

REVIEW ARTICLES

## Obstructive sleep apnea in patients with head and neck cancer: a systematic review

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**Study Objectives:** Head and neck cancers (HNCs) may modify the upper airway anatomy and thereby increase the risk for obstructive sleep apnea (OSA). If untreated, OSA is associated with adverse outcomes. Identification of risk factors for OSA in patients with HNC is essential to promote proper evaluation, treatment, and improvement of sleep-related outcomes. In this review, we assessed associations between tumor stage, cancer treatment, and OSA in the population with HNC.

**Methods:** A systematic search of PubMed, EMBASE ([Embase.com](https://www.embase.com)), Cochrane Library ([Cochranelibrary.com](https://www.cochranelibrary.com)), Scopus, and Web of Science was conducted to identify articles related to OSA in patients with HNC. A total of 215 articles were identified, of which 14 were included in the qualitative synthesis. These studies included 387 participants.

**Results:** The most common cancer type, tumor location, and cancer therapy were squamous cell carcinoma, oropharynx, and surgery, respectively. Three of six articles reported an association between surgical treatment and OSA. Conversely, associations between tumor stage, radiotherapy, and OSA were found in only a minority of studies (15%). The prevalence of OSA was between 57% and 76% pre-cancer therapy and 12% and 96% afterward.

**Conclusions:** This review suggests a potential association between HNC surgery and OSA. An association between tumor stage, radiotherapy to the head and neck, and OSA is inconclusive. Further research is needed to examine the relationship between HNC and OSA.

**Keywords:** head and neck cancer, obstructive sleep apnea, tumor stage, surgery, radiotherapy

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### BRIEF SUMMARY

**Current Knowledge/Study Rationale:** Tumors of the head and neck may modify the anatomy of the upper airway and predispose to obstructive sleep apnea. If untreated, obstructive sleep apnea is associated with adverse outcomes. This review examined associations between tumor stage, cancer treatment, and obstructive sleep apnea in patients with head and neck cancer.

**Study Impact:** Obstructive sleep apnea is frequently observed among patients with head and neck cancer. Surgical treatment of head and neck cancer may be associated with obstructive sleep apnea; therefore, sleep testing of this population should be considered.

### INTRODUCTION

Head and neck cancers (HNCs) account for 53,000 incident cases associated with a mortality of 20% per year in the United States.<sup>1</sup> Risk factors include tobacco use, alcohol consumption, and viral infections (human papillomavirus and Epstein-Barr virus).<sup>2</sup> Among HNCs, squamous cell carcinoma is the most common type. These tumors may arise from structures close to the upper airway, cause anatomical abnormalities, and predispose patients to obstructive sleep apnea (OSA).<sup>3–5</sup>

OSA is characterized by recurrent collapse of the upper airway during sleep with corresponding oxygen desaturation and arousals. Untreated OSA is associated with cardiometabolic and neurocognitive impairment.<sup>4,6</sup> Polysomnography (PSG) is the gold standard for diagnosis of OSA, with a home sleep apnea test as an alternative.<sup>5</sup> The estimated prevalence of OSA in the general adult population is approximately 10–30%.<sup>7,8</sup>

however, prevalence significantly varies by age, sex, and body mass index (BMI).

While information regarding OSA among patients with HNC is limited, an increased risk for OSA has been suggested compared with the general population.<sup>9</sup> However, it is not clear what factors in patients with HNC are possibly associated with an increased risk for OSA. This review examines the association between tumor stage, cancer therapy, and OSA in patients with HNC.

### METHODS

An experienced health science librarian (C.S.) conducted a systematic search of PubMed, EMBASE ([Embase.com](https://www.embase.com)), Cochrane Library ([Cochranelibrary.com](https://www.cochranelibrary.com)), Scopus, and Web of Science to identify articles related to OSA in patients with HNC. The search strategy and inclusion criteria were developed prior to

conducting the systematic search. Five sentinel articles were used as a means of harvesting search terms, including Medical Subject Headings (MeSH), Emtree, and keywords terms. Cited reference searching using the 5 sentinel articles was also conducted in Scopus. English-language and adult filters were used on the search results. Findings are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses or PRISMA statement,<sup>10</sup> elaboration, and explanation.<sup>11</sup>

All searches were completed by 14 August 2019. A full description of the search strategy and complete list of search terms and limits used in each database are included in the supplemental material. Citations were imported into EndNote (Thomson Reuters, New York, NY) for deduplication, then exported into Excel (Microsoft Office 2016; Microsoft Corporation, Redmond, WA) for analysis.

