Increased incidence of colorectal cancer with obstructive sleep apnea: A nationwide population-based cohort study

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ARTICLE INFO

Article history:

Received

Received in revised form

Accepted

Published online

Keywords:

Cohort study

Colorectal cancer

National Health Insurance Research Database

Obstructive sleep apnea

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ABSTRACT

Background: Epidemiological studies on the obstructive sleep apnea (OSA) and cancer relationship in humans are inconsistent. Furthermore, there are limited prospective studies on the association between OSA and the risk of colorectal cancer (CRC). This retrospective cohort study examined the longitudinal relationship between OSA and CRC in a nationwide population-based cohort.

Methods: We identified 4180 individuals newly diagnosed with OSA (the exposed cohort) and randomly selected 16,720 age- and sex-matched subjects without OSA (the nonexposed cohort) between 2000 and 2008 from Taiwan's National Health Insurance Research Database. 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 OSA and CRC.

Results: After adjusting for potential confounders, patients with OSA were associated with a significantly higher risk of CRC than those without OSA (adjusted HR, 1.80; 95% CI, 1.28–2.52). The cumulative incidence of CRC was significantly higher in the OSA cohort than in the comparison cohort (log-rank test, $p < 0.001$). Furthermore, the association between OSA and CRC appeared to be enhanced with increasing frequency of OSA medical visits (adjusted HR [95% CI] was 1.61 [0.97–2.66] and 1.86 [1.26–2.75] for one visit and two or more visits, respectively).

Conclusion: This population-based cohort study demonstrated that OSA was associated with an increased risk of CRC. Further large-scale prospective studies are needed to confirm our results.

1. Introduction

Obstructive sleep apnea (OSA) is the most common type of breathing-related sleep disorder, characterized by recurrent episodes of upper airway collapse during sleep. The prevalence of OSA defined at an apnea–hypopnea index (AHI) ≥5 was a mean of 22% (range, 9–37%) in men and 17% (range, 4-50%) in women in 11 epidemiological studies published between 1993 and 2013 [1–3]. It is well-known that OSA is an independent risk factor for cardiovascular disease, cerebrovascular disease, and metabolic diseases [4–8]. However, studies on the OSA and cancer relationship in humans are inconsistent. A number of epidemiological studies showed that overall cancer incidence rates are higher among individuals with versus those without sleep apnea [9–15], whereas two more recent studies showed no elevated risk [16,17]. Additional studies have found a relationship between sleep apnea and increased cancer mortality [18,19]. Furthermore, it is still unknown whether this association was limited to specific cancer sites or was applicable to all types of cancers. It is possible that different types of malignant cells have different adaptive responses to intermittent hypoxia and sleep fragmentation; thus, OSA may be a risk factor for poorer prognosis or higher cancer incidence in only some types of tumors.

Colorectal cancer (CRC) is a major cause of morbidity and mortality throughout the world. It accounts for over 9% of all cancer incidence [20,21]. It is the third most common cancer worldwide and the fourth most common cause of death [20]. Globally, epidemiological evidence suggests that OSA is associated with higher cancer incidence and mortality [9–15,18,19]. However, epidemiological study results on the OSA and CRC relationship in humans are mixed. Some studies showed that the risk

of CRC was positively associated with OSA [14,22,23], whereas other studies indicated an inverse association between OSA and CRC [13]. Indeed, there are limited prospective studies on the association between OSA and the risk of CRC. Accordingly, it is interesting to explore the longitudinal relationship between OSA and the risk of CRC. To examine this hypothesis, we took advantage of Taiwan's National Health Insurance Research Database (NHIRD) to evaluate the longitudinal relationship between OSA and CRC.

