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Sleep duration and risk of cancer in the Mexican American Mano-a-Mano Cohort

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SUMMARY

Background: To date, no study has investigated the association of sleep duration with cancer risk in Mexican Americans.
Analysis: Using data from the Mano-A-Mano Mexican American Cohort study, we analyzed the relationship between sleep duration and overall cancer risk among Mexican Americans.
Results: Of 10,802 subjects included in this study, 429 developed cancer during follow-up. Compared with study participants sleeping 8-9 hours per night, those sleeping less than 6 hours per night had significantly increased risk of overall cancer in both univariate and multivariate Cox regression analyses. After adjusting for social-demographic and lifestyle variables, sleeping less than 6 hours per night was associated with a 1.37-fold increased risk of overall cancer (hazard ratio = 1.37, 95% confidence interval: 1.01-1.97). In breast cancer alone, sleeping less than 6 hours per night was associated with a 1.86-fold increased risk of breast cancer (hazard ratio = 1.86, 95% confidence interval: 1.01-3.45) after adjustment for birthplace and language acculturation. In further stratified analysis, significant associations between sleeping less than 6 hours per night and overall cancer risk were evident among overweight participants, former drinkers, those with medium or high levels of physical activity, those married or living together, and those who had less than 2 hours of sitting time per day. In addition, increased cancer risk associated with long sleep duration (at least 9 hours per night) was observed among overweight participants and those with medium or high levels of physical activity.
Conclusion: Our results provide evidence to link sleep duration with cancer risk among Mexican Americans.

Introduction

Owing to the increased prevalence in modern society of sleeping difficulties and sleepiness and decreased sleeping duration per night, the relation of sleep and health has drawn increasing interest over the past decade.[1] Both insufficient sleep and too much sleep have been associated with increased risk of various chronic health problems such as obesity, diabetes, cardiovascular disease, hypertension, cancers, and all-cause mortality.[2–14] To date, various studies that have examined the association of sleep duration with cancer risk have found that both short and long sleep durations are associated with increased risks of various types of cancer,[12–22] although the results are mixed and no consensus has been reached for any type of cancer. Furthermore, none of these studies have been conducted among Mexican Americans, one of the fastest-growing populations in United States.[23]

In fact, investigation of the relationship between sleep duration and cancer risk among Mexican Americans is of particular interest because sleep problems disproportionally affect racial and ethnic minorities among adults in the United States,[24–30] including non-Hispanic Blacks, Hispanics, American Indians, and others. Mexican Americans also have unique social-demographics that may further enhance the interest of studying the relationship between sleep duration and cancer risk. For example, in our previous analysis, we found that being born in the United States and high language acculturation were associated with short sleep duration among Mexican Americans. Both of these factors also are known risk factors for several types of cancer among Mexican Americans.[31,32] Three out of 4 Mexican Americans are either overweight or obese,[33,34] which is known to be associated with both sleep problems and various types of cancer. Thus, the associations between sleep duration and cancer risk

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observed in other populations may not be the same in Mexican Americans.

In the current study, we analyzed sleep duration in relation to cancer incidence among Mexican American study participants identified from the Mano-A-Mano Mexican American Cohort study. Our hypothesis was that abnormal sleep duration is associated with increased risk of overall cancer among Mexican Americans.

