http://dx.doi.org/10.5665/sleep.2626

Associations of Self-Reported Sleep Duration and Snoring with Colorectal Cancer Risk in Men and Women

Xuehong Zhang, MD, ScD[1]; Edward L. Giovannucci, MD, ScD[1,2,3]; Kana Wu, PhD[2]; Xiang Gao, MD, PhD[1,2]; Frank Hu, MD, PhD[1,2,3]; Shuji Ogino, MD, PhD, MS[4,5]; Eva S. Schernhammer, MD, DrPH[1]; Charles S. Fuchs, MD[1,4]; Susan Redline, MD, MPH[6]; Walter C. Willett, MD, DrPH[1,2,3]; Jing Ma, MD, PhD[1]

[1]*Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA;* [2]*Department of Nutrition, Harvard School of Public Health, Boston, MA;* [3]*Department of Epidemiology, Harvard School of Public Health, Boston, MA;* [4]*Department of Medical Oncology, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA;* [5]*Department of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA;* [6]*Division of Sleep Medicine, Department of Medicine, Brigham and Women's Hospital and Beth Israel Deaconess Medical Center, Boston, MA*

Study Objectives: We assessed the relationship between sleep duration, snoring and colorectal cancer risk.
Design: Prospective cohort studies.
Setting: United States.
Participants: A total of 30,121 men aged 41 to 79 years in the Health Professionals Follow-up Study and 76,368 women aged 40 to 73 years in the Nurses' Health Study.
Interventions: None.
Measurements and Results: We queried information on sleep duration and snoring in 1986/87. Cox proportional hazards regression models were used to estimate multivariable hazard ratios (HRs, 95% CIs). We documented 1,973 incident colorectal cancer cases (709 men and 1,264 women) over a 22-year follow-up period. Compared to sleep an average 7 h, ≥ 9 h of sleep was significantly associated with a higher risk of colorectal cancer among men (HR = 1.35, 95% CI: 1.00, 1.82), and to a lesser degree, among women (HR = 1.11, 95% CI: 0.85, 1.44). The risk associated with longer sleep was restricted to individuals who regularly snored (men: HR = 1.80, 95% CI: 1.14, 2.84; women: HR = 2.32, 95% CI: 1.24, 4.36) and to overweight individuals (i.e., BMI ≥ 25 kg/m^2) (men: HR = 1.52, 95% CI: 1.04, 2.21; women: HR = 1.37, 95% CI: 0.97, 1.94). Short sleep duration (≤ 5 h) was not associated with an increased risk of colorectal cancer in the entire sample or in subgroups stratified by snoring or BMI.
Conclusions: Longer sleep duration was associated with an increased risk of developing colorectal cancer among individuals who were overweight or snored regularly. This observation raises the possibility that sleep apnea and its attendant intermittent hypoxemia may contribute to cancer risk.
Keywords: Sleep duration, snoring, colorectal cancer, incidence, prospective study
Citation: Zhang X; Giovannucci EL; Wu K; Gao X; Hu F; Ogino S; Schernhammer ES; Fuchs CS; Redline S; Willett WC; Ma J. Associations of self-reported sleep duration and snoring with colorectal cancer risk in men and women. *SLEEP* 2013;36(5):681-688.

INTRODUCTION

Despite progress in prevention,[1] colorectal cancer remains the third most commonly diagnosed cancer and the third leading cause of death due to cancer in both women and men in the United States.[2] Efforts to continue identifying modifiable risk factors are warranted.

Both short and long sleep duration has been associated with an increased risk of cardiovascular disease,[3,4] breast cancer,[5-7] and overall mortality.[8,9] One recent case-control study[10] reported a significant association between short sleep duration and an increased risk of colorectal adenomas, precursors of colorectal cancer. This finding suggested a potential role of sleep duration in colorectal carcinogenesis, although the association with long sleep duration was not tested due to small number of cases in that study. Short or long sleep duration might affect colorectal cancer risk through associations with weight gain,[11,12] obesity,[11] diabetes,[13] and insulin resistance,[14] which are all risk factors for colorectal cancer.[15,16] However, while a meta-analysis and a recent study described associations between long[8] and short sleep duration and overall cancer risk,[17] to the best of our knowledge, no published data have examined the relation of sleep duration to risk of colorectal cancer specifically and whether the associations differ by overweight/obesity status (a factor associated with insulin resistance). In addition, although intermittent hypoxemia, which occurs with sleep disordered breathing, has been associated with tumorigenesis,[18,19] studies of cancer incidence have not considered whether the association of sleep duration and cancer may be modified by sleep disordered breathing.

We therefore examined whether sleep duration was associated with risk of colorectal cancer in large prospective cohorts of men (the Health Professionals Follow-up Study)[20] and women (the Nurses' Health Study).[21] We hypothesized that individuals with either shorter or longer sleep duration had increased risk of colorectal cancer. Furthermore, we specifically evaluated whether this relationship was modified by regular snoring (a marker of sleep apnea or disordered breathing) or overweight.

