Association between Sleep Duration and Colorectal Adenomas: Findings from a Case–Control Study in Vietnam

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ABSTRACT

Background: Colorectal cancer is one of the leading cancers worldwide and in Vietnam. Adenomas are important precursors of colorectal cancer. Study on the association between sleep duration and development of colorectal adenoma (CRA) is limited, particularly among Vietnamese population.

Methods: We conducted an individually matched case–control study of 870 CRA cases and 870 controls in a large-scale colorectal screening program involving 103,542 individuals ages ≥40 years old in Hanoi, Vietnam. Sleep duration was categorized in three groups: short: ≤6 hours/day, normal: 7 to 8 hours/day, and long: >8 hours/day. Conditional logistic regression was used to evaluate the association between sleep duration and adenomas risk after controlling for potential confounders.

Results: Overall, short-sleep duration was associated with increased risk of having CRA compared with normal duration [OR, 1.48; 95% confidence interval (CI), 1.12–1.97]. This pattern was present in both females (OR, 1.58; 95% CI, 1.14–2.18) and males (OR, 1.45; 95% CI, 1.08–1.93), with advanced adenomas (OR, 1.61; 95% CI, 1.09–2.38) and non-advanced adenomas (OR, 1.66; 95% CI, 1.19–2.32). Furthermore, the association between CRA development and short-sleep duration was more apparent among females who were nondrinker, nonobese, physically active, with proximal or both sided adenomas and with cardiometabolic disorder. Among males, the short-sleep duration was associated with CRA risk among never-smoking, cardiometabolic disorders, and obese.

Conclusions: Short-sleep duration was associated with increased prevalence of both advanced and non-advanced CRAs among Vietnamese population.

Impact: Findings from this study showed that maintaining an adequate sleep duration may have an important implication for colorectal adenoma prevention and control.

Introduction

Colorectal cancer is the third most common cancer in men, the second in women, and the second leading cause of cancer death worldwide (1). Vietnam, a low- and middle-income country (LMIC) with a total population of more than 96 million which ranks the 14th most populous country worldwide, has been experiencing rapid economic development over the past two decades (i.e., 7–8% annual growth rate; ref. 2). A combination of the widespread adoption of a Western lifestyle and improvement of life expectancy has resulted in a drastic increase in cancer incidence and mortality in Vietnam (3). Cancer now accounts for approximately one-fifth of all deaths (3, 4).

In Vietnam, colorectal cancer is the fifth most common type of cancer in incidence and cancer-related mortality among both sexes combined (5) and its incidence has been increasing. In 2018, the age-standardized incidence rate of colorectal cancer in Vietnam was 13.4 per 100,000 population and age-standardized mortality rate due to colorectal cancer was 7.0 per 100,000 population (5). The colorectal cancer incidence in Ho Chi Minh City, the largest city in Vietnam, showed an increase from 7.5 per 100,000 population during 1995 to 1998 to 11.1 per 100,000 population during 2008 to 2012 in men and from 5.3 per 100,000 population during 1995 to 1998 to 7.2 per 100,000 population during 2008 to 2012 in

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women (6). Currently, colorectal cancer screening programs are undertaken in most European countries, Canada, specific regions in North and South America, other Asia countries, and Oceania (7). Nevertheless, in Vietnam, due to the limited infrastructure, resources, and health literacy, a population-based colorectal cancer screening program has never been conducted.

CRA is considered an important precursor for colorectal cancer because the majority of colorectal cancer arise from adenomas through the well-established adenoma–carcinoma sequence (8–10). Data from the Prostate, Lung, Colorectal and Ovarian Cancer Randomized Trial showed a 3-fold increased risk of colorectal cancer among subjects with advanced adenoma compared with those without adenomas (11). Risk reduction, early detection, and management of asymptomatic individuals, such as those with adenomas, remain high priorities for a successful program for colorectal cancer control and prevention.

Because of the increasing incidence rate of colorectal cancer even after recognition of a number of modifiable risk factors for CRA (12–17), identifying additional modifiable risk factors for these precursor lesions is important for improving colorectal cancer prevention and control. Sleep is imperative for physical and mental health (18). Sleep-related problems are becoming increasingly common in modern societies with 20% to 40% reported prevalence among general population (19). Over recent decades the prevalence of short-sleep has increased whereas the long-sleep pattern has been downtrending (20). Although the normal adequate range of sleep for adults is defined between 7 and 8 hours, the National Sleep Foundation has defined <6 hours sleep duration as insufficient sleep (21). Recently, there has been an increased attention toward understanding the extent of sleep duration problems at the population level and the associations between these sleep disturbance patterns and various health outcomes, including cancers (22).

Previous studies have suggested a higher risk of CRA among short- or long-duration sleepers (23, 24). However, the true effect of altered sleep duration on CRA risk has not been fully elucidated and some studies fail to support any significant association between either short or long-sleep duration and CRA incidence (25). Furthermore, a large proportion of evidence on CRA risk factors is based on Caucasian and African American populations. Therefore, well-designed studies are warranted to evaluate the association between understudied risk factors such as sleep duration and the risk of CRAs worldwide, including Asian populations.

The objective of the current analysis was, therefore, to determine the association between sleep duration and the risk of CRAs in a first-ever case–control study conducted in Hanoi, Vietnam, which was developed from the first population-based colorectal cancer screening program in Vietnam, targeting both men and women ages 40 years or older.

