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SCIENTIFIC INVESTIGATIONS

Risk of obstructive sleep apnea after treatment of head and neck squamous cell carcinoma: a cross-sectional study

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Study Objectives: Head and neck squamous cell carcinoma (HNSCC) or its treatment may be associated with an increased risk of obstructive sleep apnea (OSA). However, reported relationships between OSA risk factors and HNSCC are inconsistent. This study examined associations between tumor variables and risk of OSA at least 1 year after completion of treatment for HNSCC.

Methods: This cross-sectional study included HNSCC patients of a large academic medical center. Inclusion criteria were age ≥ 18 years, cancer free for at least 1 year, and absence of tracheostomy or mental impairment. The STOP-BANG questionnaire, with a threshold ≥ 3, was used to classify HNSCC patients into elevated and low OSA risk. Tumor characteristics and treatment types were obtained from medical records. Descriptive statistics were used to compare characteristics between OSA risk groups. Unadjusted and age-adjusted logistic and linear regression models were used to explore associations between exposures and OSA risk.

Results: Among 67 participants, 85% were males, mean age was 62.0 years (8.0 standard deviation), mean body mass index was 28.7 kg/m^2 (4.6 standard deviation), and mean neck circumference was 16.3 inches (1.2 standard deviation). Three-quarters of participants received chemoradiation only. Elevated OSA risk was observed in 60% of the participants. Tumor location, tumor stage, and type of cancer treatment were not different between OSA risk groups. Hyperlipidemia was more common in the elevated OSA risk group vs the low-risk group (n = 16, 40% vs n = 2, 7%, P = .004). Age-adjusted analysis showed a trend toward 2-fold increased odds of elevated OSA risk in patients with tumors at the base of the tongue in comparison to other locations (odds ratio = 2.3, 95% confidence interval 0.9, 6.4). No associations between tumor stage, cancer treatment, and elevated OSA risk were observed.

Conclusions: Elevated OSA risk was common after HNSCC treatment. However, measured HNSCC characteristics generally were not different between elevated and low OSA risk groups. Given the high frequency of OSA that appears likely to exist in HNSCC patients, clinicians should inquire about OSA features in patients with a history of HNSCC.

Keywords: head and neck squamous cell carcinoma, obstructive sleep apnea, tumor location, tumor stage, cancer treatment

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Data on obstructive sleep apnea in patients with head and neck squamous cell carcinoma are limited. This study examined associations between head and neck squamous cell carcinoma characteristics, therapy, and risk of obstructive sleep apnea in patients who were cancer-free for at least 1 year.

Study Impact: Given the high frequency of elevated risk for obstructive sleep apnea in patients with a history of head and neck squamous cell carcinoma and lack of tumor or treatment-specific variables with predictive value for this sleep disorder, physicians should have a low threshold to screen and test for obstructive sleep apnea in this group.

INTRODUCTION

Head and neck tumors that arise close to the upper airway may predispose patients to obstructive sleep apnea (OSA).[1,2] Head and neck squamous cell carcinoma (HNSCC) is the most common malignant tumor of this anatomical region,[3] and risk factors include tobacco use, alcohol use, and infection by human papillomavirus (HPV).[4] In the United States, HNSCC comprises 3% of all cancers.[5] The majority of patients with HNSCC are treated with chemoradiation.[6]

The reported prevalence of OSA in adults ranges between 9 and 38%.[7] An increased prevalence of OSA among patients with HNSCC compared to the general adult population has been reported (66% before and 51% after cancer treatment).[8] Indeed, both the characteristics and treatment of HNSCC have been proposed as risk factors for OSA. However, current evidence to support these relationships is limited.[9]

Identification of risk factors for OSA among patients with a history of HNSCC could help guide OSA screening and testing in this population. This study, therefore, aims to

examine associations between tumor location, tumor stage, cancer treatment, and the risk of OSA among participants at least 1 year disease-free of HNSCC. We hypothesized that tumor location, tumor stage, or cancer treatment are associated with elevated risk of OSA at least 1 year free of HNSCC.

METHODS

Study population and sample

This cross-sectional study recruited a sample of adults diagnosed with HNSCC who received care at the University of Michigan Rogel Cancer Center or Otolaryngology Clinic from July 1, 2017, to June 30, 2018. The Electronic Medical Record Search Engine (EMERSE)[10] and HNSCC key terms were used to identify potential candidates. Inclusion criteria were age ≥ 18 years and completion of curative treatment for HNSCC greater than 1 year prior to enrollment. Exclusion criteria were the presence of tracheostomy, mental impairment, and non-English speakers. Patients closer to treatment were excluded to avoid assessment during periods when residual inflammation or wound healing could still compromise the upper airway.