METHODS

Study Population and Assessment of Sleep Duration

The Health Professionals Follow-up Study (HPFS)[20] is a prospective cohort study of 51,529 U.S. male professionals

Submitted for publication June, 2012
Submitted in final revised form October, 2012
Accepted for publication November, 2012
Address correspondence to: Xuehong Zhang, 401 Park Drive, Suite 301 West, Boston, MA 02115; Tel: (617) 519-3550; Fax: (617) 432-2435; E-mail: xuehong.zhang@channing.harvard.edu
Jing Ma, 181 Longwood Ave, Boston, MA 02115; Tel: (617) 525-2708; Fax: (617) 525-2008; E-mail: jing.ma@channing.harvard.edu

who were aged 40 to 75 years at baseline in 1986. The Nurses' Health Study (NHS)[21] is a prospective cohort study of 121,700 registered female nurses who were aged 30 to 55 years at baseline in 1976 in the U.S. A biennial questionnaire has been sent to participants in each cohort since 1986 and 1976, respectively, to collect information on demographics, lifestyle factors, and disease endpoints. The follow-up rate has been > 90% for NHS and HPFS. Both studies have been approved by the institutional review board at the Harvard School of Public Health and Brigham and Women's Hospital, Boston, Massachusetts. Return of the questionnaires was considered to imply informed consent, and we also obtained written consent from each participant to obtain and review medical records.

In 1986, NHS participants were asked to "indicate total hours of actual sleep in a 24-hour period" and "do you snore?" The same question was asked in the HPFS 1987 questionnaire and was subsequently included in both cohorts in 2000. Response categories for sleep duration were identical between the two cohorts: "5 hours or less, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, or 11 hours or more." The validity of self-reported sleep duration in NHS has been described in detail elsewhere.[9] Briefly, self-reported average time spent sleeping was highly reproducible and correlated well with sleep duration as assessed by sleep diaries (Spearman $r = 0.79$; $P < 0.0001$).[9] Response categories for snoring were "Regularly, occasionally, never" in NHS and "Every night, most nights, a few nights a week, occasionally, never" in HPFS. We defined regular snorers as those who reported snoring regularly in NHS and those who snored every night, most nights, or a few nights a week in HPFS. We defined non-snorers as those who only occasionally or almost never snored.

A total of 83,027 women answered the sleep duration question in 1986. In HPFS, 33,579 men reported sleep duration. Participants in both cohorts who did not answer the sleep question did not differ substantially from respondents according to age, BMI, physical activity, endoscopy screening, family history of colorectal cancer, alcohol consumption, or major dietary factors. We further excluded participants with ulcerative colitis, and those who died or reported colorectal cancer or any other cancer (except non-melanoma skin cancer) before 1986 for NHS and 1988 for HPFS. A total of 76,368 women and 30,121men remained to form the baseline population for this analysis.

Identification of Incident Colorectal Cancer Cases

In both cohorts, participants reported cancer and other disease outcomes on biennial questionnaires. Researchers received participants' permission to obtain their medical records and pathological reports and, while blinded to exposure information, abstracted the information on anatomic location, stage, and histological type of the cancer. Colorectal cancer and subsites were defined according to the International Classification of Diseases, Ninth Revision (ICD-9).[22]

Assessment of Other Variables

We obtained information on potential colorectal cancer risk factors such as height, body weight, physical activity (MET-h/w), cigarette smoking, aspirin use, family history of colorectal cancer, snoring, antidepressant drug use, and menopausal status and postmenopausal hormone use (women only) on the biennial questionnaires. In addition, almost every 4 years, we collected information on dietary factors using baseline and subsequent validated food frequency questionnaires in the NHS[23] and in the HPFS.[24] These factors included consumption of red meat, processed meat, alcohol, folate, calcium, and vitamin D. In 1988, women participating in NHS were asked how many years in total (never, 1-2, 3-5, 6-9, 10-14, 15-19, 20-29, and ≥ 30 years) they had worked rotating night shifts.[25]

Statistical Analyses

We calculated person-time for each participant from the date of baseline questionnaire return to the date of death, loss to follow-up, colorectal cancer diagnosis, or the end of follow-up (May 31, 2008, for the NHS; January 31, 2008, for the HPFS), whichever came first. We used a Cox proportional hazards regression model[26] to calculate hazard ratios (HRs, 95% CIs) and adjusted simultaneously for age (in months) and year of questionnaire return. We observed no violation of the proportional hazard assumption based on the likelihood ratio test that compared the model with and without the interaction terms between sleep duration and age or follow-up time. We conducted all analyses using the SAS software (Version 9.2; SAS Institute Inc). All statistical analyses were two-sided, with a P-value < 0.05 indicating significance.

In addition to age, in multivariate models, we adjusted for established or potential risk factors for colorectal cancer including BMI and diabetes (see Table 2 for variable categorizations). In women, we used the information provided in the 1986 questionnaire for these factors. In men, for non-dietary factors, we used information provided in the 1988 questionnaire; for dietary factors, we used the information provided in the 1986 questionnaire because no food frequency questionnaire was administered in 1988. In addition, we conducted sensitivity analysis adjusting for marital status, education level, sedentary activity (TV watching as a surrogate), waist to hip ratio, history of hypertension, depression (antidepressant use as a surrogate), and cardiovascular disease. Since results were essentially unchanged with adjustment for these latter factors, they were not included in the final model. Because sleep duration may be influenced by undiagnosed cancer, we conducted lag-time analyses, excluding cases that occurred within the first 4 years after assessment of sleep duration.