Materials and Methods

Study population

Data used in this analysis were collected from a case–control study of CRA as part of the Vietnam Colorectal Cancer and Polyps Research (VinCAPR). Details of the VinCAPR were described elsewhere (17, 26). Briefly, this colorectal screening program was conducted among 672,742 eligible persons ages 40 years or older. All participants were recruited from six districts of Hanoi, namely, Hai Ba Trung, Hoang Mai, Gia Lam, Thuong Tin, Thanh Oai, and Chuong My. The screening enrollment was carried out between January 01, 2018 and October 31, 2019. An immunochemical fecal occult blood test (iFOBT) Kit was distributed to 103,542 consented individuals of whom 84,369 returned the kits to Vinmec Times City Hospital (Vinmec TC), Hanoi. Among those who returned the kits, 80,330 individuals were 40 years or older, and 4,887 had a positive test (i.e., the concentration of blood detected in the sample ≥100 ng hemoglobin/1 mL). We invited all patients with positive iFOBT results for a colonoscopy at the Vinmec TC, of whom 2,278 underwent the colonoscopy and adenoma(s) were found and confirmed pathologically in 932 patients. Among the remaining 2,028 individuals who did not undergo the colonoscopy at Vinmec TC, 581 were unreachable due to wrong phone number or not answering the phone after three attempts, the others refused to have colonoscopy, had contraindication for colonoscopy or underwent colonoscopy at other hospitals. We invited all adenoma patients for a follow-up survey. Sixty-two patients refused to participate in-person interview, leaving a total of 870 adenoma cases (**Fig. 1**).

Written informed consents were obtained from all study participants. This study was approved by the Institutional Review Boards (IRB) of Vinmec Healthcare System and the University of Pittsburgh.

Control selection

Controls were randomly selected from 75,443 individuals who had negative iFOBT results and individually matched to cases in 1 to 1 ratio by age (±5 years old), gender, and residential district.

Assessment of exposure and other covariates

During the in-person interview, a trained interviewer used structured questionnaires to collect information on: (i) sociodemographic features, (ii) disease history, (iii) physical activity, (iv) dietary history, (v) personal habits and lifestyle, (vi) employment history, (vii) menstrual and reproductive history, (viii) contraceptive and hormone use, (ix) familial cancer history, (x) physical development and body measurement, and (xi) anthropometric measurement.

During the interview, participants were asked the following question for sleep duration "On average, how many hours do you usually sleep each day including daytime sleeping?," with the following answer choices: (i) less than 5 hours; (ii) 5 hours; (iii) 6 hours; (iv) 7 hours; (v) 8 hours; (vi) 9 hours; (vii) 10 hours; (viii) 11 hours; and (ix) more than 11 hours. Body mass index (BMI) was calculated by self-reported of weight in kilograms divided by height squared in meters. Waist and hip circumference were taken and rounded to nearest one decimal point. Waist–hip ratio (WHR) was calculated by taking the waist-circumference over hip-circumference. Regarding the smoking habits the following variables were included: smoking status (i.e., never-, current-, and former-smokers) whereas former and current smokers had additional information on: (i) age of starting and age of quitting smoking, (ii) number of cigarettes per day and (iii) number of years of smoking. Current smoking status was defined as smoking at least one cigarette per day continuously for the last 6 months. Former smokers were those who has stopped smoking at the time of interview. Ever-smokers included current smokers and former-smokers. Current regularly drinking status was defined as consumption of one or more drinks per day continuously for the last 3 months. Comorbidity was defined if an individual reported one of the following diseases: cardiometabolic disorders, chronic hepatitis, liver cirrhosis, chronic gastritis, peptic, gastric and duodenal ulcers, allergy, asthma, emphysema, chronic bronchitis, tuberculosis, arthritis, systemic lupus erythematosus, inflammatory bowel disease, gout, and/or prostatic hypertrophy. Cardiometabolic disorders

