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Sleep duration and cancer risk in women

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INTRODUCTION

Recently, interest has increasingly focused on the importance of sleep in the promotion of health [1-4]. This interest has been fueled by the fact that over a third of the U.S. population reports insufficient sleep [4] and mounting scientific evidence that sleep disturbances are associated with increased risks of a number of chronic health conditions, including cardiovascular disease, diabetes, and cancer [5-13]. To date, the limited number of published studies on sleep duration and cancer risk have yielded provocative, yet highly inconsistent results, reporting elevated risks associated with both short and long sleep durations as well as no associations for a variety of cancer sites [14-31]. These inconsistencies may partially be a reflection of different mechanistic pathways operating for different cancer sites [13]. The objective of the current study was to conduct an analysis of sleep duration and risk of all cancer sites combined, as well as for the five most commonly-diagnosed cancer sites among a large, prospective cohort of California women. Additionally, we evaluated the sleep-associated risks for cancers of the breast, endometrium and ovary combined, which as a group all share an estrogen-mediated etiology [32].

MATERIALS AND METHODS

Study Population

The study population for these analyses was drawn from the California Teachers Study (CTS), a large on-going prospective study of female professional school employees in California. Participants in the CTS are 133,479 women who responded to a 1995-96 mailing to 329,000 active and retired female enrollees in the State Teachers Retirement System (STRS). Although information on the characteristics of STRS members is quite limited, the sociodemographic profile of CTS members appears to be representative of STRS members as a whole [33]. A full description of the CTS cohort is presented elsewhere [33]. The use of

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human subjects in the CTS has been approved by the Institutional Review Boards at all participating institutions and by the California Committee for the Protection of Human Subjects, California Health and Human Services Agency.

For the present analyses, CTS participants were excluded (in sequence) for the following reasons: lived outside California at baseline (n=8,867); agreed to breast cancer research only (n=18); had an unknown history of prior cancer (n=662); had a prior history of invasive cancer (n=13,142); asked to be removed from the study after joining (n=1); or had unknown or invalid information about sleep duration (n=9,180). The resulting eligible study population was comprised of 101,609 women. Other than being slightly older, and less likely to be pre-menopausal and report comorbidities, the characteristics of the subjects in the current analysis were similar to those of the full CTS cohort.

Outcome Assessment

The CTS cohort is followed annually for cancer diagnosis, death, and change of address. State and national mortality files, as well as reports from relatives, are used to ascertain date and cause of death. Address changes for continued follow-up are obtained by several methods including annual mailings, notifications of moves received from participants, and linkages to nationwide consumer reporting companies and the U.S. Postal Service National Change of Address database. Cancer outcomes are identified through annual linkages with the California Cancer Registry (CCR), a legally mandated statewide population-based cancer reporting system. Case ascertainment for the CCR is estimated to be 99% complete [34].

For the purposes of our analyses, a woman was considered a cancer case if she was diagnosed with a primary invasive carcinoma, identified through the annual linkages of the CTS to the CCR, after joining the cohort and before January 1, 2012. Site-specific analyses were focused on the five most common invasive cancers diagnosed among CTS participants and included: breast (SEER site code = 26000; n=5,053), colorectal (SEER site codes = 21041-21049, 21051, 21052; n=983), melanoma (SEER site code = 25010; n=749), lung (SEER site code = 22030; n=820), and endometrial (ICDO3 code = C54.1, C54.9; n=957). The analysis of endometrial cancers excluded 21,464 women identified as having had a hysterectomy (either by self-report on their baseline questionnaire or via linkage to statewide hospitalization discharge data files) prior to the completion of their baseline questionnaire, and women with hysterectomy during the follow-up period were censored at the time of their hysterectomy. The “All Sites” group included 12,322 cases of any prospectively-diagnosed invasive cancer. We further defined a group of “Estrogen-mediated” cancers (n=6,458) as incident cases of invasive breast, endometrial, or ovarian (SEER site code = 27040; n=443) cancer.