To test the priori hypotheses, we specifically evaluated whether the sleep duration and colorectal cancer association was stronger among regular snorers or overweight individuals. As exploratory analyses, we also evaluated whether the association with sleep duration differed by alcohol consumption (< 10 g/d, ≥ 10 g/d in women; < 15 g/d, ≥ 15 g/d in men), family history of colorectal cancer (yes, no), physical activity (< median, ≥ median, in each cohort), menopausal status (premenopausal, postmenopausal), and years of shift work (0-14, ≥ 15 years, women only). In these stratified analyses, given the relatively small number of cases for short sleepers (i.e., ≤ 5 h) in HPFS, we used ≤ 6 h as the lowest category. Because initial analyses did not reveal significant associations with short sleep, further post hoc analyses only examined associations for the long sleepers (≥ 9 h) compared to the reference group (7 h). We constructed cross-product terms between the 2 sleep duration groups (i.e., ≥ 9 vs. 7 h) and each of the variables considered for effect modification and tested whether beta-coefficients of the cross product terms were statistically significant using a Wald test. We further conducted stratified analysis by history of endoscopy/sigmoidoscopy screening (yes, no) to assess potential detection bias. Lastly, using information on sleep duration collected from the baseline and year 2000, we calculated HRs for colorectal cancer diagnosed after 2000 according to 4 cross-classified categories of sleep duration (i.e., optimal: defined as 7 h vs. suboptimal: defined otherwise). We also conducted interaction analyses to evaluate whether the associations with "changes" in sleep duration in these 2 time periods differ by BMI at baseline or weight change in these 2 time periods.

RESULTS

We documented a total of 1,973 incident colorectal cancer cases: 1,264 cases in NHS (1986-2008) and 709 cases in HPFS (1988-2008). At baseline, the median age was 53 for women and 56 for men. Selected lifestyle and potential confounding factors were compared across hours of sleep duration (Table 1). Individuals with ≥ 9 h of sleep per day tended to smoke more, consume more alcohol, and were less likely to be physically active. In contrast, the short sleepers (≤ 5 h), especially for the male health professionals, tended to smoke less, consume less alcohol, and to be more physically active. In addition, among women, those with ≥ 15 years of rotating night shift work were most likely to report short sleep duration (≤ 5 h).

Habitual regular snoring was slightly more frequent in those with long or short sleep hours compared with individuals with median of 7 h of sleep (Table 1). Regular snorers had a higher mean BMI than non-snorers (28.3 vs. 25.1 kg/m^2 in men; 26.0 vs. 25.3 kg/m^2 in women) and tend to be overweight (65% vs. 41% in men; 55% vs. 37% in women).

The hazard ratios of colorectal cancer in relation to sleep duration are presented in Table 2 for men and Table 3 for women. In both men and women, the age-adjusted results were quite similar to the multivariable-adjusted results. In men, compared to those with 7 h of sleep, men with ≥ 9 h of sleep per day had a suggestively increased risk of colorectal cancer (HR = 1.35; 95% CI: 1.00, 1.82) (Table 2). Results were similar when stratified by endoscopy/sigmoidoscopy screening or excluding cases within the first 4 years after assessment of sleep duration (data not shown). In women, the hazard ratios for both ≥ 9 h and ≤ 5 h of sleep were generally above 1.0 although not statistically significant (Table 3). No apparent or consistent pattern was seen by cancer sub-sites. In addition, no clear patterns were seen when sleep duration were examined in the 2 time periods using cross-classified sleep variables from baseline and 2000; results did not differ by BMI at baseline or weight change in these 2 time periods (data not shown).

We found no association between snoring and colorectal cancer risk in men or women; the multivariate-adjusted HRs were 0.79 (95% CI: 0.59, 1.06) for men who snored every night and 1.07 (95% CI: 0.87, 1.32) for women who regularly snored. However, when the association with sleep duration stratified by snoring, we found that the positive association with ≥ 9 h of sleep appeared to be restricted to individuals who regularly snored in both men (HR = 1.80; 95% CI: 1.14, 2.84) and women (HR = 2.32; 95% CI: 1.24, 4.36; Table 4). The interaction between sleep duration and snoring was borderline significant for women (P = 0.05; Figure 1).

We further found that the positive association with ≥ 9 h of sleep was restricted to overweight individuals (i.e., BMI ≥ 25 kg/m^2) (HR = 1.52; 95% CI: 1.04, 2.21 for men; HR = 1.37; 95% CI: 0.97, 1.94 for women). Figure 2 shows the joint associations of BMI and sleep duration.

