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The Association Between Sleep Disorders and the Risk of Colorectal Cancer in Patients: A Population-based Nested Case–Control Study

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Abstract. *Aim: To investigate the risk of colorectal cancer in patients with sleep disorders. Materials and Methods: We identified 7,355 participants with colorectal cancer between January 1, 2000, and December 31, 2013, from the Longitudinal Health Insurance Database 2005 of the Taiwan National Health Insurance Research Database; 29,420 controls were also identified from the same database based on frequency matching on age, sex, and index date of the cases. Diagnoses of sleep disorders by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) in the cases and controls prior to the index date were assessed. The risk of colorectal cancer in patients with sleep disorders was estimated with multivariate logistic regression analyses. Results: The mean age of the 36,775 patients was 63.05 years, and 56% of them were males. The risk of colorectal cancer was higher in patients with sleep disorders compared to those without [adjusted odds ratio (OR)=1.29, 95% confidence interval (CI)=1.13–1.47]. The risk of colorectal cancer was higher in patients having sleep disorders with depression compared to those without the condition (adjusted OR=5.69, 95% CI=4.01-6.98). Conclusion: The risk of colorectal cancer in patients with sleep disorders was found to be significantly higher by case–control study and particularly pronounced among those with sleep disorders with depression, exhibiting a joint effect on colorectal cancer risk.*

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Colorectal cancer (CRC) is the most common cancer in the adult population worldwide (1). The Ministry of Health and Welfare in Taiwan reported CRC as the most commonly diagnosed cancer. Mortality rates have increased rapidly and the age-standardized incidence rate was 34.0 per 100,000 in the year of 2002 and 43.0 in in the year of 2015 in Taiwan (2).

The risks of CRC have been extensively examined in the context of diet behavior, physical activity, and obesity (3,4). In recent decades, an increasing number of studies have provided evidence that sleep duration is correlated with the prevalence and incidence of developing CRC. Thompson *et al*. found that shorter duration of sleep significantly increases risk of colorectal adenomas (5). Another study revealed that longer sleep duration was associated with an increased risk of CRC progressing among individuals who were overweight or snored regularly (6). Lu *et al*. investigated the data from three cohort studies by a meta-analysis approach and suggested that long sleep duration increased risk of CRC, and the mechanism remains unclear (7).

Sleep is understood to play a pivotal role in human health, including the association of sleep loss with dysregulation of immune system function (8). Sleep deprivation is associated with increasing insulin resistance and decreasing insulin sensitivity (9). Previous studies have extensively investigated the association between the risk of sleep disorders and chronic diseases, such as type 2 diabetes (10), hypertension