Sleep Duration

Sleep duration was ascertained from the CTS baseline questionnaire, a mailed self-administered survey, completed in 1995-96 (<http://www.calteachersstudy.org/surveys/BaselineL.pdf>), based on response to the question: “In the past year, on average, how many hours per day did you spend sleeping (none, <1, 1, 2, 3-4, 5-6, 7-9, 10 or more)?”.

Participants who reported fewer than 3 hours of sleep per night were excluded as these were considered invalid answers. Sleep duration was then categorized into three groups for analysis: 3-6, 7-9, and 10 or more hours per day of sleep.

Covariate Information

Data on potential covariates were gathered from the CTS baseline questionnaire and included information on: age at baseline; race/ethnicity; recent physical activity; body mass index (BMI); alcohol consumption; smoking status, smoking duration and intensity, age at smoking initiation and years since quitting; menopausal status and hormone therapy (HT) use at baseline; family history of cancer; age at menarche; parity; breastfeeding history; use of non-steroidal anti-inflammatory drugs (NSAIDs); history of colorectal polyps; dietary intake of calcium, folate, fiber, iron, vitamin D and fat; total caloric intake; dietary consumption of red meat, organ meat, pork, poultry, fish, processed meat, total meat; and comorbidity defined by self-report (no/yes) of any of the following conditions: high blood pressure, heart attack, myocardial infarction, stroke, or diabetes, or reported taking medication to treat high blood pressure. Measures of neighborhood socioeconomic status (SES) and urbanization were constructed based on 2000 U.S. census block group data linked to the baseline residential address of CTS participants. Methods for constructing these neighborhood sociodemographic metrics were developed as part of prior analyses in this cohort and are described in detail elsewhere [35,36]. Missing information for each covariate was coded as missing and included as a category in the multivariate models.

Follow-up

Follow-up time was calculated as the number of days between the time a woman joined the cohort (i.e., the date she completed her baseline questionnaire) and the earliest of four dates: the date of her primary invasive cancer diagnosis; the date of her first non-California residential address lasting 4 months or longer; the date of her death; or December 31, 2011. Women who were diagnosed with *in situ* cancer during the follow-up period were censored at the time of their diagnoses.

Statistical Analysis

Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs) associated with sleep duration, using ages at the start and end of follow-up (in days) to define time on study. Sleep duration was modeled as a categorical variable, using 3-6, 7-9 (referent group), and 10 or more hours per day of sleep as the groupings. All initial models were stratified by age at baseline (in single year increments) and adjusted for race/ethnicity. Assessment of important covariates was conducted by individually adding each of the potential confounders listed above to these initial age-stratified and race/ethnicity adjusted models, and keeping as covariates only those variables whose addition changed the regression coefficient for the sleep duration variable by 10% or more [37]. This resulted in different multivariate models for each of the cancer outcomes, as detailed in the footnote of Table 2. Linear tests for trend across categories of sleep duration were performed by using the median value of each category as a continuous variable in the models.

To account for the possibility that sleep duration could be influenced by physiologic changes associated with the development of cancer prior to diagnosis, we conducted sensitivity analyses in which we repeated our risk analyses after excluding cases who were diagnosed within two years of the start of the follow-up period (n=1,488 for all cancer sites) .

All models were run using the PHREG procedure in SAS Version 9.3 (SAS Institute, Cary, NC). Statistical significance was based on p-values of < 0.05.

RESULTS

Similar to the CTS cohort as a whole, study subjects were predominantly non-Hispanic white (87%) and middle-aged (mean = 52 years; range = 22 to 104 years at baseline). The distributions of selected characteristics by categories of sleep duration are presented in Table 1 (distributions are shown only for those characteristics which were included as covariates in risk models for at least one of the site-specific or groups of cancer outcomes). Although these characteristics significantly differed across categories of sleep duration ($p < 0.01$), most differences were fairly modest. Compared to average sleepers (7-9 hours/day), longer sleepers (>10 hours/day) tended to be older, be more likely to be non-white, be less physically active, be overweight or obese, abstain from alcohol consumption, have ever smoked tobacco, be peri/post-menopausal and have never used hormone therapy, and report comorbidities. Overall, characteristics of short sleepers (< 6 hrs/night) tended to be similar to those of average sleepers, with the exception that they were slightly more likely to be non-white, be less physically-active, be overweight or obese, report comorbidities, and live in suburban or urban neighborhoods.