Data collection

Potential study participants were identified by a medical record review, and informed consent was obtained from each participant. Demographic, anthropometric, substance use (tobacco and alcohol), comorbidities, tumor features, and cancer therapy data were obtained from chart review. Of note, tumor stage was assigned according to the American Joint Committee on Cancer's staging manual eighth edition. Participants completed the STOP-BANG questionnaire[11] to provide a measure of OSA risk. Given limitations to in-person interaction during the coronavirus disease 2019 (COVID-19) pandemic, all participants completed the questionnaire online through Qualtrics software. Body mass index (BMI) was calculated from height and weight reported in the electronic medical record, and neck circumference was based on collar size. This study was compliant with regulations and approved by the Protocol Review Committee of the Rogel Cancer Center and the University of Michigan Institutional Review Board.

STOP-BANG questionnaire

The STOP-BANG is among the most commonly used questionnaires available for OSA screening. The eight questions of this tool ask about sleep symptoms, hypertension, demographics, and anthropometric measures. Each item is assigned 1 point if positive, and the total summed score ranges from 0–8.[11] STOP-BANG questionnaire sensitivities and specificities from a variety of populations (sleep clinic, surgical, renal disease, bus drivers, and general population) have been pooled. Corresponding sensitivities for mild, moderate, and severe OSA (with a STOP-BANG score threshold of ≥ 3) are 88%, 90%, and 93%, and specificities are 42%, 36%, and 35%, respectively.[12] For the purpose of this study, participants with a STOP-BANG score ≥ 3 points were classified at elevated risk for OSA, whereas scores of ≤ 2 points were considered low risk.

Statistical analyses

Descriptive statistics of participants' demographic and health characteristics were stratified by OSA risk status. We compared OSA risk groups using *t* tests for continuous variables and chi-square and Fisher's exact tests for categorical variables.

Informed by causal diagrams and prior studies, we selected age and BMI as potential confounders to be included in the adjusted statistical models. However, as HNSCC therapy may modify posttreatment BMI[13]—a typical predictor for OSA risk—we hypothesized that this anthropometric measure could mediate the relationship between HNSCC and OSA risk. Therefore, the analyses were not adjusted for BMI. Logistic and linear regression models, unadjusted and age-adjusted, were used to examine associations between tumor characteristics and OSA risk as well as cancer treatment and OSA risk. Statistical significance was set at a $P < .05$. All calculations were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

A total of 2,700 patients with HNSCC were identified from the electronic medical record search. Of those, 259 patients met the inclusion criteria, all were invited to the study, and 67 consented to participate. Age, sex, BMI, alcohol consumption, HNSCC location, HPV infection status, proportions of hypertension, and hyperlipidemia were similar between the study participants (n = 67) and those who were eligible but did not enroll in the study (n = 192).

Of the 67 participants, 57 (85%) were men, mean age was 62.0 years (7.7 standard deviation [SD]), mean BMI was 28.7 kg/m^2 (4.6 SD), mean neck circumference was 16.3 inches (1.2 SD), and mean time between end of cancer treatment and OSA screening was 61.2 months (42.9 SD). The majority of participants (n = 40, 60%) had elevated risk for OSA (STOP-BANG ≥ 3), and 14 (21%) had a diagnosis of OSA prior to this study. Among participants with a previous OSA diagnosis, 13 obtained elevated risk, one low risk for OSA, and none had further OSA testing after completing cancer treatment. Comparisons between elevated and low-risk OSA groups demonstrated statistically significant differences in hyperlipidemia prevalence (n = 16, 40% vs n = 2, 7%, $P = .004$). In contrast, alcohol consumption, smoking, other comorbidities, and long-term cancer treatment sequelae were similar between OSA risk groups (**Table 1**).

