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Original Contribution

Sleep Disturbance and Incidence of Thyroid Cancer in Postmenopausal Women The Women's Health Initiative

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Sleep disturbance has been found to be associated with numerous adverse health outcomes, including cancers. However, no epidemiologic study has examined the relation between sleep disturbance and thyroid cancer risk. A total of 142,933 postmenopausal women who were 50–79 years of age and enrolled in the Women's Health Initiative between September 1, 1993, and December 31, 1998, were followed up for a mean of 11 years. Cox proportional-hazard regression models were used to estimate hazard ratios and 95% confidence intervals for sleep disturbance (insomnia and sleep duration) and risk of thyroid cancer. Insomnia score was measured using a validated 5-item Women's Health Initiative Insomnia Rating Scale. Overall, a total of 295 thyroid cancer cases were identified. After adjustment for potential confounders, women with greater insomnia scores had a significantly higher risk of thyroid cancer than did women with low scores (hazard ratio = 1.44, 95% confidence interval: 1.01, 2.05). The significant association between insomnia score and thyroid cancer was confined to nonobese women (hazard ratio = 1.71, 95% confidence interval: 1.12, 2.62) and was not seen in obese women (hazard ratio = 0.94 95% confidence interval: 0.48, 1.84) (*P* for interaction = 0.07). In conclusion, postmenopausal women with greater insomnia scores, especially nonobese women, had a significantly increased risk of thyroid cancer. More studies are needed to confirm these findings.

insomnia; sleep disorder; sleep disturbance; risk factors; thyroid cancer

Abbreviations: CI, confidence interval; HR, hazard ratio; WHI, Women's Health Initiative; WHIIRS, Women's Health Initiative Insomnia Rating Scale.

Thyroid cancer is the most common endocrine malignancy. Although thyroid cancer is a relatively uncommon cancer, its incidence rate has been increasing sharply since the mid-1990s (1). According to the recent US annual report to the nation on the status of cancer (1975–2006), thyroid cancer incidence rose annually by 5.8% among men and 7.4% among women, and it is the fastest-increasing cancer in both men and women (2). Some of this increase could be explained by improved detection of very small papillary tumors and by changes in diagnostic criteria. However, studies have shown that medical surveillance and more sensitive diagnostic procedures cannot completely explain the observed increases (3); thus, other possible explanations should be explored. Still, little is known about the etiology of thyroid cancer except that increased risk is associated with ionizing radiation exposure, particularly in childhood; prior benign thyroid disease (4); and probably obesity (5).

Sleep disturbances, manifested primarily as sleep deprivation and disruptions in circadian synchronization, are increasingly common in today's society as a result of occupational and personal pressures (6, 7). Inadequate sleep duration and poor sleep quality have been found to be associated with numerous adverse health outcomes, including total mortality, cardiovascular and gastrointestinal disease, and metabolic disorders, such as insulin resistance, type 2 diabetes mellitus, and obesity (8, 9). Epidemiologic studies also have reported that night-shift workers are at a

significantly increased risk of developing several different malignancies, including breast, colon, prostate, and endometrial cancers (10).

It has been observed that sleep deprivation was associated with elevated thyroid-stimulating hormone concentration (11), which has been linked to an increase in thyroid cancer in some studies (12–15). Thus, it is biologically plausible that sleep disturbance might increase risk of developing thyroid cancer. However, no epidemiologic study has directly examined the relation between sleep disturbance and thyroid cancer risk.

To fill this gap, we used the Women's Health Initiative (WHI), a large prospective study, to investigate the association between sleep disturbance, including insomnia and sleep duration, and the risk of thyroid cancer. Furthermore, we assessed the interaction between sleep disturbance and obesity status to test whether these sleep characteristics might influence cancer risk via alterations in appetite regulation that lead to obesity (16), which is a risk factor for several cancers, including thyroid cancer (5).

MATERIALS AND METHODS

Women's Health Initiative

The WHI was designed to address the major causes of morbidity and mortality in postmenopausal women (17) and includes both multicenter clinical trials and an observational study. Details of the scientific rationale, eligibility requirements, and baseline participant characteristics of the WHI have been published elsewhere (18–22). Briefly, a total of 161,808 women 50–79 years of age were recruited at 40 clinical centers throughout the United States between September 1, 1993, and December 31, 1998. The WHI clinical trial includes 4 overlapping components: 2 hormone therapy trials (27,347 women), a dietary modification trial (48,835 women), and a calcium/vitamin D supplementation trial (36,282 women). Participants in the observational study included 93,676 women who were screened for the clinical trials but proved to be ineligible or unwilling to participate or who were recruited through a direct invitation for the observational study. The study was overseen by institutional review boards at all 40 clinical centers and at the coordinating center, as well as by a study-wide data and safety monitoring board. All participants in the WHI gave informed signed consent and were followed up prospectively.