2. Methods

2.1. Data source

The present study was a retrospective cohort study using claims data from the NHIRD in Taiwan. The NHIRD is a large database provided by a single-payer, universal, compulsory health care system for nearly all 23.7 million residents and enrolls approximately 99% of the population of Taiwan. The NHIRD contains comprehensive health care information, including demographic data of insured individuals, data of clinical visits, diagnostic codes, and prescription details. The NHIRD has been used for high-quality epidemiological studies [24,25] and has shown good validity [26,27]. The data of this study was obtained from the Longitudinal Health Insurance Database (LHID 2000), a subset of the NHIRD. The LHID 2000 dataset contains historical ambulatory and inpatient care data for 1 million randomly sampled beneficiaries enrolled in the NHI system in 2000. The LHID 2000 database allows researchers to approach the medical service use history of these patients. There were no significant differences in the distributions of age, sex, and healthcare costs between the individuals in the LHID and NHIRD.

The present study has been approved by the Institutional Review Board of Fu-Jen Catholic University (FJU-IRB NO: C104014).

2.2. Study cohorts

The selection of study subjects is shown in Fig. 1. We conducted a nationwide retrospective cohort study based on patients ≥20 years old with a diagnosis of OSA by retrieving all patients from January 1, 2000, to December 31, 2008, in the NHIRD.

Subjects with OSA were identified from the database using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 327.23 (central sleep apnea), 780.51 (insomnia with sleep apnea), 780.53 (hypersomnia with sleep apnea), and 780.57 (unspecified sleep apnea). These codes have been used and reported in previous epidemiological studies [28–30]. Patients with OSA diagnosed before 2000 were excluded to prevent overestimation of the risk of incident events. To create a non-OSA cohort, we randomly selected patients without a history of OSA. We designated the index date as the date of OSA diagnosis for the subjects with OSA (the exposed group) and the matched date of physician visits for subjects without OSA (the nonexposed group). In addition, we defined the time from 2000 to 2002 as the exposure period to determine the OSA status for each subject.

For improved accuracy and comparability of data, we followed these steps for quality control: subjects who were <20 years (exposed group, n = 470; nonexposed group, n =36,158) and of unknown sex (exposed group, n = 9; nonexposed group, n = 379) were excluded. Before the beginning of follow-up (January 1, 2000), subjects who had been diagnosed with cancer (with ICD-9-CM codes from 140 to 240; exposed group, n = 2,349; nonexposed group, n = 169,720) were also excluded. To mitigate potential selection bias, we matched our subjects 1:4 by age and sex. Overall, our study sample included 4180 subjects with OSA (the exposed group) and 16,720 subjects without OSA (the nonexposed group).

2.3. Outcome

The outcome of interest was incident CRC (ICD-9-CM codes 153, 153.0, 153.1, 153.2, 153.3, 153.6, 153.7, 153.8, 153.9, 154, 154.0, 154.1, 154.2, 154.3, 154.8, and 159.0). The length of follow-up for people who developed incident CRC was the period from the index date to the date of first diagnosis of CRC in inpatient or outpatient records. The censored time of people who did not have CRC was the period from the index date to either December 31, 2013, or the date of withdrawal from the National Health Insurance. To enhance the accuracy of outcomes, we also used the Catastrophic Illness Dataset to confirm the diagnosis of CRC. In Taiwan, to receive a certificate of catastrophic illness, a cancer patient must hold an official certificate of diagnosis issued by a hospital with confirmation by laboratory results, histology, and/or diagnostic imaging. Therefore, the Catastrophic Illness Dataset is a complete and accurate data source to track the development of CRC among study subjects.

2.4. Covariates

In order to control for confounding factors, we identified covariates from the NHIRD, including age, sex, and chronic diseases that have been reported to have associations with risk of CRC [18]. The chronic diseases under consideration included chronic obstructive pulmonary disease (ICD-9-CM codes 490, 491, 492, 493, 494, 495, and 496), diabetes mellitus (ICD-9-CM code 250), coronary artery disease (ICD-9-CM codes 410, 411, 412, 413, and 414), hypertension (ICD-9-CM codes 401, 402, 403, 404, and 405), alcohol-related conditions (ICD-9-CM codes 571.0, 571.1, 571.2, and 571.3 for alcoholic liver disease, and 303 for alcohol dependence), hypercholesterolemia (ICD-9-CM codes 272.0, 272.1, 272.2, and 272.4), peptic ulcer