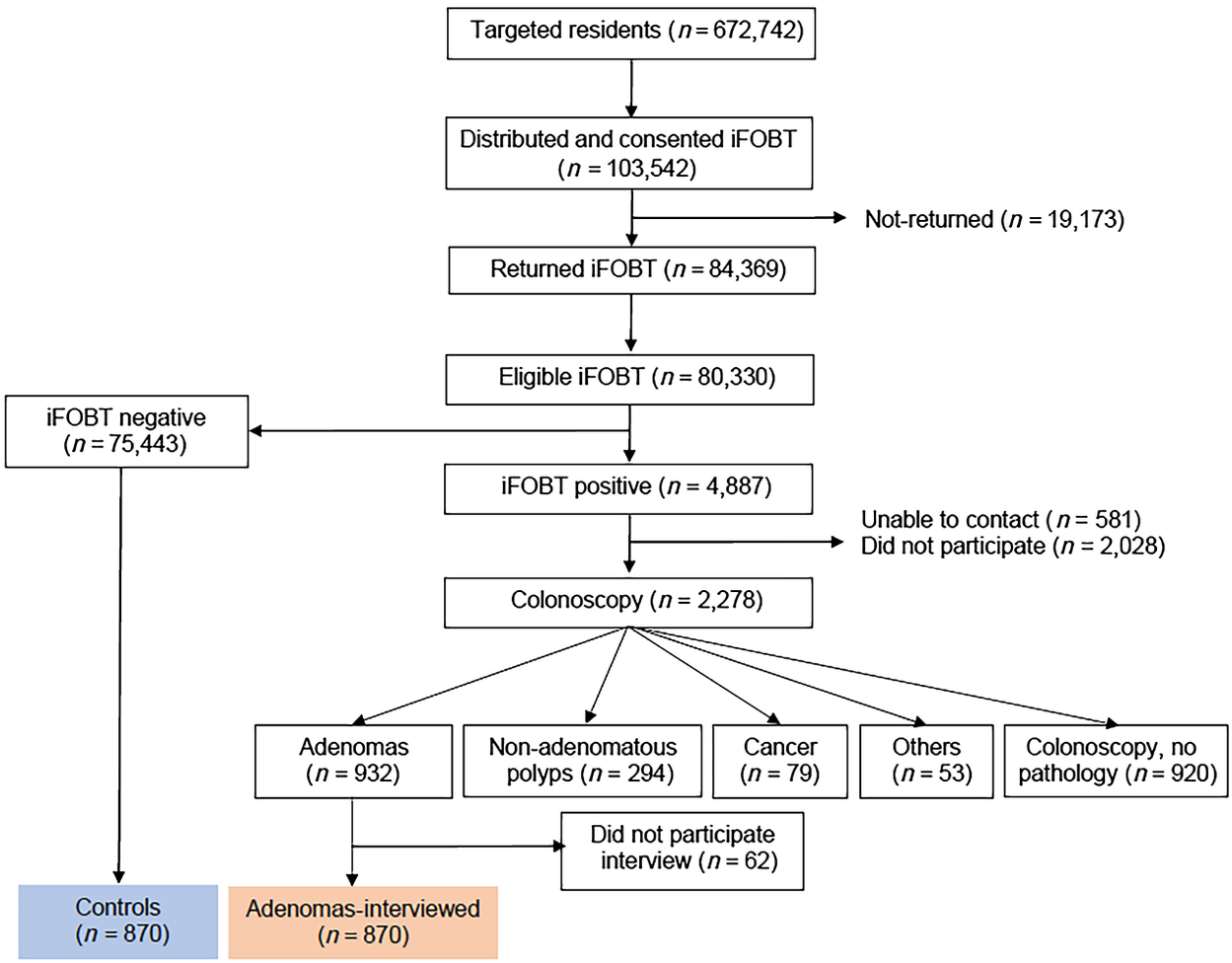

Figure 1.
Flow chart case–control study design in this study. The flow chart shows the process used to select cases and controls for this study of the association sleep duration and the risk of colorectal adenomas/polyps. *n*, number of individuals.

was defined when participants reported any of the following conditions and/or diseases: diabetes mellitus (excluding gestational diabetes), high blood pressure (excluding gestational hypertension), hyperlipidemia, cardiovascular disease, stroke, and myocardial infarction.

Histopathologic evaluation

During the standard-of-care colonoscopy, biopsies obtained from suspect lesions, and all removed polyps/adenomas were histologically diagnosed on the basis of the International Classification Code-Version 10 (ICD-10; ref. 27). Advanced adenomas were defined as adenomas with any of the following features: ≥1 cm, with high-grade dysplasia, with tubulovillous or villous histology. Adenomas smaller than 1 cm diameter, and without advanced histology findings were categorized as non-advanced adenoma (11). For the purpose of current analysis, only information of adenomas was included. The anatomic location of the detected adenoma was also recorded. The proximal colon included the cecum, ascending, hepatic flexure, and transverse colon, whereas distal colon included splenic flexure, descending, sigmoid colon, and rectum.

Statistical analysis

Means and SD were calculated for continuous variables while counts and proportions were computed for categorical variables. To compare the distributions of continuous and categorical variables between cases and controls, *t* test or ANOVA, and χ^2 tests were applied, respectively.

Logistic regression models were used to determine the association between sleep duration and the prevalence of CRAs. ORs and their corresponding 95% CIs of CRAs with short (≤6 hours/day) or long-sleep duration (>8 hours/day) categories compared with normal sleep duration (i.e., 7–8 hours/day) were derived from the multivariable logistic regression models adjusted for potential confounders: education, marital status, smoking status (i.e., ever versus never), smoking year, pack-year, alcohol drinking status (i.e., ever vs. never), weekly physical activity (i.e., yes vs. no), family history of cancer (i.e., yes vs. no), and number of comorbidity (i.e., 0, 1, and ≥2). An ordinal variable for BMI was used for the linear trend test for adenomas risk.

We also performed stratified analysis by smoking status (i.e., ever smokers vs. never smokers), alcohol drinking status (i.e., ever drinkers

vs. never drinkers), weekly physical activity (i.e., yes vs. no), family history of cancer (i.e., yes vs. no) adenoma types (i.e., advanced adenomas vs. non-advanced adenomas), adenomas location (i.e., proximal, distal, both sided), cardiometabolic disorders (i.e., yes vs. no). For above stratified analyses except by gender, we used conditional logistic regression models with adjustment for matched variable (i.e., sex, age, and residential district). Interaction terms between sleep duration and selected covariates were created to evaluate the differences in odds of colorectal adenomas/polyps in stratified analysis in the logistic regression models.

