Increased Incidence of Oral Cancer in Patients With Obstructive Sleep Apnea: Results From National Insurance Claims Data 2007–2014

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Few studies have shown an increased risk of oral cancer in patients with obstructive sleep apnea syndrome (OSAS). We investigated the association between OSAS and oral cancer using data from the Korea National Health Insurance Service database. A total of 198,574 male patients who were newly diagnosed with OSAS between 2007 and 2014 were included. A control group of 992,870 participants was selected using propensity score matching, and the hazard ratio for oral cancer (95% confidence interval) was calculated. The incidence of oral cancer among patients with OSAS was significantly higher than that of the controls (1.25 [1.01–1.54]). Regarding oral cancer incidence by sex, there was no increase in the hazard ratio in males, but it increased to 2.29 (2.29 [1.38–3.70]) in females. In particular, the incidence of oral cancer was the highest in patients aged 40–65 years (1.38 [1.07–1.75]).

Keywords Obstructive sleep apnea; Oral cancer; Incidence; Korea.

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is clinically characterized by recurrent episodes encompassing both apnea and hypopnea, accompanied by a minimum 4% decline in oxygen saturation and concurrent manifestations of functional impairment, as outlined in clinical guidelines [1]. OSAS stands as a prevalent and notably debilitating disorder, with a documented prevalence of 9.1% among middle-aged men and 4.0% among middle-aged women [2]. Extensive research has consistently underscored the grave health implications of untreated OSAS, manifesting in a strong association with conditions such as hypertension, type 2 diabetes, stroke, and cardiovascular disease [3-5].

Oral cancers develop on the surface of the tongue, inside the cheeks, palate, lips, or gums [6]. The incidence of oral cancer is 8.0/100,000, and it is the most common cancer of the head and neck. It occurs more often in men and older adults, and the use of alcohol and tobacco and human papillomavirus (HPV) infection are known triggers [6]. The overall 5-year survival rate is not low at 65%, but depending on the occurrence site, serious problems with speaking and swallowing may occur after surgical treatment, and a large cosmetic defect may remain. Therefore, it is important to prevent oral cancer by avoiding triggers as much as possible. However, further research on unknown triggers is needed.

Several studies have been published recently on the association between OSAS and various cancers [7-9]. Two major theoretical grounds have been proposed for OSAS causing or worsening cancer [7-9]. First, oxygen radicals generated during repeated apnea and hy-
perventilation cause oxidative stress, inflammation, DNA damage, and cancer development. Second, frequent sleep fragmentation disrupts the circadian rhythm, which leads to problems in the regulation of genes related to cancer development. An association between oral cancer and OSAS has also been frequently reported, and in most cases, OSAS is caused by mechanical obstruction of the upper airway due to oral cancer. It has also been reported that a few patients with oral cancer develop OSAS due to narrowing of the upper airway after surgery or radiation therapy [10-12]. However, no studies have examined whether there is an increased risk of oral cancer in patients with OSAS. As mentioned above, patients with OSAS might be at an increased risk of various cancers due to the overproduction of oxygen radicals and sleep fragmentation. In particular, the oral cavity may be further affected because it is the area where snoring and apnea occur. Mechanical stimulation of the oral mucosa due to vibration [13] and dryness due to mouth breathing [14] may cause inflammation, change the oral microbiome, and ultimately increase the incidence of cancer [15]. However, a large number of patients with OSA must be observed for a long period of time to prove this uncertain association. This study aimed to investigate whether the incidence of oral cancer was increased in patients with OSAS using large-scale data.

METHODS

The National Health Insurance System (NHIS) constitutes a comprehensive public medical insurance framework, encompassing nearly 97% of the South Korean populace. This system yields extensive and reliable datasets pertaining to medical diagnoses, medical interventions, prescription patterns, and diverse patient demographic information. Diagnoses are established through the Korean Classification of Diseases, 7th edition, a derivative of the 10th edition of the International Classification of Diseases. Researchers seeking to harness NHIS data for their investigations are required to secure approval from their respective local institutional review boards prior to commencing their studies. In this study, we delineated the OSAS group as comprising individuals aged 20 years or older who were newly diagnosed with OSAS (coded as G47.30) during the period from 2007 to 2014. Subsequently, we employed propensity score matching based on sex and age to establish the control group, comprising participants without an OSAS diagnosis. The number of individuals in this control group was fivefold that of the OSAS group. The primary endpoint of our investigation was to ascertain the incidence of newly diagnosed oral cancer. Notably, participants with any prior history of cancer diagnosis were excluded from the study. Our data collection encompassed baseline information such as age, sex, and income level, which was categorized into quintiles predicated on health insurance premium payments. Additionally, we compiled data pertaining to comorbidities, including conditions such as hypertension, dyslipidemia, diabetes, chronic obstructive pulmonary disease, stroke, and ischemic heart disease, utilizing a predefined operational definition founded on insurance claims data, as outlined in Supplementary Table 1 (in the online-only Data Supplement).