(ICD-9-CM codes 531, 532, and 533), liver cirrhosis and chronic hepatitis (ICD-9-CM code 571), and inflammatory bowel disease (ICD-9-CM codes 555 and 556). Nevertheless, epidemiologic data have consistently reported a positive association among obesity, smoking and CRC [31,32]. Unfortunately, data on obesity and cigarette smoking were not available from the NHIRD. Nevertheless, obesity-related diseases (ICD-9-CM code 250, diabetes mellitus; ICD-9-CM codes 401, 402, 403, 404, and 405, hypertension; ICD-9-CM codes 272.0, 272.1, 272.2, and 272.4, hypercholesterolemia; and ICD-9-CM codes 410, 411, 412, 413, and 414, coronary artery disease) and smoking-related diseases (ICD-9-CM codes 490, 491, 492, 493, 494, 495, and 496, chronic obstructive pulmonary disease) were used as substitute variables of obesity and smoking and were treated as potential confounders in multivariable Cox proportional hazard regression models. In addition, patients with cystic fibrosis (ICD-9-CM code 277.0), acromegaly (ICD-9-CM code 253.0), and prostate cancer (ICD-9-CM code 185) under long-term androgen deprivation therapy would be at an elevated risk for CRC [20]. Therefore, these disease diagnosis codes were also included in multivariable Cox proportional hazard regression models.

2.5. Statistical analysis

We examined the differences between the exposed and nonexposed cohorts in categorical or continuous descriptive statistics using the χ^2 test and analysis of variance when appropriate. The Kaplan–Meier method was used for survival analysis to estimate the cumulative incidence of CRC in the study cohorts, and the log-rank test was performed to compare the risk of incident CRC between the OSA and non-

OSA cohorts. In addition, we used Cox proportional hazard regression models to compute the hazard ratios (HRs) and accompanying 95% confidence intervals (CIs) after adjustment for potential confounders. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, NC). A p value of < 0.05 and a CI not containing 1 were considered statistically significant in 2-tailed tests.

3. Results

The characteristics of study cohorts and potential confounders are shown in Table 1. Of the data identified from January 1, 2000 to December 31, 2008, we included 4180 patients as the OSA cohort and 16,720 matched nonexposed cohort. The study population was predominantly Han Chinese. As we had matched the study subjects, the age and sex distributions were comparable between the cohorts. The mean age for the OSA and non-OSA cohorts was 45.97 and 45.64 years, respectively. The percentage of male subjects in these 2 cohorts was 80%. Compared with the non-OSA cohort, subjects with OSA had a significantly higher proportion of comorbidities, including hypertension, diabetes mellitus, hypercholesterolemia, coronary artery disease, peptic ulcer, liver cirrhosis and chronic hepatitis, stroke, chronic obstructive pulmonary disease, and inflammatory bowel disease ($p < 0.0001$).

As demonstrated in Table 2, there were 53 and 132 incident CRC in the OSA and non-OSA cohorts during the follow-up period of 35,445.12 and 155,244.15 person-years, respectively. The OSA cohort had a significantly higher incidence of CRC than the non-OSA cohort (14.95 vs 8.5 per 10,000 person-years). The Kaplan–Meier

curves of cumulative incidence for the OSA cohort and the comparison cohort are illustrated in Fig. 2. The OSA cohort had a higher risk of incident CRC than the comparison cohort, and the log-rank test revealed a significant difference over the entire Kaplan–Meier curve. The longer the follow-up, the greater the difference between these 2 cohorts. As shown in Table 2, there was a significant positive association between OSA and the risk of CRC after adjustment for potential confounders (adjusted HR, 1.80; 95% CI, 1.28–2.52). An examination of the association among subgroups showed that an increase in the risk of CRC associated with OSA was consistently present in both men and women and in all age groups.