Materials and methods

Study population

The current study included data from 10,802 Mexican American adults aged 20-60 years, identified from Mano-A-Mano, an Mexican American cohort study. Participants did not have self-reported cancer, diabetes, or cardiovascular diseases at the time of enrollment. Data were obtained from individuals in a large population-based cohort of Mexican-origin households recruited in the Houston, TX, area. This cohort, for an ongoing prospective study of first- and second-generation Mexican-origin immigrant households in Houston, was initiated in July 2001 and is maintained by the Department of Epidemiology at The University of Texas MD Anderson Cancer Center. A detailed description of the sampling and recruitment strategy has been published previously.[35] Briefly, participants were recruited through block-walking in predominantly Mexican American neighborhoods, from community centers and local health clinics, and via networking through currently enrolled participants. Of the identified eligible households, about 88% agreed to participate in the study. After obtaining written informed consent from participants, trained bilingual research interviewers conducted structured face-to-face interviews lasting around 45 minutes using a standardized and validated questionnaire in the participant's preferred language, either Spanish or English. The questionnaire elicited information on birthplace and residential history, social and demographic characteristics, lifestyle behaviors, levels of physical activity, personal medical history, family history of chronic disease, acculturation, and occupational exposures. Participants are annually followed up via a telephone call to update information on selected exposures and new diagnoses of selected chronic diseases, including cancer, type 2 diabetes, and hypertension. The incidence of cancer in the cohort was confirmed with the Texas Cancer Registry. Self-reported 24-hour sleep duration data were available at baseline for all participants in our study. Our study was approved by the Institutional Review Board of The University of Texas MD Anderson Cancer Center, and all methods were in accordance with the relevant guidelines and regulations.

Statistical analysis

Statistical analyses were performed using the Stata software package (version 13; StataCorp, College Station, TX). Various studies have examined the association between sleep duration and cancer risk.[12–21] However, there is no consensus on how to select the cut points, in particular between 6 and 9 hours. In the current study, we grouped the study participants into 4 categories: <6, 6-8, 8-9, and at least 9 hours per night. Our selection was decided based both on the hypothesized biological effects on cancer risk as well as on the frequency distribution of sleep duration within our study population. The differences in the distributions of social-demographic and lifestyle variables between cancer cases and controls were evaluated using the χ^2 test. Association between cancer risk and sleep duration was assessed using univariate and multivariable-adjusted Cox proportional hazards regression models. Adjusted hazard ratios (HRs) and 95% confidence intervals (95% CIs) were estimated, and potential confounding factors were adjusted for as appropriate. All statistical tests were 2-sided, and P values of less than .05 were considered statistically significant. In the power calculation, we estimated to have at least 80% of power to detect an HR of 1.15 at significance level of .05 in the analysis between sleep duration and overall/breast cancer risk shown in Table 2. We had at least 80% of power to detect an HR of 1.52 at significance level of .05 in the stratified analysis shown in Table 3.

Results

We identified a total of 429 cancer cases among 10,802 study subjects during follow-up. Table 1 summarizes basic social-demographic characteristics and lifestyle behaviors for both the cancer cases and noncancer controls. Study participants were divided into 4 groups according to their sleep duration: less than 6 hours, 6-8 hours, 8-9 hours, and at least 9 hours per night. The distribution of sleeping hours per night differed significantly between cancer cases and controls ($P = .006$). Participants with cancer were more likely to sleep <6 hours per night than the controls (13.75% vs 9.57%). In term of social-demographic characteristics, a clear trend of increasing numbers of cancer cases was observed with increasing age at enrollment ($P <$

Table 1
Distribution of characteristics among participants by case-control status