Finally, an suggestive increased colorectal cancer risk associated with sleep ≤ 5 h was only observed among women who had ≥ 15 years of shift work (HR = 1.50; 95% CI: 0.94, 2.39; n = 19 cases). No apparent pattern was seen by alcohol consumption, family history of colorectal cancer, physical activity, or menopausal status (women only).

DISCUSSION

In these two large cohorts of middle-aged to elderly men and women, we found that men with long sleep duration (≥ 9 h per day) had a significantly increased risk of developing colorectal cancer compared with those with 7 h of sleep. In subgroup analyses, men or women who were overweight or who were regular snorers and who reported sleeping ≥ 9 h per day were at an approximately 1.4 to 2-fold increased risk of developing colorectal cancer compared to overweight or regular snorers with 7 h of sleep per day. These associations were independent of known colorectal cancer risk factors.

To the best of our knowledge, our study is the first to report a significant positive association of colorectal cancer with long sleep duration, especially among those who are overweight or regular snorers. There are several potential mechanisms for these positive associations. Individuals with ≥ 9 h of sleep may spend less time in physical activity and more time in sedentary behaviors. However, adjustment for physical activity and sedentary behaviors (TV watching as a surrogate) did not alter our findings. Alternatively, individuals reporting long sleep duration may spend more time in bed but actually get less sleep and experience poorer sleep quality due to frequent awakenings. Low sleep efficiency and reduced slow wave sleep may result in increased cortisol secretion, inflammation and insulin resistance[27-29] and may contribute to the development of obesity.[30] Longer sleep also may reflect exposures to high levels of somnogenic cytokines, such as interleukin-1 (IL-1) and tumor necrosis factor (TNF-α), which may have direct pro-inflammatory effects on tumorigenesis.[18,19] Thus, an association between long sleep and colorectal cancer may reflect the effects of increased inflammatory mediators among individuals who sleep longer.

A novel finding of this study was evidence for a stronger association with long sleep hours among regular snorers. Snoring is a cardinal symptom of sleep apnea, and has been used as a surrogate for sleep disordered breathing, a common disorder associated with recurrent episodes of sleep disruption and intermittent hypoxemia. Sleep disruption may reduce sleep quality, increase sleepiness, and result in longer reported sleep durations. Intermittent hypoxemia has been shown in animal models to promote tumor growth, possibly through release of pro-angiogenic mediators resulting in cell proliferation.[31-33] There has been little prior work that has addressed the association of snoring or sleep disordered breathing with cancer. Among the two studies we identified, one case-control study has reported an increased, albeit nonsignificant increase in colonic polyps in

Table 1—Age-standardized characteristics by sleep duration in the Health Professionals Follow-up Study (in 1988) and in the Nurses' Health Study (in 1986)

Characteristics	HPFS: Sleep duration (hours per day)				
	≤ 5 h (n = 641)	6 h (n = 5,819)	7 h (n = 14,356)	8 h (n = 7,823)	≥ 9 h (n = 1,482)
Age, mean (SD), y	58 (10)	56 (9)	55 (9)	57 (10)	61 (10)
Body mass index (kg/m^2), mean (SD)*	25.7 (3.4)	25.6 (3.2)	25.3 (3.0)	25.4 (3.1)	25.7 (3.3)
Physical activity (MET-h/w), mean (SD)†	31.1 (34.1)	29.1 (34.5)	28.4 (32.2)	29.3 (33.3)	27.0 (32.1)
History of colorectal cancer in a parent or sibling (%)	10	8	9	8	8
Ever smokers (%)	39	43	42	43	46
Regular aspirin use (%)‡	35	40	40	41	41
Dietary intake, mean (SD)					
Total energy (kcal/d)	1,983 (665)	1,978 (623)	2,003 (604)	2,019 (618)	2,082 (638)
Alcohol consumption (g/d)	10.0 (16.3)	10.5 (14.5)	11.0 (14.8)	12.7 (16.4)	16.0 (19.8)
Total calcium intake (mg/d)§	894 (507)	903 (423)	906 (413)	905 (438)	883 (401)
Total vitamin D intake (IU/d)§	431 (402)	419 (322)	406 (302)	397 (294)	379 (271)
Total folate intake (µg/d)§	502 (339)	493 (282)	481 (267)	474 (268)	444 (245)
Beef, pork, or lamb as a main dish (servings/w)	1.6 (1.8)	1.7 (1.6)	1.8 (1.6)	1.9 (1.7)	2.0 (1.6)
Processed meat intake (servings/w)	1.1 (1.7)	1.2 (1.8)	1.2 (1.9)	1.3 (1.9)	1.3 (1.9)
Worked on rotating night shift ≥ 15 years (%)			NA		
Snoring regularly (%)‖	12	10	10	11	12
History of diabetes (%)	4	3	3	3	5