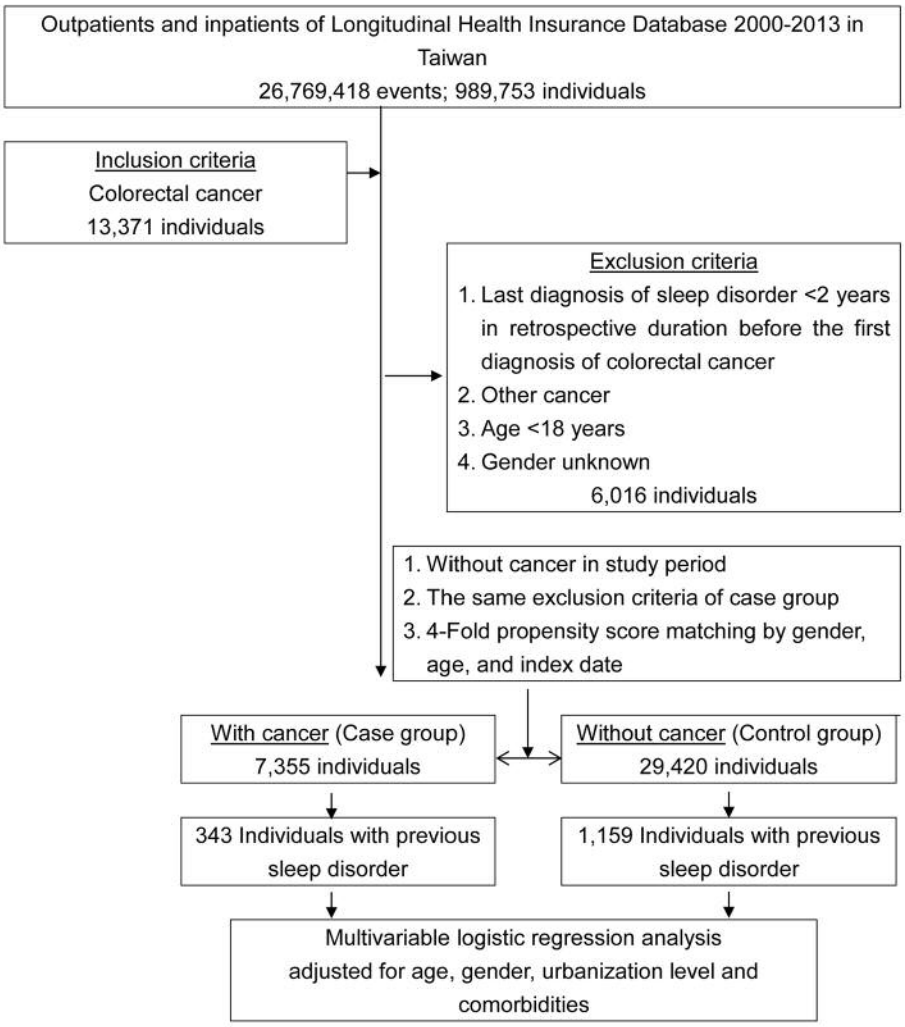

Figure 1. T*he flowchart of our study design (nested case–control study) from the National Health Insurance Research Database in Taiwan.*

(11), and coronary arterial diseases (12). Recently, emerging evidence suggests that sleep disturbances may also increase the risk of several types of cancer, such as of the breast (13), liver (14), and prostate (15). However, longitudinal observational studies surveying the associations between sleep disorders and CRC are limited. Therefore, the aim of this study was to evaluate the risk of CRC incidence among patients with sleep disorders, using a nationwide, health claims research database.

Materials and Methods

Data source. Taiwan's National Health Insurance program launched a single-payer system on March 1, 1995. As of 2017, 99.9% of Taiwan's population was enrolled. In this study, the data were collected from the Longitudinal Health Insurance Database 2005 (LHID2005), a subset of National Health Insurance Research Database 1,000,000 people among the entire population were randomly selected. National Health Research Institutes encrypted all personal identification before the release of LHID2005 to protect patient privacy. In the LHID2005 dossier, the disease diagnosis codes are based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) (16). The Ethics Review Board of Tri-Service General Hospital, National Defense Medical Center (TSGHIRB No.1-106-05-169), approved this study.

Identification of case and controls. Patients were defined as incident CRC cases if they had diagnoses of ICD9-CM codes for CRC (ICD-9 CM 153-154) in the period between 2000 and 2013. Controls were patients without CRC, frequency matched by sex, age group, and index date, with a control-to-case ratio of 4:1 (Figure 1).

Identification of sleep disorders and comorbidity. The risk factors explored in this study were sleep disorders, which were defined with the criteria of having at least three outpatient diagnoses identified

Table I. *Characteristics of study patients*.

	Total		Cases		Controls		
Variable	n	%	n	%	n	%	*p*-Value*
Total	36,775		7,355	20.00	29,420	80.00	
Gender							0.999
Male	20,675	56.22	4,135	56.22	16,540	56.22	
Female	16,100	43.78	3,220	43.78	12,880	43.78	
Age (mean±SD), years	63.05±14.52	63.07±17.04	63.05±13.82	0.916			
Age group, years							0.999
18-40	2,655	7.22	531	7.22	2,124	7.22	
45-64	11,980	32.58	2,396	32.58	9,584	32.58	
≥65	22,140	60.20	4,428	60.20	17,712	60.20	
Comorbidities							
T2DM	7,759	21.10	1,589	21.60	6,170	20.97	0.235
Hypertension	6,310	17.16	1,291	17.55	5,019	17.06	0.316
Depression	564	1.53	235	3.20	329	1.12	<0.001
Stroke	1,101	2.99	228	3.10	873	2.97	0.551
Dementia	680	1.85	127	1.73	553	1.88	0.384
CKD	586	1.59	109	1.48	477	1.62	0.434
Urbanization level							<0.001
1 (Highest)	11,456	31.15	2,725	37.05	8,731	29.68	
2	16,546	44.99	3,362	45.71	13,184	44.81	
3	2,671	7.26	360	4.89	2,311	7.86	
4 (Lowest)	6,102	16.59	908	12.35	5,194	17.65	
Sleep disorder	1,502		343	4.66	1159	3.94	<0.001