A modified scheme of the Oxford Centre for Evidence-based Medicine for ratings of individual studies was used to determine the level of evidence of selected articles.<sup>12</sup> This scheme stratifies the level of evidence from 1 to 5, with 1 having the most robust evidence (randomized controlled trials) and 5 the weakest (expert opinion).

## RESULTS

The search strategy identified 215 articles (PubMed, 72; EMBASE, 51; Scopus, 55; Web of Science, 37; and Cochrane Library, 0). After removal of 11 duplicates, 204 studies were screened and 186 excluded as they were not relevant to OSA in HNC. Of the remaining 18 studies, 4 were excluded for the following reasons: a secondary analysis of previously published research, lack of objective sleep measures, and systematic reviews that contained early data before most of the reviewed articles were published or had a different approach to the present review. The current systematic review included a total of 14 studies (Figure 1) in the qualitative synthesis.<sup>13–26</sup> Two reviewers, R.G. and G.L.D., screened all articles with an overall 93% agreement rate. The disagreements were resolved by discussion.

### Characteristics of the studies

Table 1 summarizes characteristics of studies and participants. The search found articles published from 2001 to 2019. Most studies were conducted in the United States (3),<sup>13,22,24</sup> followed by Brazil (2),<sup>15,21</sup> Canada (2),<sup>14,18</sup> Taiwan (2),<sup>19,23</sup> China (1),<sup>26</sup> France (1),<sup>25</sup> Germany (1),<sup>17</sup> Israel (1),<sup>20</sup> and The Netherlands (1).<sup>16</sup>

Eleven of the 14 studies were cross-sectional, 2 were prospective cohort studies,<sup>23</sup> and 1 was a single-arm trial.<sup>14</sup> Most articles included in the current review had a level 4 evidence according to the modified scheme of the Oxford Centre for Evidence-based Medicine. The primary aims of most studies were to describe the prevalence of OSA in patients with HNC and to examine OSA as an outcome of surgical techniques or radiotherapy (RT).

### Participants

The total number of participants in this review was 387. The sample size range of individual studies was 14–56. The majority of studies had less than 25 participants, and most were men, with

a 4:1 ratio of men to women. The mean age was  $60.4 \pm 5$  years (range: 27–89 years), and the mean BMI was  $25.5 \text{ kg/m}^2$  (range:  $15\text{--}70 \text{ kg/m}^2$ ).

### Head and neck cancer

Table 2 summarizes HNC characteristics. While the most common tumor was squamous cell carcinoma, other types included nasopharyngeal carcinoma, lymphoma, sarcoma, adenocarcinoma, melanoma, and a few rare tumors. Tumor locations in descending order of frequency were oropharynx, larynx, oral cavity, tongue, nasopharynx, tonsils, nasal cavity, and salivary gland. The tumor, nodes, and metastasis (TNM) system by the American Joint Committee on Cancer and the Union for International Cancer Control was the standard for tumor staging in most studies.<sup>27</sup> This system combines the 3 tumor features to stratify patients in prognostic stage groups from 0 to IV. Stages 0–II correspond to early disease with better prognosis and stages III–IV are advanced stages with worse prognosis.<sup>27</sup> Only 4 studies described a stage group, with the majority of participants having advanced disease.<sup>15,18,20,25</sup> Surgery was the most common cancer therapy, followed by RT and chemoradiation. Only 1 study reported human papillomavirus status.<sup>24</sup>

Of the 7 reports that examined the relationship between tumor stage and OSA,<sup>14,16,18–20,24,25</sup> only 1 found an increased proportion of OSA among participants with advanced tumor stages in comparison to those with early tumor stages.<sup>16</sup>