Risk estimates for each of the site-specific and grouped cancer outcomes associated with short and long sleep durations are presented in Table 2. Overall, with the exception of lung cancer, point estimates generally were near or below one for short sleepers and above one for long sleepers; confidence intervals, however, tended to be wide and include 1.0. Tests for trend suggested a statistically significant increased risk associated with increasing sleep durations for the group of estrogen-mediated ($p = 0.04$) cancers. When the data were stratified by menopausal status at baseline, we continued to see an approximate 30% increase in risk for the estrogen-mediated cancers associated with long sleeping durations among peri/post menopausal women but the number of cases in the long sleep category among pre-menopausal women was insufficient to evaluate ($n = 9$) (*data not shown*). When we repeated these analyses excluding the cases diagnosed within two-years of baseline, the HRs for long sleep duration tended to increase slightly and the HR for the estrogen-mediated cancers became statistically significant for the long sleepers (HR=1.31, 95% CI = 1.02 – 1.68 for 10+ hours/night). While the confidence intervals in these subset analyses generally became wider, the test for trend for endometrial cancer became statistically significant ($p < 0.05$).

CONCLUSIONS

The results from these analyses suggest that longer sleep may be associated with increased risks of estrogen-mediated cancers only. Our results provided no evidence of risk associated with short sleep duration. Our analyses, however, were hindered by a number of limitations

that merit some discussion. Perhaps most importantly, our ascertainment of sleep duration was based on questions that were asked as part of a series of questions pertaining to physical activity, and were not designed specifically to study sleep as a risk factor per se. Thus, information on sleep duration was not collected on a continuous scale and the categories of duration were primarily designed to capture times for more active activities such as running or walking, which are usually performed for shorter time periods than would be typical for sleeping. Consequently, the categories of sleep duration that we used in our analyses were not ideally-suited to evaluating sleep. We had to use the broad 7-9 hours/day category as our referent; a category that only included 7-8 hours/day, which is considered the optimum sleep duration for most adults [4], would have been more ideal. If risks associated with longer sleep times begin to increase at time intervals of less than 10 hours, this could have had the effect of diluting our risk estimates. Furthermore, this categorization resulted in the vast majority of our study population (73%) classified into our referent group and relatively few cases (generally < 50 cases) in our long sleepers group, further limiting our statistical power to detect risks.

Similar to other epidemiologic studies on this topic, our assessment of sleep duration was based on self-report, and only on nocturnal sleep, which is likely to have introduced some degree of misclassification of exposure. While the prospective nature of our study eliminates the problem of differential recall bias, we can not discount the possibility of non-differential misclassification. There is evidence, however, that one-time self report of habitual sleep habits may be reasonably accurate at capturing sleep duration [38,39]. We also did not have information on psychosocial factors such as fatigue, anxiety and depression nor on other sleep conditions such as apnea or restless leg syndrome that may be important confounders.

Despite these limitations, our study has some notable strengths. Its prospective cohort design offers the opportunity to avoid selection and recall biases which can occur in case control studies, and the availability of excellent cancer outcome data over the follow-up period of nearly 15 years, provided substantial numbers of cases, at least for the average and short sleepers. The fact that limiting our analyses to exclude cases diagnosed within the first two years of follow-up did not substantially change our results suggests that our findings are not simply a reflection of reverse causality due to effects of early-stage disease on sleep duration prior to clinical diagnosis. Furthermore, while we did not have information on the full complement of potential covariates for all of the individual cancer sites we examined, we did have information for the most important covariates for breast and other hormonal cancers as well as for colorectal cancers, which were the predominant cancers diagnosed in our study population.

