Original Article

# Short Duration of Sleep Increases Risk of Colorectal Adenoma

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**BACKGROUND:** Short duration and poor quality of sleep have been associated with increased risks of obesity, cardiovascular disease, diabetes mellitus, and total mortality. However, few studies have investigated their associations with risk of colorectal neoplasia. **METHODS:** In a screening colonoscopy-based case-control study, the Pittsburg Sleep Quality Index (PSQI) was administered to 1240 study participants before colonoscopy. **RESULTS:** Three hundred thirty-eight (27.3%) of the participants were diagnosed with incident colorectal adenomas. Although there was no appreciable difference in the overall PSQI score between cases and adenoma-free controls (5.32 vs 5.11; $P = .37$), the authors found a statistically significant association of colorectal adenoma with the PSQI component 3, which corresponds to sleep duration ($P = .02$). Cases were more likely to average less than 6 hours of sleep per night (28.9% vs 22.1% in controls, $P = .01$). In multivariate regression analysis adjusted for age, gender, race, smoking, family history of colorectal cancer, and waist-to-hip ratio, individuals averaging less than 6 hours per night had an almost 50% increase in risk of colorectal adenomas (OR = 1.47; CI = 1.05-2.06, $P$ for trend = .02) as compared with individuals sleeping at least 7 hours per night. Cases were also more likely to report being diagnosed with sleep apnea (9.8% vs 6.5%, $P = .05$) and more likely to have worked alternate shifts (54.0% vs 46.1%, $P = .01$), although these differences were not significant in multivariate models. **CONCLUSIONS:** Shorter duration of sleep significantly increases risk of colorectal adenomas. The authors' results suggest sleep duration as a novel risk factor for colorectal neoplasia. ***Cancer* 2011;117:841–7.** *© 2010 American Cancer Society.*

**KEYWORDS:** sleep duration, quality of sleep, colorectal adenoma, Pittsburgh Sleep Quality Index.

**Sufficient** sleep on a daily basis is an important correlate of healthy living. Acute sleep deficits have been associated with negative health outcomes such as impaired glucose tolerance, higher levels of evening cortisol and other endocrine factors, elevated markers of systemic inflammation, increased blood pressure, and daytime cognitive dysfunction.[1-5] Although less studied, long-term chronic sleep deficits have been associated with all-cause mortality, incident coronary heart disease, incident diabetes, and weight gain.[6-10]

Emerging evidence suggests that disruption in the circadian rhythm may also increase risks of several types of cancer. In particular, night shift work has been associated with increased risks of cancer in the breast, endometrium, prostate, and colorectum.[11-15] Whereas published work suggests a link between circadian rhythm and tumorigenesis, the relationship of sleep quality and duration with cancer development has been understudied, and most studies reported thus far were limited to breast cancer or cancer survivors. The first study to report an association of sleep with breast cancer in a cohort of females found a decreased risk of breast cancer among women who consistently slept longer hours.[16] Subsequent reports in 2 other cohort studies also suggested an inverse association between short sleep duration and risk of breast cancer[17,18]; however, another study did not observe this association.[19] The effects of sleep duration and overall sleep quality on the risk of colorectal neoplasia are largely unknown.

Here we evaluate the associations of the duration and quality of sleep, as well as shift work and diagnosis of sleep apnea, with the development of colorectal adenomas, a well established precursor of colorectal cancer, in a prospectively

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recruited population of patients undergoing routine colorectal cancer screening. We hypothesize that short duration and poor quality of sleep are associated with increased risk of colorectal adenoma.

