Original Article

Insomnia Increased the Risk of Colorectal Cancer

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Key Words
Insomnia;
Colorectal cancer;
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Purpose. Insomnia is a common sleep disorder that affects 25% of Taiwanese adults. However, the association between insomnia and colorectal cancer (CRC) is still unclear. This study examined the risk of CRC among patients with insomnia and analyzed CRC risk based on the duration of follow-up for insomnia.
Methods. We identified 54,578 individuals newly diagnosed with insomnia and randomly selected 163,734 age- and sex-matched subjects without insomnia between 2000 and 2006 from Taiwan's National Health Insurance Research Database (NHIRD). The Kaplan-Meier method was used for calculating the cumulative incidence of CRC in each cohort. Cox proportional hazard regression models were used to estimate hazard ratios (HRs) and the accompanying 95% confidence intervals (CIs) for the association between insomnia and CRC.
Results. The insomnia group showed a significantly higher incidence rate of CRC compared to the control group, with rates of 18.52 and 12.21 per 10,000 person-years, respectively. The relative risk of developing CRC in the insomnia group was 1.53 times higher than that in the non-insomnia group (adjusted HR, 1.53; 95% CI, 1.41 to 1.66). Each annual visit for insomnia-related issues was associated with a 39-65% increase in the risk of colorectal cancer compared to the control group.
Conclusions. The findings of this cohort study, based on a population, provide evidence of an association between insomnia and an elevated risk of CRC. Further large-scale prospective studies are needed to confirm our results.

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Insomnia is a common sleep disorder that affects 25% of Taiwanese adults.[1] Persistent insomnia is associated with mortality,[2] and a growing body of evidence suggests that it is correlated with the prevalence of chronic diseases, such as hypertension[3] and hypercholesterolemia.[4] However, the association between insomnia and CRC has yielded inconsistent results in previous studies.[5-8] Further investigation is needed to address this public health concern. Compared with those in Western countries, fewer studies in Taiwan have explored the relationship between insomnia and the risk of CRC. Therefore, this study utilized data

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from Taiwan's NHIRD to examine the risk of CRC among patients with insomnia and analyzed CRC risk based on the duration of follow-up for insomnia.

Material and Methods

Data sources

The NHIRD of Taiwan was created in 1995, alongside the implementation of a comprehensive universal healthcare system. The NHIRD encompasses the medical records of the entire population of Taiwan, totaling 23.74 million individuals, with an impressive coverage rate of 99.6% as of 2009. For this study, pertinent data were gathered from the NHIRD, and a sample of 1,000,000 participants was randomly selected from the entire population. The NHIRD contains disease diagnosis codes that adhere to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

Study population

Using data obtained from the Longitudinal Health Insurance Database (LHID) 2000, we conducted a cohort study on a population-based sample of patients aged > 20 years who had been diagnosed with unspecified insomnia (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] codes 780.52) and specific non-organic sleep disorders (ICD-9-CM codes 307.4). The study period was from January 1, 2000, to December 31, 2006. The date of enrollment was determined as the date of initial diagnosis of insomnia. To ensure the study's focus, we excluded patients who had been diagnosed with cancer (ICD-9-CM codes 140-210) before enrollment, resulting in the exclusion of 5615 patients. Additionally, patients who visited fewer than three outpatient departments were excluded. All participants were followed up until the occurrence of the first diagnosis of CRC (ICD-9-CM codes 153 and 154), death, withdrawal from health insurance, or December 31, 2013, whichever event occurred earlier (Fig. 1).

Outcome

The two groups were followed from the beginning of the study to the onset of insomnia, and the endpoints of this study was the diagnosis of CRC, withdrawal from the LHID, or December 31, 2013. The diagnostic codes for CRC were the ICD-9-CM codes 153 and 154.

Definitions of the other variables

Age, sex, comorbidities, and urbanization levels were included in the analysis. Age was divided into 5 groups, with 10-year intervals. The comorbidities considered were hypertension, diabetes mellitus (DM), hyperlipidemia, coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), liver cirrhosis, and chronic hepatitis. Patients with any of these comorbidities were classified as having comorbidities.[9]

Statistical analysis

All analyses were performed using the SPSS software package (version 21; SPSS Inc., Chicago, Illinois, USA). Descriptive statistics, such as percentages, average values, and standard deviations, were reported. The differences in the distribution of age, gender, and comorbidities between the groups with and without insomnia were compared using the chi-squared test for categorical variables and t-test for continuous variables. Furthermore, we quantified the effects of age, sex, and comorbidities on CRC incidence rates per person-year in both groups. A Cox proportional hazards regression model was used to assess the influence of insomnia on CRC risk. The hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. The CRC-free risk difference between the two groups was estimated using the Kaplan-Meier method with log-rank test. Statistical significance was set at $p < 0.05$.