All statistical analyses were conducted using Stata version 14.1 (StataCorp). All *P* values were two-sided and 0.05 was used as a threshold of statistical significance.

Data availability

Data are available with relevant request from the corresponding author and from the Research Management Department, Vinmec Healthcare System, 458 Minh Khai Street Vinh Tuy Ward, Hai Ba Trung District, Hanoi, Vietnam. Phone: +84-243-975-0028; Fax: +84-243-974-3557. E-mail: v.rmo@vinmec.com.

Results

The mean (SD) age at enrolment for cases and controls were 60.3 (8.7) years and 59.7 (8.7) years, respectively. The sociodemographic characteristics and selected factors of study participants are presented in Supplementary Table S1. Compared with controls, CRA cases had significantly higher frequency of current smokers, higher mean years of smoking, higher prevalence of current drinking, higher prevalence of positive family history for colorectal cancer and higher prevalence of two or more comorbidities (all $P < 0.05$). There were no statistically significant differences between cases and controls with respect to education, marital status, weight, height, BMI, waist-hip-ratio, smoking pattern (mean cigarettes/day, mean pack-years of smoking), weekly physical activity, and family history of any cancer or cardiometabolic disorders.

Subjects with shorter sleep were older, had lower BMI, less likely to have a smoking history compared with subjects with normal range sleep (**Table 1**).

The association between sleep duration with the prevalence of adenomas are presented in **Table 2**. Overall, less than 6-hour sleep was associated with the risk of having CRA (OR, 1.48; 95% CI, 1.12–1.97). The positive association between short sleep and prevalence of adenomas was detected among both men and women (OR, 1.45; 95% CI, 1.08–1.93 and OR, 1.58; 95% CI, 1.14–2.18 respectively, $P_{\text{interaction}^*} = 0.96$). Furthermore, the short-sleeper were at higher odds of having both advanced or non-advanced CRA (OR, 1.61; 95% CI, 1.09–2.38 and OR, 1.66; 95% CI, 1.19–2.32, respectively). Among non-advanced adenomas, the association between short-sleep and CRA was detected in both men (OR, 1.55; 95% CI, 1.00–2.38) and women (OR, 1.62; 95% CI, 1.10–2.38; $P_{\text{interaction}^*} = 0.41$; **Table 2**).

Results from stratified analyses by tobacco smoking, alcohol drinking, BMI, weekly physical activity, cardiometabolic disorders, adenoma location by sex are shown in **Table 3**. There was a significant association with adenomas among never-drinker female compared with those with normal sleep duration (OR, 1.59; 95% CI, 1.14–2.21). Furthermore, there was a significant association between short-sleep and adenomas in nonobese subjects (OR, 1.88; 95% CI, 1.21–2.92), and in females with proximal or both sided adenomas (OR, 2.12; 95% CI, 1.09–4.11 and OR, 2.67; 95% CI, 1.37–5.21, respectively). Similarly, a positive association was noted among nonobese females (OR, 1.67; 95% CI, 1.10–2.54) as well as women with any weekly physical activity (OR, 1.72; 95% CI, 1.12–2.63).

Among male subset, short-sleep duration was positively associated with increased prevalence of adenomas in nonsmokers (OR, 1.70; 95% CI, 1.05–2.74; $P_{\text{interaction}^*} = 0.91$) as well as men with overweigh/obesity (OR, 1.57; 95% CI, 1.02–2.43; $P_{\text{interaction}^*} = 0.56$). Furthermore, positive association between short-sleep duration and adenomas risk was seen among men without physical activity (OR, 1.61; 95% CI, 1.02–2.54; $P_{\text{interaction}^*} = 0.52$) and with positive history of cardiometabolic disorders (OR, 1.62; 95% CI, 1.05–2.50; $P_{\text{interaction}^*} = 0.81$; **Table 3**).

Discussion

In a first-ever case–control study of CRAs in Vietnam that was based on a large-scale of colorectal cancer screening program and included 870 cases with individually matched 870 controls, we found a significant association between short-sleep duration and the prevalence of adenomas. This association was more evident among females with proximal or both sided adenomas, no drinking history, nonobese, and physically active. In male subjects, the association between short asleep and CRA was more notable among nonsmokers as well as obese/overweight subjects and those with no regular physical activity.

Our finding is consistent with a previous case–control study including 1,240 cases of routine colonoscopy screening, which showed the higher odds for adenomas among those with short-sleep duration (23). Yet, this study was conducted in different populations (i.e., more than 61% Caucasian and 37% African-Americans). Furthermore, study in a large cohort of postmenopausal women showed both short-sleep and long-sleep are associated with increased colorectal cancer risk, suggesting an U-shaped association pattern (28). Again, such study had different outcome (colorectal cancer) and different population with a majority of Caucasians, followed by African-Americans and Hispanic and less than 3% of Asians/Pacific Islanders. This study showed increased prevalence of adenomas in those with longer sleep duration among males with BMI <23 kg/m^2 (but not among females) and among those with proximal adenomas. However, it should be noted that the number of long-sleepers with proximal adenomas was small. There was no other significant increased colorectal cancer risk among long-sleepers across this studied population. Although most previous studies have reported the association between long-sleep duration and colorectal cancer risk (29), there are numerous conflicting reports on the association between sleep duration and colorectal cancer risk. A large-scale study by Titova and colleagues (30) among 367,586 UK Biobank participants, using Mendelian randomization approach reported genetic liability to short-sleep duration was linked with a nonsignificant higher odds of colorectal cancer, yet no impact of long-sleep duration on the colorectal cancer risk was found.

