Sleep Duration and Risk of Liver Cancer in Postmenopausal Women: The Women's Health Initiative Study

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Abstract

Background: Sleep duration has been associated with nonalcoholic fatty liver disease, but its association with liver cancer remains unknown.

Material and Methods: In the prospective Women's Health Initiative Study, 139,368 postmenopausal women reported sleep habits at baseline (1993–1998). We ascertained 175 incident liver cancer cases during an average 13.8 years of follow-up through August 2014. We used multivariable Cox proportional hazard regression models to estimate a hazard ratio (HR) and its 95% confidence interval (95% CI) for risk of liver cancer in association with nocturnal sleep duration.

Results: Compared to women reporting 6–8 hours of sleep, the HR for liver cancer was 1.94 (95% CI 1.07–3.53) for women reporting ≥ 9 hours of sleep. Among the obese women, the HR associated with ≥ 9 hours of sleep was 3.18 (95% CI 1.84–8.60). The HR was 0.93 (95% CI 0.34–2.53) among nonobese women (p value for interaction = 0.18). Short sleep duration (≤ 5 hours) was not associated with liver cancer risk.

Conclusion: Long sleep duration was associated with a moderate increase in liver cancer risk in obese postmenopausal women in the United States. Larger study is needed to confirm our observation on effect modification by adiposity status.

Keywords: sleep, liver cancer, risk factor, circadian rhythm, obesity, WHI

Introduction

THE PREVALENCE OF sleep disorders increases as people age. Sleep disorders are common among both premenopausal and postmenopausal women.¹ The sleep-wake cycle is a manifestation of circadian rhythms. Circadian rhythm disruption has been linked to alterations in inflammatory and immune systems,^{2,3} cell cycle and DNA damage response,⁴ glucose homeostasis,⁵ leptin resistance,⁶ and insulin-like growth factor 1.⁷ Circadian rhythm that regulates daily oscillations in physiologic processes can affect cancer development through these mechanisms. Clinical studies have shown alterations in circadian clock gene expression in cancers of stomach,⁸ liver,⁹ and colorectal cancer with liver

metastasis.¹⁰ Observational studies have shown short or long sleep duration, as one manifestation of circadian rhythm misalignment, was associated with increased risk of stomach and colon-rectum cancers.^{11–13}

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease and a risk factor for liver cancer.^{14,15} NAFLD patients with sleep apnea and daytime sleepiness were found to have severe liver damage.¹⁶ NAFLD has also been associated with short sleep duration and poor sleep quality,^{17–19} as well as long sleep duration.²⁰ In a study conducted in Japan, the proportion of NAFLD was lowest in the group with a sleep duration of 6–7 hours and highest in the group with sleep durations of ≤ 6 and > 8 hours in women.²¹

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The association between sleep duration and liver cancer has not been evaluated in an epidemiologic study. Therefore, we investigated the association between self-reported sleep characteristics, including nocturnal sleep duration, sleep disturbance, daytime napping, and snoring with incident liver cancer risk in the prospective Women's Health Initiative (WHI) Study. We hypothesized that short or long sleep duration would be associated with risk of liver cancer in postmenopausal women and secondarily, the association would differ by adiposity status because short sleep duration and poor sleep quality have been associated with high adiposity.¹²

Materials and Methods

Study population

Detailed information on study population, recruitment methods, and research protocols of the WHI Study was described previously.²² A total of 161,808 postmenopausal women aged 50 to 79 who met eligibility criteria were enrolled at 40 clinical centers across the United States from 1993 to 1998 (baseline). The WHI Study consists of 68,132 women enrolled in four overlapping Clinical Trials (WHI-CTs) and 93,676 women enrolled in an Observational Study (WHI-OS). The CTs included women who did not receive active interventions, a dietary modification trial, a hormone therapy trial, and a calcium and vitamin D trial. For this analysis, we excluded women who reported having prior cancer (other than nonmelanoma skin cancer) ($n = 14,849$) or unknown cancer history ($n = 1406$), had missing data on sleep duration ($n = 669$), follow-up <1 year ($n = 1264$), or had daily energy intake of <600 kcal or >5000 kcal ($n = 4252$) at baseline. The final analytic cohort included 139,368 women.

