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REVIEW ARTICLES

# Association of obstructive sleep apnea and nocturnal hypoxemia with all-cancer incidence and mortality: a systematic review and meta-analysis

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**Study Objectives:** Biological models suggest that obstructive sleep apnea (OSA) is potentially carcinogenic. We aimed to clarify the inconsistent epidemiological literature by considering various traditional and novel OSA severity indices.

**Methods:** We systematically searched PubMed, Embase, Scopus, and the Cochrane Library for observational or randomized studies of associations of OSA, measured by diagnostic codes or any index, each with all-cancer incidence or mortality in adults, compared with participants with no/mild OSA. Two reviewers independently selected studies, extracted data, and evaluated study bias using the Newcastle-Ottawa scale and quality of evidence using GRADE (Grading of Recommendations Assessment, Development, and Evaluation). We performed inverse variance-weighted, random-effects meta-analyses and sensitivity analyses.

**Results:** We included 20 observational studies (5,340,965 participants), all with moderate/low bias, from 1,698 records. Based on T90 (sleep duration with oxygen saturation < 90%), patients with OSA who had moderate (T90 > 1.2%, hazard ratio [HR] = 1.28, 95% confidence interval [CI] = 1.07–1.54) and severe nocturnal hypoxemia (T90 > 12%, HR = 1.43, 95% CI = 1.16–1.76) experienced 30%–40% higher pooled all-cancer risk than normoxemic patients, after multiple adjustment for covariates including obesity. Furthermore, severe nocturnal hypoxemia nearly tripled all-cancer mortality (HR = 2.66, 95% CI = 1.21–5.85). Patients with apnea-hypopnea index–defined severe OSA, but not moderate OSA, had higher all-cancer risk (HR = 1.18, 95% CI = 1.03–1.35) but similar all-cancer mortality as patients without OSA. An OSA diagnosis was not associated with all-cancer risk. Evidence quality ranged from low to moderate. Insufficient evidence was available on the oxygen desaturation index, lowest/median saturation, and arousal index.

**Conclusions:** In patients with OSA, nocturnal hypoxemia is independently associated with all-cancer risk and mortality. Future studies should explore if risk differs by cancer type, and whether cancer screening and OSA treatment are beneficial.

**Systematic Review Registration:** Registry: PROSPERO; URL: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=220836; Identifier: CRD42021220836.

**Keywords:** obstructive sleep apnea, cancer, polysomnography, intermittent hypoxia, repetitive hypoxia, nocturnal hypoxia, apnea-hypopnea index

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### BRIEF SUMMARY

**Current Knowledge/Study Rationale:** Biological models suggest that obstructive sleep apnea (OSA) is potentially carcinogenic. However, epidemiological studies are inconsistent, possibly because traditional indices of OSA severity may be inadequate in predicting cancer risk.

**Study Impact:** In this meta-analysis of observational studies, moderate and severe nocturnal hypoxemia, as measured by sleep duration with < 90% oxygen saturation (T90), predicted all-cancer risk and mortality, while OSA severity stratified by the traditional apnea-hypopnea index was associated with all-cancer risk but not mortality. An OSA diagnosis alone was not associated with all-cancer incidence. Future studies should assess OSA via a broader variety of indices, explore associations with specific cancer types, and investigate whether cancer screening or OSA treatment is beneficial.

## INTRODUCTION

Obstructive sleep apnea (OSA) is highly prevalent, yet underdiagnosed and undertreated. Globally, close to 1 billion adults aged 30–69 years experience OSA, with over 400 million of them having moderate to severe disease.[1] The repetitive upper airway collapse and oxygen desaturation in OSA cause disrupted sleep, daytime sleepiness, poor productivity, and decreased quality of life.[2] The accompanying autonomic dysfunction and inflammatory cascades aggravate cardiovascular diseases, such as hypertension, ischemic heart disease, arrhythmias, and stroke,[3–5] as well as neuropsychiatric disorders such as Alzheimer disease, vascular dementia, anxiety, and depression.[6–8]

Emerging evidence over the last decade suggests that OSA could adversely modify the incidence and prognosis of cancer.[9]

As cancer is the second-leading cause of death worldwide,[10] the implications are enormous. The theoretical foundation for this relationship is rooted in repetitive hypoxia and reoxygenation, which is a metabolic driver of carcinogenesis.[5,11–17] Intermittent hypoxia in OSA, as opposed to chronic hypoxia in other respiratory conditions, has been shown in animal models and cell lines to be a particularly potent enhancer of various hallmarks of cancer, such as angiogenesis, immune evasion, and metastasis.[9,18]