T2DM, Type 2 diabetes; CKD, chronic kidney diseases. *Chi-square/Fisher exact test on category variables and *t*-test on continuous variables.

with the ICD-9 code. These codes included 780.5 (sleep disturbance), 780.50 (sleep disturbance, unspecified), 780.52 (insomnia, unspecified), 780.51, 780.53, 780.57 (sleep apnea syndrome), 307.4 (specific disorders of sleep of nonorganic origin), 780.54 (hypersomnia, unspecified), 780.55 (disruptions of 24-h sleep–wake cycle, unspecified), 780.56 (dysfunctions associated with sleep stages or arousal from sleep), 780.58 (sleep-related movement disorder, unspecified), 780.59 (sleep disturbance, other) in the period between 2000 and 2013.

The comorbidities evaluated in this study included type 2 diabetes (ICD-9-CM 250), hypertension (ICD-9-CM 401-405), depression (ICD-9-CM 296.2–296.3, 300.4, 311), stroke (ICD-9-CM 430-438), dementia (ICD-9-CM 290, 294.1, 331.0) and chronic kidney disease (ICD-9-CM 585).

Statistical analysis. Descriptive statistics were used for characteristic information, including the percentage, mean, and standard deviation. Chi-squared and *t*-tests were used to evaluate the distributions of categorical and continuous variables between case and controls. The incidence densities of CRC were calculated according to age, sex, comorbidities, and urbanization level. Unconditional multiple logistic regression analyses were performed to evaluate the risks of CRC associated with sleep disorders with and without adjusting for age, sex, and comorbidities, respectively. Adjusted models with significant covariates were constructed through backward selection using the likelihood ratio test. Subgroup analyses were conducted with stratification by different types of sleep disorder. All analyses were performed using SPSS version 21 (IBM, Armonk, NY, USA). A *p*-value of less than 0.05 was considered significant.

Results

Demographic data. Table I shows the demographic characteristics of patients with and without CRC from 2000 to 2013. The mean age of the total 36,775 patients was 63.05±14.52 years and 56.22% of them were males. Age and sex were frequency-matched between the case and control groups to ensure no significant differences in the distributions of the two variables existed. Compared with those in the control group, the comorbidity of depression was more prevalent in the case group (Table I). Among 7,355 patients with CRC, the proportion of those with sleep disorders was 4.66% (343/7,355), while 3.94% (1,159/29,420) of the control group had a sleep disorder ($p<0.001$).

Factors of CRC using logistic regression. Table II shows participants aged 45-64 years, or ≥65 years [adjusted odds ratio (AOR)=1.51; 95% confidence interval (CI)=1.22–1.88; AOR=1.88, 95% CI=1.52-2.33, respectively] had significantly higher risk of CRC compared with those aged 18-40 years (controls). There was also a significantly higher risk of cancer for patients with comorbidities (AOR: type 2

diabetes=1.15; 95% CI=1.01-1.31; depression=3.48, 95% CI=2.51-4.82; stroke=1.21, 95% CI=1.01-1.43, chronic kidney disease=2.01, 95% CI=1.50-2.71, respectively) compared with those in the control groups.

Risk of CRC stratified by sleep disorder subgroups using logistic regression. Table III shows a 1.29-times higher risk of CRC in patients with sleep disorders compared to those in the control group (AOR=1.29, 95% CI=1.13-1.47). Multivariate logistic regression analyses revealed that in the case of CRC, those previously diagnosed with sleep apnea or insomnia had a higher risk of developing CRC (AOR=1.76, 95% CI=1.54-2.00; AOR=1.54, 95% CI=1.35-1.75). In addition, patients with sleep disorders and depression had a significantly higher risk of developing CRC compared with those without these conditions (AOR=5.69; 95% CI=4.01-6.98) (Table IV).