Case ascertainment

Cases of incident liver cancer were ascertained through August 29, 2014 from annual self-administered questionnaires. The diagnosis was then verified and adjudicated through centralized review of pathology reports, discharge or consultant summaries, operative and radiology reports, or tumor registry abstracts.²³ A total of 86% of adjudicated liver cancer cases had pathologically confirmed diagnosis.

Data collection and exposure assessment

Detailed information on demographic characteristics, medical history, medication use, reproductive history, family cancer history, psychosocial factors (pain and fatigue), and history of liver diseases (chronic active hepatitis, cirrhosis, or yellow jaundice) was queried during the baseline screening visit by interviewer-administered structured questionnaires. Self-administered food frequency questionnaire was used to collect food intake information. Women also completed a questionnaire to provide detailed information on sleep habits and psychosocial factors in the past 4 weeks using the following 10 questions: (1) "Did you take any kind of medication or alcohol at bedtime to help you sleep?"; (2) "Did you fall asleep during quiet activity like reading, watching TV, or riding in car?"; (3) "Did you nap during the day?"; (4) "Did you have trouble falling asleep?"; (5) "Did you wake up several times at night?"; (6) "Did you wake up earlier than you planned to?"; (7) "Did you have trouble getting back to sleep after you woke up too early?"; (8) "Did

you snore?"; (9) "Overall, how was your typical night's sleep during the past 4 weeks?"; and (10) "About how many hours of sleep did you get on a typical night during the past 4 weeks?" For each question, the score ranges from 0 to 4. Question no. 9 was used to define sleep quality that ranges from very sound or restful, sound or restful, average quality, restless, and to very restless. Question no. 10 was used to define sleep duration with categories of ≤ 5 , 6, 7, 8, 9, and ≥ 10 hours. For all other questions, a five-point scale (0, <1, 1–2, 3–4, and ≥ 5 times/week) was used to evaluate the response, with an additional choice of "Don't know" for self-reported snoring. Using questions 4–7 and 9, Levine et al. developed a 5-item Women's Health Initiative Insomnia Rating Scale (WHIIRS)²⁴ to define sleep disturbance. These items are intended to assess sleep latency, sleep maintenance, insomnia, early morning awakening, and sleep quality. The summary score ranges from 0 to 20 and was used to define sleep disturbance.²⁵ The higher score indicates more sleep disturbance. Reliability and validity of the 5-item WHIIRS have been evaluated.²⁶

The Institutional Review Boards at Baylor College of Medicine and Michael E. DeBakey VA Medical Center approved this analysis. All women gave their informed consent before their inclusion in the study.

Statistical analysis

Univariate and age- and multivariable-adjusted Cox proportional hazard regression models were used to estimate hazard ratios (HRs) and their 95% confidence intervals (95% CIs) for incident liver cancer in association with sleep exposure variables. Person-years of follow-up were calculated beginning at the second year of follow-up to the date of first diagnosis of liver cancer, death, lost to follow-up, or August 29, 2014. For self-reported nocturnal sleep duration, we collapsed 7–8 hours and further 6–8 hours as the reference, less than 5 hours as short sleep duration, and 9 and ≥ 10 hours as long sleep duration category. We classified sleep disturbance into four categories (score 0–3, 4–6, 7–10, and ≥ 11) based on approximate quantile distribution of WHIIRS. Daytime napping and snoring variables were collapsed into two categories, <1 and ≥ 1 time/week. Sleep disturbance, daytime napping, and snoring were secondary exposures of interest.

