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Original Article

Sleep apnea increased incidence of primary central nervous system cancers: a nationwide cohort study

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ABSTRACT

Introduction: Obstructive sleep apnea (OSA) was associated with increased incidence of all cancers. We aimed to determine the risk for primary central nervous system (CNS) cancers in patients with sleep apnea syndrome.
Methods: A total of 23,055 incident cases of newly diagnosed sleep apnea syndrome (sleep apnea group) were identified between 2000 and 2003 in the medical claims database of Taiwan's National Health Institute (NHI) program and were matched by age and gender to patients without OSA (comparison group) in the same period. The occurrence of primary malignant CNS cancers was measured 2 years after the index date over a 10-year period.
Results: The incidence density of primary CNS cancers (per 10,000 individual-years) was 2.14 and 1.28, respectively, for the OSA and comparison groups. The overall risk for developing primary CNS cancers was significantly higher in the OSA group (adjusted hazard ratio [HR], 1.54; $P = 0.046$) after adjusting for age, gender, and obesity, among other variables. Subgroup analysis revealed a significantly higher risk for primary brain cancers but not primary spinal cord cancers in the OSA subgroup (adjusted HR, 1.71; $P = 0.027$). The analysis also revealed a significantly higher risk for primary CNS cancers in the insomnia with OSA subgroup (adjusted HR, 2.20; $P = 0.001$) and in the OSA without surgical treatment subgroup (adjusted HR, 1.831; $P = 0.003$).
Conclusions: OSA, especially with insomnia, may increase the risk for primary CNS cancer development, though surgical treatment may reduce this risk in participants with OSA.

1. Introduction

Patients with obstructive sleep apnea (OSA) and poor quality of sleep may be at increased risk for obesity, diabetes mellitus (DM), cardiovascular disease, cognitive impairment and total mortality [1,2]. OSA also may contribute to several organ system dysfunctions including auditory [3] and ophthalmic [4] degeneration, as well as overactive bladder [5]. However, little information is available regarding the association of OSA and tumor formation. Evidence shows that tumor hypoxia and its related molecular mediators regulate multiple steps of tumorigenesis, including tumor formation, progression, and response to therapy [6]. Hypoxia also plays a role in glioma tumorigenesis [7]. The progression of low-grade astrocytoma to glioblastoma multiforme may be mediated by hypoxia-induced phenotypic changes and subsequent clonal selection of cells that overexpress hypoxia-responsive molecules [7,8]. From these experimental observations, we hypothesized that OSA and subsequent tissue hypoxia might lead to cancer formation. However, this relationship in humans has not yet been firmly established.

A previous study showed that short duration of sleep increased the risk for colorectal adenoma [9]. It has been reported that an adequate night of sleep may reduce the risk for breast cancer [10,11]. Recently, OSA was associated with increased incidence of all cancers, especially in men and patients younger than the age of 65 years in a large multicenter Spanish cohort study [12]. Thus it seems that sleep apnea may increase the risk for malignant tumors at various sites. Because the central nervous system (CNS) is a high oxygen-demanding organ, it may be prone to hypoxia damage. Moreover, tissue hypoxia resulting from sleep

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apnea may increase the risk for cancer formation, but it remains unclear if OSA can increase the risk for primary CNS cancers in humans. Therefore, our study aimed to address this concern.

2. Materials and methods

2.1. Study design and data collection

Our study used data retrieved from the medical claims database of Taiwan's National Health Institute (NHI) program. In Taiwan, National Health Care is obligatory and individuals rarely are excluded from this system. Thus the NHI program covers more than 96% of the population in the country and has contracted with 97% of all hospitals and clinics in Taiwan [13]. The study protocol was approved by the Institutional Review Board of Dalin Tzu Chi Hospital. Further, this board waived the need for written inform consent, as the files of participants were delinked from the database.

In the period between January 2000 and December 2003, a cohort of 23,055 participants (ages, 20–50 years) with newly diagnosed sleep apnea (*The International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] codes 780.51, 780.53 and 780.57) was identified as the sleep apnea group from the population of visitors to the outpatient departments of all hospitals and clinics in Taiwan between 2000 and 2003. Sleep apnea was diagnosed by polysomnography (PSG) showing an apnea-hypopnea index of greater than five events per hour. However, PSG was less available and less frequently performed in Taiwan in early 2000. Therefore, OSA was diagnosed by clinical symptoms (i.e., persistent snoring and apnea with witness). The date of the first diagnosis of OSA in the database between 2000 and 2003 was defined as the index date, and participants with OSA before the year 2000 were excluded to ensure that no study participant had OSA prior to the beginning of the study. In addition, we divided the OSA group into two subgroups: insomnia with sleep apnea (ICD-9-CM codes 780.57 and 785.51) subgroup and hypersomnia with sleep apnea (ICD-9-CM code 780.53) subgroup.