A meta-analysis by Chen and colleagues (29) compared the impact of short- or long-sleep duration on the colorectal cancer risk across ethnicities. Interestingly, they reported disparity across ethnic groups as the short-sleep duration strongly associated with the cancer risk among Asian subpopulation, which was based on four cohorts (31–33) in Japan and Singapore and one case–control study including 1,779 incident cases (34) recruited from China, yet did not yield a significant effect in American or European populations (29).

The association between sleep duration and CRA could be explained by a number of potential plausibility. Sleep duration may be a surrogate measure of exposure to light and the resultant melatonin secretion as protective factor against cancer. Melatonin has been indicated with promising health outcomes and as a protective factor against progression of various types of tumors including colorectal cancer (35). Experimental study has supported the antiproliferative and proapoptotic role of

Table 1. Distributions of baseline characteristics among study participants (both cases and controls) by sleep duration in this study.

Characteristics	≤6 hours/night ($n = 800$) *n* (%)	7–8 hours/night ($n = 723$) *n* (%)	>8 hours/night ($n = 169$) *n* (%)	*P* value
Mean age (±SD), years	61.7 ± 8.5	58.8 ± 8.7	57.2 ± 8.2	<**0.0001**
Sex (%)				
Male	449 (56.1)	423 (58.5)	122 (72.2)	**0.001**
Female	351 (43.9)	300 (41.5)	47 (27.8)	
Highest level of education (%)				
No formal education	22 (2.7)	18 (2.5)	6 (3.5)	<**0.01**
Primary school	128 (16.0)	81 (11.2)	30 (17.7)	
Secondary school	341 (42.6)	333 (46.0)	72 (42.6)	
High school	161 (20.1)	141 (19.5)	35 (20.7)	
Professional education	78 (9.7)	59 (8.2)	13 (7.7)	
College or higher	70 (8.7)	90 (12.6)	12 (7.1)	
Marital status				
Married	706 (88.2)	672 (92.9)	159 (94.1)	**0.002**
Single/separated/divorced/widowed	94 (11.8)	51 (7.1)	10 (5.9)	
Mean weight (kg ± SD)	55.9 ± 8.6	57.4 ± 8.7	57.8 ± 9.1	**0.001**
Mean height (cm ± SD)	158.7 ± 6.9	159.5 ± 7.6	161.7 ± 7.2	<**0.0001**
BMI (kg/m^2)	21.1 ± 2.6	22.5 ± 2.6	22.0 ± 2.7	**0.02**
Smoking status				
Never smoker	529 (66.1)	442 (61.1)	94 (55.6)	**0.03**
Former smoker	163 (20.4)	143 (19.8)	44 (26.0)	
Current smoker	107 (13.4)	135 (18.7)	31 (18.3)	
Mean cigarettes/day (±SD)[a]	13.9 ± 9.5	11.7 ± 7.9	12.2 ± 8.1	0.009
Mean years of smoking (±SD)[a]	29.8 ± 13.0	29.7 ± 13.1	27.5 ± 14.6	0.38
Alcohol drinking status (%)				
Nondrinker	459 (57.4)	396 (54.8)	80 (47.3)	0.15
Former drinker	41 (5.1)	39 (5.4)	10 (5.9)	
Current drinker	290 (36.3)	283 (39.1)	79 (46.8)	
Alcohol consumption				
≤1 drink/week	47 (14.2)	48 (14.9)	12 (13.5)	0.33
1.1–7 drinks/week	70 (21.2)	47 (14.6)	15 (16.9)	
7.1–14 drinks/week	56 (16.9)	57 (17.7)	11 (12.4)	
>14 drinks/week	158 (47.7)	170 (52.8)	51 (57.3)	
Any weekly physical activity				
Yes	467 (58.5)	410 (58.4)	80 (47.3)	**0.03**
No	332 (41.6)	312 (43.2)	89 (52.7)	
Family history of cancer (%)				
No	600 (75.0)	544 (75.2)	134 (79.3)	0.30
Yes	198 (24.8)	173 (23.9)	35 (20.7)	
Family history of colorectal cancer (%)				
No	169 (84.9)	157 (90.8)	29 (82.9)	0.18
Yes	30 (15.1)	16 (9.3)	6 (17.1)	
Cardiometabolic disorders				
Yes	387 (48.4)	312 (43.2)	56 (33.1)	**0.001**
No	413 (51.6)	411 (56.9)	113 (66.9)	
Comorbidity (number) (%)				
0	193 (24.1)	200 (27.7)	56 (33.1)	0.08
1	188 (23.5)	156 (21.6)	41 (24.3)	
≥2	419 (52.4)	367 (50.8)	72 (42.6)	

Note: Bold text indicates *P* value < 0.05.
[a]Only among current and former smokers.

melatonin in development of colorectal cancer (36). In addition, melatonin exerts antioxidant and anti-inflammatory effects that may promote DNA repair mechanisms (37, 38).