We evaluated for potential confounding effects of medical history, multiple demographic, lifestyle, anthropometric, reproductive, and psychosocial factors. None was associated with both sleep duration and liver cancer risk at $p < 0.25$ level. Nevertheless, age at screening, race/ethnicity (white, black or African American, Asian, Hispanic, and others), employment (not currently employed vs. employed), pain (<75 vs. ≥ 75 score), fatigue (0–100, continuous), coffee (drink coffee daily vs. not), alcohol servings per week (continuous), hormone replacement therapy (no, current, past), body mass index (BMI) (<30 vs. ≥ 30 kg/m²), and type 2 diabetes (yes vs. no) were included in multivariable models according to literature review. Age at menopause was included in the model because its removal changed the risk estimate by 10%. We also evaluated whether adjustment for trial assignment (observational study, hormone therapy [placebo, estrogen alone, and estrogen plus progestin], dietary modification, and calcium/vitamin D) would change the risk estimates. We

assessed the proportional hazards assumption of major exposure variable by generating an interaction term with age at screening in a Cox regression model.

We then conducted the analyses stratified by obesity (BMI <30 kg/m² vs. BMI ≥30 kg/m²). We used 6–8 hours of sleep as the reference group to increase study power. Statistical interaction was assessed using a Wald test. In sensitivity analyses, we examined the association between sleep duration and incident liver cancer risk by excluding women reporting use of sleep medication more than twice per week (*n* = 12,018) because of the suggested carcinogenic effect of hypnotic medications.²⁷ We also excluded those who reported having chronic liver diseases at baseline (*n* = 2904), those who lost to follow-up in the first 5 years of study (*n* = 5850), or African American women (*n* = 11,793).

All statistical tests were two-sided, and *p* < 0.05 indicates statistical significance. SAS 9.4 (SAS institute, Inc., Cary, NC) was used in statistical analysis.

Results

The study cohort consisted of 139,368 women with an average age at screening of 63.2 years. A total of 175 incident liver cancer cases were ascertained during a mean duration of 13.8 years of follow-up. A total of 8.1% reported ≤5 hours, 27.5% reported 6 hours, 60.1% reported 7–8 hours, and 4.3% reported ≥9 hours of nocturnal sleep, respectively. The proportion of self-reported liver diseases was 2.6%, 2.4%, 2.3%, and 2.1% in women reporting ≤5, 6, 7–8, and ≥9 nocturnal sleep hours, respectively (Table 1). In addition, we found that women who were lost to follow-up in the first 5 years were more likely to report to have slept 5 or less hours compared to the women who were not lost to follow-up in the first 5 years (12.8% vs. 7.9%). We also found that African American women were more likely to report to have slept 5 or less hours compared to other ethnic groups (18.5% vs. 7.12%). African American women were also more likely to be obese compared to other ethnic groups (50% vs. 28%) (data not shown in tables).

Table 2 shows age-adjusted and multivariable-adjusted risk estimates for liver cancer according to sleep exposures. Compared to women reporting 7–8 hours of nocturnal sleep, women with long sleep duration (≥9 hours) had an increased risk of liver cancer (HR_{adjusted} = 1.88; 95% CI 1.02–3.45). The adjustment for race/ethnicity did not change the risk estimate. The adjustment of BMI/diabetes attenuated the risk estimates slightly for both short and long sleep hours (Table 2). The risk estimate remained the same after the adjustment for trial assignment. Liver diseases may be in the causal pathway from sleep duration to liver cancer. Nevertheless, the adjustment of liver diseases at baseline attenuated the association slightly (HR_{adjusted} = 1.85; 95% CI 1.01–3.40). Compared to women reporting 6–8 hours of nocturnal sleep, women with long sleep duration (≥9 hours) had an increased risk of liver cancer (HR_{adjusted} = 1.94; 95% CI 1.07–3.35). Short sleep duration (≤5 hours), daytime napping, snoring, and sleep disturbance were not associated with liver cancer risk in multivariable models (Table 2).

The association between long or short sleep duration and liver cancer did not significantly differ by BMI status (*p*-value for interaction = 0.18). However, we did not observe the positive association between long sleep duration and liver

cancer risk in women with BMI <30 kg/m² (HR_{adjusted} = 0.93, 95% CI 0.34–2.53). The HR was 3.98 (95% CI 1.84–8.60) among obese women (Table 3).

