Sleep Medicine 15 (2014) 1016–1020

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Sleep apnea and the subsequent risk of breast cancer in women: a nationwide population-based cohort study

Wei-Pin Chang [a], Mu-En Liu [b,c], Wei-Chiao Chang [d], Albert C. Yang [b,c], Yan-Chiou Ku [e], Jei-Tsung Pai [a], Yea-Wen Lin [a], Shih-Jen Tsai [b,c,*]

[a] Department of Healthcare Management, Yuanpei University, HsinChu, Taiwan
[b] Department of Psychiatry, Taipei Veterans General Hospital, Taipei, Taiwan
[c] Division of Psychiatry, School of Medicine, National Yang-Ming University, Taipei, Taiwan
[d] Department of Clinical Pharmacy, School of Pharmacy, Taipei Medical University, Taipei, Taiwan
[e] Nursing Department, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan

ARTICLE INFO

Article history:
Received 26 February 2014
Received in revised form 8 May 2014
Accepted 27 May 2014
Available online 25 June 2014

Keywords:
Sleep apnea
Breast cancer
Women
Population-based study
Taiwan population

ABSTRACT

Background: Hypoxia plays an important role in the development of solid tumors. Intermittent hypoxia is the hallmark of sleep apnea (SA). We tested the hypothesis that SA may increase the risk of breast cancer in Taiwan by using a population-based data set.
Methods: Our study cohort consisted of women diagnosed with SA between January 2003 and December 2005 ($n = 846$). For each SA patient, five age-matched control women were randomly selected as the comparison cohort ($n = 4230$). All participant cases were followed for 5 years from the index date to identify the development of breast cancer. Cox proportional-hazards regression was performed to evaluate the 5-year breast-cancer-free survival rates.
Results: Forty-four women developed breast cancer during the 5-year follow-up period, among whom 12 were SA patients and 32 were in the comparison cohort. The adjusted hazard ratio (HR) of breast cancer in patients with SA was higher [HR, 2.09; 95% confidence interval (CI), 1.06–4.12; $P < 0.05$] than that of the controls during the 5-year follow-up. Despite not meeting statistical significance, we found increases in the risk of breast cancer in women aged 30–59 years (HR, 2.06; 95% CI, 0.90–4.70) and ≥60 years (HR, 3.05; 95% CI, 0.90–10.32) compared with those aged 0–29 years.
Conclusion: The findings of our population-based study suggest an association between SA and an increased risk of breast cancer in women.

1. Introduction

Sleep apnea (SA) is a common sleep disorder characterized by multiple cessations of breathing during sleep that lead to intermittent hypoxia and sleep fragmentation. Each apnea, the period of the cessation of breathing, can last from 10 s to several minutes. The severity of SA is categorized as mild, moderate, or severe, based on the number of apneas per hour, and it is the most frequent medical cause of daytime sleepiness. Untreated SA has been shown to increase the risk of motor vehicle accidents [1], and evidence indicates that SA is a risk factor for diabetes and cardiovascular disease-related mortality and morbidity [2–6].

In a case report series, obstructive SA was present in patients with head and neck cancer at a prevalence of 76% (13/17), suggesting an association between obstructive SA and malignancies of the oral cavity and oropharynx [7]. In a cohort of 4910 suspected obstructive SA patients, Campos-Rodriguez et al. demonstrated that increased overnight hypoxia in severe SA was associated with an increased incidence of cancer [8]. Data from both animal and epidemiological studies also suggest a possible relationship between cancer progression and survival and the severity of SA [9–11].

The most common type of breast cancer originates in the milk ducts. Breast cancer occurs in both men and women, but is far more prevalent in women. Various seemingly unrelated factors have been shown to increase the risk of breast cancer. Hormone use, alcohol consumption, obesity, and nulliparity are each associated with a modest increase (<2-fold) in the risk of breast cancer. A family history of first-degree relatives with breast cancer is also associated with an increase (>2-fold) in the risk of breast cancer [12,13].

Hypoxia plays important roles in tumorigenesis, tumor angiogenesis, and metastasis [14]. Hypoxia leads to an adaptive re-

* Corresponding author at: Department of Psychiatry, Taipei Veterans General Hospital, No. 201, Shih-Pai Road, Sec. 2, 11217, Taipei, Taiwan. Tel.: +886 2 2875 7027 ext. 276; fax: +886 2 2872 5643.
E-mail address: tsai610913@gmail.com (S.-J. Tsai).

http://dx.doi.org/10.1016/j.sleep.2014.05.026
1389-9457/

sponse, orchestrated by hypoxia-inducible factor-1 (HIF-1), which is crucial for carcinogenesis and tumor progression [15]. Hypoxia is a microenvironmental selection force during somatic evolution in breast carcinogenesis. The level of HIF-1α is increased during carcinogenesis in breast tissue, and is associated with other tumor biomarkers, such as vascular endothelial growth factor [16]. Chen et al. recently demonstrated that the role of HIF-1α differs in the response, proliferation, and tumor progression phases of carcinogenesis in breast tissues [17].

Frequent, intermittent hypoxia in long-term SA may therefore lead to tumor carcinogenesis [18], thereby influencing the risk of breast cancer. However, evidence in support of this hypothesis is lacking, and no increased incidence of any type of cancer has been reported among women with long-term, frequent SA. Therefore, we examined the incidence of breast cancer during the first 5 years following a diagnosis of SA in a nationwide population-based cohort to determine the association between SA and subsequent breast cancer risk in women.