Results

A total of 54,578 newly diagnosed cases of insom-

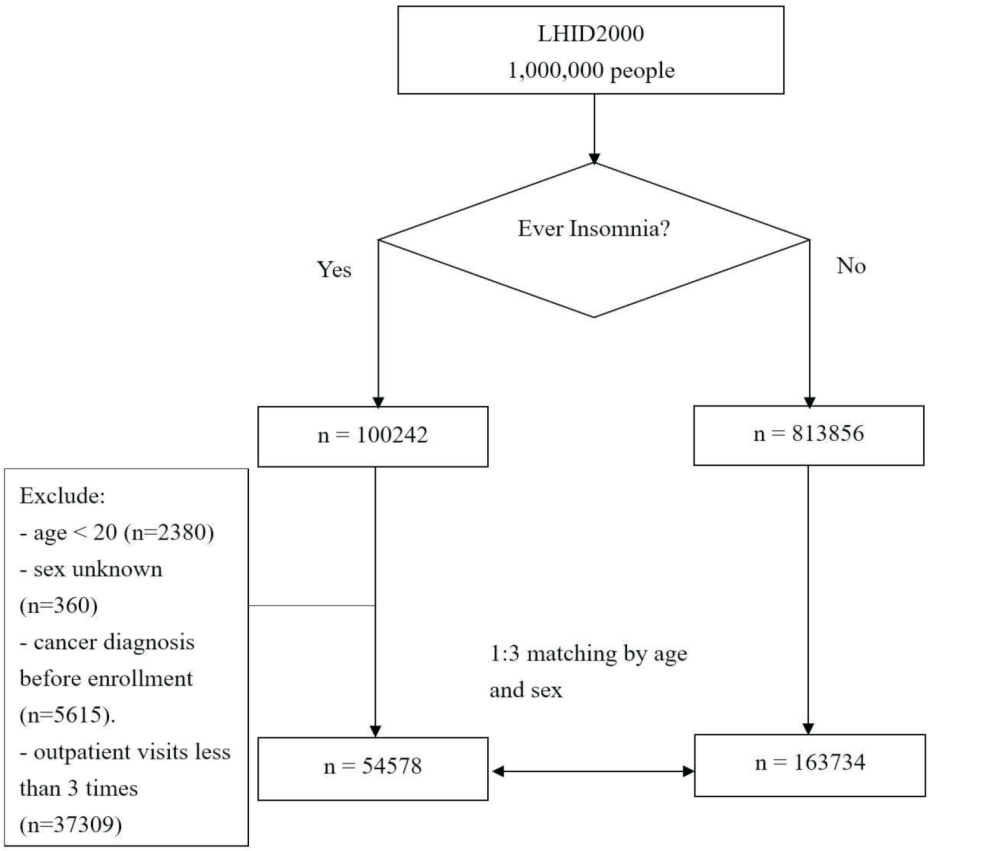

Fig. 1. A flowchart of the present study.

nia were identified, and 163,734 participants without insomnia were included in the comparison group. The subjects in both groups were followed up until the conclusion of the study, which was on December 31, 2013. Both groups consisted of a higher proportion of women than men and predominantly included individuals aged 60 years and above. In the population analysis of the insomnia and control groups, a higher number of individuals with comorbidities, such as hypertension, DM, hyperlipidemia, CAD, COPD, liver cirrhosis, and chronic hepatitis, were found in the insomnia group than in the control group. These differences were significant (Table 1).

To evaluate the cumulative incidence, we employed the Kaplan-Meier survival analysis. The insomnia cohort exhibited a higher risk of developing incident colorectal cancer (CRC) than the control cohort. The log-rank test revealed a significant difference over the entire Kaplan-Meier curve (log-rank test; $p < .001$; Fig. 2). The longer the follow-up period, the greater the difference between the two cohorts.

Throughout the follow-up period, the incidence rate of CRC was significantly higher in the insomnia group than in the non-insomnia group (18.52 vs. 12.21 per 10,000 person-years). The relative risk of developing CRC in the insomnia group was 1.53 times higher than that in the non-insomnia group (adjusted hazard ratio [HR], 1.53; 95% CI, 1.41 to 1.66; Table 2).