Table II. *Logistic regression of colorectal cancer variables.*

Variable	AOR	95% CI	95% CI	*p*-Value
Gender				
Male	1.06	0.95	1.17	0.316
Female	Reference			
Age group, years				
18-40	Reference			
45-64	1.51	1.22	1.88	<0.001
≥65	1.88	1.52	2.33	<0.001
T2DM				
Without	Reference			
With	1.15	1.01	1.31	0.030
Hypertension				
Without	Reference			
With	0.95	0.84	1.08	0.428
Depression				
Without	Reference			
With	3.48	2.51	4.82	<0.001
Stroke				
Without	Reference			
With	1.21	1.01	1.43	0.035
Dementia				
Without	Reference			
With	1.31	0.85	2.01	0.221
CKD				
Without	Reference			
With	2.01	1.50	2.71	<0.001
Urbanization level				
1 (Highest)	0.80	0.68	0.94	0.007
2	0.85	0.73	0.98	0.024
3	0.74	0.59	0.93	0.009
4 (Lowest)	Reference			

T2DM, Type 2 diabetes; HTN, hypertension; CKD, chronic kidney diseases; AOR, odds ratio adjusted for variables listed in the table, CI, confidence intervaI.

Discussion

The present study found that sleep disorders were significantly associated with a higher risk of CRC, particularly in those individuals with depression. These results suggest that sleep disorders may be a novel risk factor for CRC. Moreover, when a patient suffered both sleep disorders and depression, the risk of CRC was 5.69-times higher compared with the control group. This reflects a joint effect between sleep disorders and depression on increasing the risk of CRC. To the best of our knowledge, this is the first retrospective case–control study examining the association between sleep disorders and the risk of CRC.

Although the physiological mechanisms remain unclear of the association between sleep disorders and CRC, we inferred a potential mechanism from previous studies that may provide some insights into our observation. Some evidence supports the notion that the disruption of circadian rhythm is involved in the decreased production of melatonin and interference in the stability of clock genes, which could potentially promote the development of cancer (17-19). Previous study indicated that the mechanisms of action of circadian genes in cancer include the down-regulation of PER2 and the up-regulation of β-catenin protein levels (19), which causes proliferation of colon cancer cells and the formation of intestinal and colonic polyps. This suggests that the disruption of the peripheral intestinal circadian clock may contribute to intestinal epithelial neoplastic transformation of human CRC (20). Circadian disruption is classified as "probably carcinogenic" to humans by the International Agency for Research on Cancer (IARC) (21).

Melatonin is a natural hormone linked to DNA repair. Reiter has suggested mechanisms of cancer inhibition through melatonin (17). Previous evidence has also supported melatonin as restraining cancer growth and increasing immune function (18). Sleep disruption may affect the secretion of melatonin and is associated with decrease in the function of removing free radicals and protecting against oxidative DNA damage (20, 22).

Inadequate sleep may reduce the release of immune-stimulating hormones, such as growth hormone, prolactin, and dopamine, which may affect the natural state of the immune system (23). Impaired sleep was shown to have an effect on the performance of pro-inflammatory cytokine genes including interleukin-6 (IL6) and tumor necrosis factor-α (*TNFA*) (24). Activation of cellular and genomic markers of inflammation may also contribute to the development of CRC (25).

Sleep deprivation increases the sensitivity to dextran sodium sulfate (DSS) shown to induce colitis in animal studies (26). An epidemiological study also indicated that sleep of less than 6 hours or a more than 9 hours per day is associated with an increased risk of ulcerative colitis (27). The association between ulcerative colitis and CRC is also

Table III. *Factors of colorectal cancer stratified by sleep disorder subgroups using logistic regression.*

	With sleep disorder			Without sleep disorder			With *vs*. without			
Subgroup	Exposure	Person-years	Rate*	Exposure	Person-years	Rate*	Ratio	AOR	95% CI	*p*-Value
Total	343	20,208.18	16.97	1,159	165,801.05	6.99	2.43	1.29	1.13-1.47	<0.001
Sleep apnea	27	20,208.18	1.34	67	165,801.05	0.40	3.35	1.76	1.54-2.00	<0.001
Insomnia	233	20,208.18	11.53	660	165,801.05	3.98	2.90	1.54	1.35-1.75	<0.001
Other	109	20,208.18	5.39	468	165,801.05	2.82	1.91	1.02	0.89-1.16	0.183

AOR, Odds ratio adjusted for the variables listed in Table II; CI, confidence interval. ICD-9-CM code: Sleep apnea: 780.51, 780.53, and 780.57; insomnia: 780.52; other: 307.4, 780.50, 780.54-780.56, and 780.59. *Per 10^3 person-years.

acknowledged by Yashiro *et al*. (28). The abovementioned pathophysiological factors may explain the association between sleep disorders and CRC shown in this study.