All participants with OSA were further divided into a surgical treatment group if they received surgical treatment for their OSA and a nonsurgical treatment group if they did not receive surgical treatment. The same database was used to randomly select the comparison group (patients without OSA in the same period). Participants in the comparison group were matched (1:3) by age within 2 years and gender to participants in the OSA group. Participants with other respiratory abnormalities (ICD-9-CM code 786.09), apnea (ICD-9-CM code 786.03), history of primary malignant CNS cancers (ICD-9-CM codes 191–192), or metastatic CNS cancers diagnosed before the index date and within 2 years after the index date were excluded.

2.2. Study end point

To avoid a possible reverse causal relationship between OSA and primary CNS cancers, new diagnosis of primary malignant CNS cancers (including brain cancers and spinal cord cancers) 2 years after the index date was defined as the end point in our study. However, the association of OSA with all cancers or other types of cancer was not tested. The observation period began on the index date, which was the same for both the sleep apnea group and the comparison group, and ended on the date of CNS cancer diagnosis or date of censoring before or on December 31, 2009. The length of follow-up was calculated for each patient diagnosed with primary CNS cancers. The completion date was defined as the date of death or the date of withdrawal from the NHI program.

2.3. Statistical analysis

The significance of the differences in age, gender and baseline comorbidities between the OSA group and the comparison group was assessed using t tests or χ^2 tests. The incidence of primary CNS cancers was estimated for the two groups. Cox proportional hazards regression models were used to assess the effects of OSA syndrome on primary CNS cancer risk after adjustment for age, gender and comorbidities. By doing so, we were able to test if OSA was an independent risk factor for primary CNS cancers. Nevertheless, the possibility remained that some comorbidities were intermediate variables between OSA and primary CNS cancers.

The comorbidities included obesity (ICD-9-CM codes 278.0, 278.00, 278.01, and 278.02), coronary artery disease (CAD) (ICD-9-CM code 4140), hypertension (HTN) (ICD-9-CM codes 401–405), DM (ICD-9-CM code 250), hyperlipidemia (ICD-9-CM code 272), chronic kidney disease (CKD) (ICD-9-CM codes 585–586), chronic hepatitis (ICD-9-CM codes 070 and 571.4), liver cirrhosis (ICD-9-CM codes 571, 571.2, 571.5, and 571.6), cerebrovascular diseases (CVD) (ICD-9-CM code 438), Parkinson disease (PD) (ICD-9-CM codes 332 and 094.82), and Alzheimer disease (AD) (ICD-9-CM codes 290.4, 294.1, and 331.0). A 2-tail P value of less than 0.05 was considered to indicate statistical significance. We used SAS 9.1 statistical software (SAS Institute, Inc., Cary, NC, USA) to perform the analysis.

3. Results

3.1. Participant characteristics

Table 1 shows the clinical characteristics of both study cohorts. All comorbidities, including obesity, CAD, HTN, DM, dyslipidemia, CKD, chronic hepatitis, liver cirrhosis, CVD, PD and AD were more prevalent in the OSA group than in the comparison group.

3.2. Incidence of primary CNS cancers

During the 10-year follow-up period, we identified 38 cases (0.16%) of primary CNS cancer (brain [n = 32] and spinal cord [n = 6]) in the OSA group and 85 cases (0.12%) of CNS cancer (brain [n = 65] and spinal cord [n = 20]) in the comparison group (Table 1).

Table 1
Clinical characteristics of both study cohorts.

	Sleep apnea group (n = 23,055)	Comparison group (n = 69,165)	P values
Mean age ± SD, y	37.6 ± 8.2	37.6 ± 8.2	0.85
Gender (M:W), %	66.8:33.2	66.8:33.2	>0.99
Obesity, %	4.1	0.1	<0.001
CAD, %	2.1	0.3	<0.001
HTN, %	17.9	3.9	<0.001
DM, %	8.1	2.4	<0.001
Dyslipidemia, %	15.3	2.6	<0.001
CKD, %	1.2	0.3	<0.001
Chronic hepatitis, %	23.6	5.1	<0.001
Liver cirrhosis, %	2.2	0.5	<0.001
CVD, %	3.3	0.6	<0.001
Parkinson disease, %	0.3	0.04	<0.001
Alzheimer disease, %	0.1	0.02	<0.001
Incidence density of CNS cancers (/10,000 individual-years)			
Brain+spine	2.14	1.28	
Brain	1.80	0.98	
Spine	0.34	0.30	

Abbreviations: SD, standard deviation; y, years; M, men; W, women; CAD, coronary artery disease; HTN, hypertension; DM, diabetes mellitus; CKD, chronic kidney disease; CVD, cerebrovascular diseases; CNS, central nervous system.