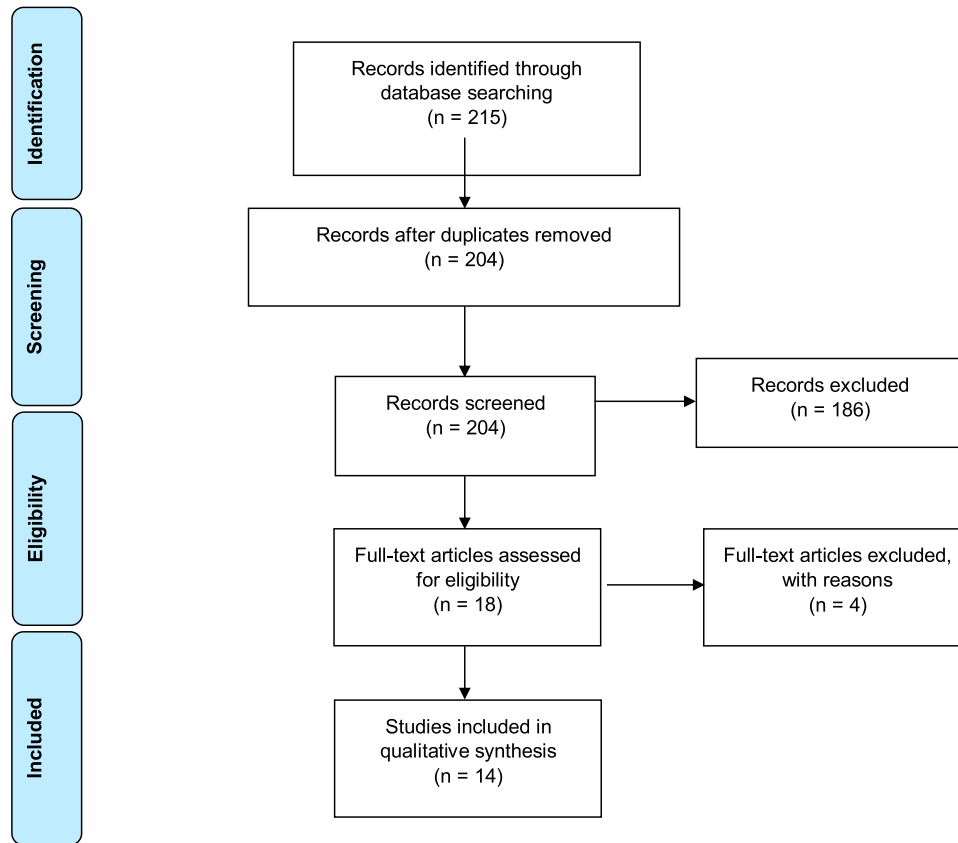
Among the 7 studies that examined associations between HNC surgery and OSA,<sup>17–19,21,25,26</sup> 3 showed evidence of a relationship. One study described worse and more frequent OSA postsurgery compared with presurgery (82% vs 57%). In addition, OSA was more severe in participants treated with supracricoid partial laryngectomy vs vertical partial laryngectomy.<sup>26</sup> In contrast, worse OSA with vertical partial laryngectomy than with horizontal partial laryngectomy<sup>21</sup> and increased odds of OSA in relation to surgical vs nonsurgical treatment (odds ratio = 5.5)<sup>18</sup> were observed in other articles.

Of the 8 studies that explored relationships between treatment of HNC with RT and OSA,<sup>17–19,21–25</sup> only 1 reported increased odds of OSA with RT use vs non-RT (odds ratio = 11.47).<sup>22</sup>

### Self-reported sleep measures

Table 3 summarizes sleep measures and characteristics of OSA in HNC. The vast majority of studies (85%) used self-reported measures of sleep variables and a minority used scales for quality of life. Eleven studies used the Epworth Sleepiness Scale (ESS) alone or in combination with other scales. The ESS is an 8-item questionnaire that measures daytime sleepiness, with scores ranging from 0 to 24. A score of 10 or above indicates excessive daytime sleepiness.<sup>28</sup> Alternative ESS thresholds (ie, 8 or 12) were utilized in several reports,<sup>18,20,26</sup> and thus limit comparisons across studies. Two of 4 studies that examined the relationship between ESS score and apnea-hypopnea index (AHI) found a correlation.<sup>21,25</sup> Three articles explored differences in ESS scores between participants with HNC with or without OSA, and only 1 reported statistical significance.<sup>22</sup> Other scales included OSA symptom questionnaires, the Pittsburg Sleep Quality Index, Functional Outcomes of Sleep

Figure 1—PRISMA flow diagram.



PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 1—Summary of studies and characteristics of patients with head and neck cancer tested for obstructive sleep apnea.

| Study, Country/Year                             | Study Design       | Level of Evidence <sup>a</sup> | n  | Age, Mean (Range), y      | Male/Female, n/n | BMI, Mean (Range), kg/m <sup>2</sup> |
|---|--------------------|--------------------------------|----|---------------------------|------------------|--------------------------------------|
| Friedman et al, <sup>13</sup> USA/2001          | Cross-sectional    | 4                              | 24 | 64.8 (39–89)              | 21/3             | 22 (16–31)                           |
| Payne et al, <sup>14</sup> Canada/2005          | Single-arm trial   | 2                              | 17 | 64 (42–76)                | 14/3             | 27 (16–37)                           |
| Israel et al, <sup>15</sup> Brazil/2006         | Cross-sectional    | 4                              | 22 | 63.5 (50–80)              | 20/2             | 25 (19–31)                           |
| Nesse et al, <sup>16</sup> The Netherlands/2006 | Cross-sectional    | 4                              | 33 | 62 (38–87)                | 23/10            | 25 (16–35)                           |
| Steffen et al, <sup>17</sup> Germany/2009       | Cross-sectional    | 4                              | 31 | 64.5 <sup>b</sup> (48–77) | 22/9             | 25 <sup>b</sup> (18–35)              |
| Qian et al, <sup>18</sup> Canada/2010           | Cross-sectional    | 4                              | 24 | 60.2 [S: 64, NS: 54]      | 16/8             | 28 (15–47)                           |
| Chan et al, <sup>19</sup> Taiwan/2012           | Cross-sectional    | 4                              | 26 | 52 (32–71)                | 24/2             | 25 (19–36)                           |
| Gilat et al, <sup>20</sup> Israel/2013          | Cross-sectional    | 4                              | 15 | 57 (27–79)                | 5/10             | 24                                   |
| Teixeira et al, <sup>21</sup> Brazil/2013       | Cross-sectional    | 4                              | 14 | 64.9 (41–84)              | 13/1             | 26 (19–29)                           |
| Faiz et al, <sup>22</sup> USA/2014              | Cross-sectional    | 4                              | 56 | 60 <sup>b</sup> (28–87)   | 43/13            | 29 <sup>b</sup> (12–70)              |
| Lin et al, <sup>23</sup> Taiwan/2014            | Prospective cohort | 2                              | 18 | 49                        | 15/3             | Pre: 24; post: 21                    |
| Huyett et al, <sup>24</sup> USA/2017            | Cross-sectional    | 4                              | 16 | 61.6 <sup>b</sup> (48–75) | 13/3             | 30 <sup>b</sup> (22–39)              |
| Loth et al, <sup>25</sup> France/2017           | Cross-sectional    | 4                              | 51 | 61.1 (44–76)              | 37/14            | 23 (16–33)                           |
| Ouyang et al, <sup>26</sup> China/2019          | Prospective cohort | 2                              | 40 | (44–67)                   | 37/3             | Pre: 23.3; post: 23.6                |

<sup>a</sup>Level of evidence ranged from 1 to 5 with lower numbers representing higher level of evidence (based on a modified scheme of the Oxford Centre for Evidence-based Medicine for ratings of individual studies). <sup>b</sup>Median was used instead of the mean. BMI = body mass index, NS = nonsurgical, S = surgical.

**Table 2—Characteristics of head and neck tumors and relationship between tumor stage, cancer treatment, and obstructive sleep apnea.**