Our findings in women showed an approximate 1.6-time increased risk of CRA among short-duration sleepers. This notion was also consistent with several previous studies. For instance, a case–control study by Thompson and colleagues (23) showed a similarly elevated risk of CRA among women with less than 6-hour sleep (OR, 1.58; 95% CI, 1.03–2.43; $P_{trend} = 0.04$), whereas among men the association was not significant (OR, 1.31; 95% CI, 0.74–2.34; $P_{trend} = 0.25$). This association was independent of obesity and of insulin resistance as two potential underlying mechanisms.

In this study, significant increased CRA risk was found among female (but not male) short-sleepers with proximal adenomas or both sided adenomas. No such association was found among those with distal adenomas, both males and females. The different pattern of

Table 2. Overall and sex-specific associations between sleep duration and CRA.

	Overall		Advanced adenomas		Non-advanced adenomas	
	Cases/ controls	OR (95% CI)[a]	Cases/ controls	OR (95% CI)[a]	Cases/ controls	OR (95% CI)[a]
Overall						
7–8 hours	326/397	1.00	144/175	1.00	182/222	1.00
≤6 hours	435/365	**1.48 (1.12–1.97)**	184/154	**1.61 (1.09–2.38)**	251/211	**1.66 (1.19–2.32)**
>8 hours	88/81	1.43 (0.81–2.50)	44/38	1.40 (0.79–2.48)	44/43	1.34 (0.79–2.28)
Male						
7–8 hours	194/229	1.00	100/124	1.00	94/105	1.00
≤6 hours	240/209	**1.45 (1.08–1.93)**	125/108	**1.50 (1.00–2.25)**	115/101	**1.55 (1.00–2.38)**
>8 hours	65/57	1.53 (0.99–2.35)	38/29	1.79 (0.99–3.25)	27/28	1.48 (0.78–2.84)
Female						
7–8 hours	132/168	1.00	44/51	1.00	88/117	1.00
≤6 hours	195/156	**1.58 (1.14–2.18)**	59/46	1.53 (0.84–2.79)	136/110	**1.62 (1.10–2.38)**
>8 hours	23/24	1.22 (0.64–2.32)	6/9	0.73 (0.21–2.49)	17/15	1.54 (0.71–3.32)
$P_{interaction}$[b]		0.96		0.71		0.41

Note: Bold text indicates P value < 0.05.

[a]Model adjusted for education level (≤primary school, secondary school, ≥high school), marital status (married vs. single/separated/divorced/widowed), smoking status (i.e., ever vs. never), smoking pack-years, drinking status (i.e., ever vs. never), weekly physical activity (i.e., yes vs. no), family history of cancer (i.e., yes vs. no), number of comorbidity (i.e., 0–1 vs. ≥2), and BMI (<23 vs. ≥23).

[b]Interaction with sex.

association between adenoma locations may be attributed to the differences in molecular mechanisms of tumorigenesis and progression of proximal and distal colon cancer.

Different pattern of association between two sexes may be partly explained by the association between estrogen and melatonin excretion. Melatonin has a disruptive effect on estrogen-dependent cell signaling, leading to a reduction of estrogen-stimulated cells (39). A similar hormonal interaction between estrogen and melatonin metabolites may be involved in other association with adenomas in females in this study. Also, estrogen is known to induce a protective effect against initiation and development of adenomas (40).

Another finding of this study was the stronger association between short-sleep duration and the odd of having adenomas among women with regular physical activity. This interesting finding may be attributed to the enhanced level of circulating anabolic hormones, insulin-like growth factor (IGF-1), or dehydroepiandrosterone which has been highlighted among older women (41). Physical activity affects the function and circulation of these hormones via expression of membrane transporter proteins and receptors (41, 42). Therefore, the strong association between the short-sleep duration and adenomas risk in women may be partly explained by these hormonal interactions. However, further studies are warranted to elucidate this phenomenon.

Our finding specifically suggested the association between limited sleep duration and development of CRA in participants with no drinking history, with advanced or non-advanced adenomas. This may suggest the influence of limited sleep duration in the earlier stages of tumorigenesis. There is proven difference in various cellular mechanisms including cell proliferation, differentiation, and apoptosis and DNA repair between day and night time (43). Furthermore, the expression of cytochrome P450 enzymes, involved in the process of detoxification of carcinogens and other exogenous molecules, follows a rhythmic pattern. The maximum level of most P-450 transcripts, have been reported to occur before subjective dawn at a time with minimal light (44). Some studies have showed an enhanced risk of colorectal cancer among nightshift workers (43, 45). A number of circadian clock genes (i.e., *PER1*, *PER2*, *PER3*, and *CLOCK*) have been extensively linked with carcinogenesis via affecting DNA repair and apoptosis (46). Although a number of clock genes are playing pivotal roles in regulating the circadian rhythm, a differential expression of various single nucleotide polymorphisms in *PER3* and *CLOCK* genes have been reported between Asian and Caucasian subjects (47).

Furthermore, another aspect which should be considered in the interpretation of these results is the role of ethnic background in the baseline melatonin secretion. Evidence shows a lower-level of melatonin excretion in Asian than in Caucasian subjects (8, 48). Therefore, the findings should also be interoperated based on the specific ethnicity of study population.

Strengths of our study include a population-based case–control study design where both CRA cases and control individuals were from a population-based screening program, thus reducing the risk of selection bias. Second, a comprehensive questionnaire implemented in this study allowed us to control for potential confounding factors while evaluating the association between sleep duration and adenomas prevalence.