Characteristics	NHS: Sleep duration (hours per day)				
	≤ 5 h (n = 3,470)	6 h (n = 19,555)	7 h (n = 31,661)	8 h (n = 18,086)	≥ 9 h (n = 3,596)
Age, mean (SD), y	54 (7)	53 (7)	53 (7)	53 (7)	54 (7)
Body mass index (kg/m^2), mean (SD)*	26.4 (5.7)	25.7 (5.0)	25.1 (4.6)	25.2 (4.7)	25.7 (5.2)
Physical activity (MET-h/w), mean (SD)†	16.1 (25.1)	15.6 (20.9)	15.7 (20.7)	15.5 (22.8)	14.0 (20.5)
History of colorectal cancer in a parent or sibling (%)	8	8	8	8	8
Ever smokers (%)	32	34	35	35	34
Regular aspirin use (%)‡	41	40	38	37	40
Dietary intake, mean (SD)					
Total energy (kcal/d)	1,737 (572)	1,746 (531)	1,775 (519)	1,790 (524)	1,834 (560)
Alcohol consumption (g/d)	4.8 (9.6)	5.7 (10.1)	6.2 (10.2)	6.7 (11.4)	7.9 (13.9)
Total calcium intake (mg/d)§	1,049 (542)	1,078 (517)	1,093 (502)	1,081 (506)	1,066 (517)
Total vitamin D intake (IU/d)§	331 (262)	340 (258)	343 (248)	344 (255)	343 (257)
Total folate intake (µg/d)§	396 (233)	404 (226)	407 (220)	403 (222)	398 (228)
Beef, pork, or lamb as a main dish (servings/w)	2.1 (1.4)	2.2 (1.4)	2.2 (1.3)	2.2 (1.4)	2.3 (1.4)
Processed meat intake (servings/w)	1.0 (1.3)	1.0 (1.2)	1.0 (1.2)	1.0 (1.3)	1.1 (1.4)
Worked on rotating night shift ≥ 15 years (%)	14	8	5	5	6
Snoring regularly (%)‖	10	10	9	10	12
History of diabetes (%)	5	3	2	3	4

*Body mass index was calculated as weight in kilograms divided by the square of height in meters. †MET denotes metabolic equivalent. MET-h/w = sum of the average hours/week spent in each activity × MET value of each activity. ‡Regular aspirin user was defined as consumption of ≥ 2 325-mg tablets per week. Non-regular user was defined otherwise. §Nutrient values were energy-adjusted intake. ‖Regular snoring was defined as those who reported regular snoring in NHS and those who reported snoring every night, most nights, or a few nights a week in HPFS.

those reporting a doctor diagnosis of sleep apnea.[10] In the other Wisconsin Sleep Cohort, sleep disordered breathing was associated with increased total cancer mortality.[34]

Prior studies have reported "U" shaped associations between sleep duration and mortality,[8,9,35] cardiovascular disease,[3,4] obesity,[11] and diabetes.[13] One recent case-control study in a sample of patients undergoing routine colonoscopy screening reported that when compared with individuals sleeping ≥ 7 h per night, individuals reporting < 6 h per night had a 47% increase in risk of developing adenomas (OR = 1.47, 95% CI: 1.05, 2.06).[10] In our study, the hazard ratios for the short sleepers (i.e., ≤ 5 h of sleep) were all above 1.0 in women, but not statistically significant; in men, the hazard ratios were less than one. In contrast to many other studies, several health habits were more favorable in the short sleep sleepers compared to those sleeping longer in the male health

Table 2—Hazard ratios (95% CIs) of colorectal cancer according to hours of sleep per day in the Health Professionals Follow-up Study (1988-2008)

		≤ 5 h	6 h	7 h	8 h	≥ 9 h
Colorectal cancer	Cases (total = 709)	10	135	291	218	55
	Age-adjusted*	0.69 (0.36,1.30)	1.14 (0.93,1.41)	1.0 (reference)	1.24 (1.03,1.48)	1.43 (1.06,1.93)
	Multivariable-adjusted†	0.67 (0.35,1.28)	1.14 (0.93,1.41)	1.0 (reference)	1.22 (1.01,1.46)	1.35 (1.00,1.82)
Colon cancer	Cases (total = 547)	8	101	231	164	43
	Age-adjusted*	0.66 (0.32,1.35)	1.07 (0.84,1.36)	1.0 (reference)	1.17 (0.95,1.43)	1.40 (1.00,1.97)
	Multivariable-adjusted†	0.63 (0.31,1.29)	1.08 (0.85,1.37)	1.0 (reference)	1.16 (0.94,1.42)	1.32 (0.94,1.86)
Proximal colon cancer	Cases (total = 244)	4	42	99	78	21
	Age-adjusted*	0.71 (0.26,1.94)	1.06 (0.74,1.53)	1.0 (reference)	1.25 (0.92,1.69)	1.62 (1.00,2.64)
	Multivariable-adjusted†	0.71 (0.25,1.95)	1.12 (0.77,1.62)	1.0 (reference)	1.23 (0.91,1.67)	1.57 (0.96,2.56)
Distal colon cancer	Cases (total = 218)	4	43	97	61	13
	Age-adjusted*	0.83 (0.30,2.27)	1.07 (0.74,1.54)	1.0 (reference)	1.07 (0.77,1.48)	1.01 (0.56,1.83)
	Multivariable-adjusted†	0.82 (0.29,2.27)	1.06 (0.73,1.52)	1.0 (reference)	1.07 (0.77,1.49)	1.01 (0.56,1.84)
Rectal cancer	Cases (total = 162)	2	34	60	54	12
	Age-adjusted*	0.79 (0.19,3.25)	1.42 (0.93,2.18)	1.0 (reference)	1.49 (1.02,2.17)	1.54 (0.81,2.93)
	Multivariable-adjusted†	0.80 (0.19,3.33)	1.43 (0.93,2.20)	1.0 (reference)	1.45 (0.99,2.12)	1.43 (0.74,2.74)