We conducted several sensitivity analyses to verify the robustness of our study finding. The results are presented in Table 4 using 6–8 hours as the reference category. In general, the associations between long sleep duration and liver cancer risk were strengthened. The association between short sleep duration and liver cancer was not seen. A statistically non-significant increased risk associated with short sleep duration was noted when we excluded African American women from the analysis; the adjusted HR was 1.38 (95% CI 0.79–2.43) (Table 4).

Discussion

In this large prospective cohort of postmenopausal women, we found that self-reported long nocturnal sleep duration was associated with moderately increased risk of liver cancer compared to normal sleep hours among obese women. Sleep hygiene can be modified and promoted among women.²⁸ Our study suggested a novel way for risk stratification and liver cancer prevention.

Evidence for the association between sleep duration and cancer risk is accumulating, but inconsistent.^{12,29} Thus far, two meta-analyses found long sleep duration was associated with an increased risk for colorectal cancer compared to 7–8 hours.^{30,31} In the prospective California Teachers Study, longer sleep duration (>10 hours per night) was associated with an increased risk of colorectal and breast cancers.³² The association between sleep and liver cancer was examined in one registry-based study in Taiwan. It found a significantly increased liver cancer risk in those with nonapnea sleep disorder compared to normal healthy subjects without sleep disorder (unadjusted HR = 1.12, 95% CI 1.06–1.18). However, this ecological study did not consider any confounding factors or examine the association between sleep duration and liver cancer.³³ Our study did not find short sleep duration to be associated with risk of liver cancer.

Sleep-related complaints are common in patients with chronic liver diseases.³⁴ Several studies conducted in Asia have investigated the association between sleep duration and risk of NAFLD. Three studies showed short sleep duration to be associated with an increased risk of NAFLD,^{18,35,36} whereas one Chinese prospective study showed long sleep duration (>8 hours) as a risk factor for NAFLD compared with 7–8 hours sleep duration in middle-aged and elderly people, although in men the association was attenuated after considering BMI.²⁰ In our study, short sleep duration was not associated with risk of liver cancer and the association between long sleep duration and liver cancer risk was attenuated slightly after obesity and diabetes were considered in the model. Approximately 2.5% of women reported having chronic liver diseases in our study population. The adjustment of liver diseases in the statistical models slightly attenuated the association between long sleep duration and liver cancer.

We only observed the positive association between long sleep duration and liver cancer among obese women. This was an unexpected finding because short sleep duration, rather than long sleep duration, has been associated with high adiposity in several epidemiological researches conducted in

TABLE 1. BASELINE CHARACTERISTICS OF PARTICIPANTS BY THEIR HABITUAL SLEEP DURATION IN THE WOMEN'S HEALTH INITIATIVE STUDY, UNITED STATES, 1993–2014