The following participants were excluded from the original cohort of 161,808 for this analysis: 14,849 women who had a history of cancer (except nonmelanoma skin cancer) at baseline, 783 women who joined but provided no follow-up information, and 3,243 women who had missing values for the main exposures. After exclusions, 142,933 women remained for further analysis.

Measurement of exposures, outcome, and confounders

Sleep disturbance measurement. At enrollment, participants were asked 10 sleep-related questions covering the prior 4 weeks, including: 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 television, or riding in a 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? 10) About how many hours of sleep did you get on a typical night during the past 4 weeks?

Using these questions, Levine et al. (23) developed a 5-item Women's Health Initiative Insomnia Rating Scale (WHIIRS). The WHIIRS is computed from the aforementioned questions 4–7 and 9 and is summed from the 5 components. These items are intended to assess sleep latency, sleep maintenance insomnia, early morning awakening, and sleep quality. For each question, the score ranges from 0 to 4. The summary score ranges from 0 to 20, where a higher score indicates greater insomnia. Reliability and validity of the 5-item WHIIRS have been evaluated in 2 studies (24). It was reported that the WHIIRS has very good short-term test-retest reliability and acceptable internal consistency. In a different sample of 459 WHI women (24), responses on the WHIIRS were compared with objective measures of sleep as measured by a wrist actigraphy recorder. Results showed that differences in sleep latency, sleep efficiency, and waking after sleep onset, as measured by the recorder, could be detected by the WHIIRS. Validity of the WHIIRS also was supported by correlations with many measures known to be related to sleep, including the depression scale from a short form of the Center for Epidemiologic Studies Depression Scale (25) and 8 subscales of the RAND 36-item Health Survey (26). In addition to the 2 studies, Levine also looked at WHIIRS in a clinical trial among 850 postmenopausal women who were not participating in the WHI (27) and found that the construct validity of the WHIIRS was supported.

In the present study, we used the validated 5-item WHIIRS as our main exposure, called insomnia score. We classified the score for insomnia into 4 categories (0–3, 4–6, 7–10, and ≥11) on the basis of the distribution of this variable. In addition, we assessed the impact of self-reported sleep duration (≤6 hours, 7 or 8 hours, ≥9 hours) on the risk of thyroid cancer development.

Follow-up and ascertainment of cases. Incident thyroid cancer cases were identified by self-administered questionnaires (administered every 6 months in the WHI clinical trial through 2005, annually in the WHI clinical trial after 2005, and annually in the WHI observational study throughout the study), with all cases confirmed by medical record review. All primary thyroid cancer cases then were coded centrally in accordance with the Surveillance Epidemiology and End Results (National Cancer Institute) coding guidelines. For these analyses, participants were followed up to first thyroid cancer diagnosis, date of death, loss to follow-up, or end of WHI clinical trial or observational study follow-up (September 30, 2010), whichever occurred first.

Statistical analysis

The distribution of demographic characteristics by different levels of sleep disturbance is presented in Table 1. A

Table 1. Baseline Characteristics of Participants by Level of Insomnia Score Among 142,933 Women at Enrollment in the Women's Health Initiative, United States, 1993–1998