Furthermore, we performed an analysis of the risk of CRC associated with the frequency of OSA clinical visits. We divided the frequency of OSA visits into two categories: one visit and two or more visits. The HR for the association between the risk of CRC and OSA was relatively greater for subjects with two or more visits than that for subjects with only 1 visit (adjusted HR [95% CI], 1.86 [1.26–2.75], and 1.61 [0.97–2.66], respectively). In addition, there was a significant trend toward an increase in risk for CRC with increased OSA clinical visits ($p < 0.001$).

4. Discussion

This is the first large-scale population-based study on the association between OSA and the risk of CRC. This study based on claims data from Taiwan's NHIRD revealed a significantly increased risk of CRC associated with OSA (adjusted HR, 1.80; 95% CI, 1.28–2.52).

It has been found that perturbations in sleep architecture and continuity may initiate, exacerbate, or modulate the phenotypic expression of multiple diseases [33]. It is well known that OSA is an independent risk factor for cardiovascular disease, cerebrovascular disease, and metabolic disease [4–8]. Furthermore, the intermittent hypoxia that is attendant to sleep-disordered breathing has been implicated in increased incidence and more adverse cancer prognosis [34]. Some studies have demonstrated that CRC development may be associated with sleep apnea and hypoxic environments [9,10,12,22,23]. Specifically, a case-control study revealed that the detection rate of advanced colorectal neoplasia in patients with OSA was significantly higher than in the asymptomatic average-risk population [9]. Findings in the current study provide additional support for an association between OSA and CRC risk. Moreover, the present study demonstrated that the HR of CRC appeared to increase with increasing frequency of clinical visits for OSA. This suggests that the severity of OSA, as indicated by frequency of clinical visits, is a significant risk predictor of CRC. However, conceptually, individuals with frequent physician visits may have a higher likelihood of detection of CRC. Thus, early detection bias may account for an overestimation in the risk of CRC associated with OSA in the current study.

With regard to the mechanisms likely to be involved in the development of CRC in patients with OSA, we hypothesize that systemic mechanisms, such as intermittent hypoxia and oxidative stress, might be decisively involved in colorectal carcinogenesis. Indeed, a Spanish group led by Ramon Farré examined the impact of intermittent hypoxia on tumor volume and weight in a murine model of melanoma

and found that intermittent hypoxia mimicking OSA enhances tumor growth and increases lung metastasis [35,36]. In this sense, chronic and intermittent hypoxia have been shown to play a key role in regulating various stages of tumor formation and progression [34,37,38]. Recent studies have found that elevation of reactive oxygen species (ROS) levels during the reoxygenation periods of intermittent hypoxia can modify gene expression through the regulation of the activity of some transcription factors and signaling pathways involved in carcinogenesis [34,39]. In addition, both chronic and intermittent hypoxia and ROS can activate transcription factors, such as hypoxia-inducible factor−1, which are known to promote angiogenesis and enhance tumor progression [39–41]. Patients with OSA experience periods of intermittent hypoxemia induced by repetitive obstructions of the upper airway during sleep. As these oxygen desaturations of arterial blood are translated into intermittent events of oxygen partial pressure at the tissue level [42], patients with OSA could be more prone to develop malignancies.

The results of the present study need to be interpreted within the context of some limitations. First of all, OSA is largely undiagnosed in populations, and the use of medical claims datasets might underestimate the prevalence of OSA and bias the assessment of CRC risk associated with OSA. In addition, it has been noted that studies that are based on insurance claims or other third-party data are often flawed because the information on confounding factors contained in insurance data is often limited [27,43]. In the present study, information on important confounders such as obesity, smoking habits, and dietary patterns were not available in the NHIRD. In this study, we used obesity-related diseases (eg, hypertension, diabetes mellitus,