	<i>Hours of sleep per night</i>			
	≤5	6	7–8	≥9
No. of participants (<i>n</i> = 139,368)	11,299	38,312	83,794	5963
% of participants	8.1	27.5	60.1	4.3
Demographics				
Age at screening, years, mean (SD)	63.0 (7.5)	62.9 (7.3)	63.0 (7.1)	63.7 (7.1)
Race/Ethnicity (%)				
White, non-Hispanic	66.5	78.6	87.7	85.2
Black	19.8	11.7	5.8	7.8
Hispanic	6.1	4.1	3.2	4.5
Asian/Pacific Island	4.9	3.8	1.9	1.1
Other	2.7	1.7	1.3	1.3
Education (no college), %	40.8	33.4	30.3	34.0
Employment ^a (currently working), %	61.3	57.6	63.2	75.1
Smoking status ^b , (% ever)				
Past smoker	38.7	41.4	42.5	44.9
Current smoker	8.4	7.5	6.3	7.2
Smokers ^c , (% ≥20 years smoking)	56.1	54.2	52.9	56.4
Smokers ^c , no. of cigarette smoked/day, mean (SD)	3.5 (1.4)	3.5 (1.3)	3.4 (1.3)	3.6 (1.4)
Weekly alcohol servings ^d , mean (SD)	1.7 (4.2)	2.1 (4.5)	2.6 (5.0)	3.1 (6.0)
Physical activity (MET), mean (SD)	10.9 (13.7)	12.1 (13.7)	12.9 (13.7)	12.3 (14.3)
Waist-to-hip ratio, mean (SD)	0.82 (0.08)	0.82 (0.08)	0.82 (0.08)	0.82 (0.08)
BMI, kg/m ² , mean (SD)	29.2 (6.5)	28.2 (6.0)	27.6 (5.7)	28.4 (6.1)
Daily coffee consumption (% yes)	65.4	71.3	73.8	71.9
Medical history				
Liver disease (% yes)	2.6	2.4	2.3	2.1
Treated type 2 diabetes (% yes)	7.2	4.5	3.6	5.0
Cardiovascular disease (% yes)	21.0	17.8	16.3	18.7
Hypertension (% yes)	40.0	34.9	31.5	35.6
Reproductive factors				
Pregnant ever (% yes)	91.4	91.3	90.7	90.3
Oral contraceptive use ever (% yes)	39.4	41.6	43.0	40.8
Age at menopause, years, mean (SD)	47.1 (7.1)	48.0 (6.5)	48.5 (6.1)	48.2 (6.4)
Hormone replacement therapy (% yes)				
Former user	26.7	23.3	21.5	21.6
Current user	36.5	43.4	46.7	44.1
Psychosocial factors				
Depression ^e (% CES-D/DIS >0.06)	73.0	84.9	90.5	85.8
More fatigue ^f (% score ≤65)	67.2	54.5	47.0	57.4
More pain ^g (% score <75)	48.1	34.8	29.1	35.5
More social strain ^h (% score >10)	15.2	9.6	6.6	7.3
Care giving (% ≥3 times/week)	19.8	16.3	14.3	14.6
Clinical trial assignments				
Observation (%)	7.9	26.8	68.8	4.5
Calcium/vitamin D (%)	7.9	28.7	59.7	3.7
Dietary modification (%)	7.9	28.3	60.0	3.9
HRT E-alone (%)	12.9	30.2	53.2	3.7
HRT E+P (%)	7.9	28.7	59.2	4.2

^aNot working was defined as no full or part time work.^bSmoking status by “Ever” versus “Never,” with “Never” defined as answering “No” to “Have you smoked 100 cigarettes in your life?”^cDefined as current and past smokers.^dDefined as current and past drinkers with serving size standardized across all alcohol types.^eDepression (CES-D ranges from 0 to 1). A higher score indicates a greater likelihood of depression. Center for Epidemiologic Studies Depression Scale >0.06 was used to indicate depression.^fFatigue score (ranges from 0 to 100). A higher score indicates less fatigue.^gPain score (ranges from 0 to 100). A higher score indicates a more favorable condition.^hSocial strain score (ranges from 4 to 20). A higher score indicates more strain.

BMI, body mass index; CES-D, Center for Epidemiologic Studies Depression Scale; DIS, National Institute of Mental Health's Diagnostic Interview Schedule; HRT, Hormone replacement therapy; MET, metabolic equivalent of task; SD, standard deviation.

TABLE 2. HAZARD RATIOS AND 95% CONFIDENCE INTERVALS OF LIVER CANCER BY SLEEP DURATION AND HABITS IN THE WOMEN'S HEALTH INITIATIVE STUDY, UNITED STATES, 1993–2014

