

Correlation between sleep apnea and CNS tumors - meta-analysis

Abstract

Background: Sleep apnea is a disorder of breathing in which obstruction of the upper airway or inhibition of brain stem respiratory motor output can lead to severe obstructive sleep apnea. It is affecting 425 million adults aged 30-69 globally, with the highest number of affected individuals being in China, the USA, Brazil, and India. Risk factors include age, male sex, family history, menopause, craniofacial deformities, and drinking and smoking. Between 1975-1977 and 2009-2015, the five-year relative survival for all malignant brain tumors increased from 23% to 36%. About 83570 people were diagnosed with brain and other CNS tumors in the United States, and 18600 died from the disease. Sleep apnea has been linked to several pathogenic processes, including sleep fragmentation, persistent systemic inflammation, and immunological dysfunction.

- Objectives:**
1. To associate sleep apnea and CNS tumor in patients.
 2. To determine the common type of brain tumor associated with the sleep apnea.
 3. To investigate the incidence of CNS association to sleep apnea with respect to age.

Design: Meta-analysis study.

Settings: A search for articles related to sleep apnea and CNS cancer was done using PUBMED and Cochrane Library through 42 years using keywords.

Materials and Methods: We used different keywords to expand the literature search including "sleep apnea with brain tumor", and "sleep apnea with CNS tumor". On PUBMED we found 162 results for "sleep apnea with brain tumor" and 124 results for "sleep apnea with CNS tumor" therefore a total of 286 results were found. Likewise, at Cochrane Library, 11 results were found for "sleep apnea with a brain tumor. We also used Google Scholar for data mining. All data were recorded by at least 3 authors and consensus data were entered into and analyzed for descriptive statistics using Microsoft Excel.

Main Outcome Measures: Relation between sleep apnea and central nervous system tumors.

Sample Size: 70 articles.

A search for articles related to sleep apnea and brain cancer was done using PUBMED and Cochrane Library through 42 years.

Results: A total of 70 articles were enrolled which met the inclusion criteria defined below. The highest number of publications were contributed by the USA, Japan, and China in this study. All 70 articles reported on Brain tumors and Sleep Apnea including 11 articles reported tumors in children under 10 years, 16 articles reported young patients (10-40 years), 11 articles middle aged patients (40-60 years) and 3 articles reported old patients (60-75 years). The total number of citations of 66 articles after the search is 2904.

Conclusion: Given the fundamental principles, it is now clear how sleep apnea influences the growth of CNS malignancies. The crucial open topic right now is how we might employ specific medicines to reduce the prevalence of CNS malignancies brought on by sleep apnea. More study must be done on sleep apnea, especially given how serious it is.

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Introduction

Sleep apnea involves a recurrent obstruction in breathing (apneas or hypopneas) due to upper airway obstruction or brain stem respiratory motor output inhibition leading to low oxygen levels and high carbon dioxide levels.¹ Common sleep apnea symptoms comprise loud snoring, sleep interruption, and daytime fatigue, while risk factor includes age, male gender, obesity, family history, menopause, craniofacial deformities, and certain lifestyle choices like drinking and smoking. The severity of sleep apnea is assessed using the apnea-hypopnea index (AHI) along with indicators like nocturnal hypoxemia and sleep fragmentation. However, the gold standard test for screening

and diagnosing sleep apnea is a polysomnogram.² According to Benjafield et al, globally 936 million adults aged 30-69 years have mild to severe obstructive apnea and 425 million adults aged 30-69 years have moderate to severe apnea with China, USA, Brazil, and India having the highest number of affected individuals respectively.³

A brain tumor whether benign or malignant can manifest through symptoms like headache, focal neurological deficit, seizure, decreased alertness, disorientation, and change in behavior.⁴ Brain cancer ranks among the eighth most common cancer in people over 40 years and stands as the fifth leading cause of cancer-related deaths for males ages 40-59 in the USA.⁵ Between 2008 and 2017, the malignant brain tumor

rate declined by 0.8% per year but rose in children by 0.5%-0.7%. The survival rate for all malignant brain tumors increased from 23% to 36% between 1975-2015, especially in younger age patients.⁶ The number of new cases of Brain and CNS tumors worldwide in both genders of all ages was 308103, with mortality contributing to 251329 cases. Similarly, in Asia, it was 166925 and North America 27526, with a mortality of 137646 and 20690 respectively in the diseased individual.⁷