The most common tumor location was the base of the tongue, in 33 (49%) of the participants, followed by the tonsils (n = 23, 35%), larynx (n = 5, 7%), and other sites including soft palate, mouth floor, oral tongue, vocal cord, posterior pharynx, and nasopharynx (n = 6, 9%). The majority of participants had a tumor stage I or II (n = 58, 87%), were HPV-positive (n = 62, 93%), and received treatment only with chemoradiation (n = 50, 75%). Other treatment options included radiotherapy alone (n = 11, 16%), surgery only (n = 3, 4.5%), and a combination of modalities (n = 3, 4.5%). Of importance, none of the participants with laryngeal tumors were treated with surgery. No difference in tumor location, tumor stage, HPV status, cancer treatment, or total radiation dose was observed between OSA

Table 1—Demographic and health characteristics of 67 patients at least 1 year free of head and neck squamous cell carcinoma screened for obstructive sleep apnea at Michigan Medicine.

	Total Sample, n (%)	Elevated OSA Risk, n (%)*	Low OSA Risk, n (%)*
Sample size, n	67	40 (60)	27 (40)
Age (SD), y	62.0 (7.7)	61.7 (7.1)	63.2 (8.5)
Body mass index (SD), kg/m^2	28.7 (4.6)	29.6 (4.5)	27.3 (4.1)
Neck circumference (SD),** inches	16.3 (1.2)	16.5 (1.3)	15.8 (0.5)
Alcohol intake (SD), g/wk	57 (73)	68 (87)	37 (47)
Male	57 (85)	37 (92)	20 (74)
Female	10 (15)	3 (8)	7 (26)
Smoking	28 (42)	15 (38)	13 (48)
Hypertension	23 (34)	20 (50)	3 (11)
Hyperlipidemia	18 (26)	16 (40)	2 (7)
Diabetes	7 (10)	5 (13)	2 (7)
Hypothyroidism	21 (31)	12 (30)	9 (33)
Anxiety	13 (19)	5 (13)	8 (30)
Depression	16 (24)	9 (23)	7 (26)
Gastroesophageal reflux	13 (19)	9 (23)	4 (15)
Xerostomia	12 (18)	6 (15)	6 (22)
Dysphagia	11 (16)	7 (18)	4 (15)

*Based on STOP-BANG score with a cutoff ≥ 3 points. **n = 18 missing (6 high and 12 low risk). OSA = obstructive sleep apnea, SD = standard deviation.

risk groups (**Table 2**). Further, the presence and severity of mucositis, esophagitis, dysphagia, dermatitis, xerostomia, and dysgeusia during cancer treatment were similar between OSA risk groups (data not shown).

The mean STOP-BANG score was 3.0 (1.4 SD), 3.8 (1.2 SD), and 1.8 (0.4 SD) in the total sample, the elevated OSA risk, and the low OSA risk group, respectively. The frequency of positive STOP-BANG items varied by OSA risk groups. In particular, snoring, daytime sleepiness, observed apneas, hypertension, BMI, and neck circumference were higher in the elevated OSA risk group, while age and sex were similar between these groups.

Table 2—Tumor characteristics of 67 patients, at least 1 year free of head and neck squamous cell carcinoma, screened for obstructive sleep apnea with the STOP-BANG questionnaire.

Characteristics	Overall Sample, n (%) (n = 67)	Elevated OSA Risk, n (%)* (n = 40)	Low OSA Risk, n (%)* (n = 27)
Tumor location			
Base of the tongue	33 (49)	23 (58)	10 (37)
Other**	34 (51)	17 (42)	17 (63)
Tumor stage			
I–II	58 (87)	34 (85)	24 (89)
III–IV	9 (13)	6 (15)	3 (11)
Human papillomavirus			
Positive	57 (93)	36 (95)	21 (91)
Negative	4 (7)	2 (5)	2 (9)
Cancer treatment			
Chemoradiation	50 (75)	28 (70)	22 (81)
Other***	17 (25)	12 (30)	5 (19)
Mean total radiation dose, Gy (SD)	65.7 (14.9)	65.6 (15)	65.7 (14)

*Based on STOP-BANG score with a cutoff ≥ 3 points. **Other tumor locations included tonsil, larynx, and other less-frequent sites. ***Radiotherapy, surgery, or a combination of modalities. OSA = obstructive sleep apnea, SD = standard deviation.

Age-adjusted logistic regression models suggested a 2-fold increased odds of elevated OSA risk approaching statistical significance in participants with tumors at the base of the tongue in comparison to other locations (odds ratio = 2.3, 95% confidence interval 0.9, 6.4). A similar analysis was conducted between participants with tumors of the base of the tongue and tonsils subsites obtaining similar odd ratios (odds ratio = 2.1, 95% confidence interval 0.7, 6.4). However, associations between tumor stage or cancer therapy and OSA risk were nonsignificant (odds ratio =1.4, 95% confidence interval 0.3, 6.1 and odds ratio = 0.5, confidence interval 95% 0.2, 1.7, respectively) (**Table 3**). In age-adjusted models, associations between STOP-BANG scores and tumor location, tumor stage, and cancer treatment were similarly nonsignificant (**Table 4**).

