade, and stage was used to identify two groups of invasive epithelial ovarian cancer: type I including endometrioid, clear cell, low-grade serous, and mucinous carcinomas and malignant Brenner tumors, and type II including high-grade serous carcinoma, carcinosarcoma, undifferentiated carcinoma, and mixed carcinoma (18). There were 117 type I and 607 type II ovarian cancer.

For 167 ovarian cancer cases who were solely identified from the cause of death, the end of follow-up was date of death. For other women, follow-up duration was defined as baseline to the date of ovarian cancer diagnosis, date of death, loss to follow-up, or end of study period (September 28, 2018), whichever happened first.

Covariates

Data on covariates were collected at baseline for the study participants. The potential confounders used in multivariable analyses included age (continuous), race/ethnicity (black or African-American, Hispanic or Latina, non-Hispanic white, and other), BMI (<25, 25–<30, ≥30), physical activity as a continuous variable (METs/week), smoking (past smoker, current smoker, and never smoker), alcohol intake (<7 drinks/week, ≥7 drinks/week), age at menarche (<12, 12–13, 14–15, ≥16), parity [0 (combining never pregnant and never had term pregnancy), 1, 2, 3, 4, ≥5], family history of breast or ovarian cancer (yes/no), use of oral contraceptives (yes/no), menopausal symptoms (yes in case of hot flashes or night sweats, no in case of neither hot flashes nor night sweats), postmenopausal hormone therapy (yes/no), depressive symptoms (yes/no), and treatment arms in each CT (not enrolled, intervention group, or control group). Depression scores were computed from a short (6-item) form of the Center for Epidemiologic Studies Depression (CES-D) Scale plus two questions from the National Institute of Mental Health's Diagnostic Interview Schedule (DIS). We categorized depressive symptoms as no/yes based on a previously established cutpoint of 0.06 (19).

Statistical analysis

Participants' characteristics were compared among women with different levels of sleep duration and between women with insomnia (≥9 on the WHIIRS) and without. Means ± SDs were used to describe continuous characteristics, while proportions were used for categorical variables. ANOVA and t test were used for continuous variables, and χ^2 tests were used to analyze categorical variables.

The Cox proportional hazards model was used to calculate HRs and 95% confidence intervals (CI) of ovarian cancer according to the exposures of interest. Associations by the histotype (serous, invasive serous, nonserous; type I, type II) were also evaluated. For each histotype, the event variable was coded as 1 (failed) if the study participant was diagnosed with this histotype and 0 with any other histotype. Women with ovarian cancer in other histotypes were censored at the time of diagnosis. $P_{\text{heterogeneity}}$ across histotypes (serous/nonserous; type I/type II) was calculated using logistic regression model which took serous ovarian cancer or type II ovarian cancer as the reference, excluded noncases and entered sleep measurements as continuous variables (20).

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In the Cox models, potential confounders included age at baseline, race/ethnicity, body mass index, physical activity, smoking, alcohol intake, age at menarche, parity, family history of breast or ovarian cancer, use of oral contraceptives, postmenopausal hormone therapy, depressive symptoms, and treatment arms in each CT. The assumption of the proportional hazards in the Cox model was checked on the basis of the Schoenfeld residuals, and the assumption was met.

Similar to previous studies (21, 22), we examined whether the associations between sleep duration, sleep quality, sleep disturbance, and insomnia and overall ovarian cancer/serous ovarian cancer/invasive serous/type II ovarian cancer were modified by hysterectomy at baseline (yes/no), age at baseline (<70, ≥70), obesity status (BMI <30, ≥30), prior use of oral contraceptives (yes/no), postmenopausal hormone therapy (yes/no), parity (nulliparous, 1–2, ≥3), depression (yes/no) and WHI component (OS/CTs). Interactions between each factor and sleep habits were tested by entering multiplicative interaction terms into the models.

We performed two sensitivity analyses. First, we estimated HRs and CIs for ovarian cancer incidence in relation to a combination of insomnia and sleep duration (insomnia and

Table 1. Characteristics of participants by average hours of sleep and insomnia at baseline in the WHI ($n = 109{,}024$).