When the subjects were divided into five age groups, the CRC risks of the groups with insomnia were significantly higher than those of the groups without insomnia (adjusted HRs of the five groups were 1.65 [95% CI, 0.73-3.75], 2.1 [95% CI, 1.43-3.1], 1.53 [95% CI, 1.22-1.92], 1.47 [95% CI, 1.24-1.74], and 1.52 [95% CI, 1.37-1.68], respectively). Both men and women showed a significantly higher risk of CRC in the insomnia group than in the non-insomnia

Table 1. Comparison of baseline demographic status and comorbidity in insomnia and control groups

Variable	Comparison cohort N = 163374 (%)	Insomnia cohort N = 54578 (%)	*p*-value
Age, years (SD)*	52.93 (17.5)	52.92 (16.0)	0.990
20-30	13245 (8.09)	4415 (8.09)	1.000
30-40	24966 (15.25)	8322 (15.25)	
40-50	36297 (22.17)	12099 (22.17)	
50-60	32394 (19.78)	10798 (19.78)	
≥ 60	56832 (34.71)	18944 (34.71)	
Sex			1.000
Female	103395 (63.15)	34465 (63.15)	
Male	60339 (36.85)	20113 (36.85)	
Comorbidity			
Hypertension	48474 (29.61)	27553 (50.48)	< 0.001
DM	23412 (14.30)	12432 (22.78)	< 0.001
Hyperlipidemia	16688 (10.19)	11366 (20.83)	< 0.001
CAD	17150 (10.47)	13498 (24.73)	< 0.001
COPD	29814 (18.21)	19408 (35.56)	< 0.001
Liver cirrhosis & chronic hepatitis	17378 (10.61)	12100 (22.17)	< 0.001

* t-test.

Abbreviation: CRC, colorectal cancer; DM, diabetes mellitus; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease.

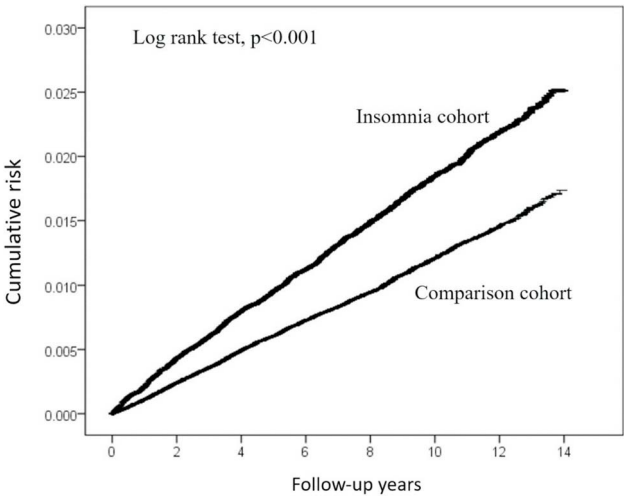

Fig. 2. Kaplan-Meier curve of colorectal cancer in the comparison cohort and the insomnia cohort.

group (adjusted HRs were 1.59 [95% CI, 1.41-1.8] in men and 1.48 [95% CI 1.33-1.65] in women, respectively). The insomnia group had a significantly higher risk of CRC than the non-insomnia group, regardless of the presence of comorbidities, such as hypertension, DM, hyperlipidemia, CAD, COPD, liver cirrhosis, and chronic hepatitis (Table 2).

Furthermore, the risk of CRC increased with the frequency of clinical visits per year due to insomnia (Table 3). Our results indicated that this risk tended to increase with the frequency of clinical visits. When the clinical visit was < 5, 5 to 9, 10 to 23 and > 23 times per year, the risk of CRC increased by 39%, 48%, 58%, and 65% respectively, compared with the comparison group. These results demonstrated that the risk of CRC was with insomnia in a longitudinal observation study.

Discussion

Quality sleep is vital for optimal human functioning and various physiological and behavioral processes. The disruption of these intricate mechanisms can lead to a range of symptoms associated with inadequate sleep, either individually or in combination. Sleep disorders have been linked to impaired healing, an increased risk of cancer recurrence, compromised cognitive abilities, decreased work productivity, drug or medication abuse, strained relationships, and elevated healthcare costs.[10]

Previous studies have established a connection

Table 2. Incidence rates and adjusted HR of CRC by age, gender, urbanization level, and comorbidities