Variable	Controls, n (%)	Cases, n (%)	*P* value
Overall	10,373 (100)	429 (100)	
Sleep duration			
<6 h per night	993 (9.57)	59 (13.75)	
6 to <8 h per night	4307 (41.52)	180 (41.96)	
8 to <9 h per night	4003 (38.59)	136 (31.70)	
≥9 h per night	1070 (10.32)	45 (10.49)	.006
Age at enrollment, y			
21-30	1946 (18.76)	16 (3.73)	
31-40	3473 (33.48)	59 (13.75)	
41-50	2352 (22.67)	91 (21.21)	
50-60	1488 (14.34)	107 (24.94)	
>60	1114 (10.74)	156 (36.36)	<.001
Sex			
Male	2062 (19.88)	103 (24.01)	
Female	8311 (80.12)	326 (75.99)	.042
Marital status			
Married/living together	8126 (78.34)	311 (72.49)	
Other	2234 (21.54)	118 (27.51)	.004
Education levels			
Less than high school	6097 (58.78)	272 (63.40)	
High school graduate	2323 (22.39)	83 (19.35)	
College	1947 (18.77)	74 (17.25)	.156
Place of birth			
Mexico	7813 (75.32)	256 (59.67)	
United States	2560 (24.68)	173 (40.33)	<.001
Language acculturation			
Low	6601 (63.64)	242 (56.41)	
High	3718 (35.84)	185 (43.12)	.002
BMI category			
Underweight/normal weight	1501 (14.47)	50 (11.66)	
Overweight	3423 (33.00)	146 (34.03)	
Obese	5425 (52.30)	233 (54.31)	.257
Smoking status			
Never	7571 (72.99)	255 (59.44)	
Former	1526 (14.71)	94 (21.91)	
Current	1274 (12.28)	80 (18.65)	<.001
Alcohol drinking			
Never	6993 (67.42)	270 (62.94)	
Former	1015 (9.79)	71 (16.55)	
Current	2343 (22.59)	88 (20.51)	<.001
Physical activity			
Low	7461 (71.93)	330 (76.92)	
Medium + high	2812 (27.11)	95 (22.14)	.022
Sitting, h/d			
<2	2967 (28.60)	115 (26.81)	
2-4	4234 (40.82)	175 (40.79)	
4-6	1952 (18.82)	75 (17.48)	
>6	1194 (11.51)	63 (14.69)	<.001

Table 2
Sleep duration and risk of overall cancer

Sleep duration	Unadjusted	Model 1[a]	Model 2[b]	Model 3[c]
Overall				
<6 h per night	1.78 (1.31-2.42)	1.63 (1.19-2.22)	1.42 (1.04-1.94)	1.37 (1.01-1.87)
6 to <8 h per night	1.20 (0.96-1.51)	1.18 (0.94-1.48)	1.17 (0.93-1.46)	1.15 (0.92-1.44)
8 to <9 h per night	Reference	Reference	Reference	Reference
≥9 h per night	1.28 (0.91-1.79)	1.21 (0.86-1.70)	1.19 (0.85-1.67)	1.11 (0.79-1.57)
Breast cancer only				
<6 h per night	1.92 (1.04-3.54)	1.86 (1.01-3.45)	1.61 (0.87-3.00)	1.71 (0.92-3.18)
6 to <8 h per night	1.19 (0.75-1.89)	1.18 (0.74-1.87)	1.14 (0.72-1.80)	1.17 (0.73-1.87)
8 to <9 h per night	Reference	Reference	Reference	Reference
≥9 h per night	1.56 (0.82-2.97)	1.53 (0.80-2.92)	1.52 (0.80-2.91)	1.38 (0.69-2.74)

[a] Adjusted for birthplace and language acculturation.
[b] Adjusted for birthplace, language acculturation, age, sex, marital status, and education level.
[c] Adjusted for birthplace, language acculturation, age, sex, marital status, education level, smoking status, drinking status, sitting time, physical activity, and BMI category.

.001). Compared with their counterparts, men and persons married or living together had a higher risk of cancer ($P = .042$ and 0.004, respectively). Participants with cancer were more likely born in the United States ($P < .001$) and more likely to have higher language acculturation ($P = .002$) than their counterparts. We observed no significant differences in relation to body mass index (BMI) category. However, the distribution between cases and controls significantly differed by smoking status ($P < .001$), alcohol status ($P < .001$), levels of physical activity ($P = .022$), and hours spent sitting per day ($P < .001$). Compared with controls, cancer cases were more likely to be smokers, ever drinkers, physically inactive, and sitting many hours per day.