Variable	Insomnia Score Level (WHIIRS)[a]								*P* Value[b]
	0–3 (*n* = 39,607)		4–6 (*n* = 39,227)		7–10 (*n* = 36,427)		≥11 (*n* = 27,622)		
	%	Mean	%	Mean	%	Mean	%	Mean	
Age at baseline, years		62.5		63.1		63.4		63.3	<0.0001
Ethnicity, white non-Hispanic	81.3		83.0		84.8		82.9		<0.0001
Education, college graduate or above	44.2		40.5		38.4		32.0		<0.0001
Body mass index[c]		27.6		28.0		28.0		28.4	<0.0001
Physical activity, METs/week		13.7		12.5		11.9		11.3	<0.0001
Smoking status									<0.0001
Never smokers	52.3		50.7		49.7		49.4		
Former smokers	39.3		41.5		42.8		42.2		
Current smokers	29.8		26.1		23.5		20.5		
Alcohol intake, ≥7 drinks/week	10.9		11.6		12.3		11.6		<0.0001
Family history of cancer	44.6		46.7		47.5		48.0		<0.0001
Previous thyroid disease (yes)	21.0		23.5		25.0		25.1		<0.0001
Hormone therapy use									<0.0001
Estrogen alone	27.4		29.2		30.9		32.4		
Estrogen plus progestin	23.1		21.7		21.1		19.5		
Mixed use	5.2		5.6		5.9		5.8		
Depression score (CES-D/DIS)									
Mean score		0.01		0.02		0.04		0.10	<0.0001
Score ≥0.06	10.3		17.5		28.2		44.0		<0.0001

Abbreviations: CES-D, Center for Epidemiologic Studies Depression Scale; DIS, National Institute of Mental Health's Diagnostic Interview Schedule; METs, metabolic equivalents; WHIIRS, Women's Health Initiative Insomnia Rating Scale.

[a] Sleep disturbance level was classified into 4 categories (WHIIRS: 0–3, 4–6, 7–10, and ≥11). The cutpoints were "quasi-quartiles" based on distribution of the ordinal scale 0–20 from WHIIRS.

[b] *P* values were obtained from analysis of variance when the exposures were continuous and from chi-square tests when the exposures were categorical.

[c] Weight (kg) / height $(m)^2$.

chi-squared test was used to evaluate differences for categorical covariates, and analysis of variance was used for continuous variables.

Cox proportional-hazards regression models were used to estimate hazard ratios and 95% confidence intervals of thyroid cancer associated with insomnia score and sleep duration. We estimated both age-adjusted and multivariable-adjusted hazard ratios and 95% confidence intervals. In the multivariable-adjusted models, on the basis of literature review, we considered potential confounders including the following: age at enrollment (<55, 55–59, 60–64, 65–69, 70–74, or ≥75 years); ethnicity (American Indian or Alaska Native, Asian or Pacific Islander, black or African American, Hispanic/Latino, non-Hispanic white, or other); educational level (high school or less, some college or technical training, or college or above); smoking status (never, former, or current); body mass index (weight (kg) / height $(m)^2$) (<18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, 35.0–39.9, or ≥40); recreational physical activity (total metabolic equivalent tasks per week: <5, 5 to <12, or ≥12); alcohol intake (nondrinker, past drinker, or current drinker (including frequency: <1 drink/month, 1 drink/month to <1 drink/week, 1 to <7 drinks/week, or ≥7 drinks/week)); history of hormone therapy use (none, estrogen alone, estrogen and progestin, or mixed); family history of any cancer (yes or no); history of prior thyroid disease (an answer of yes or no to the question, "Did a doctor ever say that you had a thyroid gland problem (not including thyroid cancer)?"); and depression score, which was computed from a short form of the Center for Epidemiologic Studies Depression Scale and 2 questions from the National Institute of Mental Health's Diagnostic Interview Schedule (25). The depression score ranges from 0 to 1, with a higher score indicating a greater likelihood of depression. We utilized the widely used cutoff values of 0.06 and 0.009, which initially were developed by Burnam (25), to indicate moderate and mild depression symptomatology.

Different study cohorts (those who participated in the WHI observational study or clinical trials and those with different treatment assignments for the 3 WHI clinical trials) were treated as strata in the Cox model to take account of possible different baseline hazards in different

Table 2. Hazard Ratios and 95% Confidence Intervals for Thyroid Cancer Incidence Associated With Sleep Disturbance, Women's Health Initiative, United States, 1993–2010[a]

Exposure	No. of Cases	Total No.	Age Adjusted		Multivariable Adjusted	
			HR	95% CI	HR	95% CI
Insomnia score level (WHIIRS)						
0–3	65	39,607	1		1	
4–6	82	39,277	1.29	0.93, 1.79	1.26	0.91, 1.75
7–10	84	36,427	1.44	1.04, 2.00	1.39	1.00, 1.93
≥11	64	27,622	1.49	1.06, 2.11	1.44	1.01, 2.05
P for trend			0.01		0.03	
Sleep duration, hours						
≤6	90	51,165	0.81	0.63, 1.04	0.79	0.61, 1.02
7–8 (ref)	195	85,618	1		1	
≥9	10	6,150	0.75	0.40, 1.42	0.74	0.39, 1.39

Abbreviations: HR, hazard ratio; CI, confidence interval; WHIIRS, Women's Health Initiative Insomnia Rating Scale.