This study found a higher risk of CRC compared to the reference group in two subgroups of patients with sleep disorder, sleep apnea and insomnia. A previous study demonstrated a heightened risk for cancer development in individuals suffering from insomnia, parasomnia or obstructive sleep apnea (15). Another study showed that a short sleep duration is associated with a higher risk of CRC development (5, 6). Moreover, a longer sleep duration (≥9 hours/per night) is also associated with an increased risk for developing CRC among individuals who snored or overweight (6). Zhang *et al*. raises the possibility that obstructive sleep apnea and intermittent hypoxemia may contribute to cancer risk (6). Furthermore, intermittent hypoxia and sleep fragmentation caused by obstructive sleep apnea was associated with a poorer prognosis or higher incidence of cancer (29). Further studies are required to investigate sleep problems as a modifiable risk factor in the context of the progression of CRC.

Our findings revealed that the risk for CRC in patients with both sleep disorder and depression was significantly higher (5.69-fold) than for patients without these conditions (sleep disorders 1.29-fold, depression 3.48-fold). Therefore, the joint effect of sleep disorder and depression is in need of attention. To our knowledge, this is the first longitudinal population-based study on the risk of CRC associated with sleep disorders combined with depression. Determining the mechanism explaining the observed association was not the aim of this study. Prior evidence supported a bidirectional association between sleep disorders and depression (30). Depression is suggested to suppress the immune system causing an elevation of IL6 (31) and an increased concentration of C-reactive protein (32), each of which has been associated with an increased risk of CRC (32, 33). On the contrary, the Nurses' Health Study indicated depressive symptoms were unrelated to the risk of colorectal adenomas (34). We understand that factors involving CRC are complex combinations of risks and interactions among multiple variables, further suggesting that the confirmed associations were independent of these possible pathways. It is important for further studies to clarify the direct or indirect effects of sleep disorders and depression on the relationship to CRC.

Table IV. *Colorectal cancer risk stratified by sleep disorders and depression using logistic regression.*

Sleep disorder	Depression	AOR	95% CI	*p*-Value
Without	Without	Reference (1.00)		
With	Without	1.29	1.13-1.47	<0.001
Without	With	3.48	2.50-4.83	<0.001
With	With	5.69	4.01-6.98	<0.001

AOR, Odds ratio adjusted for the variables listed in Table II; CI, confidence interval. Joint effect (interaction term): colorectal cancer × depression, $p<0.001$.

There are several potential limitations of the present study. Firstly, the National Health Insurance Research Database does not provide detailed information, such as physical activity, alcohol consumption, tobacco use and diet behaviors, which may have resulted in residual confounding. Secondly, body mass index and obesity were not variables included in our study. It is crucial to note that a previous study reported obesity having a direct and independent relationship with CRC, suggesting an association between obesity and CRC (4). We suggest that future studies should consider investigating the effect of obesity, and sleep disorders on CRC. Thirdly, despite the meticulous design of this study and its control of confounding factors, biases might remain from possibly unmeasured or unknown confounding factors, such as the onset of depression, stage of CRC at diagnosis and medication that might have influenced the results. A prospective cohort study is suggested in order to evaluate the relationship between sleep disorders and CRC.

Conclusion

The present study revealed that sleep disorders are associated with an increased prevalence of CRC. Both sleep disorders and depression of patients have a synergistic effect on CRC, compared to the reference group. Sleep disorder might be a new risk factor for the development of CRC. Healthcare providers should, perhaps, pay more attention to the association between chronic sleep problems and the risk of developing CRC.

Conflicts of Interests

This study was performed without financial support and there are no conflicts of interest to declare.

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