*Adjusted for age (in months). †Adjusted for age (in months), smoking before age 30 (0, 1-4, 5-10, or > 10 pack-years), history of colorectal cancer in a parent or sibling (yes, no), history of endoscopy (yes, no), regular aspirin use (yes, no), physical activity (< 3, 3-< 27, ≥ 27 MET-h/w), snoring (regularly, occasionally, almost never), body mass index (< 25, 25-< 30, ≥ 30 kg/m^2), history of diabetes (no, yes), beef, pork, and lamb as a main dish (tertiles), consumption of processed meat (tertiles), alcohol consumption (0-< 5, 5-< 10, 10-< 15, or ≥ 15 g/d), energy-adjusted total calcium intake (quintiles), total folate (quintiles), and total vitamin D intake (quintiles).

Table 3—Hazard ratios (95% CIs) of colorectal cancer according to hours of sleep per day in the Nurses' Health Study (1986-2008)

		≤ 5 h	6 h	7 h	8 h	≥ 9 h
Colorectal cancer	Cases (total = 1,264)	64	318	486	332	64
	Age-adjusted*	1.15 (0.88,1.49)	1.05(0.91,1.21)	1.0 (reference)	1.17 (1.02,1.35)	1.14 (0.88,1.48)
	Multivariable-adjusted†	1.10 (0.85,1.44)	1.04(0.90,1.20)	1.0 (reference)	1.16 (1.01,1.33)	1.11 (0.85,1.44)
Colon cancer	Cases (total = 1,004)	51	245	391	261	56
	Age-adjusted*	1.13 (0.84,1.51)	1.01(0.86,1.18)	1.0 (reference)	1.14 (0.98,1.34)	1.24 (0.93,1.64)
	Multivariable-adjusted†	1.09 (0.81,1.46)	1.00(0.85,1.18)	1.0 (reference)	1.13(0.96,1.32)	1.20 (0.91,1.59)
Proximal colon cancer	Cases (total = 611)	29	154	237	162	29
	Age-adjusted*	1.07 (0.73,1.58)	1.05 (0.85,1.28)	1.0 (reference)	1.16 (0.95,1.42)	1.04 (0.71,1.54)
	Multivariable-adjusted†	1.06 (0.72,1.57)	1.05 (0.85,1.28)	1.0 (reference)	1.14 (0.93,1.40)	1.02 (0.69,1.50)
Distal colon cancer	Cases (total = 375)	21	86	148	94	26
	Age-adjusted*	1.20 (0.76,1.91)	0.93 (0.72,1.22)	1.0 (reference)	1.10 (0.85,1.43)	1.54 (1.01,2.35)
	Multivariable-adjusted†	1.11 (0.70,1.77)	0.92 (0.70,1.20)	1.0 (reference)	1.08 (0.83,1.40)	1.47 (0.96,2.24)
Rectal cancer	Cases (total = 260)	13	73	95	71	8
	Age-adjusted*	1.23 (0.69,2.19)	1.23 (0.90,1.67)	1.0 (reference)	1.30 (0.95,1.77)	0.73 (0.35,1.51)
	Multivariable-adjusted†	1.17 (0.65,2.10)	1.20 (0.88,1.63)	1.0 (reference)	1.29 (0.95,1.76)	0.71 (0.35,1.47)

*Adjusted for age (in months). †Adjusted for age (in months), postmenopausal hormone use (premenopausal, never, past, or current user), and factors listed in Table 2 footnote.†

professionals. In particular, men sleeping < 5 h per night reported the highest levels of physical activity and both men and women who were short sleepers reported lower energy consumption than the long sleepers. Since both cohorts were health professionals, it is possible that the correlates of sleep duration differ from those in more general population samples and these health professionals with shorter sleep choose to sleep less in order to exercise or work longer.

Several potential limitations merit discussion. First, objective measurements of sleep duration, snoring, sleep quality, and sleep disordered breathing were unavailable. Self-reported sleep duration and snoring data obtained from questionnaires may result in misclassification, which could bias the results to either direction. In addition, long sleep duration may represent multiple comorbidities[36] and may have been influenced by undiagnosed subclinical diseases, raising concerns

Table 4—Multivariable hazard ratios* for colorectal cancer by sleep duration and BMI and snoring for men in the Health Professionals Follow-up Study (1988-2008) and for women in the Nurses' Health Study (1986-2008)