2. Methods

2.1. Database

The National Health Insurance Research Database (NHIRD) was established, and is managed, by the Taiwan National Health Research Institutes (NHRI). The NHIRD provides comprehensive health care data to researchers, including the enrollment files, claims data, catastrophic illness files, and various data regarding drug prescriptions. Our study data used the Longitudinal Health Insurance Database (LHID) 2005, a subset of the NHIRD. The LHID 2005 contains historical ambulatory data and inpatient care data for one million randomly sampled beneficiaries enrolled in the National Health Insurance (NHI) system between 1997 and 2010. The NHI provides comprehensive health care insurance for ~22.96 million residents of Taiwan. The NHRI has reported that there are no statistically significant differences in age or sex between the randomly sampled group and all beneficiaries of the NHI program. Because the NHI released the LHID 2005 database for research purposes, our study was exempt from full review by our institutional review boards.

2.2. Study population

The LHID 2005 was used to conduct a matched case-controlled study. A study cohort was compared with a control cohort to examine the relationship between SA and breast cancer in women. The study participants were linked to their claims data to identify the first diagnosis of SA based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 327.23, 780.51, 780.53, and 780.57. For data accuracy, the included subjects were required to have received polysomnography and all ICD-9 codes were assigned by the otolaryngologist, pulmonologist, or neurologist. The date of the initial diagnosis of SA was assigned as the index date for each SA patient. Each SA cohort patient was matched based on age and index year to five randomly identified beneficiaries without SA to create the comparison cohort. Female patients diagnosed with breast cancer (ICD-9-CM code 174.X) before or after the study period were excluded from both cohorts. We also identified relevant comorbidities, including hypertension (ICD-9-CM 401.X-405.X), diabetes mellitus (ICD-9-CM 250.X), and hyperlipidemia (ICD-9-CM 272.X).

2.3. Level of urbanization

For our analysis of urbanization, all 365 townships in Taiwan were stratified into seven levels according to the standards established by the Taiwanese NHRI based on a cluster analysis of the 2000 Taiwan census data, with Level 1 referring to most urbanized and Level 7 referring to least urbanized. The criteria on which these strata were determined included the population density (persons/km^2), the number of physicians per 100,000 people, the percentage of people with a college education, the percentage of people aged >65 years, and the percentage of agricultural workers. Because levels 5, 6, and 7 contained few SA cases, they were combined into a single group, thereafter referred to as level 5.

2.4. Statistical analysis

Pearson χ^2-tests were performed to examine the differences in the categorical data between the SA and comparison cohorts, including the urbanization level, monthly income, region, and comorbidities. Survival analysis using the Kaplan–Meier method was also performed, and used the log-rank test to compare the survival distributions between the cohorts. The survival period was calculated for patients who suffered from SA until an occurrence of hospitalization, an ambulatory visit for breast cancer, or the end of the study period (December 31, 2010), whichever came first. After adjusting for monthly income, urbanization level, and the comorbidities as potential confounders, Cox proportional-hazards analysis stratified by age group and index year was performed to examine the risk of breast cancer during the 5-year follow-up in both cohorts. The age group factors in both groups were further classified. Stratified analysis was also performed regarding the underlying status of hypertension, diabetes, and hyperlipidemia to assess the association between SA and breast cancer events. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated to quantify the risk of breast cancer. Two-sided $P < 0.05$ was considered significant.

3. Results

Figure 1 shows the research design flowchart. The SA cohort contained 846 female patients, and 4230 female patients were included in the comparison cohort. The distributions of demographic characteristics and the comorbidities for the SA and comparison cohorts are shown in Table 1. Hypertension ($P < 0.001$), hyperlipidemia ($P < 0.001$), diabetes ($P < 0.001$), obesity ($P < 0.001$), alcohol use disorder ($P < 0.001$), and higher monthly income ($P = 0.002$) were more prevalent in the SA cohort than in the comparison cohort.

During the 5-year follow-up, 12 SA patients (1.4%) and 32 patients in the comparison cohort (0.8%) developed breast cancer. The

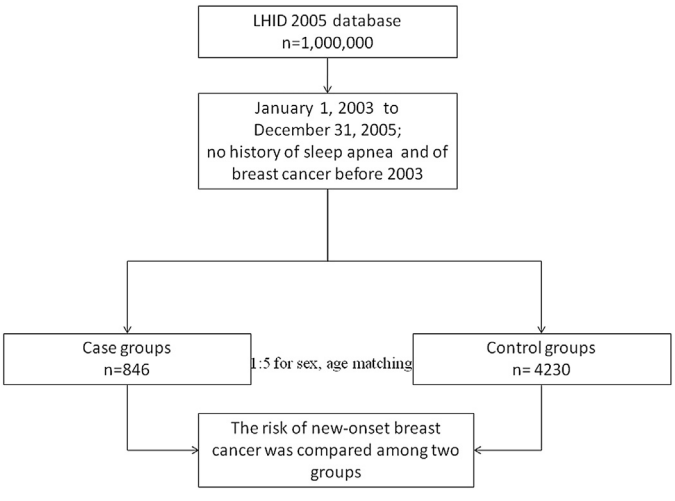

Fig. 1. Study research design. LHID, Longitudinal Health Insurance Database.