Our study also has some limitations. First, due to the cross-sectional design, a conclusion on the causality is not possible. Second, using self-reported sleep duration might lead to measurement bias, including recall bias. Third, the selection of controls from iFOBT negative participants might have included some cases in the controls due to the false-negative result. In a study of 18,296 individuals who were screened for colorectal cancer by colonoscopy and FIT test at the Health Management Center of the National Taiwan University Hospital, Chiu and colleagues (49) showed that FIT false-negative test might miss individuals with small or nonpolypoid CRAs or early-stage cancers (i.e., carcinoma *in situ* or T1) compared with later stages (i.e., T2–T4), with respective sensitivity of 66.7% and 100% (P = 0.05). Such misclassification is likely to result in an underestimation of the sleep–CRA association. Although having a control group from those with negative result in a colonoscopy would be an ideal for our case–control study design, it is more challenge in terms of logistic preparation and recontact them than having a control group from those with a FOBT-negative result. In addition, having an additional control group (i.e., of those with negative result of colonoscopy) would create a heterogeneous control pool, which poses another challenge to the downstream analysis.

Table 3. Association between sleep duration and CRA in this study, stratified by selected characteristics, overall, and by sex.

	Overall		Male		Female	
	Cases/ controls	OR (95% CI)	Cases/ controls	OR (95% CI)	Cases/ controls	OR (95% CI)
Smoking status[a]						
Never regular smoking						
7–8 hours	188/254	1.00	57/87	1.00	131/167	1.00
≤6 hours	290/239	**1.67 (1.20–2.32)**	96/84	**1.70 (1.05–2.74)**	194/155	**1.56 (1.13–2.16)**
>8 hours	44/50	1.28 (0.71–2.32)	22/26	1.36 (0.67–2.77)	22/24	1.20 (0.63–2.28)
Ever regular smoking						
7–8 hours	136/142	1.00	136/142	1.00	0/0	—
≤6 hours	145/125	1.24 (0.72–2.16)	144/125	1.26 (0.87–1.82)	1/0	—
>8 hours	44/31	1.50 (0.62–3.67)	43/31	1.59 (0.91–2.79)	1/0	—
$P_{Interaction}$		0.88		0.91		
Drinking status[b]						
Never regular drinkers						
7–8 hours	163/233	1.00	36/72	1.00	127/161	1.00
≤6 hours	244/215	**1.70 (1.17–2.48)**	57/71	1.78 (0.97–3.28)	187/144	**1.59 (1.14–2.21)**
>8 hours	36/44	1.23 (0.64–2.36)	14/23	0.97 (0.41–2.29)	22/21	1.31 (0.67–2.57)
Ever regular drinkers						
7–8 hours	160/162	1.00	157/156	1.00	3/6	1.00
≤6 hours	188/143	1.33 (0.82–2.17)	181/136	1.35 (0.97 -1.89)	7/7	2.05 (0.25–16.73)
>8 hours	52/37	1.27 (0.63–2.60)	51/34	1.66 (0.99–2.79)	1/3	0.89 (0.03–26.48)
$P_{Interaction}$		0.47		0.21		0.92
BMI status						
<23 kg/m^2						
7–8 hours	191/239	1.00	114/131	1.00	77/108	1.00
≤6 hours	257/226	**1.88 (1.21–2.92)**	134/120	1.35 (0.91—2.00)	123/106	**1.67 (1.10–2.54)**
>8 hours	62/51	1.52 (0.76–3.04)	46/34	**1.81 (1.04–3.16)**	16/17	1.57 (0.72–3.43)
≥23 kg/m^2						
7–8 hours	135/158	1.0	80/98	1.00	55/60	1.00
≤6 hours	178/139	1.32 (0.74–2.37)	106/89	**1.57 (1.02–2.43)**	72/50	1.52 (0.88–2.61)
>8 hours	26/30	0.60 (0.20–1.76)	19/23	1.09 (0.53–2.24)	7/7	0.87 (0.26–2.95)
$P_{Interaction}$		0.17		0.56		0.51
Weekly physical activity						
Yes						
7–8 hours	135/177	1.00	118/129	1.00	73/90	1.00
≤6 hours	175/157	**2.05 (1.18–3.57)**	140/120	1.34 (0.92–1.96)	119/88	**1.72 (1.12–2.63)**
>8 hours	45/44	1.71 (0.80–3.67)	30/26	1.40 (0.75–2.61)	13/11	1.50 (0.60–3.73)
No						
7–8 hours	191/219	1.00	76/100	1.00	59/77	1.00
≤6 hours	259/208	**1.55 (1.01–2.39)**	100/89	**1.61 (1.02–2.54)**	75/68	1.36 (0.81–2.29)
>8 hours	43/37	1.27 (0.61–2.66)	35/31	1.64 (0.89–3.01)	10/13	1.15 (0.44–3.00)
$P_{Interaction}$		1.00		0.52		0.64
Cardiometabolic disorders[c]						
Yes						
7–8 hours	144/168	1.00	88/89	1.00	56/79	1.00
≤6 hours	221/166	1.60 (0.97–2.64)	124/87	**1.62 (1.05–2.50)**	97/79	**1.73 (1.08–2.75)**
>8 hours	29/27	1.14 (0.43–3.02)	23/16	1.42 (0.70–2.97)	6/11	0.80 (0.27–2.40)
No						
7–8 hours	182/229	1.00	106/140	1.00	76/89	1.00
≤6 hours	214/199	**1.90 (1.27–2.84)**	116/122	1.30 (0.89–1.89)	98/77	1.48 (0.95–2.30)
>8 hours	59/54	1.34 (0.77–2.36)	42/41	1.51 (0.90–2.54)	17/13	1.53 (0.68–3.43)
$P_{Interaction}$		0.57		0.81		0.71
Adenomas location[d]						
Proximal						
7–8 hours	55/74	1.00	24/29	1.00	31/45	1.00
≤6 hours	83/71	**1.93 (1.04–3.56)**	31/31	1.43 (0.60–3.45)	52/40	**2.12 (1.09–4.11)**
>8 hours	20/10	3.1 (1.17–8.18)	11/5	3.43 (0.85–13.91)	9/5	3.17 (0.89–11.36)
Distal						
7–8 hours	154/169	1.00	82/97	1.00	72/72	1.00
≤6 hours	184/165	1.33 (0.92–1.91)	104/88	1.39 (0.89–2.17)	80/77	1.02 (0.64–1.63)
>8 hours	42/39	1.26 (0.72–2.2)	34/29	1.66 (0.89–3.1)	8/10	0.85 (0.31–2.32)