<i>Sleep variable</i>	<i>No. of cases</i>	<i>No. of noncases</i>	<i>HR^a (95% CI)</i>	<i>HR^b (95% CI)</i>	<i>HR^c (95% CI)</i>
Duration					
≤5 hours	17	11,282	1.38 (0.83–2.31)	1.10 (0.63–1.94)	1.07 (0.61–1.89)
6 hours	43	38,269	0.96 (0.67–1.37)	0.90 (0.61–1.32)	0.89 (0.60–1.32)
7–8 hours	103	83,691	1.00	1.00	1.00
≥9 hours	12	5951	1.68 (0.92–3.05)	1.88 (1.02–3.45)	1.85 (1.01–3.39)
≤5 hours	17	11,282	1.40 (0.85–2.32)	1.15 (0.66–1.99)	1.11 (0.64–1.92)
6–8 hours	146	121,960	1.00	1.00	1.00
≥9 hours	12	5951	1.70 (0.94–3.06)	1.94 (1.07–3.53)	1.88 (1.04–3.41)
Sleep disturbance					
0–3	40	37,764	1.00	1.00	1.00
4–6	55	37,629	1.33 (0.89–2.00)	1.22 (0.78–1.91)	1.21 (0.78–1.90)
7–10	48	35,095	1.24 (0.81–1.89)	1.11 (0.70–1.77)	1.11 (0.70–1.77)
≥11	30	26,371	1.07 (0.67–1.72)	0.85 (0.50–1.45)	0.86 (0.50–1.47)
Daytime naps^d					
<1 time/week	104	96,766	1.00	1.00	1.00
≥1–2 times/week	68	41,862	1.40 (1.02–1.90)	1.16 (0.83–1.64)	1.12 (0.80–1.57)
Snoring^d					
<1 time/week	38	35,159	1.00	1.00	1.00
≥1–2 times/week	42	32,281	1.25 (0.81–1.95)	1.22 (0.76–1.95)	1.13 (0.70–1.82)
Unknown	95	71,197	1.18 (0.81–1.72)	1.10 (0.73–1.67)	1.08 (0.71–1.63)

^aModel 1: HR adjusted for age at screening.

^bModel 2: Model 1 plus race/ethnicity (white, black or African American, Asian, Hispanic, and others), employment (not currently employed vs. employed), pain (<75 vs. ≥75 score), fatigue (0–100, continuous), coffee (drink daily vs. not), alcohol servings per week (continuous), hormone replacement therapy (no, current, and past).

^cModel 3: Model 2 plus BMI (<30 vs. ≥30 kg/m²) and type 2 diabetes (yes vs. no).

^dDaytime naps and snoring were collapsed from five categories into two.

CI, confidence interval; HR, hazard ratio; ref, reference; WHIIRS, Women's Health Initiative Insomnia Rating Scale ≥1–2 times/week.

children, younger adults, and older individuals.^{37–39} Sleep deprivation has been associated with insulin resistance and type 2 diabetes.⁴⁰ In Western societies, changes in leptin and ghrelin among those with sleep deprivation may contribute to obesity.⁴¹ However, several studies conducted in Asia did not show adiposity mediates the association between short sleep duration and hyperleptinemia and insulin resistance in women.^{42,43} The interrelationship between obesity and sleep duration may differ by populations. The possibility of obesity being an effect modifier for sleep duration and liver cancer risk in Western countries should be examined in larger studies.

The mechanisms underlying the observed positive association between long sleep duration and liver cancer are unknown. There have been a few studies showing long sleep

hours in association with metabolic syndrome. One study using the data collected from Chinese showed that long sleep hours (≥9 hours) or short sleep hours (<6 hours) were associated with an increased risk of having metabolic syndrome.⁴⁴ A meta-analysis also showed that both short and long sleep duration are associated with metabolic syndrome in adults.⁴⁵ Peripheral clock genes, which regulate 10%–15% of the transcriptome, are predominantly expressed in the liver.⁴⁶ These genes have fundamental roles in regulating energy metabolism and expression of enzymes controlling absorption and metabolism of xenobiotics. Period circadian clock 2 gene (*PER2*) mutations significantly promote liver carcinogenesis in mice.⁴⁷ A recent study found circadian rhythm phase shifts in the liver and kidney tissue in colorectal cancer patients who also had hepatic metastases.⁴⁸ This

TABLE 3. HAZARD RATIOS AND 95% CONFIDENCE INTERVAL OF LIVER CANCER IN ASSOCIATION WITH SLEEP DURATION, STRATIFIED BY BODY MASS INDEX IN THE WOMEN'S HEALTH INITIATIVE STUDY, UNITED STATES, 1993–2014