Next, we investigated the relationship between sleep duration and cancer risk (Table 2). Because both short and long sleep durations have been linked with various types of chronic diseases, we selected sleeping 8 to <9 hours per night as the reference group. In the univariate Cox regression analysis, sleeping <6 hours per night was significantly associated with increased risk of overall cancer (HR = 1.78, 95% CI: 1.31-2.42). Neither sleeping 6 to <8 hours per night nor sleeping ≥9 hours per night was associated with the risk of overall cancer. Fig. 1 shows the Kaplan-Meier survival estimates for the association between sleep duration and overall cancer risk ($P < .001$). In further multivariate analysis, we included birthplace and language acculturation in model 1; birthplace, language acculturation, age, sex, marital status, and education level in model 2; and birthplace, language acculturation, age, sex, marital status, education level, smoking status, drinking status, sitting time, physical activity, and BMI category in model 3. The association between sleeping <6 hours per night and overall cancer risk remained statistically significant in all 3 models (model 1: HR = 1.63, 95% CI: 1.19-2.22; model 2: HR = 1.42, 95% CI: 1.04-1.94; and model 3: HR = 1.37, 95% CI: 1.01-1.97). However, the strength of the association gradually declined from univariate model, model 1, model 2, and model 3.

During the follow-up, 102 women developed breast cancer. In breast cancer only, a similar association was observed between sleep duration and breast cancer risk (Table 2). In the univariate Cox regression analysis, sleeping <6 hours per night was significantly associated with increased risk of breast cancer (HR = 1.92, 95% CI: 1.04-3.54). This significant association remained after adjustment for birthplace and language acculturation in model 1 (HR = 1.86, 95% CI: 1.01-3.45) but not after further adjustment in model 2 or model 3.

In analysis further stratified by social-demographic characteristics and lifestyle behaviors, the association between sleeping duration and overall cancer risk was influenced by BMI, drinking status, physical activity, marital status, and sitting time (Table 3). For the BMI category, a significant association was observed only for overweight study participants and not for persons of normal weight or obese persons. Among overweight study participants, sleeping categories of <6 hours per night, 6 to <8 hours per night, and ≥ 9 hours per night were associated with 1.99-, 1.57-, and 1.88-fold increased risks of overall cancer (HR = 1.99, 95% CI: 1.15-3.43; HR = 1.57, 95% CI: 1.05-2.36; HR = 1.88, 95% CI: 1.08-3.26). Among former drinkers, sleeping <6 hours per night and sleeping 6 to <8 hours per night were associated

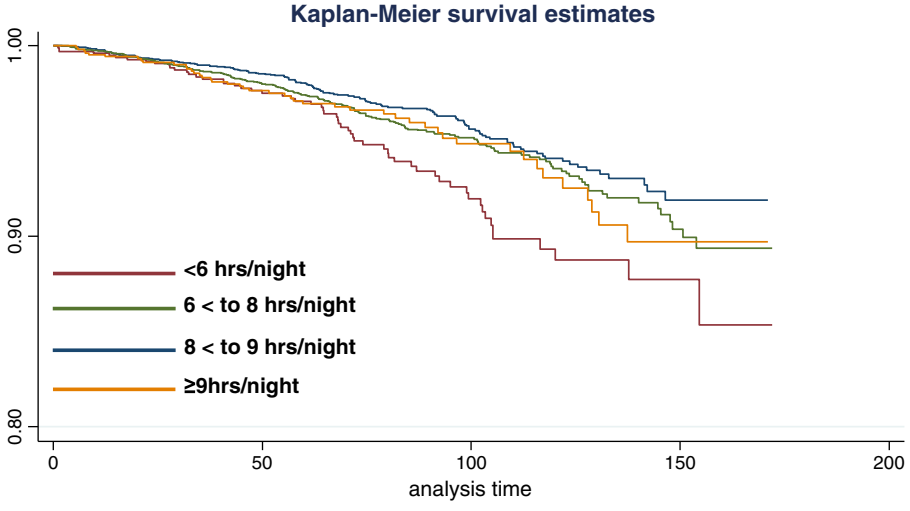

Fig. 1. Smoothed hazard estimates to assess the association between sleep duration and overall cancer risk.