Our findings are consistent with some reports in the limited but very mixed epidemiologic literature on this topic, which has reported null [15,20,26,29], inverse [17-19,24,25,28], and direct [17,22,23,26,31] associations between sleep duration and cancer risk. Recent meta-analyses of these data, while noting substantial heterogeneity in results, concluded that the evidence to date does not support an association between sleep duration and overall cancer risk [9,11,13]. Other than for breast and colorectal cancers, these meta-analyses, however, could not consider other site-specific risks due to the fact that there has not been more than one original study published for the other specific cancer sites. Meta-analyses of the three

studies of colorectal cancer suggest longer sleep to be associated with a higher risk of colorectal cancer (summary rate ratio=1.29; 95% CI: 1.09 – 1.52) [9,13]. Although not statistically significant, our finding of an approximate 40% increase in risk of colorectal cancer associated with sleep durations of 10+ hours/day, based on only 18 cases, is consistent with this conclusion. The literature on breast cancer and sleep is particularly mixed with most studies reporting no association with sleep duration [11]. There is some very limited evidence, however, that suggests, similar to our own results, longer sleep durations may be related to increased breast cancer risk, depending on the subtype of breast cancer [26] and how the sleep duration was measured and modeled [22,23]. To our knowledge, our study is the first to evaluate and report an increased risk for a group of estrogen-mediated cancers. This finding seems to be in contradiction to the results of a meta-analysis that reported longer sleep was associated with reduced risks of hormone-related cancers. The authors of this meta-analysis, however, noted significant heterogeneity ($p<0.009$) in the results, which included studies of men and a broader category of hormone-related cancer sites than in our study, including cancers of the prostate and thyroid [13].

A number of pathways have been postulated to explain the potential role of sleep in carcinogenesis, including its influence on regulation of immune function, insulin metabolism, and circadian rhythms mediated by alterations in melatonin secretion [1,2,10,40,13]. While it is well beyond the scope of our study to evaluate potential mechanisms, our findings of increased risks associated with longer sleep duration seem inconsistent with the latter two of these hypothesized pathways. Shorter, not longer, durations of sleep have been linked to a number of cancer risk factors related to insulin metabolism, including obesity, metabolic syndrome, and diabetes [41-43]. Likewise, the carcinogenic effects of circadian disruption are thought to be mediated through the suppression of melatonin, an endogenous hormone with oncostatic and potentially anti-estrogenic properties that is released primarily during nocturnal sleep and would therefore likely exert a protective effect among longer sleepers [44,40,45,46]. Thus, our finding that long sleep duration is only associated with estrogen-mediated cancers is not consistent with a circadian disruption mechanism mediated by declines in melatonin and associated elevations in estrogens. Our finding of an increased risk associated with long sleep durations is more consistent with an effect mediated through proinflammatory immune responses. Compared to short sleepers, longer sleepers have been shown to have increased serum cortisol levels and reduced killer cell activity, both of which may promote carcinogenesis [44,2], although the reason why this risk would be confined to the group of estrogen-mediated cancers is not apparent

In summary, in light of our own findings in the context of the very limited and inconsistent body of research on this topic, additional research is clearly warranted. Epidemiologic studies that expand beyond considering just sleep duration to include an evaluation of metrics of sleep disturbance and quality (including sleep efficiency, sleep onset latency, and timing of sleep) would be especially fruitful as would investigations in more diverse populations than the CTS that include more people of color, and men. Additionally, the use of biomarkers to ascertain measures of immune function, circadian disruption and glucose metabolism may help to elucidate potential mechanistic pathways, critical towards guiding potential future public health interventions. Given that sleep is a potentially modifiable risk

factor, a greater understanding of its role in carcinogenesis offers a promising avenue for cancer prevention research worthy of pursuit.