hypercholesterolemia, and coronary artery disease) and smoking-related diseases (eg, chronic obstructive pulmonary disease) as substitute variables for obesity and smoking, and put them into multivariable regression models to adjust for confounding effects of obesity and smoking. In the literature, a meta-analysis revealed a significant positive association between the Westernized diet and the risk of CRC [44]. In addition, a meta-analysis provides evidence support for the inverse association between physical activity and colon cancer. It provides a formal estimate showing that individuals can likely reduce their risk of CRC, overall, by 24% through participation in physical activity [45]. However, we lacked information on dietary patterns and physical activity from the medical claims database, which precluded regression adjustment of confounding effects of dietary patterns and physical activity. Therefore, it cannot be ruled out that there may be residual confounding for obesity, smoking, dietary patterns, and physical activity in the present study. Furthermore, obesity imposes mechanical loads on both the upper airway and respiratory system that predispose to upper airway narrowing, collapse, and airflow obstruction during sleep, and obesity is one of the strongest sleep apnea risk factors [46]. It has been noted that the mechanism of sleep apnea in nonobese patients may be different from that in obese patients. Nonobese patients may have a different arousal response to the apnea [46]. Accordingly, different mechanisms involved in the association between OSA and CRC risk may be present in obese and nonobese individuals, respectively. However, we lacked data on body mass index in the NHIRD, which precluded the assessment of CRC risk associated with OSA based on obesity status. Besides, previous studies showed that continuous positive airway pressure (CPAP), the most

effective and widely used therapy for sleep apnea, can reduce the burden of diseases linked to OSA [47, 48]. Notably, the transcriptional landscape of peripheral blood leukocytes is altered by effective CPAP therapy for OSA, and that this signature is characterized as CRC was likely to be associated with more severe levels of OSA as indicated by downregulation of a disproportionate number of genes mapping to neoplastic pathways [49]. Furthermore, the ated by medical visits in this study. Therefore, patients should receive CPAP treatment based on the presence of symptomatic or severe OSA. Apparently, CPAP treatment might reduce the risk of CRC associated with OSA. A treatment effect of CPAP may be a hidden possible association between OSA and CRC. Nevertheless, CPAP data were not available in this claims dataset, which precluded the assessment of implications of CPAP treatment on the association between OSA and CRC.

The strength of this study is that it is a national cohort study based on Taiwan's NHIRD, which contains data from Taiwan's compulsory and universal health care system, which has high coverage rate in Taiwan. This allowed us to perform our analysis in a real-life setting in an unselected patient population.

5. Conclusion

In conclusion, despite its limitations, this population-based cohort study demonstrated that OSA was associated with an increased risk of CRC. However, results should be interpreted with caution due to unmeasured confounders (eg, body mass index, smoking, dietary patterns, and physical activity). Further large-scale

prospective studies are needed to confirm our results, and the effect of CPAP treatment of OSA on colorectal tumorigenesis needs to be elucidated.

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Fig. 1. Flowchart illustrating enrollment of patients for the study cohorts

Fig. 2. Kaplan–Meier curves for the cumulative incidence of colorectal cancer in the obstructive sleep apnea cohort and the comparison cohort.

Table 1

Baseline characteristics of obstructive sleep apnea (OSA) cohort and comparison cohort.

Variable	OSA cohort	Comparison cohort	*p*
	n = 4,180	*n* = 16,720	
Age, y			
20–29	647 (15.48)	2588 (15.48)	1.000
30–39	975 (23.33)	3900 (23.33)	
40–49	1026 (24.55)	4104 (24.55)	
50–59	782 (18.71)	3,128 (18.71)	
60–70	402 (9.62)	,608 (9.62)	
>70	348 (8.33)	1392 (8.33)	
Sex			
Female	1210 (20.00)	4840 (20.00)	1.000
Male	2970 (80.00)	11,880 (80.00)	
Comorbidity			
HT	1739 (41.60)	4117 (24.62)	<0.0001
DM	789 (18.88)	1990 (11.9)	<0.0001
HC	773 (18.49)	1508 (9.02)	<0.0001
CAD	801 (19.16)	1483 (8.87)	<0.0001
Stroke	524 (12.54)	1194 (7.14)	<0.0001
PU	1,252(29.95)	2852 (17.06)	<0.0001
LCCH	941 (22.51)	1930 (11.54)	<0.0001
AL	63 (1.51)	138 (0.83)	<0.0001
COPD	1247 (29.83)	2578 (15.42)	<0.0001
Asthma	13 (0.31)	28 (0.17)	0.0607
IBD	104 (2.49)	290 (1.73)	0.0014
Acromegaly	3 (0.01)	1 (0.00)	0.0060
Prostate cancer	20 (0.10)	40 (0.19)	0.0097