[a] In the multivariable-adjusted model, we adjusted for age at enrollment, ethnicity, educational level, smoking, body mass index (weight (kg)/height $(m)^2$), recreational physical activity, alcohol intake, family history of cancer, previous thyroid disease, history of hormone therapy use, depression score, and different treatment assignments for Women's Health Initiative clinical trials.

subgroups. In addition, we assessed whether the association among insomnia score, sleep duration, and thyroid cancer was modified by obesity status, and we performed an analysis of insomnia score and sleep duration and their association with thyroid cancer stratified by obesity status. Furthermore, we performed several sensitivity analyses to confirm our results. First, to account for reverse causality (i.e., sleep disturbance caused by undiagnosed thyroid cancer), we performed all analyses after excluding the first 2 years of follow-up. Second, we performed an analysis among the subgroup of women who had updated information on sleep habits collected in year 1 for the WHI clinical trials and in year 3 for the WHI observational study (127,938 women). We used the average of the 2 scores and examined subsequent thyroid cancer risk after the second questionnaire. Third, we performed the analysis among women who had never smoked.

Tests for trend were performed by assigning the ordering number to each category and modeling this variable as a continuous variable. Interactions between obesity status and sleep disturbance were tested by entering multiplicative interaction terms into the model. The proportionality assumption was satisfied for all exposure variables of interest and potential confounding variables on the basis of graphs of scaled Schoenfeld residuals (28). All statistical analyses were conducted in SAS, version 9.2 (SAS Institute, Inc., Cary, North Carolina). All *P* values are 2 sided.

RESULTS

Over an average of 11 years of follow-up, a total of 295 thyroid cancer cases were identified. Baseline characteristics by level of insomnia score at enrollment are shown in Table 1. Compared with women with the lowest insomnia scores (WHIIRS <4), women with higher insomnia scores were significantly more likely to be older, to be white (non-Hispanic), to have higher body mass index, to consume 7 or more alcoholic drinks per week, to report a high family history of cancer, to report a history of previous thyroid disease, to report a history of estrogen-alone hormone therapy use, and to have a higher depression score and were significantly less likely to have graduated from college, to be physically active, to be a current smoker, and to report a history of estrogen-plus-progestin hormone therapy use (all *P* values < 0.05) (Table 1).

Women who had higher insomnia scores (WHIIRS ≥11) had a 44% (95% confidence interval (CI): 1, 105) excess risk of thyroid cancer compared with women with the lowest insomnia scores (WHIIRS <4) after adjustment for potential confounders (Table 2). However, we did not observe that sleep duration (either shorter or longer than 7–8 hours) was associated with risk of thyroid cancer.

Further analyses stratified by obesity status suggested that the significant association between insomnia score and thyroid cancer was confined to nonobese women (hazard ratio (HR) = 1.71, 95% CI: 1.12, 2.62) and was not seen in obese women (HR = 0.94, 95% CI: 0.48, 1.84) (*P* value for interaction = 0.07). No association was noted between sleep duration and thyroid cancer risk, regardless of obesity status (Table 3). We compared the different histology subtypes, stage, and size of the thyroid cancer lesions and did not see significant difference between different levels of insomnia and tumor histology, stage or size (Table 4).

To minimize the possibility of reverse causation (i.e., sleep disturbance could be caused by undiagnosed thyroid cancer), we performed all analyses after excluding the first

Table 3. Hazard Ratios and 95% Confidence Intervals for Thyroid Cancer Incidence Associated With Sleep Disturbance Stratified by Obesity, Women's Health Initiative, United States, 1993–2010[a]

Exposure	Nonobese (BMI[b] <30)			Obese (BMI[b] ≥30)		
	No. of Cases	HR	95% CI	No. of Cases	HR	95% CI
Sleep disturbance level (WHIIRS)[b]						
0–3	43	1	Referent	22	1	Referent
4–6	49	1.16	0.77, 1.75	33	1.48	0.86, 2.54
7–10	51	1.31	0.87, 1.97	33	1.56	0.90, 2.70
≥11	49	1.71	1.12, 2.62	15	0.94	0.48, 1.84
P for trend		0.01			0.87	
Sleep duration, hours[bc]						
≤6	58	0.84	0.61, 1.15	32	0.69	0.45, 1.06
7–8 (reference)	126	1	Referent	69	1	Referent
≥9	8	0.96	0.47, 1.96	2	0.38	0.09, 1.54

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; WHIIRS, Women's Health Initiative Insomnia Rating Scale.