Sleep apnea associated brain tumor results from the process sleep fragmentation, inflammation, hypoxia and oxidative stress leading to DNA damage and promoting malignant cell growth.⁴

The cerebellum, hippocampus, anterior cingulate gyrus, temporal, frontal, and parietal cortices showed diffuse changes in brain-affected patients with OSA in an investigation.⁸ The connection between sleep apnea and CNS tumor is incompletely studied in clinical research leaving a significant gap in our understanding in their correlation. Therefore, the purpose of this study is to associate sleep apnea and CNS tumor in patients, determine the common type of brain tumor associated with the sleep apnea and investigate the incidence of CNS tumor association to sleep apnea with respect to age. This study will help readers/researchers to better understand the association between sleep apnea and CNS tumors and provide an opportunity to further explore these associations in their future research studies.

Materials and methods

Literature search

A search for articles related to sleep apnea and brain cancer was done using PUBMED and Cochrane Library. We used different keywords to expand the literature search including “sleep apnea with brain tumor”, “sleep apnea with CNS tumor”. On PUBMED we found 162 results for “sleep apnea with brain tumor” and 124 results for “sleep apnea with CNS tumor” therefore a total of 286 results were found. After applying the filter with Humans and English we found 116 results for “sleep apnea with brain tumor” and 97 results for “sleep apnea with CNS tumor” thus a total of 213 results. Likewise, on Cochrane Library, 11 results were found for “sleep apnea with a brain tumor, however, none of the results matched our keywords. For “sleep apnea with CNS tumor”, no results were found. We also used Google Scholar for data mining.

Screening of publications for eligibility

In the study, we only included those publications for the final analyses where any kind of Brain or CNS tumor is associated with any type of sleep apnea. We removed all the duplicate entries to determine the inclusion criteria. In the final analysis, all those publications whether without full text or with full text were included.

Indexation and analyses

The data insertion in the Microsoft Excel sheet was done by 4 authors and crosschecked amongst each other. The PubMed ID, title, name of the journal, year of publication, number of citations, first author country, type of article, sample size, mean age, mean BMI, type of brain tumor, type of sleep disturbance, and any comorbidities of every publication included was recorded. The 4 authors cross-checked the entered data and differences were investigated for consensus indexation. To calculate the frequency and percentages, SPSS was used.

Results

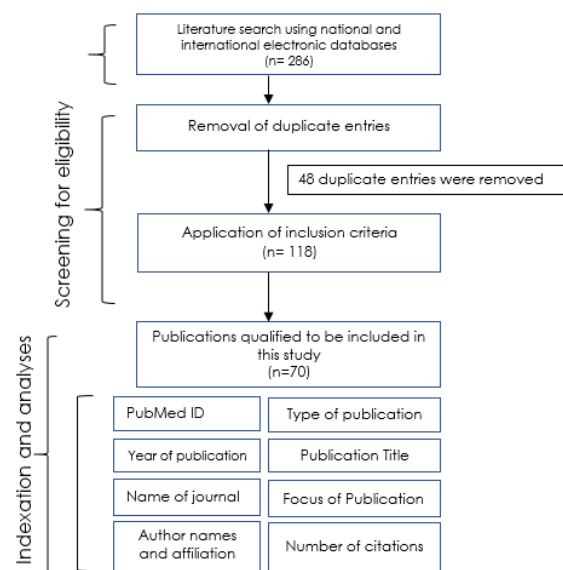
Eligible studies

According to the keywords, we filtered 286 publications in total from Pubmed. We included 118 publications in our study for meeting the inclusion criteria. A total of 48 duplicate publications were removed. For further meta-analysis, a total of 70 publications were enrolled which met the inclusion criteria defined below. These 70 articles were all human-based research.