AL, alcohol-related chronic liver disease; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HC, hypercholesterolemia; HT, hypertension; IBD, inflammatory bowel disease; LCCH, liver cirrhosis and chronic hepatitis;PU, peptic ulcer.

Table 2

Incidence rates of colorectal cancer (CRC) in study cohorts and multivariable Cox proportional hazards regression model analysis for the association between obstructive sleep apnea (OSA) and risk of CRC.

Variable	OSA cohort			Comparison cohort			Adjusted HR (95% CI)
	No. of CRC	PYs	Incidence rate (per 10,000)	No. of CRC	PYs	Incidence rate (per 10,000)	
Total	53	35,445.12	14.95	132	155,244.15	8.5	1.80 (1.28–2.52)
Age group, y							
≤30	5	13,887.61	3.60	15	62,399.18	2.40	2.21 (0.72–6.74)
40–49	13	8,843.65	14.70	23	38,631.53	5.95	2.22 (1.08–4.63)
50–59	13	6,519.75	19.94	35	28,186.33	12.42	1.63 (0.81–3.27)
60–69	12	3,407.45	35.22	32	14,889.46	21.49	2.16 (1.08–4.34)
≥70	10	2,786.65	35.89	27	11,137.65	24.24	1.17 (0.54–2.52)
Sex							
Male	37	25,120.06	14.73	98	110,064.98	8.90	1.71 (1.14–2.56)
Female	16	10,325.06	15.50	34	45,179.17	7.53	2.09 (1.12–3.91)

CI, confidence interval; HR, hazard ratio; PYs, person-years.

Hazard ratios were adjusted for sex, age, and baseline comorbidities, including hypertension, diabetes mellitus, hypercholesterolemia, coronary artery disease, stroke, peptic ulcer, liver cirrhosis and chronic hepatitis; alcohol-related chronic liver disease, chronic obstructive pulmonary disease, asthma, inflammatory bowel disease, acromegaly, and prostate cancer.

Table 3. Multivariable Cox proportional hazards regression model analysis for the association between the risk of colorectal cancer (CRC) and frequency of clinical visits for obstructive sleep apnea (OSA)

Frequency of OSA visits	No. of CRC	PYs	Incidence rate (per 10,000)	Adjusted HR (95% CI)
Comparison cohort	132	155,244.15	8.50	ref
1	18	13,650.87	13.19	1.61 (0.97-2.66)
≧2	35	21,794.25	16.06	1.86 (1.26-2.75)
Trend test				P <0.001

Abbreviations: PYs, person-years; HR, hazard ratio; CI, confidence interval.
Hazard ratios were adjusted for sex, age, and baseline comorbidities, including hypertension, diabetes mellitus, hypercholesterolemia, coronary artery disease, stroke, peptic ulcer, liver cirrhosis & chronic hepatitis; alcohol-related chronic liver disease, chronic obstructive pulmonary disease, asthma, inflammatory bowel disease, acromegaly, and prostate cancer.