[a] In each model, we adjusted for age at enrollment, ethnicity, educational level, smoking, BMI, recreational physical activity, alcohol intake, family history of cancer, previous thyroid disease, history of hormone therapy use, depression score, and different treatment assignments for Women's Health Initiative clinical trials.

[b] Weight (kg)/height (m)^2.

[c] *P* for interaction test: 0.07 for sleep disturbance and obesity status; 0.33 for duration of sleep and obesity status.

2 years of follow-up. The results were similar to those based on the whole data set (for insomnia score ≥11 vs. insomnia score <4 overall, HR = 1.43, 95% CI: 0.98, 2.09; for nonobese women, HR = 1.75, 95% CI: 1.11, 2.76). In the subgroup of women who had updated information on sleep habits after enrollment, we observed similar associations between the average sleep disturbance and subsequent thyroid cancer risk (data not shown). In addition, we observed a similar increased risk of thyroid cancer for WHIIRS ≥11 compared with WHIIRS 0–3 among women who had never smoked (for WHIIRS ≥11 compared with WHIIRS 0–3 among nonobese women, HR = 1.97, 95% CI: 1.05, 3.70).

We also analyzed the relations between other sleep-related questions that were asked on WHI questionnaires but were not included in WHIIRS. We found no significant association between thyroid cancer and the following questions: "Did you take any kind of medication or alcohol at

Table 4. Thyroid Cancer Characteristics by Levels of Insomnia, Women's Health Initiative, United States, 1993–2010

Characteristic	Levels of Insomnia (WHIIRS)								*P* Value[a]
	0–3		4–6		7–10		≥11		
	No.	Mean (SD)	No.	Mean (SD)	No.	Mean (SD)	No.	Mean (SD)	
Thyroid cancer (total)	65		82		84		64		
Histology									0.5
Papillary carcinoma	52		69		61		49		
Follicular carcinoma	6		6		12		5		
Others	7		7		11		10		
Stage									0.3
Localized	47		58		65		50		
Regional	11		20		12		8		
Distant	3		3		2		5		
Unknown	4		1		5		1		
Size, mm		22.4 (17.9)		19.6 (14.8)		16.2 (15.0)		19.9 (18.7)	0.2

Abbreviations: SD, standard deviation; WHIIRS, Women's Health Initiative Insomnia Rating Scale.

[a] *P* value for size was obtained from analysis of variance, and *P* values for histology and stage were based on chi-square tests.

bedtime to help you sleep?" "Did you fall asleep during quiet activity like reading, watching television, or riding in a car?" "Did you snore?" However, a significant association was observed for the question about napping during the day (yes vs. no: HR = 1.33, 95% CI: 1.05, 1.68). No dose-response trend was noted for the frequency of naps per week (<1, 1–2, 3–4, or ≥5).

DISCUSSION

In the present large, prospective study in postmenopausal women, we observed that women with higher insomnia scores had a significantly higher risk of thyroid cancer that was confined to nonobese women. There was no significant association between sleep duration and the risk of thyroid cancer.

It is not clear why we did not observe an association between self-reported sleep duration and thyroid cancer. It could be because self-reported sleep duration is poorly correlated with objectively measured sleep duration. It is estimated that the correlation between self-reported sleep and objectively measured sleep (via actigraphy) is about 0.47 among middle-aged men and women (29). However, we do not have objective measures of sleep duration in the WHI. It is also possible that sleep quantity is less important than poor sleep quality as a risk factor for thyroid cancer. Because this is the first study on sleep disturbance and thyroid cancer, more studies are needed to confirm, refine, or refute these findings.

In addition, the lack of association between insomnia score and thyroid cancer risk among obese women is somewhat surprising and unexplained. Obesity itself has been identified as an emerging risk factor for thyroid cancer. Obese postmenopausal women are more likely to have vasomotor symptoms that interfere with sleep (30, 31). On the other hand, inadequate sleep also could lead to obesity via alterations in appetite regulation (16). It is possible that these complex relations make it more difficult to detect the independent effect of sleep disturbance on thyroid cancer. In addition, power might be an issue among obese women, because we had only 15 cases in the WHIIRS ≥11 category. Also, it could be due to competing risks in the obese women who had WHIIRS ≥11 (e.g., cardiovascular disease mortality related with insomnia and obesity).