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Table 1Distribution of selected characteristics by self-reported sleep duration among study population (n=101,609).^a

Characteristic	Sleep Duration						X ² p-value ^b
	3-6 hrs/day		7-9 hrs/day		10 hrs/day		
	N	%	N	%			
All	26,440	100	74,211	100	958	100	
Age at baseline (years)							
20-29	972	4	3,817	5	30	3	
30-39	3,240	12	10,882	15	79	8	
40-49	7,319	28	20,417	28	135	14	
50-59	7,153	27	17,820	24	159	17	
60-69	4,303	16	11,835	16	192	20	
70-79	2,555	10	6,942	9	158	17	
80	898	3	2,498	3	205	21	0.001
Race/Ethnicity							
White	21,293	80	66,109	89	820	86	
Black	1,273	5	1,229	2	30	3	
Hispanic	1,494	6	2,833	4	46	5	
Asian/Pacific Islander	1,474	6	2,110	3	22	2	
Other/unknown	906	3	1,930	2	40	4	<0.001
Physical activity, strenuous & moderate, last 3 years (hrs/week)							
0-1.1	9,700	37	23,513	32	525	55	
1.2-4.1	8,298	31	25,397	34	202	21	
4.2	8,442	32	25,301	34	231	24	<0.001
Body Mass Index (kg/m ²)							
16-24	14,267	54	45,269	61	477	50	
25-29	6,684	25	17,158	23	237	25	
30	4,290	16	9,152	12	160	16	
Unknown/ Outlier	1,199	5	2,632	4	84	9	<0.001
Alcohol consumption (g/day)							
None	9,178	35	22,776	31	414	43	
< 20	14,196	54	41,663	56	385	40	
20	1,670	6	6,183	8	89	9	
Unknown	1,396	5	3,589	5	70	8	<0.001
Smoking status							
Never	17,573	66	49,483	67	593	62	
Former	7,161	27	20,925	28	295	31	
Current	1,558	6	3,447	5	63	6	
Unknown	148	1	356	0	7	1	<0.001
Menopausal Status/HT use ^c							
Premenopausal	10,240	39	32,131	43	219	23	

Characteristic	Sleep Duration						X ² p-value ^b
	3-6 hrs/day		7-9 hrs/day		10 hrs/day		
	N	%	N	%			
Peri/post-menopausal, No HT use	3,475	13	7,940	11	219	23	
Peri/post-menopausal, Past HT use	1,829	7	4,610	6	119	12	
Peri/post-menopausal, Current E	3,531	13	9,183	12	128	13	
Peri/post-menopausal, Current E+P	3,586	14	11,067	15	123	13	
All Other	3,779	14	9,280	13	150	16	<0.001
Co-morbidity ^d							
No	19,856	75	59,066	80	575	60	
Yes	6,584	25	15,145	20	383	40	<0.001
Neighborhood Socioeconomic Status							
Lowest quartile	6,818	26	17,076	23	235	25	
2nd quartile	6,210	23	17,673	24	239	25	
3rd quartile	6,285	24	17,619	24	220	23	
Highest quartile	5,893	22	18,036	24	205	21	
Unknown	1,234	5	3,807	5	59	6	<0.001
Neighborhood Urbanization							
Rural/town	2,525	10	8,586	12	120	13	
Non-metropolitan city	6,762	25	20,570	28	258	27	
Suburban/urban	15,921	60	41,255	55	521	54	
Unknown	1,232	5	3,800	5	59	6	<0.001

^aDistributions are presented only for those variables which were included as covariates in risk models for at least one of the site-specific or groups of cancer outcomes (see footnote of Table 2).

^bP-value based on the Pearson X² for all variables except for age and physical activity, for which the Mantel Haenszel X² was used.

^cAbbreviations: HT=hormone therapy, E=estrogen, E+P=estrogen plus progestin.

^d'Yes' = self-report of any of the following: high blood pressure, high blood pressure medications, heart attack/myocardial infarction, stroke, diabetes; 'No' = did not self-report any of those conditions.