Annual growth of publications

All articles included are published in international journals. The first publication focusing on sleep apnea and brain tumor was published in the year 1980. When doing this analysis, the latest article was published in 2022.

In total, before 2000 only 17 publications were published. 13 publications during the year 2000-2005 were published, while during 2006-2010, 5 publications were found. During 2011-2015, only 14 publications were published while in 2016-2020 a total of 15 publications were published. Since 2021 to date, 06 publications have been published. The highest number of publications (n= 7) were published in 2004. The average number of publications has been 1.6 per year up till now since 1980. (Flow chart & Figure 1)



Flowchart: The working algorithm utilized in this study.

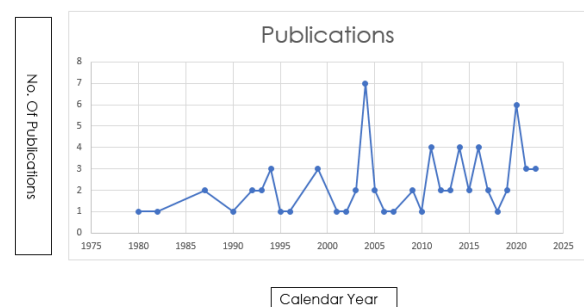


Figure 1: Annual Growth of CNS Cancer Related Publications from World During 1980 to Date

Types and research foci of publications

According to the qualified sample, all publications are included in Pubmed and Google Scholar. In our study with a total of 70 Publications, the original articles were 21, 8 articles were review articles, 38 were case reports, 1 case review, and 2 case series. The highest number of publications were contributed by the USA, Japan, and China in this study.

Top journals

In this study, the Top 4 Journals with publications were:

- 1- Journal of Clinical Sleep Medicine
- 2- Journal of Clinical Endocrinology and Metabolism
- 3- Pediatrics
- 4-American Journal of Respiratory and Critical Care Medicine

Identification and description of studies

From the articles which met the inclusion criteria, Brain tumors reported in patients with sleep apnea were included for further study. The different types of tumors reported in our study are (1 on supratentorial tumor, 1 on malignant tumor, 3 on brain stem tumor, 3 on suprasellar tumor, 5 on mixed type brain tumor, 1 on medullary tumor, 1 on diffuse midline glioma, 5 on CNS tumor, 1 on brain tumor, 16 on pituitary adenoma, 1 on pediatric brain tumor, 5 on brainstem glioma, 2 on ganglioglioma, 3 on ependymoma, 1 on cerebellar hemangioblastoma, 3 on craniopharyngioma, 1 on frontobasal tumor, 1 on posterior fossa tumor, 1 on prolactinoma, 1 on intracranial mature teratoma, 2 on astrocytoma, 2 on germinoma, 2 on medulloblastoma, 1 on epidermoid tumor, 1 on bulbar hemangioblastoma, 1 on lipoma, 1 on acoustic neuroma, 1 on malignant glial tumor and 2 articles reported arachnoid cyst). Among 70 articles reported on Brain tumors and Sleep Apnea, 24 articles were obstructive sleep apnea, 19 article were central sleep apnea and 27 were both obstructive and central sleep apnea. According to the age, 11 articles reported tumors in children under 10 years. 16 articles reported tumors in patients (10-40 years), 11 articles reported tumors in middle-aged patients (40-60 years), and 3 articles reported tumors in old age patients (60-75 years).

In this research, the most common CNS tumors were found to be Pituitary Adenoma in 16 articles, 5 articles mentioned Brain Stem Glioma and about 5 articles mentioned different types of CNS tumors. 10 articles mentioned Mix type apnea and 9 articles mentioned Obstructive sleep apnea associated with pituitary Adenoma. The brainstem glioma was most associated with Central sleep apnea in 5 articles, while 2 articles mentioned mixed-type apnea and 1 mentioned Obstructive sleep apnea. CNS tumor was most associated with Obstructive sleep apnea in 3 articles and mixed type in 2 articles.

Most of the research in our meta-analysis was found to be associated with CNS tumors and mixed Type of sleep apnea which is both Obstructive and Central.