<i>BMI <30 kg/m² (n = 97,824)</i>				<i>BMI ≥30 kg/m² (n = 41,544)</i>		
<i>Sleep duration</i>	<i>No. of cases</i>	<i>HR^a (95% CI)</i>	<i>HR^b (95% CI)</i>	<i>No. of cases</i>	<i>HR^a (95% CI)</i>	<i>HR^b (95% CI)</i>
≤5 hours	8	1.07 (0.52–2.21)	0.96 (0.46–2.01)	9	1.81 (0.88–3.69)	1.40 (0.61–3.20)
6–8 hours	100	1.00	1.00	46	1.00	1.00
≥9 hours	4	0.85 (0.31–2.32)	0.93 (0.34–2.53)	8	3.28 (1.55–6.96)	3.98 (1.84–8.60)

^aModel 1: HR adjusted for age at screening.

^bModel 2: Model 1 plus race/ethnicity (white, black or African American, Asian, Hispanic, and others), employment (not currently employed vs. employed), pain (<75 vs. ≥75 score), fatigue (0–100, continuous), coffee (drink daily vs. not), alcohol servings per week (continuous), hormone replacement therapy (no, current, and past), BMI (<30 kg/m² vs. ≥30 kg/m²), and type 2 diabetes (yes vs. no). Wald *p*-value = 0.18 for interaction term between obesity and sleep duration.

TABLE 4. SENSITIVITY ANALYSES ON THE ASSOCIATION BETWEEN SLEEP DURATION AND LIVER CANCER

<i>Sleep duration (hours)</i>	<i>No. of cases</i>	<i>No. of noncases</i>	<i>HR^a (95% CI)</i>	<i>HR^b (95% CI)</i>	<i>HR^c (95% CI)</i>
No lost to follow-up in 5 years					
≤5	16	10,542	1.41 (0.84–2.36)	1.17 (0.66–2.06)	1.14 (0.65–2.00)
6–8	139	117,137	1.00	1.00	1.00
≥9	12	5672	1.79 (0.99–2.36)	2.05 (1.13–3.72)	2.02 (1.11–3.66)
Non-African American					
≤5	16	9085	1.65 (0.98–2.78)	1.43 (0.82–2.52)	1.38 (0.79–2.43)
6–8	131	112,826	1.00	1.00	1.00
≥9	12	5505	1.90 (1.05–3.43)	2.10 (1.16–3.82)	2.06 (1.13–3.76)
No liver diseases at baseline					
≤5	14	11,042	1.28 (0.74–2.22)	1.03 (0.56–1.88)	1.00 (0.54–1.83)
6–8	132	119,418	1.00	1.00	1.00
≥9	11	5847	1.72 (0.93–3.18)	1.93 (1.04–3.60)	1.90 (1.02–3.55)
Not taking sleep medication more than twice a week					
≤5	10	7533	1.37 (0.79–2.38)	1.20 (0.67–2.17)	1.16 (0.65–2.10)
6–8	117	94,556	1.00	1.00	1.00
≥9	10	4607	1.76 (0.95–3.26)	2.11 (1.13–3.94)	2.08 (1.12–3.88)

^aModel 1: HR adjusted for age at screening.

^bModel 2: Model 1 plus ethnicity (white, black or African American, Asian, Hispanic, and others), employment (no vs. currently employed), pain (<75 vs. ≥75 score), fatigue (0–100, continuous), coffee (drink coffee each day, yes vs. no), alcohol servings per week (continuous), and hormone replacement therapy (no, current, and past).

^cModel 3: Model 1 plus BMI (<30 vs. ≥30 kg/m²), and type 2 diabetes (yes vs. no).

finding strongly suggests a systemic effect of peripheral clocks on cancer development. Alternatively, long sleep duration may be an indicator for circadian rhythm disruption, comorbidity, and lack of energy as the consequence of liver damage. Sleep disturbances can alter the balance of inhibitory and stimulatory cytokines.⁴⁹ Biomarker studies related to sleep duration may help further elucidate biological mechanisms underlying the association between sleep duration and cancer.