Previous epidemiologic studies have shown that poor sleep quality and inadequate sleep duration are associated with numerous adverse health outcomes, such as total mortality, cardiovascular disease, and type 2 diabetes mellitus (8, 9). Epidemiologic studies also have reported that night shift workers are at a significantly increased risk of developing breast (32–35), colon (36), prostate (37, 38), and endometrial cancer (39) compared with workers who did not report any rotating night shift work. Only a few studies have examined sleep duration and breast cancer risk in humans, but findings are conflicting. Two prospective cohort studies (40, 41) provide some support for a decreased risk of breast cancer in long sleepers (≥9 hours), whereas 2 other studies reported contradictory results (1, 42). To our knowledge, the present study is the first study to examine the association between sleep disturbance and thyroid cancer.

The biologic mechanism by which sleep disturbance might be associated with an increased risk of thyroid cancer is unknown. One plausible biologic mechanism is via elevated thyroid-stimulating hormone level due to sleep disturbance (11), which could lead to an increased risk of thyroid cancer (12–15). Several plausible biologic models that explain how sleep disturbance can influence the development of cancer in general have been proposed (43). One possible mechanism is impaired immune function (44). Both laboratory studies of acute sleep deprivation and observational studies of poor sleepers have reported that sleep disturbances can lead to a suppression of immune function and a shift in the balance of cytokine production from a predominance of type 1 cytokines, including anticancer cytokines such as interleukin-2 and interferon-γ, to type 2 cancer-stimulatory cytokines such as interleukin-10 (45, 46). It has been suggested that sleep disturbance could impair immune response by disrupting circadian rhythms at the level of immune cells as a result of disrupted endocrine and physiologic circadian rhythms (45). Another possible mechanism is reduced production of melatonin caused by exposure to light at night (43). Melatonin has been demonstrated to suppress the initiation phase of tumorigenesis and inhibit the proliferation of human cancer cell lines in experimental studies (10). However, the null association between sleep duration and thyroid cancer risk noted in our study, along with inconsistent findings on sleep duration from other studies of other cancers, suggests that impaired immune system function and inflammation might play a more important role than melatonin deficiency for thyroid cancer. Like other cancer types, thyroid cancer also is influenced by inflammation. For example, studies have shown that thyroid cancer frequently occurs in one of the most common autoimmune thyroid diseases, Hashimoto's thyroiditis (47).

Another proposed model is that sleep might influence cancer risk via alterations in levels of appetite-regulating hormones, such as leptin and ghrelin (16), that lead to increased appetite and subsequently obesity, which is a risk factor for several cancers (48). In addition, there could be changes in waking behavior; increased daytime fatigue due to poor sleep quality could lead to decreased physical activity, lethargy, or changes in eating behavior. A recent pooled analysis of 5 prospective studies found that obesity was positively associated with thyroid cancer risk in both men and women (5). However, our analyses stratified by obesity status indicated that the significant association between sleep disturbance and thyroid cancer was confined to nonobese women, which suggests that changes in hormones involved in appetite regulation might not be a major pathway for the observed association.

Strengths of our study include its prospective design, detailed information on potential confounders, and validated cancer diagnoses. However, it has some limitations as well. First, our sleep disturbance measures relied on self-reporting of sleep habits through questionnaires, rather than more objective means such as wrist-actigraphy or polysomnography. This exposure misclassification is most likely to be

nondifferential; thus, it could bias our estimates of effect toward the null. Second, we lacked information on ionizing radiation exposure (an important risk factor for thyroid cancer), which might confound our results. Our results would be overestimated if ionizing radiation exposure were associated with an increased level of sleep disturbance. However, there is no literature reporting that ionizing radiation exposure is associated with sleep disturbance. Thus, our results are unlikely to be entirely confounded by ionizing radiation. Finally, the study was conducted in postmenopausal women, so our findings might not be generalizable to other populations.

In conclusion, postmenopausal women with greater sleep disturbance, especially nonobese women, had a significantly increased risk of thyroid cancer. More large prospective studies are needed to confirm this finding and to examine the possible biologic mechanisms for the association.

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