The data were summarized as mean values ± standard deviation for age and as proportions for all other categorical variables. Group comparisons were conducted using either the Student’s t-test or the chi-squared test, as appropriate. The incidence of oral cancer was determined by dividing the number of events by the person-time product at risk. A Cox proportional hazards model was applied to assess the hazard ratio of OSAS on the relative incidence of oral cancer, with stratification for covariates that included income level, diabetes, hypertension, and dyslipidemia status. Two models were employed: Model 1, which remained unadjusted for covariates, and Model 2, which was adjusted for income levels, as well as hypertension, diabetes, and dyslipidemia status. Variations in hazard ratios were examined according to age and sex. The results are reported as mean values and the corresponding 95% confidence intervals (CI). All statistical analyses were conducted utilizing SAS version 9.4 (SAS Institute, Cary, NC, USA) and R version 3.2.3 (The R Foundation for Statistical Computing, Vienna, Austria).

Ethical Approval

As this study exclusively utilized publicly available data, the Institutional Review Board of Konkuk University Hospital (KUMC 2020-03-040) granted an exemption from the requirement to obtain informed consent.

RESULTS

Between the years 2007 and 2014, a total of 198574 male patients were newly diagnosed with OSAS, while a corresponding control group of 992870 participants was identified. Demographic data characterizing the OSAS and control cohorts are comprehensively presented in Supplementary Table 2 (in the online-only Data Supplement).

Among the 992870 control participants, 444 individuals were diagnosed with oral cancer during the study period, resulting in an incidence rate of 0.094 when considering person-time. Conversely, 113 out of the 198574 patients in the OSAS patient cohort developed oral cancer, yielding an incidence rate of 0.119, which notably exceeded that of the control group. Analysis using the Cox proportional hazards model revealed that the hazard ratio for the incidence of oral cancer in the OSAS group remained statistically significant in both Model 1, which lacked adjustments (hazard ratio [HR] = 1.27; 95% CI: 1.03–1.56), and Model 2, which incorporated adjustments for income level and
various comorbidities including diabetes, hypertension, and dyslipidemia (HR = 1.25; 95% CI: 1.01–1.54).

We also conducted a stratified analysis based on age and sex using Model 2. The hazard ratio exhibited the most pronounced increase within the group aged ≥ 40 years and < 65 years (HR = 1.38; 95% CI: 1.07–1.75), whereas no significant increase was observed in the age groups < 40 years or ≥ 65 years. Importantly, while no substantial change in hazard ratio was observed in males, a substantial increase was evident in females, with a hazard ratio of 2.29 (95% CI: 1.38–3.70). Detailed results are comprehensively summarized in Tables 1 and 2.

### DISCUSSION

While OSAS has gained attention as a potential risk factor for various cancers, there is no definitive consensus on its association with oral cancer [7-9]. However, this analysis suggests that the risk of oral cancer is most significantly increased in individuals aged 40 to 65 with OSAS, particularly females.

Hypoxic damage is often proposed as a potential mechanism linking OSAS and cancer [16]. Chronic hypoxia within tumors is known to promote tumor growth and metastasis [16]. In this study, the overall hazard ratio for oral cancer in patients with OSAS was 1.25, indicating a moderately increased risk. The risk is believed to rise with a higher apnea-hypopnea index (AHI) value. However, this study could not confirm AHI due to data limitations. Additionally, gene-level analysis suggests that severe OSAS may negatively impact cancer-related genes, implying a need to address OSA in oral cancer patients [17].

Studies have revealed a higher prevalence of OSAS in patients with oral cancer, especially in cases involving tongue cancer [18]. The relationship between lesion size and OSAS severity remains unclear, with some studies finding a strong link while others did not [10-12]. However, it is important to be vigilant for oral cancer in patients with OSAS.

Treatment for oral cancer, such as surgery, chemotherapy, and radiotherapy, can affect OSAS. Surgical interventions in the oral cavity may lead to airway obstruction, and radiation therapy can result in structural changes that impact airway function, potentially leading to OSAS. Postoperative radiation and chemotherapy can also induce swelling, further complicating the evaluation [19].

This study indicates a higher incidence of oral cancer in individuals with OSAS and suggests a potential bidirectional relationship between OSAS and oral cancer. Thus, it is important to consider these findings when managing patients with OSAS or oral cancer. However, the study had limitations, such as not accounting for factors like smoking, alcohol consumption, nutritional status, HPV infection, and potential biases in the data source. Future research should aim to provide a more comprehensive understanding of this complex relationship.

### Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.17241/smr.2023.01928.

### Availability of Data and Material

The datasets generated or analyzed during the current study are available in the National Health Insurance Service repository (https://nhiss.nhis.or.kr/bd/ay/bdaya001iv.do).

### Author Contributions


### Conflicts of Interest

The authors have no potential conflicts of interest to disclose.
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REFERENCES