Despite the strong biological plausibility, epidemiological evidence is inconclusive, with initial studies reporting higher cancer incidence and mortality among patients with OSA[19–21] and subsequent studies, including a nationwide analysis of 5.6 million individuals, reporting no association.[22,23] The inconsistency is to the extent that 2 previous meta-analyses on this topic,[24,25] published just 3 months apart in 2015 and using almost identical primary studies, came to the exact opposite conclusions. All included studies in these meta-analyses used only the traditional apnea-hypopnea index (AHI) to grade OSA severity, which treats cessations (apnea) and reductions in airflow (hypopnea) as equivalent events and does not account for the magnitude or duration of oxygen desaturations.[26] A variety of other indices addressing these limitations are available and better predict health outcomes, such as cardiovascular disease, perioperative complications, and mortality.[26–28] These non-AHI indices were recently investigated as predictors of cancer risk in large epidemiological studies totaling > 40,000 patients, published in the last few years.[29–31]

Given the tremendous clinical significance of the link between OSA and cancer, it is timely to clarify the inconsistent epidemiological relationship. In this systematic review and meta-analysis, we aim to comprehensively pool the associations of OSA measured by various indices, each with the overall incidence and mortality of cancer. As our focus is to compare different measures of OSA severity in relation to cancer, we will focus solely on the overall or aggregate cancer risk. Individual cancer types are numerous, each with distinct mechanisms that can be separately reviewed once the optimal indicator of OSA in predicting cancer risk has been established.

## METHODS

This review is registered on PROSPERO (CRD42021220836) and is reported in accordance with the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[32] The PRISMA checklist is included in **Table S1** in the supplemental material.

### Search strategy

We searched PubMed, Embase, Scopus, and the Cochrane Library from inception until June 6, 2021, using the following free-text search strategy: (sleep apnea OR nocturnal hypoxia OR nocturnal hypoxemia) AND cancer AND (incidence OR incident OR mortality). We did not search for "sleep-disordered breathing," as this is a heterogeneous umbrella term that includes primary snoring, OSA, central sleep apnea, and sleep-related hypoventilation syndromes.[33,34] We also hand-searched the bibliographies of included articles and relevant reviews, journals, or electronic sources to identify 2 additional relevant records.[31,35]

### Study selection

Records were uploaded onto Rayyan (Qatar Computing Research Institute (QCRI), Doha, Qatar),[36] which is an online systematic review platform that enables authors to manually screen abstracts in a blinded manner. Two authors independently selected potentially eligible studies based on title and abstract followed by full-text screening. Eligibility criteria are summarized in **Table 1**. In brief, we included randomized trials or observational studies of adults aged at least 18 years, which reported the association of sleep apnea with all-cancer incidence or mortality, in comparison to healthy controls without sleep apnea or with mild disease. We accepted the presence or severity of sleep apnea measured by any index such as the AHI, respiratory disturbance index, and clinical diagnosis (eg, *International Classification of Diseases* [ICD] diagnostic codes, sleep duration with arterial oxygen saturation [$SaO_2$] < 90% [T90], oxygen desaturation index [ODI]). We accepted conference abstracts, academic dissertations, and other gray literature. We excluded case reports, reviews, letters, and non-English publications. We also excluded studies that reported a specific cancer type, as these would have introduced heterogeneity in our analysis of the overall or total cancer risk, given that existing evidence has suggested a differential risk (and indeed even a protective effect) based on cancer type.[22,37]

### Data extraction

Two authors extracted the following data from each article into a standardized extraction spreadsheet template: first author, year published, study design, setting, country, sample size, percentage male, mean/median age, body mass index (BMI), intervention/exposure, outcomes, covariates, statistical methods, and key findings.

### Risk of bias

As all included studies were observational, we used the Newcastle-Ottawa scale to evaluate the risk of bias at the study level (**Table S2** in the supplemental material).[38,39] Two authors independently graded studies as having a high (< 5 stars), moderate (5–7 stars), or low risk of bias (≥ 8 stars) as per previous reviews.[40–42]

### Statistical analysis

We found sufficient data to meta-analyze the longitudinal associations between baseline OSA measured by the AHI, ICD, and T90 with all-cancer incidence and mortality. Using the generic inverse-variance method, we separately pooled the hazard ratios (HRs) for all-cancer incidence as follows: (1) AHI (mild vs none, moderate vs none, and severe vs none), (2) T90 (moderate vs none, severe vs none), and (3) ICD (presence vs absence of diagnosis). Standard AHI cutoffs used to stratify OSA severity were as follows: none (< 5), mild (5–14), moderate (15–29), and severe (≥ 30).[43] For nocturnal hypoxemia measured by T90, cutoffs used were consistent with prior