Number of citations received

The total number of citations of 66 articles after the search is 2904. 4 articles did not receive any citations to date.

Discussion

This meta-analysis and systematic review were conducted to clarify the association between sleep apnea (both central sleep apnea

and obstructive sleep apnea) and all types of CNS tumors in all age groups. Our findings suggest that sleep apnea has a significant association with both brain and spinal cord tumor.

Our study is supported further by several other studies. According to one of the study, obesity was strongly linked to sleep-disordered breathing and excessive daytime sleepiness in CNS tumor survivors. Among 31 survivors referred for sleep issues, 26 were overweight.⁹ Weight gain can disrupt normal upper airway function during sleep by causing reduced airway space due to increased fat deposits, changes in neural mechanism, respiratory control instability, and decreased stabilization traction on the upper airway.¹⁰ The Wisconsin sleep cohort study revealed that one standard deviation change in body mass index was linked to the fourfold rise in the prevalence of disease.¹¹ Data from long-term studies such as the Sleep Heart Health study, the Wisconsin sleep cohort study, and the Cleveland family study revealed that gaining weight over time significantly speeds up the progression of obstructive sleep apnea or can result in the development of moderate to severe forms of condition.² According to a Taiwanese study, a 1.5-fold increase in the risk of central nervous system malignancy was observed over 2 years in 23055 patients with obstructive sleep apnea compared to nonapneic controls with the highest risk found in those with both OSA and insomnia.¹² According to the Brain and other central nervous system tumor statistics 2021, the most common malignant brain tumor is glioblastoma followed by diffuse/ anaplastic astrocytoma, lymphoma, and hematopoietic and meningeal tumor. Likewise, On the non-malignant side, the most common is meningioma followed by Pituitary tumor, Nerve sheath tumor, and neuroepithelial tumor.⁶

Several potential mechanisms may help us to better understand the association between CNS tumors and sleep apnea. In general, oxygen-sensing pathways, oxidative stress, inflammation, endothelial function, clonal selection, and altered immunological response are thought to play a role in the pathogenesis of tumors among sleep apnea patients. Intermittent hypoxia produces reactive oxygen species (ROS), which exacerbate oxidative stress, and inflammation and induce tumorigenesis and the hypoxia-reoxygenation cycle coupled with genetic alteration increases genetic instability, damages the endothelial barrier, facilitates tumor cell entry into the bloodstream.¹³

Result

In the present study, by combining our 70 relevant studies we found that the most common CNS tumor was Pituitary adenoma (n=16) followed by Brain stem glioma (n=5) and mixed type CNS tumor (n=5). Among the included articles on Brain tumors with Sleep Apnea, the most common associated sleep disorder was found to be Mixed type (both Obstructive and Central sleep apnea) reported in 27 articles, followed by Obstructive sleep apnea in 24 articles and central sleep apnea in 19 articles. According to the age, 11 articles reported tumors in children under 10 years, 16 articles reported tumors in patients among (10-40 years), 11 articles reported tumors in patients among (40-60 years), and 3 articles reported tumors in old age patients (60-75 years).

Strength and Limitations

The strength of this study is that this is one of the first Meta-analyses and systematic reviews to investigate the association between sleep apnea and CNS tumors. The size of the sample was adequate, and this study includes all age group patients without any geographical discrimination. Our study also has limitations. The most relevant confounding variables like lifestyle, physical activity, hours of sleep,

nutrition, smoking, and alcohol consumption have not been included in this study because no primary data was available. Nevertheless, the patient's mean age and mean BMI were included which are the most important factors that can be associated with sleep apnea.

Conclusion

Sleep apnea is strongly associated with CNS tumors and from the basic mechanisms it has been clarified how sleep apnea mediates the development of CNS tumors. Now the important unanswered question remains how we might use certain therapies to lower the incidence of CNS tumors brought on by sleep apnea. Particularly, based on the severity of sleep apnea, more research needs to be conducted regarding it.

Limitation: The most relevant confounding variables like lifestyle, physical activity, hours of sleep, nutrition, smoking and alcohol consumption have not been included in this study because no primary data was available.

Statement conflict of interest: None declared.

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