## MATERIALS AND METHODS

### *Study Population*

One thousand two hundred forty patients scheduled for routine screening colonoscopy at University Hospitals Case Medical Center in Cleveland, Ohio, and affiliated gastroenterology practices in the surrounding areas were recruited before their colonoscopic examinations. These asymptomatic patients were referred to the practices for colorectal cancer screening because they were at least 50 years old and had no colonoscopy exam within the last 10 years, or they had a positive family history of colorectal cancer that met the American Cancer Society colorectal cancer screening recommendation to undergo screening colonoscopy at a younger age.[20] Potential participants were eligible if they were at least 30 years old, did not have any inflammatory bowel disease (such as Crohn's disease or ulcerative colitis), and had never been diagnosed with colorectal cancer or polyps or any form of cancer. All participants completed a computer-aided interview conducted by a trained research assistant for collection of demographics, lifestyle, and behavioral risk factors before their colonoscopy. The interview was done over the phone, unless time constraints necessitated an in-person interview just before colonoscopy to ensure prospective collection of data. The interview included a comprehensive query of lifestyle factors such as diet, physical activity, alcohol consumption, and smoking, as well as a self-reported medical history including diagnosis of metabolic syndrome components and family history of colorectal and other cancers. Individuals were asked what they consider their race to be and given a choice of Caucasian, African American, Hispanic/Latino, Native American, Asian, or Other. For this project, all responses other than Caucasian and African American were collapsed into a single "other" category.

Fasting blood samples were obtained at the time of colonoscopy (before the procedure) and refrigerated immediately. All samples were then transported on wet ice to the research laboratory and processed the same day as collection. Each blood tube was spun for 15 minutes at 600*g*, and aliquots of plasma, serum, and concentrated buffy coat were prepared and frozen at −80°C. Height, weight, hip and waist circumferences, and blood pressure measurements were also obtained just before colonoscopy by nursing staff at the participating endoscopy laboratories. Waist-to-hip ratio (WHR) was calculated as waist circumference divided by hip circumference. Body mass index (BMI) was calculated as weight (in kg) divided by height (in meters) squared.

All participants signed a medical record release form. Medical records pertaining to colonoscopy were obtained after completion of the procedure and pathology reports. Patients were classified as cases if their colonoscopy results indicated at least one pathologically confirmed colorectal adenoma. All others were considered as controls.

The recruitment rate was 64.9% for all eligible patients, and those who completed the study did not differ from those who refused to participate with regard to age, gender, and race ($P > .05$). All participants gave informed consent. The study protocol was approved by the Institutional Review Board at University Hospitals Case Medical Center.

### *Sleep Quality Data*

In addition to the risk factor questionnaires, the Pittsburgh Sleep Quality Index (PSQI)[21] was administered via an in-person phone survey to each participant to obtain information on the subject's overall sleep quality in the past month. The PSQI asks information on various aspects of sleep quality, including how frequently one has trouble sleeping and how much sleep one has had per night. The PSQI includes 4 open-ended questions for the participants: what time they typically go to bed, how long it takes them to fall asleep, what time they wake up, and how many hours of actual sleep they get on a typical night? The question on total sleep elicited information on the average total number of hours sleep per night, which we used with the PSQI's overall sleep quality measurements to measure average sleep duration.

In addition, select questions not included in the PSQI were added to the phone survey. These questions include self-report of a diagnosis of sleep apnea (yes/no), and if the participant ever worked alternate (2nd or 3rd) shifts (yes/no).

The PSQI responses were then coded into 7 components representing different aspects of sleep, including self-reported quality, sleep latency, duration, sleep efficiency, disruptions, sleeping aid use, and daytime sleepiness—each component scoring between 0 and 3, where the higher the score, the worse the sleep quality. The

overall global PSQI score is the sum of the 7 components and thus corresponds to a value between 0 and 21.

### *Homeostasis Model Assessment—Insulin Resistance (HOMA-IR)*

Serum levels of insulin and glucose were determined from fasting blood samples. Glucose was measured using colorimetric reflectance spectrophotometry and had an overall QC range <5%. Insulin was measured using a standard ELISA assay with a mean inter-assay CV of 4.7%. Insulin resistance was calculated using the homeostasis model assessment-insulin resistance (HOMA-IR) index.[22] Both insulin and glucose measurements were available on 266 cases and 745 controls.

### *Statistical Analyses*

We first evaluated the differences in demographics and risk factors between cases and controls via univariate analyses using either a chi square test (for discrete variables) or student *t* test (continuous variables). For discrete measurements in which any one cell had fewer than 5 individuals, a Fisher exact test was used in place of the chi square test. Each component of the PSQI, as well as the global PSQI, was analyzed similarly for any statistically significant difference between cases and controls.