| Study, Country/Year                             | Cancer Type    | Cancer Site   | Cancer Staging (TNM and Stage Groups <sup>a</sup> ) | Relationship Cancer Stage and OSA | Cancer Treatment (%)                  | Relationship Cancer Treatment and OSA   |
|---|----------------|---|---|-----------------------------------|---------------------------------------|---|
| Friedman et al, <sup>13</sup> USA/2001          | SCC            | Larynx, tongue, pharynx   | N/A   | N/A                               | Surgery (100), RT (42)                | Higher frequency of OSA in RT group (analysis not performed due to small sample size) |
| Payne et al, <sup>14</sup> Canada/2005          | SCC            | Oral, oropharynx  | Tumor size (1–7 cm)                                 | No relationship                   | Surgery (76), other (24)              | N/A   |
| Israel et al, <sup>15</sup> Brazil/2006         | SCC            | Larynx  | Stage groups I and II, T1–3, N0, M0                 | No relationship                   | Surgery (100)                         | N/A   |
| Nesse et al, <sup>16</sup> The Netherlands/2006 | SCC            | Tongue, oropharynx, oral floor, tonsil  | T2–4, N0–2, M0                                      | Suggested a relationship          | Surgery (39), RT (22), combined (39)  | N/A   |
| Steffen et al, <sup>17</sup> Germany/2009       | SCC            | Oropharynx, larynx  | T1–3, N0–3, M0                                      | N/A                               | Surgery (100), RT (66)                | No relationship   |
| Qian et al, <sup>18</sup> Canada/2010           | SCC            | Oral, oropharynx  | Stage groups I–IV, T2–3, N0–2, M0                   | No correlation                    | Surgery (13), CRT (37), combined (50) | Increased odds (OR = 5.5) of OSA with surgical vs nonsurgical treatment               |
| Chan et al, <sup>19</sup> Taiwan/2012           | SCC            | Tongue  | Tumor size (1–5 cm)                                 | No relationship                   | Surgery (100), CRT (65)               | No relationship   |
| Gilat et al, <sup>20</sup> Israel/2013          | SCC<br>No SCC  | Mobile tongue   | Stage groups II–IV, T2–3, N0–1, M0                  | No relationship                   | Surgery (100), RT (87), CRT (13)      | N/A   |
| Teixeira et al, <sup>21</sup> Brazil/2013       | N/A            | Larynx  | T1–2  | N/A                               | Surgery (100), RT (36)                | Worse OSA with VPL vs HPL, but not for RT vs non-RT                                   |
| Faiz et al, <sup>22</sup> USA/2014              | SCC,<br>no SCC | Oropharynx, 21; larynx, 10; oral, 5; nasopharynx, 3; nasal cavity, 3; salivary gland, 2 | T0–4  | N/A                               | RT (79), surgery (21)                 | Increased odds of OSA (OR = 11.47) with RT vs non-RT group                            |
| Lin et al, <sup>23</sup> Taiwan/2014            | NPC            | Nasopharynx   | NA  | Not performed (small group)       | CRT (100)                             | No significant difference before and after RT   |
| Huyett et al, <sup>24</sup> USA/2017            | SCC            | Larynx, oropharynx  | T1–4, N0–2, M0                                      | No relationship                   | CRT (88), RT (12)                     | No relationship   |
| Loth et al, <sup>25</sup> France/2017           | SCC            | Oropharynx  | Stage groups III and IV, T2–4, any N, and M0        | No relationship                   | CRT (80), CRT + surgery (20)          | No relationship   |
| Ouyang et al, <sup>26</sup> China/2019          | SCC            | Larynx  | T1 N0 M0, T2 N0 M0, T3 N0 M0                        | N/A                               | Surgery (100)                         | Worse OSA in SCPL vs HPL  |

<sup>a</sup>Prognostic stage groups ranged from 0–IV with early stages (0–II) having a better prognosis. CRT = chemoradiation, HPL = horizontal partial laryngectomy, N/A = not available, NPC = nasopharyngeal carcinoma, OSA = obstructive sleep apnea, RT = radiotherapy, SCC = squamous cell carcinoma, SPCL = supracricoid partial laryngectomy, TNM = primary tumor (T), regional lymph nodes (N), and distant metastasis (M) (each item has a number assigned according to specific measures and extension of the tumor), VPL = vertical partial laryngectomy.

**Table 3—Summary of sleep measures and characteristics of obstructive sleep apnea in patients with head and neck cancer.**