	Average hours of sleep					Insomnia	
	≤5	6	7	8	≥9	Yes[a]	No
Total number of women	8,809	29,862	41,112	24,525	4,716	32,958	76,066
Age at baseline (mean ± SD, years)	63.1 ± 7.5	63.0 ± 7.3	62.9 ± 7.2	63.4 ± 7.0	63.8 ± 7.1	63.0 ± 7.2	63.4 ± 7.3
Race/ethnicity (%)							
Black or African-American	19.2	11.5	6.0	5.2	7.9	7.8	8.8
Hispanic or Latina	6.0	4.3	3.4	3.3	4.6	4.1	3.8
Non-Hispanic white	66.4	78.3	86.8	88.5	84.8	84.0	82.7
Other	8.4	6.0	3.9	3.1	2.7	4.1	4.8
Body mass index (kg/m^2, %)							
<25	30.1	34.3	38.7	37.3	33.6	34.5	37.0
25–<30	33.1	34.6	34.7	35.0	34.2	34.4	34.7
≥30	36.8	31.1	26.6	27.7	32.3	31.1	28.3
Physical activity (mean ± SD, METs/week)	11.0 ± 13.8	12.3 ± 13.8	13.0 ± 13.7	13.1 ± 14.0	12.2 ± 14.2	13.0 ± 14.1	11.7 ± 13.2
Smoking (%)							
Never	52.6	50.8	51.2	50.7	47.5	49.7	51.5
Former smoker	39.0	41.5	42.2	43.0	44.9	43.4	41.5
Current smoker	8.5	7.7	6.6	6.3	7.6	7.0	7.0
Alcohol intake (7+ drinks/week, %)	27.6	35.3	40.1	42.2	40.0	37.5	38.6
Age at menarche (years, %)							
<12	24.4	22.8	21.2	20.1	19.0	21.9	21.4
12–13	51.5	54.0	56.1	56.2	55.1	54.5	55.4
14–15	19.3	19.0	18.9	19.5	20.3	19.5	19.0
≥16	4.9	4.2	3.8	4.2	5.7	4.1	4.2
Number of term pregnancies (%)							
0[b]	11.8	11.3	11.4	11.4	12.8	10.2	12.0
1	9.9	8.8	8.4	7.6	8.6	8.2	8.6
2	23.8	25.3	25.0	24.9	24.5	24.6	25.1
3	23.0	23.7	24.8	24.8	22.7	24.9	24.0
4	15.0	15.2	15.7	16.2	15.4	16.1	15.4
≥5	16.6	15.7	14.7	15.1	16.0	15.9	15.0
Family history of breast or ovarian cancer (%)	18.5	18.5	19.0	19.4	18.6	19.5	18.6
Use of oral contraceptives (%)	39.3	41.8	43.6	42.4	41.1	42.7	42.3
Menopausal symptoms (%)	70.4	70.7	70.6	69.5	69.4	75.0	68.3
Postmenopausal hormone therapy (%)	45.7	50.0	52.9	53.3	51.1	52.6	51.1
Depressive symptoms (%)	23.8	12.7	7.6	6.8	11.4	19.9	6.2
Clinical trial assignments							
Observation (%)	7.9	26.7	37.9	23.0	4.6	30.3	69.8
Calcium/vitamin D (%)	7.9	28.8	38.0	21.6	3.7	29.3	70.7
Dietary modification (%)	7.9	28.5	38.3	21.6	3.7	28.8	71.2
HRT E-alone (%)	13.1	30.9	32.7	19.4	3.8	37.8	62.2
HRT E+P (%)	8.1	29.2	36.4	22.1	4.2	30.7	69.3
Hysterectomy at baseline (%)	34.4	28.8	25.6	25.0	24.5	30.1	25.7

Note: Differences were significant among the five groups of sleep duration with respect to all of the covariates, and between women with and without insomnia except for use of oral contraceptives and WHI component (OS/CT; ($P < 0.05$).

Abbreviations: HRT, hormone replacement therapy; SD, standard deviation; WHI, Women's Health Initiative.

[a]≥9 on the WHI Insomnia Rating Scale.

[b]Combining never pregnant and never had term pregnancy into "0" for zero term pregnancies.

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5 hours or less, insomnia and 6 hours, insomnia and 7 hours, insomnia and 8 hours, insomnia and 9 hours or more, noninsomnia and 5 hours or less, noninsomnia and 6 hours, noninsomnia and 7 hours, noninsomnia and 8 hours, noninsomnia and 9 hours or more). Second, a time-dependent analysis was used with all measures of sleep duration, sleep quality, sleep disturbance, and insomnia (up to seven measurements) obtained before ovarian cancer diagnosis or censoring.