From the open-ended question on the PSQI asking total average number of hours of sleep per night, we used the participants' self-reported hours as a separate variable outside of the PSQI. We first analyzed hours of sleep as a continuous variable, then categorized each person into one of 3 categories of average nightly sleep duration: less than 6 hours, 6 to less than 7 hours, or 7 or more hours. These cutoffs were based on the PSQI component 3 (corresponding to sleep duration), which scores each individual as 0 (>7 hours), 1 (6-7 hours), 2 (5-6 hours) and 3 (<5 hours). Because very few individuals (n = 122) reported sleeping less than 5 hours per night, we collapsed the 2 shortest duration categories into one as <6 hours.

To evaluate risk association of sleep quality parameters with colorectal adenoma, 2 main logistic regressions were performed on each component of the PSQI, as well as the global PSQI and the additional sleep measures. The base model included age, gender, and race as covariates (338 cases and 902 controls). To control for potential confounding by other known risk factors for colorectal neoplasia, the full model also included smoking, family history of colorectal cancer, and WHR (338 cases and 902 controls). Furthermore, because of the known association between sleep quality and obesity,[23] which is strongly linked to insulin resistance, and the importance of sleep in the metabolic syndrome,[24] we hypothesize that associations of sleep quality and duration with colorectal adenomas may be mediated by insulin resistance. To test this hypothesis, we further adjusted for HOMA-IR in the full model above (266 cases and 745 controls with available data). Finally, because sleep apnea patients are known to have different sleep patterns, we repeated all logistic regressions, excluding subjects who reported a diagnosis of sleep apnea.

Recently, it was reported that the association between sleep duration and measures of obesity was stronger in women compared with men.[25] Therefore, we carried out stratified analyses to explore potential gender differential associations between sleep quality or duration with colorectal adenomas.

All statistical tests were 2-sided. SAS (version 9.1, SAS Institute, Cary, NC) was used for all statistics. A $P < .05$ was considered statistically significant.

## RESULTS

Of the 1240 participants, 338 were diagnosed with incident colorectal adenomas at their colonoscopy. In general, cases were older and more likely to be male compared with controls (Table 1). There were also significant differences in the distribution of race, with African Americans more likely to be cases compared with Caucasians (Table 1). Interestingly, while there was no statistically significant difference in BMI between cases and controls ($P = .10$), on average, WHR (as a proxy for central obesity) was significantly higher among cases compared with the controls ($P = <.0001$). Current smoking was significantly more common in cases than controls, with 22.9% of cases and 14.3% of controls reporting current smoking. Family history of colorectal cancer was reported in over 20% of the study population, and did not differ between cases and controls.

Although not statistically significant, on average, cases scored higher (corresponding to poorer sleep quality) on the PSQI (Table 2), as well as most of the individual components. However, the score of component 3 of the PSQI, which corresponds to the hours of sleep per night, was statistically significantly different between cases and controls (univariate $P = .005$). Cases reported sleeping fewer hours on average than controls (6.35 vs 6.54, $P = .038$), which remained borderline significant after adjustment for age, gender, and race ($P = .07$). Further adjustment for family history, smoking, and WHR did