| Study, Country/Year                             | Sleep and Other Scales                     | Relationship Sleep Scale and OSA  | Sleep Study Device Level <sup>a</sup> | Pre/Post Cancer Treatment | Months After Cancer Treatment                 | Cutoff Index to Diagnose OSA, events/h | Frequency of OSA, %             | OSA Treatment                        |
|---|--|---|---------------------------------------|---------------------------|---|--|---------------------------------|--------------------------------------|
| Friedman et al, <sup>13</sup> USA/2001          | 10 Symptoms questions                      | N/A   | 1                                     | Post                      | N/A   | RDI 15–40, mild ≥ 40 severe            | 91.7                            | PAP, 36% adherence                   |
| Payne et al, <sup>14</sup> Canada/2005          | None                                       | N/A   | 2                                     | Pre                       | N/A   | AHI ≥20                                | 76                              | No                                   |
| Israel et al, <sup>15</sup> Brazil/2006         | ESS  | N/A   | 1                                     | Post                      | 1–72  | AHI ≥5                                 | 86                              | NA                                   |
| Nesse et al, <sup>16</sup> The Netherlands/2006 | ESS, 5 OSA symptoms questionnaire          | N/A   | 2                                     | Post                      | 6–60  | AHI ≥5 + symptoms                      | 12                              | No                                   |
| Steffen et al, <sup>17</sup> Germany/2009       | ESS, clinic visit                          | No relationship   | 3                                     | Post                      | >6  | RDI ≥20 moderate to severe             | 19                              | NA                                   |
| Qian et al, <sup>18</sup> Canada/2010           | ESS  | No correlation with AHI   | 1                                     | Post                      | 6–96  | RDI ≥5                                 | 96                              | PAP, 0% adherence due to intolerance |
| Chan et al, <sup>19</sup> Taiwan/2012           | None                                       | N/A   | 1                                     | Post                      | 6–132   | AHI ≥5                                 | 53.8                            | No                                   |
| Giati et al, <sup>20</sup> Israel/2013          | ESS  | No correlation with AHI   | 1                                     | Post                      | 24–72   | AHI ≥5                                 | 53                              | No                                   |
| Teixeira et al, <sup>21</sup> Brazil/2013       | ESS  | Positive correlation with AHI   | 1                                     | Post                      | 9–102   | AHI ≥5                                 | 92.8                            | No                                   |
| Faiz et al, <sup>22</sup> USA/2014              | ESS, PSQI                                  | ESS: Significant difference OSA vs no-OSA; PSQI: no difference                                | 1                                     | Post                      | Variable: during active cancer therapy to >60 | AHI ≥5                                 | OSA: 84; with RT: 88; no RT: 67 | PAP, 75% adherence                   |
| Lin et al, <sup>23</sup> Taiwan/2014            | ESS, SRBD symptoms, Snore VAS              | N/A   | 1                                     | Pre and Post              | Pre: N/A; post: ≥6                            | AHI ≥5                                 | Pre: 72; post: 78               | PAP, 0% adherence due to xerostomia  |
| Huyett et al, <sup>24</sup> USA/2017            | ESS FOSQ-10, UW QOL                        | No relationship   | 3, 1–3 nights                         | Post                      | >3 to 40                                      | AHI ≥5                                 | 50                              | NA                                   |
| Loth et al, <sup>25</sup> France/2017           | 1. ESS; 2. EORTC QLQ C-30; 3. EORTC H&N 35 | 1. Positive correlation with AHI; 2. significant difference OSA vs no-OSA; 3. no relationship | 3                                     | Post                      | >12   | AHI ≥10                                | 25.5                            | PAP, 36% adherence                   |
| Ouyang et al, <sup>26</sup> China/2019          | ESS  | N/A   | 1                                     | Pre and Post              | Pre: before treatment; post: 3                | AHI ≥5                                 | Pre: 57; post: 82               | No                                   |

<sup>a</sup>Sleep study devices: level 1 is an attended in-laboratory baseline polysomnography; levels 2, 3, and 4 are home sleep apnea tests. AHI = apnea-hypopnea index, EORTC H&N 35 = European Organization for Research and Treatment of Cancer Head and Neck Cancer module, EORTC QLQ-C-30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire, ESS = Epworth Sleepiness Scale, FOSQ-10 = Functional Outcomes of Sleep Questionnaire, N/A = not available, OSA = obstructive sleep apnea, PAP = positive airway pressure, PSQI = Pittsburgh Sleep Quality Index, RDI = respiratory disturbance index, RT = radiotherapy, Snore VAS = snoring visual analog scale, SRBD symptoms = sleep-related breathing-disorders symptoms, UW QOL = University of Washington Quality of Life Questionnaire.

Questionnaire, University of Washington Quality of Life Questionnaire, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ C-30), and European Organization for Research and Treatment of Cancer Head and Neck Cancer module (EORTC H&N 35). Among these less-common scales, EORTC QLQ C-30 (used only in 1 study) showed worse quality of life scores in participants with HNC with OSA vs those without OSA. The difference in scores was statistically significant.<sup>25</sup>

### Objective sleep measures

The objective measure of OSA can be performed with a variety of devices. Sleep testing device classification was assigned to 4 levels in a commonly used manner, according to the number of monitoring parameters, and the attendance of a technologist at a sleep laboratory.<sup>29</sup> Nine studies used a level 1 sleep device (in-laboratory PSG), followed by level 3 and 2 (home sleep study devices). Sleep testing occurred mostly between 3 months to 11 years post-cancer treatment. However, only 2 studies included OSA measures pre- and post-cancer treatment,<sup>23,26</sup> while 1 study performed OSA testing exclusively prior to cancer therapy.<sup>14</sup>