Tests for trend across the categories of sleep duration, sleep quality, and sleep disturbance were carried out by assigning the ordering number to each category and modeling this variable as a continuous variable. Given multiple exposure measurements and ovarian cancer subtypes, Bonferroni correction was applied, and the significance level was adjusted to 0.003 (0.05/16 tests) (16 combinations of four sleep measures (sleep duration, sleep quality, sleep disturbance level, and insomnia) and four outcomes (overall, serous, invasive serous, and type II ovarian cancer)). All analyses were conducted in STATA version 15.0 (STATA Corp.).

Results

Of 109,024 women in the analysis, there were significant differences among the five groups of sleep duration with respect to all of the covariates, and all of the significant differences existed between women with and without insomnia except for use of oral contraceptives and WHI component (OS/CT; $P < 0.05$; **Table 1**). The mean follow-up time for the whole cohort and 1,000 incident ovarian cancer cases was 15.6 and 9.3 years, respectively.

Compared with women who reported 7 hours of sleep per night, those who reported a lower or greater sleep duration had no increased risk of ovarian cancer, respectively (**Table 2**). Null associations between sleep quality, sleep disturbance level, or insomnia and ovarian cancer risk were also observed. A significant dose-response trend was not found for any variable of sleep duration, sleep quality, or sleep disturbance.

When histotype was considered, serous ovarian cancer comprised 58% of ovarian cancer in this cohort, of which 93% cases were invasive ovarian cancer. No association between sleep quality, sleep disturbance level, or insomnia and serous/nonserous ovarian cancer, or type I/type II ovarian cancer was found (**Tables 3** and **4**). However, compared with women with average sleep quality, women with restful or very restful sleep quality had a significantly lower risk of invasive serous ovarian cancer (HR: 0.73, 95% CI: 0.60–0.90, $P = 0.003$), and insomnia was associated with a higher risk of invasive serous ovarian cancer (HR: 1.36, 95% CI: 1.12–1.66, $P = 0.002$; **Table 3**). Associations with insomnia differed significantly by serous and nonserous subtypes, type I and type II subtypes ($P_{\text{heterogeneity}} = 0.001$ and $P_{\text{heterogeneity}} < 0.001$, respectively; **Tables 3** and **4**).

Table 2. HRs and 95% CIs for ovarian cancer incidence in relation to sleep habits at baseline ($n = 109{,}024$).

			Age-adjusted		Multivariable-adjusted[a]	
	N	Cases	HR	95% CI	HR	95% CI
Sleep duration, hours per night						
≤5	8,809	67	0.87	0.67–1.12	0.92	0.71–1.20
6	29,862	253	0.90	0.77–1.05	0.92	0.78–1.08
7	41,112	408	1		1	
8	24,525	232	0.96	0.81–1.12	0.95	0.80–1.11
≥9	4,716	40	0.90	0.65–1.25	0.89	0.65–1.24
P_{trend}					0.828	
Sleep quality						
Very restless or restless	17,231	151	0.94	0.78–1.14	0.94	0.78–1.14
Average	45,600	438	1		1	
Restful or very restful	46,193	411	0.90	0.79–1.03	0.90	0.78–1.03
P_{trend}					0.324	
Sleep disturbance level						
0–4	40,608	368	1		1	
5–8	35,458	324	1.01	0.87–1.17	1.00	0.86–1.17
9–20	32,958	308	1.07	0.92–1.24	1.06	0.91–1.24
P_{trend}					0.456	
Insomnia						
Yes (sleep disturbance ≥9)	32,958	308	1.06	0.93–1.21	1.06	0.92–1.22
No	76,066	692	1		1	

[a]HR and 95% CI adjusted for age at baseline, race/ethnicity (black or African-American, Hispanic or Latino, non-Hispanic white, and other), body mass index (<25, 25–<30, ≥30), physical activity, smoking (past smoker, current smoker, and never smoker), alcohol intake (<7 drinks/week, ≥7 drinks/week), age at menarche (<12, 12–13, 14–15, ≥16), parity [0 (combining never pregnant and never had term pregnancy), 1, 2, 3, 4, ≥5], family history of breast or ovarian cancer (yes/no), use of oral contraceptives (yes/no), menopausal symptoms (yes/no), postmenopausal hormone therapy (yes/no), depressive symptoms (yes/no), and treatment arms in each CT (not enrolled, intervention group, or control group).