**Table 1.** Descriptive Characteristics of Study Population

| | Cases n=338 | Controls n=902 | P[a] |
|---|---|---|---|
| Age, mean [SD], y | 57.3 [8.0] | 54.7 [8.8] | <.0001 |
| Female gender, No. (%) | 184 (54.4) | 609 (67.5) | <.0001 |
| **Race, No. (%)** | | | .011 |
| African American | 140 (41.4) | 294 (32.6) | |
| Caucasian | 190 (56.2) | 590 (65.7) | |
| Other | 8 (2.4) | 18 (2.0) | |
| **Smoking, No. (%)** | | | .0007 |
| Current | 77 (22.9) | 129 (14.3) | |
| Ever | 120 (35.7) | 323 (35.9) | |
| Never | 139 (41.4) | 449 (49.8) | |
| **Family history of colorectal cancer, No. (%)** | | | .76 |
| Yes | 81 (24.5) | 211 (23.6) | |
| No | 250 (75.5) | 682 (76.4) | |
| Body Mass Index (BMI), mean (SD), kg/m$^2$ | 29.9 (7.2) | 29.2 (6.8) | .10 |
| Waist-to-hip ratio (WHR), mean [SD] | 0.94 [0.097] | 0.91 [0.093] | <.0001 |
| **Income, No. (%)** | | | .036 |
| <$15,000 | 63 (18.7) | 115 (12.8) | |
| $15,000-$30,000 | 47 (14.0) | 119 (13.2) | |
| $30,000-$45,000 | 41 (12.2) | 98 (10.9) | |
| $45,000-$70,000 | 42 (12.5) | 164 (18.2) | |
| $70,000+ | 129 (38.3) | 357 (39.6) | |
| Don't know/refused | 15 (4.5) | 49 (5.4) | |
| Global PSQI, mean [SD] | 5.32 [3.77) | 5.11 (3.46) | .37 |
| Component 1: Sleep quality, mean [SD] | 0.99 [0.75] | 0.97 [0.74] | .66 |
| Component 2: Sleep latency, mean [SD] | 0.66 [0.86] | 0.63 [0.90] | .59 |
| Component 3: Sleep duration, mean [SD] | 1.00 [1.03] | 0.82 [0.98] | .005 |
| Component 4: Usual sleep efficiency, mean [SD] | 0.62 [0.96] | 0.61 [1.00] | .90 |
| Component 5: Sleep disruptions, mean [SD] | 1.03 [0.55] | 1.03 [0.55] | .89 |
| Component 6: Sleeping aid use, mean [SD] | 0.47 [1.00] | 0.48 [1.00] | .92 |
| Component 7: Daytime sleepiness, mean [SD] | 0.62 [0.82] | 0.62 [0.85] | .95 |
| Sleep Apnea Diagnosis, No. (%) | 33 (9.8) | 58 (6.5) | .045 |
| Average hours of sleep, mean [SD] | 6.35 [1.36] | 6.53 [1.34] | .038 |
| Ever worked alternate shift, No. (%) | 182 (54.0) | 414 (46.1) | .013 |

[a] Univariate (Student *t* or chi square test) *P* value.
[b] Compared to those averaging at least 6 hours of sleep per night.

**Table 2.** Pittsburgh Sleep Quality Index Score and Estimated Risk of Colorectal Adenoma

| | Base Model Logistic Regression[a] | | Full Model Logistic Regression[b] | | Full Model Logistic Regression with HOMA-IR[c] | |
|---|---|---|---|---|---|---|
| | OR (95% CI) | P | OR (95% CI) | P | OR (95% CI) | P |
| Global PSQI | 1.02 (0.98-1.06) | .35 | 1.01 (0.97-1.04) | .79 | 1.00 (0.96-1.05) | .92 |
| Component 1: Sleep quality | 1.07 (0.90-1.28) | .43 | 1.04 (0.87-1.25) | .69 | 0.99 (0.80-1.21) | .88 |
| Component 2: Sleep latency | 1.01 (0.87-1.18) | .85 | 0.97 (0.83-1.14) | .74 | 0.998 (0.83-1.18) | .89 |
| Component 3: Sleep duration | 1.17 (1.03-1.34) | .02 | 1.14 (1.00-1.31) | .05 | 1.15 (0.99-1.34) | .07 |
| Component 4: Usual sleep efficiency | 0.96 (0.83-1.10) | .52 | 0.93 (0.80-1.07) | .30 | 0.93 (0.79-1.10) | .39 |
| Component 5: Sleep disruptions | 0.99 (0.78-1.25) | .92 | 0.93 (0.73-1.19) | .57 | 0.96 (0.72-1.26) | .75 |
| Component 6: Sleeping aid use | 1.04 (0.91-1.19) | .56 | 1.02 (0.90-1.17) | .74 | 1.01 (0.86-1.18) | .93 |
| Component 7: Daytime sleepiness | 1.02 (0.88-1.19) | .77 | 1.00 (0.85-1.18) | .97 | 0.97 (0.81-1.16) | .73 |