In all studies, an obstructive respiratory event was defined as follows:

- Apnea: cessation of respiration for 10 seconds or longer
- Hypopnea: decreased respiratory effort of at least 30% or 50% from baseline for 10 seconds and associated with an oxygen desaturation of 3% or 4%

The number of obstructive respiratory events (apneas, hypopneas) per hour of sleep (ie, AHI for the PSG and respiratory event index for the home sleep apnea test) indicates the presence and severity of OSA.<sup>30</sup> The respiratory disturbance index (RDI) includes apneas, hypopneas, and respiratory effort-related arousal (reduction of airflow associated with arousal that does not meet the criteria for apnea or hypopnea).<sup>30,31</sup>

The most common threshold used to diagnose OSA was an AHI of  $\geq 5$  events/h. A few studies used AHI or respiratory event index thresholds  $\geq 10$  or  $\geq 20$  events/h,<sup>14,25</sup> or an RDI with thresholds of  $\geq 5$ , 15, 20, or 40 events/h.<sup>13,17,18</sup> The terms AHI and RDI were used instead of respiratory event index in several studies that objectively measured sleep with portable devices.<sup>17,24,25</sup> Only 1 study combined symptoms of OSA with AHI to diagnose OSA.<sup>16</sup>

### Obstructive sleep apnea

The prevalence of OSA ranged between 57% and 76% prior to HNC treatment and 12–96% post-treatment. However, only 2 studies assessed OSA before and after HNC therapy (using in-laboratory PSG and an AHI threshold of  $\geq 5$  events/h), and both reported an increase in the prevalence of OSA post-cancer treatment.<sup>23,26</sup>

The most frequently used OSA treatment was positive airway pressure (PAP). Five studies examined PAP therapy, reporting adherence between 0% and 75%.<sup>13,18,22,23,25</sup> Barriers to the use of PAP treatment included participants' disinterest in pursuing this therapy, xerostomia, and pressure

intolerance.<sup>18,23,25</sup> Oral appliances and tracheostomy as OSA treatments were rare.<sup>22,25</sup>

## DISCUSSION

This systematic review of published evidence suggests a possible association between HNC surgery and OSA. Conversely, data that examined associations between tumor stage, RT, and OSA are limited.

### Associations between HNC and OSA

Three articles reported associations between HNC surgery and OSA. There are several plausible explanations for these associations. First, there could be thickening of the arytenoid mucosa, loss of support after total or partial removal of the thyroid cartilage, and displacement of the tongue with reduction in the posterior airway space, as observed in those treated with supracricoid partial laryngectomy vs vertical partial laryngectomy.<sup>26</sup> It is also possible that the increase in OSA could be explained by the loss of support for the neoglottis after removal of a wing of the thyroid cartilage in participants treated with vertical partial laryngectomy vs horizontal partial laryngectomy,<sup>21</sup> and the addition of tissue that lacks normal tongue dynamics<sup>32</sup> among participants treated with oral cavity resection with radial forearm free flap reconstruction of the tongue.<sup>18</sup>

A possible association between RT and OSA was first described by Friedman et al.<sup>13</sup> Subsequently, other authors have examined this relationship,<sup>17–19,21–25</sup> but only 1 group has found evidence in support of this association.<sup>22</sup> Possible mechanisms may include lesion of the hypoglossal, vagus, or recurrent laryngeal nerves with successive dysfunction of the pharyngeal dilator muscles<sup>33</sup>; fibrosis,<sup>34</sup> which reduces the strength and retraction of the tongue base<sup>35,36</sup>; and salivary gland dysfunction, with reduced production of mucins and consequent increase in salivary viscosity and resistance of the airway.<sup>22</sup>

Only 1 of 7 articles suggested a relationship between tumor stage and OSA; however, this study was performed after cancer treatment.<sup>16</sup> Of the studies that included sleep testing prior to HNC treatment, only 1 evaluated associations between tumor size and OSA, reporting insignificant findings.<sup>14</sup> Despite the limited evidence, such data raise the possibility that mass effect and reduction in the upper airway volume<sup>37</sup> may not be a relevant mechanism for OSA as may be expected in this population.