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Table 3. HRs and 95% CIs of ovarian cancer subtype in relation to sleep habits at baseline[a,b].

		Serous ovarian cancer			Invasive serous ovarian cancer			Nonserous ovarian cancer		
	N	Cases	HR	95% CI	Cases	HR	95% CI	Cases	HR	95% CI
Sleep duration, hours per night										
≤5	8,809	33	1.05	0.72–1.53	31	1.08	0.74–1.60	22	0.77	0.48–1.21
6	29,862	122	0.96	0.76–1.20	111	0.94	0.75–1.20	94	0.91	0.70–1.19
7	41,112	196	1		182	1		147	1	
8	24,525	116	0.99	0.79–1.24	107	0.98	0.77–1.24	74	0.84	0.64–1.12
≥9	4,716	17	0.82	0.50–1.34	17	0.88	0.53–1.44	12	0.73	0.41–1.32
P_{trend}				0.731			0.772			0.813
$P_{heterogeneity}$[c]	0.961									
Sleep quality										
Very restless or restless	17,231	80	1.00	0.77–1.30	70	0.92	0.70–1.21	50	0.98	0.70–1.36
Average	45,600	219	1		212	1		140	1	
Restful or very restful	46,193	185	0.79	0.65–0.97	166	0.73	0.60–0.90[d]	159	1.10	0.87–1.38
P_{trend}				0.032			0.020			0.386
$P_{heterogeneity}$[c]	0.016									
Sleep disturbance level										
0–4	40,608	177	1		158	1		139	1	
5–8	35,458	138	0.90	0.72–1.13	131	0.96	0.76–1.21	119	0.97	0.76–1.24
9–20	32,958	169	1.25	1.01–1.56	159	1.34	1.07–1.68	91	0.82	0.62–1.08
P_{trend}				0.052			0.014			0.164
$P_{heterogeneity}$[c]	0.005									
Insomnia										
Yes (sleep disturbance ≥9)	32,958	169	1.32	1.09–1.59	159	1.36	1.12–1.66[d]	91	0.83	0.65–1.06
No	76,066	315	1		289	1		258	1	
$P_{heterogeneity}$[c]	0.001[d]									

[a]HR and 95% CI adjusted for age at baseline, race/ethnicity (black or African-American, Hispanic or Latino, non-Hispanic white, and other), body mass index (<25, 25-<30, ≥30), physical activity, smoking (past smoker, current smoker, and never smoker), alcohol intake (<7 drinks/week, ≥7 drinks/week), age at menarche (<12, 12–13, 14–15, ≥16), parity [0 (combining never pregnant and never had term pregnancy), 1, 2, 3, 4, ≥5], family history of breast or ovarian cancer (yes/no), use of oral contraceptives (yes/no), menopausal symptoms (yes/no), postmenopausal hormone therapy (yes/no), depressive symptoms (yes/no), and treatment arms in each CT (not enrolled, intervention group, or control group).
[b]Cancers determined solely by the cause of death were not included.
[c]*P* value from logistic regression model comparing serous histotype with nonserous histotype.
[d]Significant at a Bonferroni threshold.

Effect modification analysis showed that there was no modification of the associations of sleep duration, sleep quality, sleep disturbance, or insomnia with overall ovarian cancer incidence by hysterectomy at baseline (yes/no), age at baseline (<70, ≥70), obesity status (BMI <30, ≥30), use of oral contraceptives (yes/no), postmenopausal hormone therapy (yes/no), parity (nulliparous, 1–2, ≥3), depression (yes/no), and WHI component (OS/CT; all $P > 0.003$; Supplementary Table S1–S8). Similar results were observed with serous ovarian cancer and type II ovarian cancer. For invasive serous ovarian cancer, similar results were found among women with hysterectomy at baseline, ages under 70 years old, with BMI<30, without prior use of oral contraceptives, without postmenopausal hormone therapy, with parity≥3, without depressive symptoms, and participating in the OS (Supplementary Table S9–S16).