[a] Logistic regression odds ratio and *P*-value, accounting for age, gender, and race (338 cases and 902 controls).
[b] Logistic regression odds ratio and *P*-value, accounting for age, gender, race, income, smoking (ever/never/current), family history of colorectal cancer (yes/no) and waist-to-hip ratio (338 cases and 902 controls).
[c] Logistic regression odds ratio and *P*-value, accounting for age, gender, race, income, smoking (ever/never/current), family history of colorectal cancer (yes/no), waist-to-hip ratio, and HOMA-IR (266 cases and 745 controls).

**Table 3.** Risk Estimates of Colorectal Adenoma for Sleep Duration, Sleep Apnea, and Shift Work

| | | Base Model Logistic Regression[a] | | Full Model Logistic Regression[b] | | Full Model Logistic Regression With HOMA-IR[c] | |
|---|---|---|---|---|---|---|---|
| | Cases/Controls | OR (95% CI) | *P* | OR (95% CI) | *P* | OR (95% CI) | *P* |
| **Average sleep per night, h** | | | .013[d] | | .023[d] | | .027[d] |
| **>7** | 136/437 | 1.00 (referent) | | 1.00 (referent) | | 1.00 (referent) | |
| **6-7** | 100/256 | 1.24 (0.91-1.69) | | 1.24 (0.90-1.70) | | 1.40 (0.98-2.00) | |
| **<6** | 95/198 | 1.50 (1.08-2.09) | | 1.47 (1.05-2.06) | | 1.49 (1.02-2.19) | |
| Sleep apnea diagnosis | 33/58 | 1.39 (0.88-2.43) | .16 | 1.37 (0.84-2.23) | .20 | 1.44 (0.84-2.47) | .19 |
| Ever worked alternate shift | 182/414 | 1.18 (0.91-1.54) | .22 | 1.12 (0.85-1.48) | .43 | 1.16 (0.85-1.59) | .35 |

[a] Logistic regression odds ratio and *P*-value, accounting for age, gender, and race (338 cases and 902 controls).
[b] Logistic regression odds ratio and *P*-value, accounting for age, gender, race, income, smoking (ever/never/current), family history of colorectal cancer (yes/no), and waist-to-hip ratio (338 cases and 902 controls).
[c] Logistic regression odds ratio and *P*-value, accounting for age, gender, race, income, smoking (ever/never/current), family history of colorectal cancer (yes/no), waist-to-hip ratio, and HOMA-IR (266 cases and 745 controls).
[d] *P* for trend.

not materially change the risk estimate. When individuals were grouped into 3 categories of sleep duration, our analysis showed that individuals averaging less than 6 hours of sleep per night had a statistically significant increase in the risk of colorectal adenomas (OR = 1.47; 95% CI = 1.05-2.06), compared with individuals sleeping at least 7 hours per night. Both the base and full models showed a statistically significant linear dose-response relation between sleep duration and risk of adenoma (Table 3).

Cases were also more likely to report ever having worked alternate shifts than controls (54.0% vs 46.1%, $P = .01$), although this association reduced to nonsignificance after adjustment for potential confounders in the regression models (Table 3). Self-reported diagnosis of sleep apnea was also more prevalent in cases (9.8%), compared with controls (6.5%, $P = .04$), but the small numbers limited our statistical power to detect an association after adjustment for covariates.

Further adjustment for HOMA-IR did not alter our results. Indeed, a statistically significant linear trend for the categorical group of hours of sleep per night remained after adjustment for HOMA-IR (Table 3), suggesting the influence of sleep duration on colorectal adenomas is independent of insulin resistance.

Because of known differences in sleep patterns in sleep apnea patients, we repeated our full model logistic regression, excluding participants who reported sleep apnea diagnosis. This appears to have little influence on our results. In fact, the odd ratio (OR) estimates were slightly increased for shorter sleep duration (OR = 1.21; 95% CI = 0.87-1.69 for those averaging between 6 and 7 hours of sleep, and OR = 1.50 (95% CI = 1.05-2.13) for individuals reporting less than 6 hours of sleep per night, compared with those averaging at least 7 hours per night, $P_{trend} = .02$) in the full logistic regression model. There was no appreciable change in the risk estimates for PSQI scores (data not shown).