	Sleep duration (hours per day)								
	≤ 6 h		7 h		8 h		≥ 9 h		P-value for interaction
	Cases	HR (95% CIs)	Cases	HR (95% CIs)	Cases	HR (95% CIs)	Cases	HR (95% CIs)	
Snoring									
Men Non-snorers	86	1.17 (0.89, 1.53)	172	1.0 (reference)	129	1.29 (1.02, 1.63)	27	1.19 (0.78, 1.83)	
Men Regular snorers	54	0.94 (0.67, 1.31)	114	1.0 (reference)	85	1.08 (0.80, 1.45)	28	1.80 (1.14, 2.84)†	0.42
Women Non-snorers	340	1.07 (0.93, 1.24)	436	1.0 (reference)	289	1.14 (0.98, 1.33)	49	1.00 (0.74, 1.34)	
Women Regular snorers	39	0.93 (0.59, 1.45)	47	1.0 (reference)	42	1.27 (0.81, 2.00)	15	2.32 (1.24, 4.36)†	0.05
Body mass index (BMI)									
Men BMI < 25 kg/m^2	62	1.12 (0.82, 1.54)	124	1.0 (reference)	95	1.38 (1.05, 1.82)	16	1.21 (0.70, 2.11)	
Men BMI ≥ 25 kg/m^2	83	1.06 (0.80, 1.39)	167	1.0 (reference)	123	1.11 (0.87, 1.41)	39	1.52 (1.04, 2.21)‡	0.14
Women BMI < 25 kg/m^2	197	1.06 (0.88, 1.28)	276	1.0 (reference)	166	1.08 (0.89, 1.31)	25	0.84 (0.55, 1.26)	
Women BMI ≥ 25 kg/m^2	185	1.04 (0.86, 1.28)	210	1.0 (reference)	166	1.28 (1.04, 1.57)	39	1.37 (0.97, 1.94)‡	0.06

*Same factors as listed in Tables 2 & 3 footnote† except for snoring or BMI. †Pooled RR = 2.16 (95% CI: 1.49, 3.14), P-value for heterogeneity by gender = 0.74. ‡Pooled RR = 1.53 (95% CI: 1.18, 1.98), P-value for heterogeneity by gender = 0.34.

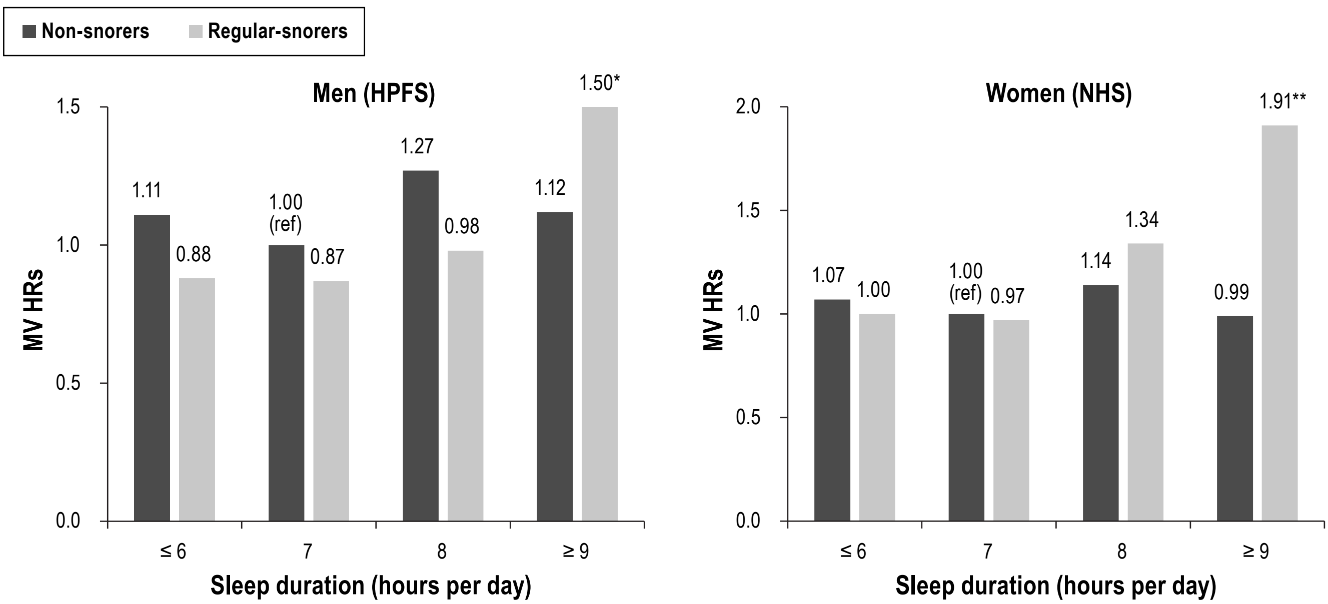

Figure 1—Multivariable hazard ratios for the joint classification of sleep duration and snoring in the Health Professionals Follow-up Study (1988-2008) and the Nurses' Health Study (1986-2008). Same covariates as Tables 2 & 3 except snoring. **Left:** Men (HPFS). *MV HR = 1.50 (95% CI: 0.99, 2.27; n = 28 cases). $P_{interaction}$ = 0.42. **Right:** Women (NHS). **MV HR = 1.91 (95% CI: 1.13, 3.21; n = 15 cases). $P_{interaction}$ = 0.05.

of reverse causality. Moreover, although changes in sleep pattern might occur during up to 22 years of follow-up, given that colorectal cancer takes decades to develop, the sleep duration queried in this study might capture the relevant long-term sleep habits. Second, we cannot rule out unmeasured residual confounding[36,37] as a possible explanation of the observed association. Third, our study had a large sample size overall, but we still had limited power examining the potential effect of short sleep hours on colorectal cancer risk in men. Lastly, our study populations were mainly of European origin, and results may not be generalizable to other ethnic groups.