The results of the sensitivity analyses were similar to main findings when a time-dependent analysis was used with all measures of sleep duration, sleep quality, sleep disturbance, or insomnia. No associations were observed between the combination of insomnia and sleep duration and ovarian cancer incidence.

Discussion

This study identified no association between sleep duration, sleep quality, sleep disturbance, or insomnia and the risk of overall ovarian cancer among postmenopausal women. However, compared with women with average sleep quality, women with restful or very restful sleep quality had a lower risk of invasive serous ovarian cancer, and compared with women without insomnia, women with insomnia had an increased risk of invasive serous ovarian cancer.

Similar to the findings of this study about sleep duration, a prospective cohort study, conducted by Hurley and colleagues, who used the data from the California Teachers Study which involved 101,609 women ages 22–104 years with a follow-up period of 15 years, found that sleep duration was not associated with risk of ovarian cancer (5). In contrast, two studies did observe an association between sleep duration and ovarian cancer (4, 6). Weiderpass and colleagues followed 45,748 Japanese women ages 40–69 years for 16 years, and found that sleep duration of 7 or more hours per day was inversely associated with epithelial ovarian cancer risk compared with less than 6 hours per day (HR: 0.4; 95% CI: 0.2–0.9; ref. 4).

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Table 4. HRs and 95% CIs of ovarian cancer subtype in relation to sleep habits at baseline[a,b].

		Type I			Type II		
	N	Cases	HR	95% CI	Cases	HR	95% CI
Sleep duration, hours per night							
≤5	8,809	8	0.94	0.44–2.02	42	1.00	0.72–1.39
6	29,862	32	1.01	0.64–1.60	147	0.88	0.72–1.09
7	41,112	46	1		253	1	
8	24,525	26	0.97	0.60–1.57	144	0.95	0.77–1.16
≥9	4,716	5	1.02	0.40–2.57	21	0.77	0.49–1.20
P_{trend}			0.992			0.858	
$P_{heterogeneity}$[c]	0.735						
Sleep quality							
Very restless or restless	17,231	14	0.75	0.41–1.38	92	0.94	0.74–1.19
Average	45,600	50	1		274	1	
Restful or very restful	46,193	53	0.99	0.67–1.46	241	0.83	0.70–0.99
P_{trend}			0.498			0.129	
$P_{heterogeneity}$[c]	0.072						
Sleep disturbance level							
0–4	40,608	51	1		220	1	
5–8	35,458	46	1.06	0.71–1.58	181	0.94	0.78–1.15
9–20	32,958	20	0.51	0.30–0.87	206	1.22	1.00–1.48
P_{trend}			0.026			0.054	
$P_{heterogeneity}$[c]	0.001[d]						
Insomnia							
Yes (sleep disturbance ≥9)	32,958	20	0.50	0.31–0.82	206	1.25	1.06–1.49
No	76,066	97	1		401	1	
$P_{heterogeneity}$[c]	<0.001[d]						

[a]HR and 95% CI adjusted for age at baseline, race/ethnicity (black or African-American, Hispanic or Latino, non-Hispanic white, and other), body mass index (<25, 25–<30, ≥30), physical activity, smoking (past smoker, current smoker, and never smoker), alcohol intake (<7 drinks/week, ≥7 drinks/week), age at menarche (<12, 12–13, 14–15, ≥16), parity [0 (combining never pregnant and never had term pregnancy), 1, 2, 3, 4, ≥5], family history of breast or ovarian cancer (yes/no), use of oral contraceptives (yes/no), menopausal symptoms (yes/no), postmenopausal hormone therapy (yes/no), depressive symptoms (yes/no), and treatment arms in each CT (not enrolled, intervention group, or control group).
[b]Cancers determined solely by the cause of death were not included.
[c]*P* value from logistic regression model comparing type I with type II ovarian cancer.
[d]Significant at a Bonferroni threshold.

However, there were only 8 cases of epithelial ovarian cancer among the women with less than 6 hours of sleep, which could not exclude the possibility that it is a chance finding. Gu and colleagues utilized the NIH-AARP Health and Diet Study cohort with 123,858 women ages 51–72 years, followed for 11 years, and found a decreased ovarian cancer risk in relation to 9 or more hours of sleep per day compared with 7–8 hours (HR: 0.50; 95% CI: 0.26–0.97; ref. 6). In that study, there were only 9 cases of ovarian cancer among the women with 9 or more hours of sleep. A meta-analysis summarized these three studies (4–6), and found no association between sleep duration and ovarian cancer (23), which is consistent with findings in this study. None of the four aforementioned studies examined the relationship between sleep duration and ovarian cancer subtypes (4–6, 23).