When the analysis was stratified by gender, we noticed a somewhat stronger association of sleep duration with colorectal adenomas in women compared with that in men (Table 4), although this difference was not statistically significant ($P_{Interaction} = .65$).

## DISCUSSION

We found that shorter sleep duration is associated with an increased risk of colorectal adenomas in a population of patients undergoing routine screening colonoscopies. In contrast, we found no evidence for an association of overall sleep quality with colorectal adenomas. This is in line with the current literature on breast cancer reporting evidence for an association of sleep duration, but not quality of sleep.[6,16-18] Individuals sleeping less than 6 hours per night have a nearly 50 percent increase in the risk of developing colorectal adenomas, compared with those sleeping more than 7 hours. This association is independent of central obesity and insulin resistance. To our knowledge, this is the first study to report a significant association of sleep duration and colorectal adenomas, supporting short duration of sleep as a novel risk factor for the development of early colorectal neoplasia.

The magnitude of increase in risk observed here is comparable to the increase in risk of colorectal cancer

**Table 4.** Gender Specific Risk Estimates of Colorectal Adenoma for Sleep Duration, Sleep Apnea, and Shift Work

| | Males | | | Females | | |
|---|---|---|---|---|---|---|
| | Cases/Controls | OR (95% CI)[a] | *P* | Cases/Controls | OR (95% CI)[a] | *P* |
| **Average sleep per night, h** | | | .25[b] | | | .04[b] |
| **>7** | 63/139 | 1.00 (referent) | | 58/143 | 1.00 (referent) | |
| **6-7** | 54/93 | 1.39 (0.85-2.28) | | 46/163 | 1.12 (0.73-1.72) | |
| **<6** | 37/55 | 1.31 (0.74-2.34) | | 73/298 | 1.58 (1.03-2.43) | |
| Sleep apnea diagnosis | 21/24 | 1.52 (0.76-3.05) | .23 | 12/34 | 1.18 (0.58-2.42) | .65 |
| Ever worked alternate shift | 100/154 | 1.39 (0.89-2.17) | .15 | 82/260 | .99 (0.69-1.43) | .96 |

[a] Logistic regression odds ratio and *P*-value, accounting for age, race, income, smoking (ever/never/current), family history of colorectal cancer (yes/no), and waist-to-hip ratio (338 cases and 902 controls).
[b] *P* for trend.

associated with having a first degree relative affected with colorectal cancer,[26] and high red meat intake.[27] Furthermore, this estimate is similar to those observed with respect to short sleep duration and breast cancer.[16-18] Thus, short sleep duration is a public health hazard leading not only to obesity, diabetes, and coronary heart disease,[7,28,30] but also, as we have now demonstrated, colorectal adenomas. Our data suggest that even a modest increase in sleep duration could have a substantial impact because of the high prevalence of colorectal adenomas, a well established precursor of colorectal cancer.

Increasing evidence strongly suggests that disruption of circadian rhythm and suppression of nocturnal production of melatonin may be the key mechanism underlying the shift work-cancer link.[15] Melatonin has been shown in animal models to reduce the number of DNA adducts and also to promote DNA repair, and thus reduce the overall amount of DNA damage and decrease cellular proliferation via cell cycle inhibition.[31-33] In the present study, we did not comprehensively evaluate disruptions to circadian rhythm, such as exposure to light at night, but rather focused on other aspects of sleep—duration and overall quality. Although the mechanisms underlying the association of sleep duration with the development of cancer are largely unknown at present, it is conceivable that sleep duration shorter than optimal (such as <6 hours) causes circadian disruption and suppression of nocturnal production of melatonin, initiating the development of colorectal adenomas.