Strengths of this study include its prospective design with long follow-up time, which minimized the potential selection or recall bias. Paralleled analyses among men and women showed consistent results of longer sleep duration and risk of colorectal cancer among regular snorers or overweight individuals, suggesting that these findings were unlikely entirely due to chance. Finally, the measurement of multiple risk factors for colorectal cancer allowed us to evaluate the potential independent effect of sleep duration.

In summary, longer sleep duration was associated with an increased risk of developing colorectal cancer among individuals who were overweight or snored regularly. Given the sparse data, more research is warranted to evaluate whether sleep duration or sleep quality is a novel risk factor for colorectal cancer and to understand the mechanisms behind this association.

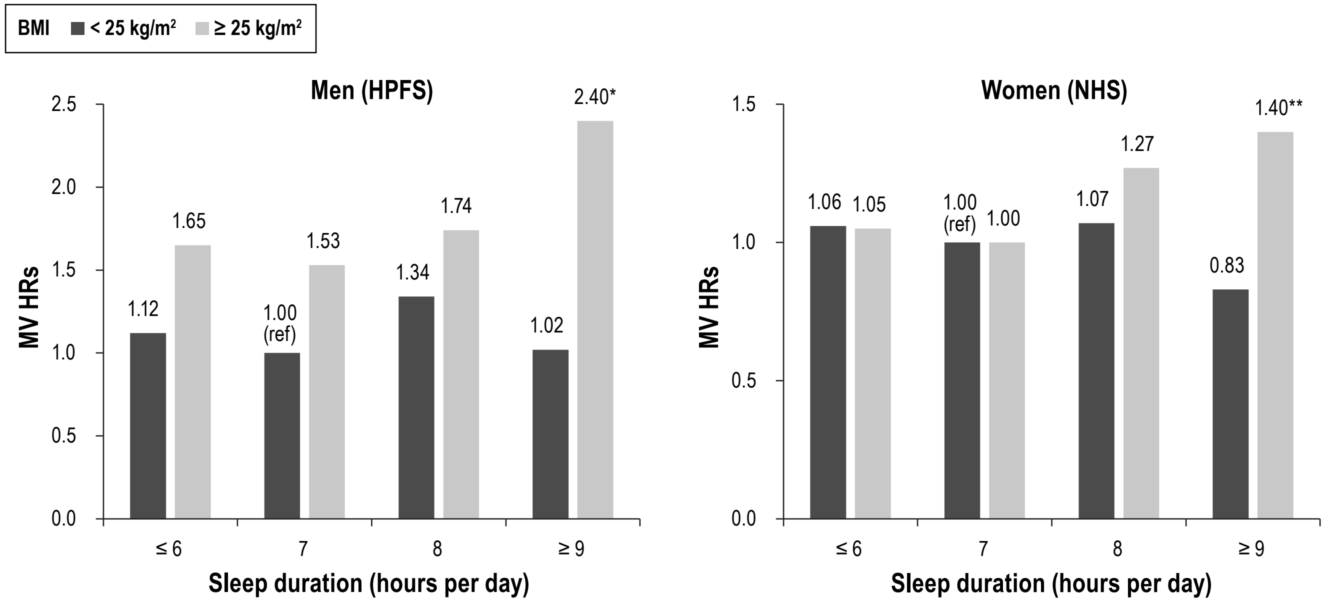

Figure 2—Multivariable hazard ratios for the joint classification of sleep duration and BMI in the Health Professionals Follow-up Study (1988-2008) and the Nurses' Health Study (1986-2008). Same covariates as Tables 2 & 3 except BMI. **Left:** Men (HPFS) *MV HR = 2.40 (95% CI: 1.65, 3.49; n = 39 cases). $P_{interaction}$ = 0.14. **Right:** Women (NHS) **MV HR = 1.40 (95% CI: 1.00, 1.97; n = 39 cases). $P_{interaction}$ = 0.06.

The novel observation of increased risk among regular snorers who sleep long raises the possibility that sleep apnea and its attendant intermittent hypoxemia may contribute to cancer risk. In addition, large prospective studies examining potential effect of sleep duration on colorectal adenomas will also be informative.

ACKNOWLEDGMENTS

The authors thank the participants and staff of the NHS and HPFS for their valuable contributions as well as the following state cancer registries for their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK,OR, PA, RI, SC, TN, TX, VA, WA, WY. This study was funded by the NIH grants CA87969, 1U54CA155626-01, and CA55075.

DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest.

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