(Continued on the following page)

Table 3. Association between sleep duration and CRA in this study, stratified by selected characteristics, overall, and by sex. (Cont'd)

	Overall		Male		Female	
	Cases/ controls	OR (95% CI)	Cases/ controls	OR (95% CI)	Cases/ controls	OR (95% CI)
Both sided						
7–8 hours	117/154	1.00	88/103	1.00	29/51	1.00
≤6 hours	168/129	**1.93 (1.22–3.05)**	105/90	1.54 (0.98–2.41)	63/39	**2.67 (1.37–5.21)**
>8 hours	26/32	1.17 (0.58–2.37)	20/20	1.13 (0.55–2.34)	6/9	1.27 (0.37–4.39)
$P_{Interaction}$		0.42		0.44		0.86

Note: Bold text indicates P value < 0.05.
[a]Model adjusted for: education level, marital status, drinking status, weekly physical activity, family history of cancer, and number of comorbidities.
[b]Model adjusted for: education level, marital status, smoking status, years of smoking, smoking pack-years, weekly physical activity, family history of cancer, and number of comorbidity.
[c]Model adjusted for: education level, marital status, smoking status, years of smoking, smoking pack-years, weekly physical activity, and family history of cancer.
[d]Model adjusted for: education level, marital status, smoking status, years of smoking, smoking pack-years, drinking status, weekly physical activity, family history of cancer, and number of comorbidity.
*Estimate was not obtained due to zero count.

In summary, to our knowledge, this study might be among the first ever to report the potential association between sleep duration and the CRA prevalence among Vietnamese population. This association between sleep deprivation and adenomas prevalence was more apparent in females with proximal or both sided adenomas and in females who were neverdrinker, nonobese, or physically active. Findings from our study suggested that maintaining adequate sleep habits may have implications to the colorectal cancer prevention and control program. Further studies are also warranted to replicate our results and to investigate the biologic mechanism of the effect of sleep deprivation on the development of CRAs.

Authors' Disclosures

No author disclosures were reported.

Authors' Contributions

C.T. Tran: Conceptualization, resources, data curation, formal analysis, supervision, validation, investigation, methodology, writing–original draft, project administration, writing–review and editing. **P. Paragomi:** Conceptualization, formal analysis, validation, methodology, writing–original draft, writing–review and editing. **M.T. Tran:** Data curation, software, formal analysis, investigation, project administration, writing–review and editing. **M.V. Nguyen:** Data curation, investigation, methodology, project administration, writing–review and editing. **T.T. Tuong:** Data curation, investigation, methodology, project administration, writing–review and editing. **Q.H. Tran:** Data curation, software, formal analysis, investigation, writing–review and editing. **L.C. Le:** Resources, investigation, writing–review and editing. **H.T. Pham:** Resources, validation, investigation, writing–review and editing. **H.T. Ha:** Validation, investigation, visualization, writing–review and editing. **N.C. Bui:** Resources, investigation, writing–review and editing. **H.H. Vu:** Resources, investigation, writing–review and editing. **P.Q. Ta:** Resources, investigation, writing–review and editing. **M.J. Shrubsole:** Resources, formal analysis, validation, investigation, methodology, writing–review and editing. **Q. Cai:** Resources, validation, investigation, methodology, writing–review and editing. **F. Ye:** Formal analysis, investigation, writing–review and editing. **S.H. Le:** Resources, data curation, investigation, writing–review and editing. **K.V. Vu:** Resources, data curation, investigation, writing–review and editing. **H.T. Tran:** Resources, data curation, investigation, writing–review and editing. **T.V. Tran:** Resources, data curation, investigation, writing–review and editing. **P. Boffetta:** Resources, investigation, writing–review and editing. **X. Shu:** Conceptualization, resources, formal analysis, validation, investigation, methodology, writing–review and editing. **H.N. Luu:** Conceptualization, resources, data curation, software, formal analysis, supervision, funding acquisition, validation, investigation, visualization, methodology, writing–original draft, project administration, writing–review and editing.

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Note

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