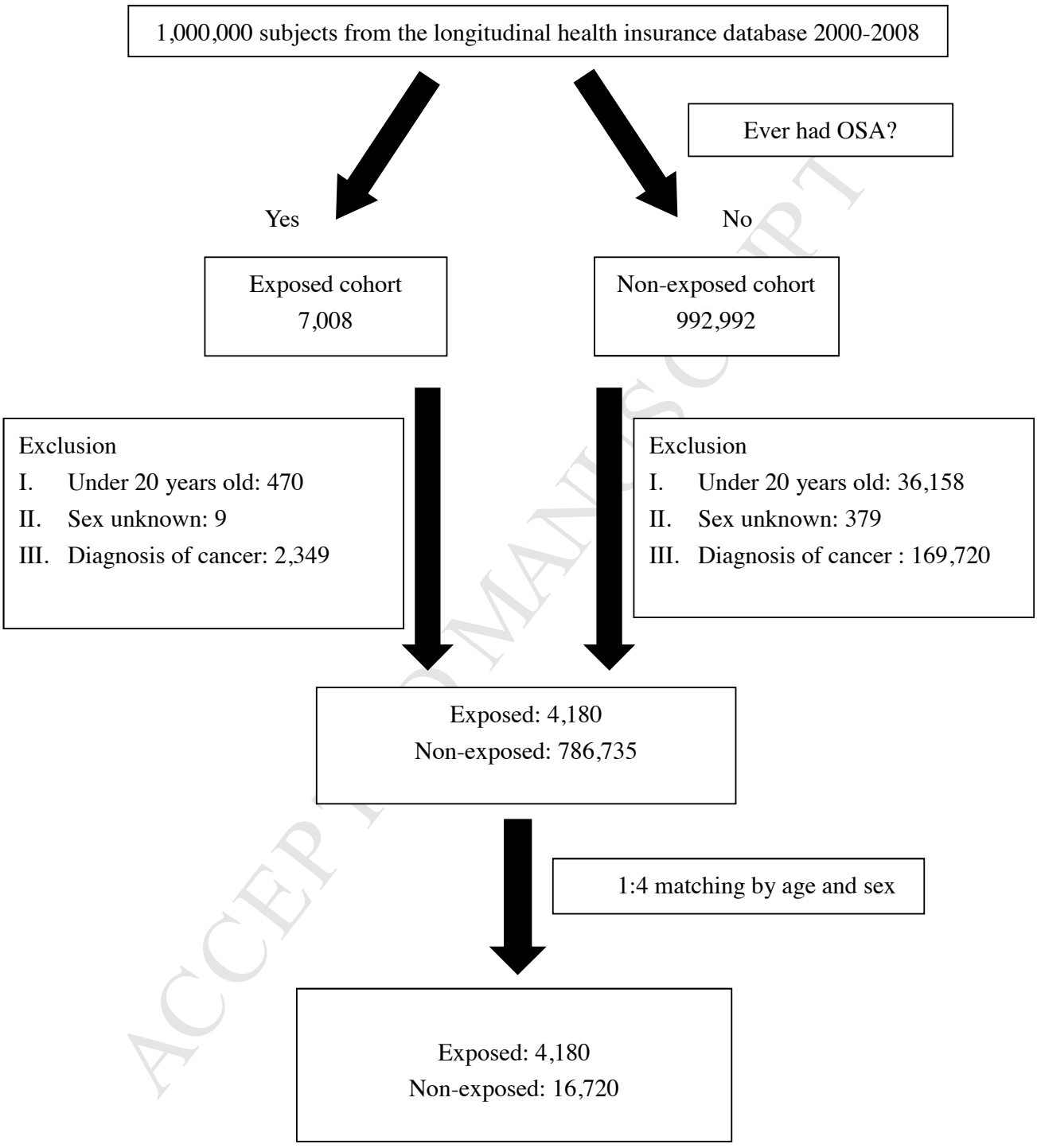

Figure 1

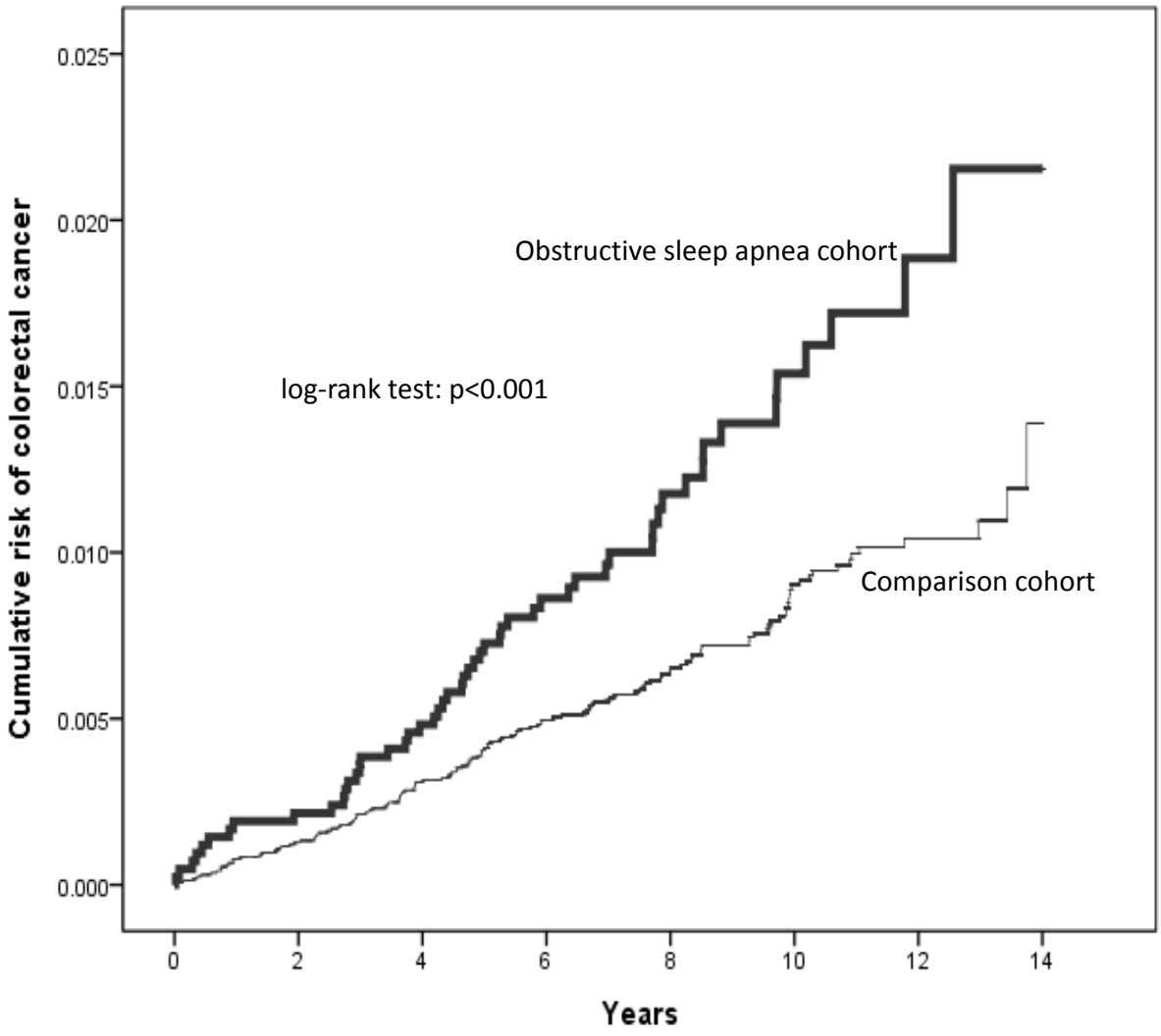

Figure 2

Highlights

- Obstructive sleep apnea (OSA) is the most common type of breathing-related sleep disorder, affecting at least 2–4% of the adult population

- Colorectal cancer (CRC) is the third most common cancer worldwide and the fourth most common cause of cancer-related death, and the incidence of CRC has rapidly increased in recent years

- The concept of patients with OSA being at higher risk of developing solid tumor malignancies have emerged in recent years.

- In this study, the relationship between the incidence of OSA and the risk of CRC was examined

- A significant association between OSA and CRC was found in an ethnic Chinese population

The authors have no commercial associations or sources of support that might pose a conflict of interest. All authors have made substantive contributions to the study and all authors endorse the data and conclusions.