Another prevailing hypothesis is that insulin resistance may underlie the link between sleep disturbance and carcinogenesis. Indeed, we have recently shown that sleep is an integral part of the syndrome of insulin resistance or the metabolic syndrome.[24] However, further adjustment for HOMA-IR in our regression analysis did not alter the magnitude or the significance level of the association between sleep duration and risk of adenoma, suggesting that insulin resistance is unlikely a mediator of our observed association.

There are a few limitations in our study. First, although all data (including the PSQI survey) were collected from all participants before their colonoscopic examinations, the cross-sectional nature of our study cannot completely dismiss the possibility of reverse causality; ie, the undiagnosed existing adenomas may have led to shorter duration of sleep among the cases. However, this scenario is extremely unlikely as we only recruited patients with no known personal history of colorectal cancer or adenomas, and most colorectal adenomas are asymptomatic. Second, although the PSQI is a well validated measure of overall sleep quality,[20] and the self-reported information on sleep apnea and alternate shift work was included in our findings, the current study does not capture all aspects of sleep that may potentially affect carcinogenesis. Third, the number of patients with a known diagnosis of sleep apnea or reporting long-term shift work is relatively small, which may have limited our statistical power to detect a potential association for sleep apnea or shift work. Lastly, under-diagnosis of sleep apnea has been well documented in the general population,[34] and we only have sleep apnea information from self-reports. Undiagnosed sleep apnea among the cases as well as the controls introduces measurement error of the exposure variable of interest; ie, sleep apnea, which in general tends to attenuate the true risk association to null.

In summary, we found in this relatively large, screening colonoscopy-based study that short duration of sleep significantly increases risk of colorectal adenomas. Our results suggest short duration of sleep as a novel risk factor for the development of early colorectal neoplasia. Effective intervention to increase duration of sleep and improve quality of sleep could be an under-appreciated avenue for prevention of colorectal cancer.