Table 3
Stratified analysis to assess the association between sleep duration and overall cancer risk[a]

	<6 h per night	6 to <8 h per night	≥9 h per night
By BMI category			
Normal	1.66 (0.61-4.52)	1.01 (0.50-2.03)	1.19 (0.41-3.45)
Overweight	1.99 (1.15-3.43)	1.57 (1.05-2.36)	1.88 (1.08-3.26)
Obese	1.08 90.71-1.64)	0.97 (0.72-1.31)	0.75 (0.45-1.25)
By drinking status			
Never	1.26 (0.86-1.84)	0.96 (0.73-1.27)	0.89 (0.56-1.39)
Former	2.42 (1.04-5.63)	2.37 (1.24-4.52)	2.24 (0.93-5.38)
Current	1.29 (0.62-2.71)	1.23 (0.72-2.08)	1.45 (0.68-3.10)
By physical activity			
Low	1.16 (0.81-1.65)	1.08 (0.84-1.39)	0.93 (0.62-1.41)
Medium and high	2.32 (1.20-4.47)	1.40 (0.83-2.36)	2.10 (1.05-4.19)
By marital status			
Not married	1.07 (0.61-1.89)	0.90 (0.57-1.41)	0.96 (0.50-1.83)
Married/living together	1.56 (1.08-2.27)	1.27 (0.98-1.66)	1.20 (0.79-1.81)
By sitting time			
<2 h	1.65 (1.13-2.27)	1.25 (0.80-1.96)	1.26 (0.62-2.58)
2-4 h	0.88 (0.50-1.57)	1.04 (0.78-1.56)	1.15 (0.66-1.98)
4-6 h	1.64 (0.79-3.41)	1.32 (0.77-2.27)	1.03 (0.45-2.33)
>6 h	1.68 (0.75-3.78)	0.94 (0.50-1.78)	1.03 (0.44-2.39)

[a] Adjusted for birthplace, language acculturation, age, sex, marital status, education level, smoking status, drinking status, sitting time, physical activity, and BMI category when appropriate.

with 2.42- and 2.37-fold increased risks of overall cancer (HR = 2.42, 95% CI: 1.04-5.63; HR = 2.37, 95% CI: 1.24-4.52). Similar association was not observed among participants who never drank or current drinkers. For physical activity, a significant association was observed only among those with medium or high levels of physical activity. Among former drinkers, sleeping <6 hours per night and sleeping ≥9 hours per night were associated with 2.32- and 2.10-fold increased risks of overall cancer (HR = 2.32, 95% CI: 1.20-4.47; HR = 2.10, 95% CI: 1.05-4.52). Among those married or living together, sleeping <6 hours per night was associated with a 1.56-fold increased risk of overall cancer (HR = 1.56, 95% CI: 1.08-2.27). Finally, among persons who had sitting times of less than 2 hours per day but not those who had at least 2 hours of sitting time per day, sleeping <6 hours per night was associated with a 1.65-fold increased risk of overall cancer (HR = 1.65, 95% CI: 1.13-2.27).

Discussion

In the current prospective cohort study of 10,802 Mexican Americans, sleeping <6 hours per night was significantly associated with increased overall cancer risk and breast cancer risk. Our study is the first to examine the relationship between sleep duration and cancer risk in Mexican Americans.

Few prospective studies have examined the association between sleep duration and overall cancer risk.[19,20] Among female participants in the National Institute of Health (NIH) the American Association of Retired Persons (AARP) Diet and Health Study Cohort, compared with sleeping 7 to 8 hours per night, sleeping less than 5 hours per night was associated with a 10% decreased risk of all cancers.[20] However, in the California Teachers Study, no significant association was observed between sleep duration and all cancer risk.[19] In the current study, we found that sleeping less than 6 hours per night was significantly associated with increased overall cancer risk compared with sleeping 8-9 hours. In further analysis, we found that the significant association was evident only among overweight participants, former drinkers, those with medium or high levels of physical activity, those married or living together, and those who had less than 2 hours sitting time per day, but not in other strata. Additionally, among overweight participants and those with medium or high levels of physical activity, those with long sleep duration (at least 9 hours per night) had an increased overall cancer risk compared with those who sleep 7 to 9 hours per night. We have no explanation for the observed difference. It may be just by chance, given the small number of cancer cases. In our power calculation, we had at least 80% of power to detect an HR of 1.52 at significance level of .05 in the stratified analysis. So, we do not have enough power to detect the association in certain strata. It may also reflect actual interactions among those variables, sleep duration, and cancer risk. In our previous analysis, those married or living together were more likely to have normal sleep duration than those not married or living separately. Furthermore, short sleep duration was associated with increased risk of obesity. Future large studies are needed to further assess the effect of social-demographic and lifestyle factors on the association between sleep duration and cancer risk.