Table 2

Estimated risk associated with sleep duration for selected cancers and groups of cancers among 101,609 eligible CTS participants: adjusted hazard ratios (HR) and 95% confidence intervals (95% CI).^{a,b}

Cancer Outcome	Sleep Duration (hours/night)	All cases diagnosed from baseline		Excluding cases diagnosed within 2-years of baseline	
		# cases	HR (95% CI)	# cases	HR (95% CI)
All Sites	3-6	3,219	0.98 (0.94, 1.02)	2,846	0.98 (0.94, 1.03)
	7-9	8,958	1.00	7,863	1.00
	10+	145	1.13 (0.96, 1.33)	125	1.16 (0.97, 1.39)
			p(trend)=0.15		p(trend)=0.23
Estrogen-mediated ^c	3-6	1,649	0.95 (0.90, 1.01)	1,438	0.96 (0.90, 1.02)
	7-9	4,736	1.00	4,091	1.00
	10+	73	1.22 (0.97, 1.54)	64	1.31 (1.02, 1.68)
			p(trend)=0.04		p(trend)=0.08
Breast	3-6	1,303	0.97 (0.91, 1.04)	1,139	0.98 (0.92, 1.05)
	7-9	3,699	1.00	3,196	1.00
	10+	51	1.13 (0.86, 1.50)	46	1.25 (0.93, 1.68)
			p(trend)=0.30		p(trend)=0.42
Colorectal	3-6	269	1.02 (0.89, 1.18)	239	1.02 (0.88, 1.19)
	7-9	696	1.00	619	1.00
	10+	18	1.45 (0.91, 2.33)	15	1.42 (0.85, 2.38)
			p(trend)=0.90		p(trend)=0.93
Endometrial	3-6	236	0.90 (0.77, 1.04)	198	0.86 (0.73, 1.01)
	7-9	708	1.00	612	1.00
	10+	13	1.16 (0.67, 2.01)	11	1.22 (0.67, 2.23)
			p(trend)=0.11		p(trend)=0.05
Melanoma	3-6	181	0.99 (0.84, 1.17)	154	0.95 (0.79, 1.14)
	7-9	559	1.00	498	1.00
	10+	9	1.44 (0.74, 2.81)	9	1.70 (0.87, 3.32)
			p(trend)=0.72		p(trend)=0.36
Lung	3-6	229	1.03 (0.88, 1.20)	209	1.07 (0.91, 1.26)
	7-9	581	1.00	511	1.00
	10+	10	0.85 (0.45, 1.60)	8	0.84 (0.42, 1.70)
			p(trend)=0.63		p(trend)=0.35
Ovarian ^d	3-6	103	0.94 (0.75, 1.17)	95	1.00 (0.79, 1.27)
	7-9	318	1.00	273	1.00
	10+	8	1.87 (0.92, 3.80)	6	1.66 (0.74, 3.75)
			p(trend)=0.31		p(trend)=0.76

^a Adjusted hazard ratios generated from multivariate age-stratified Cox proportional hazards models as follows: breast cancer adjusted for race/ethnicity, alcohol consumption and menopausal status/hormone therapy use; colorectal cancer adjusted for race/ethnicity, body mass index (BMI), alcohol consumption, menopausal status/hormone therapy use, and comorbidity; endometrial cancer adjusted for race/ethnicity, BMI, physical activity, menopausal status/hormone therapy use, and comorbidity; melanoma adjusted for race/ethnicity, physical activity, alcohol consumption,

menopausal status/hormone therapy use, comorbidity, smoking status, and neighborhood urbanization and socioeconomic status; lung cancer adjusted for race/ethnicity, BMI, physical activity, alcohol consumption, comorbidity, smoking status, and neighborhood urbanization; all sites adjusted for race/ethnicity, BMI, physical activity, alcohol consumption, comorbidity, smoking status, and menopausal status/hormone therapy use; estrogen-mediated sites adjusted for race/ethnicity, BMI and menopausal status/hormone therapy use; ovarian cancer adjusted for race/ethnicity, BMI and menopausal status/hormone therapy use.

^b Tests for trend calculated by using the midpoints of each sleep duration category and modeling as a continuous variable.

^c Includes invasive cancers of the breast, endometrium and ovary.

^d Excludes women who had an oophorectomy.