To our knowledge, ours is the first study to explore the relationship between sleep quality and sleep disturbance with the risk of ovarian cancer or ovarian cancer subtypes. With regard to the histotypes, invasive serous ovarian cancer accounted for more than half of all ovarian cancers in this study, and this study provided strong support for associations between sleep quality and insomnia with invasive serous ovarian cancer. Some studies have explored other risk factors in relation to subtypes of ovarian cancer, and found that the associations of some risk factors were stronger for invasive serous ovarian cancer than other histologic types. For example, a case–control study showed 40% increase and 40% reduction in likelihood of invasive serous ovarian cancer among women in the fourth quintile of starch and vitamin E intake compared with women in the first quintile of starch and vitamin E intake, respectively, but not for mucinous, endometrial, or other histologic types (24). The Nurses' Health Study indicated that perineal talc use modestly increased the risk of invasive serous ovarian cancer but found no association between perineal talc use and all serous, mucinous, or endometrial subtypes (25).

Each subtype of ovarian cancer has distinct cells of origin, carcinogenic pathways, histology, and clinical features (8, 26). The biologic evidence for the observed association of sleep quality and insomnia with invasive serous ovarian cancer is unknown, although there has been some literature explaining potential pathways from poor sleep to cancer risk (11, 12, 27, 28). First, poor sleep has been linked with the disruption of

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numerous modulators of immune function, and may suppress immune cancer defenses (27). Second, sleep patterns may favor cancer risk through changes in the disruption of neuroendocrine and immune circadian rhythms (11). Third, sleep disturbances can induce immune suppression and a shift to the predominance in cancer-stimulatory cytokines (12). Finally, sleep plays a specific role in the formation of immunologic memory, which is associated with the accompanying proinflammatory endocrine milieu (28). Morphologically possible origin of cells for serous ovarian cancer is fallopian tube epithelium (29), and the current findings regarding sleep measures and invasive serous subtype indicates that fallopinan tube epithelium may be more susceptible to the disruption of neuroendocrine or immune function induced by insomnia. More research is needed on this topic.

Ovarian cancer comprises several heterogenous histologic malignancies with different origins and risk factors (18, 30). In this study heterogeneity in associations with insomnia was found by serous/non-erous, and type I/type II ovarian cancer. Previous studies have explored the variation of other risk factors by ovarian cancer histotypes. For example, risk differences among serous, endometrioid, mucinous, clear cell, and other epithelial ovarian cancer were found for menopausal hormone therapy use, oral contraceptive use, parity, and BMI ($P_{\text{heterogeneity}} = 0.01, 0.03, 0.05, 0.03$, respectively; ref. 20). In a WHI study, unconjugated estradiol increased the risk of nonserous ovarian cancer, but not serous ovarian cancer ($P_{\text{heterogeneity}} < 0.01$; ref. 31).

Our study's strengths include the large prospective cohort and ovarian cancer verified by medical record review. However, our study also has limitations. First, all of the sleep measures depended on self-reported questionnaire without objective assessment through actigraphy or polysomnography. The potential misclassification of sleep habits would mostly be nondifferential with relation to ovarian cancer. Second, although a number of potential confounding factors have been adjusted in the models, residual confounding due to unmeasured confounding factors could affect the results. Third, we included cases that were only identified from the cause of death, which could result in possible misclassification for the outcome. Finally, all participants in the current study were postmenopausal women, which could also limit the generalizability to other populations.

In conclusion, our results from a large prospective cohort found no association between sleep duration, sleep quality, sleep disturbance, or insomnia with the risk of overall ovarian cancer among postmenopausal women. However, restful or very restful sleep quality was associated with a lower risk of invasive serous ovarian cancer, and insomnia was associated with a higher risk of invasive serous ovarian cancer. In addition, associations of risk of ovarian cancer with insomnia varied by subtypes. More research is needed regarding sleep habits and invasive serous ovarian cancer, and the potential biological mechanisms of sleep quality and sleep disturbance on the ovary should be better identified.

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