## CONFLICT OF INTEREST DISCLOSURES

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## REFERENCES

1. Kato M, Phillips BG, Sigurdsson G, Narkiewicz K, Pesek CA, Somers VK. Effects of sleep deprivation on neural circulatory control. *Hypertension.* 2000;35:1173-1175.
2. Meier-Ewert HK, Ridker PM, Rifai N, et al. Effect of sleep loss on C-reactive protein, an inflammatory marker of cardiovascular risk. *J Am Coll Cardiol.* 2004;43:678-683.
3. Spiegel K, Leproult R, L'hermite-Baleriaux M, Copinschi G, Penev PD, Van Cauter E. Leptin levels are dependent on sleep duration: relationships with sympathovagal balance, carbohydrate regulation, cortisol, and thyrotropin. *J Clin Endocrinol Metab.* 2004;89:5762-5771.
4. Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. *Lancet.* 1999;354:1435-1439.
5. Spiegel K, Tasali E, Penev P, Van Cauter E. Brief communication: Sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. *Ann Intern Med.* 2004;141: 846-850.
6. Ayas NT, White DP, Al Delaimy WK, et al. A prospective study of self-reported sleep duration and incident diabetes in women. *Diabetes Care.* 2003;26:380-384.
7. Ayas NT, White DP, Manson JE, et al. A prospective study of sleep duration and coronary heart disease in women. *Arch Intern Med.* 2003;163:205-209.
8. Kripke DF, Garfinkel L, Wingard DL, Klauber MR, Marler MR. Mortality associated with sleep duration and insomnia. *Arch Gen Psychiatry.* 2002;59:131-136.
9. Patel SR, Ayas NT, Malhotra MR, et al. A prospective study of sleep duration and mortality risk in women. *Sleep.* 2004;27:440-444.
10. Patel SR, Malhotra A, White DP, Gottlieb DJ, Hu FB. Association between reduced sleep and weight gain in women. *Am J Epidemiol.* 2006;164:947-954.
11. Viswanathan AN, Hankinson SE, Schernhammer ES. Night shift work and the risk of endometrial cancer. *Cancer Res.* 2007;67:10618-10622.
12. Davis S, Mirick DK. Circadian disruption, shift work and the risk of cancer: a summary of the evidence and studies in Seattle. *Cancer Causes Control.* 2006;17:539-545.
13. Kubo T, Ozasa K, Mikami K, et al. Prospective cohort study of the risk of prostate cancer among rotating-shift workers: findings from the Japan collaborative cohort study. *Am J Epidemiol.* 2006;164:549-555.
14. Schernhammer ES, Laden F, Speizer FE, et al. Rotating night shifts and risk of breast cancer in women participating in the nurses' health study. *J Natl Cancer Inst.* 2001;93: 1563-1568.
15. Schernhammer ES, Laden F, Speizer FE, et al. Night-shift work and risk of colorectal cancer in the nurses' health study. *J. Natl. Cancer Inst.* 2003;95:825-828.
16. Verkasalo PK, Lillberg K, Stevens RG, Hublin C, Partinen M, Koskenvuo M, Kaprio J. Sleep duration and breast cancer: a prospective cohort study. *Cancer Res.* 2005;65:9595-9600.
17. Kakizaki M, Kuriyama S, Sone T, et al. Sleep duration and the risk of breast cancer: the Ohsaki Cohort Study. *Br J Cancer.* 2008;99:1502-1505.
18. Wu AH, Wang R, Koh WP, Stanczyk FZ, Lee HP, Yu MC. Sleep duration, melatonin and breast cancer among Chinese women in Singapore. *Carcinogenesis.* 2008;29:1244-1248.
19. Pinheiro SP, Schernammer ES, Tworoger SS, Michels KB. A prospective study on habitual duration of sleep and incidence of breast cancer in a large cohort of women. *Cancer Res.* 2006;66:5521-5525.
20. Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *CA Cancer J Clin.* 2008;58:130-160.
21. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatric Res.* 1989;28: 193-213.
22. Matthews DR, Rudenski AS, Burnett MA, Darling P, Turner RC. The half-life of endogenous insulin and C-peptide in man assessed by somatostatin suppression. *Clin Endocrinol Oxf.* 1985;23:71-79.
23. Jennings JR, Muldoon MF, Hall M, Buysse DJ, Manuck SB. Self-reported sleep quality is associated with the metabolic syndrome. *Sleep.* 2007;30:219-223.
24. Nock NL, Li L, Larkin EK, Patel SR, Redline S. Empirical evidence for "syndrome Z": a hierarchical 5-factor model of the metabolic syndrome incorporating sleep disturbance measures. *Sleep.* 2009;32:615-622.
25. St-Onge MP, Perumean-Chaney S, Desmond R, Lewis CE, Yan LL, Person SD, Allison DB. Gender Differences in the Association between Sleep Duration and Body Composition: The Cardia Study. *Int J Endocrinol.* 2010;2010:726071.
26. Fuchs CS, Giovannucci EL, Colditz GA, Hunter DJ, Speizer FE, Willett WC. A prospective study of family history and risk of colorectal cancer. *N Engl J Med.* 1994;331: 1669-1674.
27. Larsson SC, Wolk A. Meat consumption and risk of colorectal cancer: a meta-analysis of prospective studies. *Int J Cancer.* 2006;119:2657-2664.
28. Ayas NT, White DP, Al-Delaimy WK, et al. A prospective study of self-reported sleep duration and incident diabetes in women. *Diabetes Care.* 2003;26:380-384.
29. Taheri S, Lin L, Austin D, Young T, Mignot E. Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. *PLoS Med.* 2004;1:e62.
30. Blask DE, Sauer LA, Dauchy RT. Melatonin as a chronobiotic/anticancer agent: cellular biochemical and molecular mechanisms of action and their implications for circadian-based cancer therapy. *Curr Top Med Chem.* 2002;2:113-132.
31. Blask DE, Dauchy RT, Sauer LA. Putting cancer to sleep at night –the neuro-endocrine/circadian melatonin signal. *Endocrine.* 2005;27:179-188.
32. Reiter RJ. Mechanisms of cancer inhibition by melatonin. *J Pineal Res.* 2004;37:213-214.
33. Young T, Evans L, Finn L, Palta M. Estimation of the clinically diagnosed proportion of sleep apnea syndrome in middle-aged men and women. *Sleep.* 1997;20:705-706.