Variable	Comparison cohort			Insomnia cohort			HR (95% CI)	Adjusted HR (95% CI)
	Event	PYs	Rate	Event	PYs	Rate		
Total	2014	1649199	12.21	1058	571137	18.52	1.52 (1.41-1.64)	1.53 (1.41-1.66)
Demographic								
Age group								
20-30	16	139779	1.14	10	45615	2.19	1.92 (0.87-4.24)	1.65 (0.73-3.75)
30-40	69	260530	2.65	51	87934	5.8	2.18 (1.52-3.13)	2.10 (1.43-3.10)
40-50	252	374052	6.74	129	129187	9.99	1.47 (1.19-1.81)	1.53 (1.22-1.92)
50-60	459	325460	14.1	222	113565	19.55	1.37 (1.17-1.61)	1.47 (1.24-1.74)
≥ 60	1218	549378	22.17	646	194835	33.16	1.51 (1.38-1.66)	1.52 (1.37-1.68)
Sex								
Female	1096	1047677	10.46	571	365537	15.62	1.49 (1.35-1.65)	1.48 (1.33-1.65)
Male	918	601521	15.26	487	205599	23.69	1.55 (1.39-1.73)	1.59 (1.41-1.80)
Comorbidity								
Hypertension								
No	1163	1162466	10	444	278891	15.92	1.60 (1.43-1.78)	1.85 (1.65-2.08)
Yes	851	486733	17.48	614	292245	21.01	1.19 (1.07-1.32)	1.28 (1.15-1.42)
Diabetes								
No	1598	1415891	11.29	799	439568	18.18	1.62 (1.48-1.76)	1.64 (1.50-1.80)
Yes	416	233308	17.83	259	131569	19.69	1.09 (0.98-1.28)	1.20 (1.02-1.41)
Hyperlipidemia								
No	1779	1477755	12.04	848	449290	18.87	1.57 (1.45-1.71)	1.58 (1.45-1.72)
Yes	235	171444	13.71	210	121847	17.23	1.24 (1.03-1.50)	1.31 (1.08-1.59)
CAD								
No	1709	1479272	11.55	714	427624	16.7	1.45 (1.33-1.58)	1.55 (1.41-1.70)
Yes	305	169927	17.95	344	143513	23.97	1.33 (1.14-1.55)	1.45 (1.24-1.70)
COPD								
No	1542	1352575	11.4	638	366392	17.41	1.53 (1.40-1.68)	1.63 (1.48-1.80)
Yea	472	296624	15.91	420	204745	20.51	1.25 (1.13-1.46)	1.34 (1.17-1.53)
Liver cirrhosis & chronic hepatitis								
No	1772	1473631	12.02	828	442885	18.7	1.56 (1.43-1.69)	1.55 (1.42-1.69)
Yes	242	175568	13.78	230	128252	17.93	1.30 (1.08-1.55)	1.42 (1.18-1.71)

Model adjusted for age, sex, low income, hypertension, DM, hyperlipidemia, CAD, COPD, and liver cirrhosis & chronic hepatitis.
Abbreviation: CRC, colorectal cancer; DM, diabetes mellitus; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; PYs, person-years; rate, incidence rate, per 10,000 person-years; CI, confidence interval; HR, hazard ratio.

Table 3. Incidence rates of CRC and multivariable Cox proportional hazards analysis for the association between insomnia and the risk of CRC according to the frequency of clinical visits

Frequency of insomnia visits	Event	PYs	Rate	Crude HR (95% CI)	Adjusted HR (95% CI)
Comparison cohort	2014	1649199	12.21	ref	ref
< 5	232	146167	15.87	1.30 (1.14-1.49)	1.39 (1.21-1.60)
5-9	245	143565	17.07	1.40 (1.23-1.60)	1.48 (1.29-1.70)
10-23	262	134502	19.48	1.60 (1.40-1.82)	1.58 (1.39-1.81)
> 23	319	146902	21.72	1.78 (1.58-2.00)	1.65 (1.46-1.87)
p for trend				< 0.0001	< 0.0001

Model adjusted for age, sex, low income, hypertension, DM, hyperlipidemia, CAD, COPD, and liver cirrhosis & chronic hepatitis.
Abbreviation: CRC, colorectal cancer; DM, diabetes mellitus; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; PYs, person-years; rate, incidence rate, per 10,000 person-years.

between insomnia, the most prevalent sleep disorder, and an increased risk of CRC. Our study found similar results.[11,12] One possible explanation for this association is the frequent co-occurrence of insomnia with mood disorders, pain, and fatigue, which collectively activate a complex pathogenetic mechanism.[13] This mechanism involves hormonal systems, various neurotransmitters, immune functions, excessive cytokine responses, interleukins, and tumor necrosis factor-alpha (TNF-α). These factors disrupt the normal functioning of the hypothalamic-pituitary-adrenal (HPA) axis, which regulates the physiological changes relevant to the development of cancer.[14]