The association between HNC and OSA could be confounded by common risk factors, such as age, sex, smoking, and alcohol use. The age of participants in these studies, predominantly 55–65 years old, corresponds to the typical age for development of both HNC and OSA,<sup>38,39</sup> while the male-to-female 4:1 ratio is expected for HNC,<sup>40</sup> as well as for OSA in premenopausal women. In postmenopausal women, the frequency of OSA is almost equal to males.<sup>41,42</sup> Most participants had a normal BMI, but some were overweight and obesity was rare. The observed BMI distribution may be attributed to feeding difficulties reported post-RT (dysphagia, xerostomia, and trismus).<sup>43,44</sup> Thus, in the HNC population—unlike other

populations—it is possible that BMI is not an important factor in OSA.<sup>5</sup>

Alcohol and tobacco use are common risk factors for OSA in populations without HNC.<sup>45,46</sup> However, in HNC participants, 4 studies explored a relationship between the use of alcohol, tobacco, and OSA, but none found evidence of an association.<sup>14,19,24,25</sup>

### Sleep testing, prevalence, and treatment of OSA in HNC

Heterogeneous OSA assessment across studies limits the interpretation of their findings—for example, level 1 and 2 sleep testing devices are more precise than level 3 and 4 devices that are likely to underestimate the presence and severity of OSA<sup>47</sup> and use of different cutoff values or an alternative index (RDI) to measure OSA.

The prevalence of OSA pre- and post-cancer treatment ranged between 57% and 76% and 12% and 96%, respectively.<sup>13–26</sup> The 3 studies that examined OSA pre-cancer treatment reported more consistent proportions compared with post-treatment, despite heterogeneity in participants' age, tumor features (type, location, and treatment), and sleep-assessment methods.<sup>14,23,26</sup>

A wider range of OSA frequency was reported in HNC participants post-oncologic treatment, despite similarities of demographics and tumor features. Variation in study designs (ie, exclusion and inclusion criteria, OSA assessment strategies, and thresholds) could explain the differences in OSA frequency among these studies. For example, the 3 studies with the lowest prevalence (12–25.5%) had some differences that set them apart from the rest.<sup>16,17,25</sup> The first one with an OSA prevalence of 12% screened all participants (n = 33) for OSA symptoms and daytime sleepiness (ESS). Only those with a positive screening (n = 10) underwent a PSG, and the prevalence calculation included participants not tested with PSG.<sup>16</sup> The second study with an OSA prevalence of 19% required an RDI  $\geq 20$  events/h without symptoms,<sup>17</sup> and the third one with an OSA proportion of 25.5% required a respiratory event index of  $\geq 10$  without symptoms.<sup>25</sup> This may explain a lower count of OSA cases; however, other studies with similar parameters and cutoff values reported higher frequency,<sup>13,14</sup> suggesting that other variables may be involved.

Of interest, 2 studies reported an increase in OSA prevalence post-treatment vs pretreatment despite differences in tumor characteristics and oncologic treatment protocols.<sup>23,26</sup>

In 5 studies that examined OSA therapy, PAP was the most common. However, adherence to PAP therapy was unsurprisingly variable (0–75%) and influenced by disinterest in pursuing PAP therapy, pressure intolerance, and xerostomia. Lower adherence may be improved through increased patient support, as has been observed in other populations with similar proportions of PAP therapy compliance.<sup>48</sup>

It should be noted that there are several limitations to the available data. The majority of the studies used a cross-sectional design, which decreases their strength of evidence. In addition, many studies had small sample sizes and insufficient statistical power to detect an effect. Although not unexpected, there was heterogeneity between studies regarding tumor type, tumor location, cancer treatment, methods of sleep testing, and inconsistent use of OSA definitions.

Direct comparisons between studies were, therefore, not always possible, and neither was a meta-analysis.

## CONCLUSIONS

Available data suggest a potential association between HNC surgery and OSA. Evidence of associations between tumor stage, RT to the head and neck, and OSA is limited. The use of PAP therapy to treat OSA in patients with HNC is feasible, but barriers to treatment could hamper OSA care. Given the literature gap demonstrated through this systematic review, further research is warranted to disentangle the relationship between HNC and OSA.

## ABBREVIATIONS

AHI, apnea-hypopnea index  
 BMI, body mass index  
 ESS, Epworth Sleepiness Scale  
 HNC, head and neck cancer  
 OSA, obstructive sleep apnea  
 PAP, positive airway pressure  
 PSG, polysomnography  
 RDI, respiratory distress index  
 RT, radiotherapy

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