Strengths of our study include a prospective design, a large sample size of liver cancer in the U.S. women cohort, a long follow-up time, and adjudication of incident cancer cases. The possibility of reverse causality was less likely because we excluded study participants censored in the first year of follow-up.

This study also has several limitations. We used self-reported sleep duration information. Our analyses were confined to postmenopausal women. The results may not be generalizable to men or younger women, owing to sleep and endocrine differences by age and sex.⁵⁰ This finding may not be generalized to Asian countries where hepatitis virus infection is more common. We did not have data on viral infection for our study participants. However, the prevalence of hepatitis B or C infection in Western countries is low in general (<2%).⁵¹ Nevertheless, we could not exclude the possibility that some women might have undiagnosed NAFLD. It would be interesting to examine the interrelationship among sleep duration, liver diseases, and liver cancer in future study. Last, subgroup analysis had the limited power to detect the heterogeneity by obesity. The test of interaction between obesity and sleep duration was insignificant partially because the small number of cases arose among women with extreme sleep duration. Although African American women were more likely to report having extreme short or long sleep, the sample size was too small to conduct stratified analysis by ethnic groups. The ethnic disparity of sleep duration on cancer risk deserves further investigation.⁵²

Conclusion

Our finding of moderately increased risk of incident liver cancer in obese postmenopausal women with longer sleep duration needs to be replicated in other study populations. Understanding the biological connection between sleep disorders and liver diseases may provide novel insight into the etiology of liver cancer. Sleep duration or sleep trait is an important phenotype that has not been considered in cancer prevention and risk estimate. However, more studies emerge to show that sleep duration is related to obesity and cancer. If the association between sleep duration and cancer risk is proved to be causal, the prevention opportunity may be harnessed because circadian homeostasis of liver metabolism has been shown to suppress hepatocarcinogenesis in animal models⁵³ and sleep disorders are potentially modifiable.

Acknowledgments

The work was funded, in part, by the Cancer Prevention Research Institute of Texas (RP150587, PI: H.B.E.-S.). Sponsor has no role in study design; in the collection, analysis, and interpretation of data; in writing the report; and in the decision to submit the article for publication. This work and the Women's Health Initiative (WHI) program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health; U.S. Department of Health and Human Services through contracts N01WH22110, 24152, 32100–2, 32105–6, 32108–9, 32111–13, 32115, 32118–32119, 32122, 42107–26, 42129–32, and 44221; and the Cancer Center Support Grant NIH:NCI P30CA022453. This material is also a result of work done with the support and use of facilities at the Houston VA HSR&D Center for Innovations in Quality, Effectiveness and Safety (CIN13-413). The sponsors/funders have no role in design and conduct of the study, collection, management, analysis, and interpretation of the data, and preparation, review, or approval of the article. The views expressed in this article are those of the authors and do not

necessarily represent the views of the NIH, the Department of Veterans Affairs, the U.S. government, or Baylor College of Medicine. We acknowledge the dedicated effort of the investigators and staff at the WHI clinical centers, the WHI Clinical Coordinating Center, and the National Heart, Lung, and Blood program office (listing available at www.whi.org). We also recognize the WHI participants for their commitment to the WHI program. For a list of all the investigators who have contributed to WHI science, please visit: www.whiscience.org/publications/WHI_investigators_longlist.pdf

Authors' Contributions

Study concept and design: L.J. and H.B.E.-S. Acquisition of data: H.S.-H. and L.J. Analysis and interpretation of data: K.E.R., L.C., H.B.E.-S., D.L.W., and L.H. Drafting of article: K.E.R. and L.J. Critical revision of the article for important intellectual content: K.E.R., L.J., H.B.E.-S., D.L.W., L.H., and H.S.-H. Statistical analysis: K.E.R. and L.C. Study supervision: L.J.

Author Disclosure Statement

No competing financial interests exist.

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