DISCUSSION

In this sample of 67 patients free of HNSCC for at least 1 year, we found that 60% had an elevated OSA risk. However, there were no clear associations between tumor location, tumor stage, or cancer treatment and elevated OSA risk. Of note, we observed gaps between the prevalence of elevated OSA risk (60%) and records of OSA diagnosis (21%) in this sample, suggesting a substantial proportion of undiagnosed OSA among HNSCC patients. These findings shed light on a unique population that may be vulnerable to OSA but not considered a high priority for OSA evaluation after HNSCC therapy.

Despite the absence of statistically significant associations between the proposed tumor characteristics and OSA risk, the estimated 2-fold increased odds of elevated OSA risk among participants with tumors of the base of the tongue vs other tumor sites is biologically plausible, thus noteworthy. Most oropharyngeal cancers arise from the base of the tongue or tonsils,[14] and their clinical presentation may include snoring and OSA.[1] In addition, HNSCC therapy has been proposed as a risk factor for OSA.[9] Particularly, radiation applied to the tumor bed may predispose to OSA at least by 2 mechanisms: first, the compromise of the tongue's function to maintain the upper airway patency[15] by inducing fibrosis of its muscular structure and affecting its dynamics,[16–18] and second, cranial nerve lesions—particularly of the hypoglossal nerve—that may affect the tone of the upper airway dilator muscles,[19] predisposing to airway collapse. If an association exists between tumors of the base of the tongue and OSA risk, then infections by high-risk HPV—mostly types 16, 18, and 33[20,21]—should be considered as possible risk factors for OSA as these are responsible for the majority of tumors in this anatomical region, independently of other classic HNSCC-predisposing factors.[14,22,23] In this study, as the large majority of participants had HPV-positive tumors (n = 62, 93%), exploration of the relationships between HPV infection status and elevated OSA risk was limited.

The tumor staging system for HNSCC combines tumor location, TNM system (tumor size, lymph node involvement, and metastasis), and, more recently, HPV status (only for oropharyngeal tumors). Staging groups range from I–IV, with I–II corresponding to early disease and III–IV to advanced disease.[24] In agreement with our findings, prior studies that examined relationships between HNSCC stage and OSA did not find any association[9]; however, most previously studied samples had advanced cancer stage,[25,26] in contrast to this study where most participants had early-stage HNSCC. The use of older editions of the American Joint Committee on Cancer's staging manual may explain the observed difference in the tumor stage between previous and present studies as older versions of the manual (seventh and prior editions) did not include HPV status and overestimated oropharyngeal cancer staging.[24] A recent study in newly diagnosed patients with HNSCC found a positive correlation between tumor size and OSA severity before cancer treatment.[27] Of note, participants in the present study were cancer-free at the time of the OSA screening; thus, they were unlikely affected by the plausible mass effect and reduced upper airway volume mechanism suggested by the study mentioned above.

The most common treatment of HNSCC is a combination of chemotherapy and radiotherapy.[6] A recent systematic review suggested an association between HNSCC surgery and OSA, whereas other treatment modalities did not show a clear relationship with OSA.[9] In the present study, the high proportion of chemoradiation use and the consistency of the total radiation dose received by the participants limited analyses between cancer treatment groups in relation to OSA risk.

Beyond HNSCC characteristics and treatment, traditional risk factors common to these tumors and OSA were also evaluated. For example, tobacco and alcohol use were not associated with elevated OSA risk or STOP-BANG scores. These findings were likely influenced by the large proportion of oropharyngeal and HPV-positive tumors prevalent among study participants, where smoking and alcohol use are usually less common.

The prevalence of OSA in the general adult population, evaluated by sleep apnea testing, is reported to be between 9 and 38%.[7] Similarly, the prevalence of elevated OSA risk in the general adult

Table 3—Associations of tumor location, stage and treatment with risk of obstructive sleep apnea among 67 patients at least 1 year free of head and neck squamous cell carcinoma.