The findings of the current study regarding the correlation between specific sleep factors and CRC are consistent with those of previous studies. Mirghani et al. conducted a comprehensive review of 12 studies and observed associations between CRC and both inadequate sleep duration (< 7 hours) and excessive sleep duration (> 9 hours).[15] Similarly, Chen et al. obtained comparable results, indicating that individuals who slept for 7-8 hours per day were at a 9% lower risk of CRC than those with longer or shorter sleep durations.[6]

In the current study, the risk of CRC showed a consistent upward trend with the duration of insomnia during the follow-up period. This finding is consistent with those of previous studies, which indicate that insufficient sleep may contribute to the onset of various chronic illnesses.[16] Among individuals with chronic insomnia, heightened activity in the HPA axis and sympathetic system response has been observed, resulting in elevated levels of plasma cortisol.[17]

In the present study, after accounting for potential confounding factors, such as age, sex, and comorbidities, we found that patients with insomnia were at 53% higher risk of CRC compared to the comparison cohort. This finding is consistent with those of previous studies. Furthermore, our results revealed that the risk of CRC tended to frequency of clinical visits due to insomnia was categorized as < 5, 5-9, 10-23, and > 23 times per year, the risk of CRC increased by 39%, 48%, 58%, and 65%, respectively. The findings of this longitudinal observational study provide evidence of an association between insomnia and an elevated risk of CRC.

The present study has several limitations that should be acknowledged. First of all, due to the nature of the NHIRD database, certain important variables, such as laboratory data, physical status, functional capacity, alcohol use, and psychological status, were not included in our analysis. Taiwan's medical claims database lacks important confounders, such as obesity, smoking habits, and physical activity, which are necessary to assess the association between insomnia and CRC risk. As a substitute, we used obesity-related diseases (such as hypertension, DM, hyperlipidemia, and CAD) and smoking-related diseases (such as COPD) as proxy variables for obesity and smoking status. These substitute variables were included in the multivariate regression models to account for the confounding effects of obesity and smoking. Secondly, sleep duration, sleep apnea, and depression were not considered as variables in our study, despite previous research indicating their potential association with CRC. Future studies should explore the impact of sleep duration, obstructive sleep apnea, and the occurrence of depressive episodes on CRC development. Furthermore, patients with insomnia often take hypnotic medications, but these medications were not included in the subgroup analyzed in this study. Commonly used drugs such as benzodiazepine[18,19] and tricyclic antidepressants[20-22] have been studied for their potential impact on the risk of colorectal cancer, but there is currently no consensus on this matter. Finally, the presence of unmeasured or unknown factors, such as the onset of depression, stage of CRC at diagnosis may have introduced biases that affected the results. A prospective cohort study would be beneficial to validate the relationship between sleep disorders and CRC.

Conclusion

Insomnia may play a vital role in onset of CRC, particularly in people aged between 20 and 40-years old, who are more prone to developing CRC. In other words, sleep disorders should be considered risk factors for CRC. More attention should be paid to the association between chronic sleep disorders and the risk of developing CRC.

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This study was approved by the Institutional Review Board of Fu-Jen Catholic University (FJU-IRB No: C104014).

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原　著

失眠增加罹患大腸直腸癌之風險

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目的　失眠是一種常見的睡眠疾患，佔臺灣成年人中的 25%。然而當前對於失眠與結直腸癌之間的關聯仍不清楚。本研究目的為討論失眠患者患結直腸癌的相關風險及可能原因。

方法　本研究從臺灣國民健康保險研究資料庫於 2000 年至 2006 年間，選取了 54,578 名新診斷的失眠患者，並隨機選擇了 163,734 名符合年齡及性別條件的非失眠受試者作為對照組。採用 Kaplan-Meier 方法計算了結直腸癌的累積發生率。並使用 Cox 風險回歸模型推估失眠與結直腸癌之間的風險比及其伴隨的 95% 信賴區間。

結果　失眠組與對照組相比，結直腸癌的發病率顯著較高，分別為 18.52 和 12.21 (每 10,000 人/年)。失眠組患結直腸癌的相對風險比非失眠組高 1.53 倍 (95% 信賴區間為 1.41 至 1.66)。與對照組相比，每年因失眠問題就醫之次數與結直腸癌風險增加呈正相關，高約 39-65%。

結論　本研究結果顯示失眠會導致罹患結直腸癌之風險增加，但仍須更完善且大型的前瞻性研究來佐證我們的成果。

關鍵詞　失眠、結直腸癌、臺灣國民健康保險研究資料庫。