In our study, we found that sleeping less than 6 hours per night was significantly associated with increased breast cancer risk (HR = 1.86, 95% CI: 1.01-3.45). Breast cancer is the most studied cancer in terms of its relationship with sleep duration. In a recent meta-analysis, a longer sleep duration was associated with increased risk of breast cancer, especially estrogen receptor–positive disease.[18] However, in another meta-analysis, no significant association was observed between sleep duration and breast cancer risk.[14] In the individual prospective analyses, the results are likewise mixed. For example, using data from the Southern Community Cohort Study, compared with the reference group (8 hours), Black women who reported shorter sleep duration had an increased risk of estrogen receptor–negative and progesterone receptor–negative breast cancer.[16] In the National Institute of Health (NIH) the American Association of Retired Persons (AARP) Diet and Health Study Cohort, compared with sleeping 7 to 8 hours per night, sleeping less than 5 hours per night was associated with reduced risk of breast cancer.[20] In the California Teachers Study, no significant association was observed between sleep duration and breast cancer risk.[19]

Several molecular pathways have been suggested to play a role in the effects of sleep duration on cancer, with the most prominent ones being insulin metabolism, circadian rhythms, and immune function.[1,12,36,37] Although evaluation of potential mechanisms is beyond the scope of the current study, our observation that short sleep duration was associated with increased risk of overall cancer and breast cancer is consistent with our knowledge of insulin metabolism and circadian rhythms pathways. Short sleep duration has been associated with increased cancer risk factors related to insulin metabolism, including obesity, metabolic syndrome, and diabetes.[4,38] Similarly, the

carcinogenic effects of circadian disruption are thought to be mediated through the suppression of melatonin, an endogenous hormone with potentially antiestrogenic properties that is released primarily during nocturnal sleep and would therefore likely exert a defensive effect among long sleepers.[37,39–41] Our observation that long sleep duration is associated with increased risk of overall cancer among overweight participants and those with medium or high levels of physical activity can possibly be explained as an effect mediated through proinflammatory immune responses. Compared with short sleep, longer sleep may lead to increased serum cortisol levels and reduced killer cell activity, both of which may promote carcinogenesis.[39]

Thus, from experimental and mechanistic grounds, sleep may contribute to the development of cancer. However, in epidemiological studies, the results are mixed. In most of the studies, the ascertainment of sleep duration was based on self-reported questionnaire data at one point in time and only on nocturnal sleep, which is likely to have introduced a certain degree of misclassification. Many studies did not have an evaluation of metrics of sleep disturbance and quality. Also, many of the studies did not have information on fatigue, anxiety, and depression or on other sleep conditions such as apnea or restless leg syndrome, all of which affect sleep duration. In addition, in a recent publication by Erren et al[22] of the meta-analyses of cancer incidence among some 1,500,000 study individuals in 13 countries, they offered 8 sets of recommendations for future epidemiological studies which must consider the complexity of multidirectional relationships between sleep and cancer. For examples, instead of just duration and quality, the future epidemiological studies need to consider "when we sleep," chronotype variations among the population, and sleep duration variations across the years. Knowing that sleep is a potential modifiable risk factor, a greater understanding of its role in cancer risk is of particular interest in cancer prevention research. Epidemiologic studies that incorporate the recommendations would be especially successful and have significant ramifications to improve public health.

Disclosure

Authors have declared that there are no any competing financial interests in relation to the work described.

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