Variable	n	Unadjusted, OR (95% CI)	Age-adjusted, OR (95% CI)
Base of tongue vs other*	67	2.3 (0.8, 6.3)	2.3 (0.9, 6.4)
Stage III–IV vs I–II	67	1.4 (0.3, 6.2)	1.4 (0.3, 6.1)
CR only vs other**	67	0.5 (0.2, 1.7)	0.5 (0.2, 1.7)

*Tonsil, larynx, and other locations. **Radiotherapy, surgery, or a combination of modalities. CI = confidence interval, CR = chemoradiation, OR = odds ratio.

Table 4—Associations of tumor location, stage, and treatment with STOP-BANG scores in a sample of 67 patients at least 1 year free of head and neck squamous cell carcinoma.

Variable	n	Unadjusted, Beta (95% CI)	Age-Adjusted, Beta (95% CI)
Base of tongue vs other*	67	0.4 (−0.3, 1.1)	0.4 (−0.3, 1.1)
Stage III–IV vs I–II	67	−0.02 (−1.0, 1.0)	−0.04 (−1.0, 0.9)
CR only vs other**	67	−0.4 (−1.2, 0.4)	−0.5 (−1.3, 0.3)

*Tonsil, larynx, and other locations. **Radiotherapy, surgery, or a combination of modalities. CI = confidence interval, CR = chemoradiation.

population, obtained by screening tools such as the Berlin[28] and STOP-BANG questionnaires, ranges from 6.3–38.6%.[11,29,30] These variations are attributed to the age distributions, the questionnaire, and the cutoff value used to define OSA risk.[29,30] The elevated OSA risk prevalence using the STOP-BANG questionnaire with a cutoff ≥ 3 points has been reported as 38% in a middle-age population[30] and 27.5% in older adults (mean age 57 years [16 SD]).[11] The observed proportion of elevated OSA risk in the present study (60%) nearly doubles the reported prevalence among older adults. An increased prevalence of elevated OSA risk, in the absence of clear recommendations on OSA screening and testing in patients who have had HNSCC, may lead to underrecognition and treatment, as suggested by the disproportion (ratio 3:1) of participants with elevated OSA risk vs those with a formal OSA diagnosis observed in our study. If untreated, OSA could lead to adverse cardiovascular, metabolic, cognitive, mental health, and quality-of-life consequences, which may further compromise outcomes for HNSCC patients.[31–38]

Of the eight STOP-BANG items, only age and sex were similar between the OSA risk groups. The typical age for HNSCC diagnosis (> 50 years)[39] corresponds to a positive STOP-BANG age item.[11] Indeed, the vast majority of study participants (n = 65, 97%) were older than 50 years, independent of their OSA risk group; therefore, there was no difference in distribution. Sex distribution was also similar between OSA risk groups, likely attributed to the small number of women enrolled in the study (n = 10) in comparison to men (ratio women:men 1:5.7).

The present study has several strengths that merit discussion. First, this study has the largest sample size among prior studies that have examined associations between HNSCC and OSA risk. Second, assessments of tumor location and HPV status as OSA risk factors are novel.

However, this article has several limitations. This study did rely on the STOP-BANG scores rather than objective assessments to identify increased risk for OSA. While objective OSA testing is required to elucidate potential relationships between HNSCC and OSA, the cost of these assessments would have been difficult to justify for a sample of this size in an early-stage study. The STOP-BANG is well-validated (although not in the population with HNSCC) and offers a cost-effective alternative, widely used in diverse clinical and research settings. The small number of women in the sample limited sex-specific analysis but is likely to reflect in part the demographics of HNSCC. Selection bias cannot be ruled out as patients concerned about their sleep would be more likely to participate in this study. Data on pain management with opioids, which may increase the risk of sleep-disordered breathing, were not collected. Finally, despite the sizeable sample, the heterogeneity of HNSCC treatments and HPV status were not high, which may have limited our ability to evaluate their potential impact.

CONCLUSIONS

This study demonstrated that elevated OSA risk is common—affecting the majority of study participants—at 1 year or more after HNSCC has been absent. Despite this increased prevalence, no clear-cut associations between tumor location, tumor stage, cancer treatment, and elevated risk for OSA were found. The reported findings suggest that clinicians should consider evaluation of post-HNSCC patients, particularly those with oropharyngeal tumors, for signs and symptoms of OSA.

ABBREVIATIONS

BMI, body mass index
HNSCC, head and neck squamous cell carcinoma
HPV, human papillomavirus
OSA, obstructive sleep apnea
SD, standard deviation

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