**Table 1**—Predefined eligibility criteria for the systematic review.

| | Inclusion Criteria | Exclusion Criteria |
|---|---|---|
| Population | Adults aged at least 18 years | |
| Intervention/exposure | Presence or severity of sleep apnea measured by any index such as the apnea-hypopnea index (AHI), respiratory disturbance index (RDI), clinical diagnosis (eg, *International Classification of Diseases* [ICD] diagnostic codes, sleep duration with arterial oxygen saturation < 90% [T90], oxygen desaturation index [ODI]) | |
| Comparators | Healthy controls without sleep apnea or with mild disease | |
| Outcomes | All-cancer incidence or mortality | Incidence or mortality of specific cancer types or sites |
| Study design | Randomized trials or observational studies, either published in peer-reviewed journals as full-length articles, or indexed as gray literature (conference abstracts, academic dissertations) | Case reports, reviews, letters, and non-English publications |

publications: none/mild (< 1.2), moderate (1.2–12), and severe (> 12),[21,30,31] except for 1 study that defined mild T90 as < 2.1%.[29] We repeated these analyses for all-cancer mortality, with the exclusion of ICD due to insufficient studies. We favored maximally covariate-adjusted estimates where available, and also included 2 studies that reported standardized incidence ratios in the pooled analysis,[44,45] as these sufficiently approximate HRs.[46] We used random-effects models in all analyses to account for anticipated heterogeneity in the observational estimates,[47] and assessed between-study heterogeneity using the $I^2$ statistic.[48] We considered an $I^2$ < 30% to indicate low heterogeneity between studies, 30%–60% to indicate moderate heterogeneity, and > 60% to indicate substantial heterogeneity. For outcomes with significant heterogeneity, we performed prespecified sensitivity analyses that included only studies that fulfilled the following characteristics: (1) median duration of follow-up ≥ 5 years, (2) adjustment for ≥ 1 covariate, (3) adjustment for obesity, (4) moderate or low risk of bias, and (5) prospective studies. There were insufficient studies (< 10 per outcome) to assess publication bias via visual inspection of funnel plot asymmetry, Egger's bias, or trim-and-fill as planned.[49–51] We conducted all analyses using Review Manager (RevMan, version 5.4; The Cochrane Collaboration, London, United Kingdom)[52] in accordance with statistical approaches from the Cochrane Handbook, and considered a 2-sided *P* value < .05 as statistically significant.

### Certainty of evidence

We evaluated the quality of pooled evidence at the outcome level (**Table S3** in the supplemental material) using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system.[53]

## RESULTS

The study selection process is summarized in **Figure S1** in the supplemental material. We included 21 articles from 1,510 nonduplicated records after excluding irrelevant articles based on title, abstract, and full-text screening.[19–23,29–31,37,44,45,54–63] There were 20 unique studies, as 1 study was reported in 2 records.[60,63]

### Study characteristics

The 20 included studies (**Table 2**) comprised a combined cohort of 5,340,965 patients. All studies had a moderate or low risk of bias based on the Newcastle-Ottawa scale (**Table S2**). All studies reported OSA, except for 2 studies that reported sleep apnea that mainly comprised OSA with some cases of central sleep apnea.[19,44] A sensitivity analysis excluding these studies did not change our findings. Across the 20 cohorts, 12 were retrospective, 7 were prospective, and 1 was a case-cohort study. Eleven studies were conducted in North America, 5 studies in Europe, 2 studies in Oceania, 1 in South America, and 1 in Asia. The majority of studies adjusted for age, sex, and BMI. Follow-up duration ranged from 3.5 to 22 years.

### Cancer incidence

#### *OSA measured by AHI*

Compared with patients without OSA, patients with severe OSA based on the AHI (**Figure 1**) had significantly higher pooled hazards of incident cancer (hazard ratio [HR] 1.18, 95% confidence interval [CI] 1.03–1.35, $I^2$ = 29%). In contrast, patients with mild OSA or moderate OSA were not at increased risk of incident cancer. Seven of 8 primary studies[20,21,23,29,30,54,56] had adjusted for important confounders, such as age, sex, and BMI, of which 6 studies[20,21,23,29,30,58] adjusted for smoking use, and 2 studies[29,56] adjusted for diabetes, hypertension, cardiac disease, and chronic obstructive pulmonary disease (COPD). One conference abstract did not provide information on covariates.[62] For the meta-analysis on severe OSA, which had some heterogeneity ($I^2$ = 29%), prespecified sensitivity analyses (**Table S4** in the supplemental material) showed that, when including only studies with (1) a median duration of follow-up ≥ 5 years, (2) adjustment for ≥ 1 covariate, or (3) moderate or low risk of bias, the association remained significant. Among the 2 prospective studies (pooled HR 1.59, 95% CI 0.79–3.19, $I^2$ = 72%) and the 5 studies that adjusted for obesity (pooled HR 1.23, 95% CI 0.99–1.53, $I^2$ = 42%), the association lost significance, although heterogeneity increased. The exclusion of 1

**Table 2**—Characteristics of included studies.

| Study | Study Design | Sample Size | Country | Median Age (y) | % Male | Covariates | Measurement of OSA | Cancer Type(s) Included (%total cancers) | Median Follow-up Duration (y) | NOS Risk of Bias |
|---|---|---|---|---|---|---|---|---|---|---|
| Agostinelli 2020[31] | Retrospective clinic-based cohort | 37,998 | United States | NR | NR | Age, sex, BMI, hypertension, COPD, coronary artery disease, diabetes, center, race, and ethnicity | PSG (AHI, T90) | NR | 5.9 | 6 |
| Brenner 2019[54] | Retrospective clinic-based cohort | 5,243 | Israel | All: 51 (± 13.1)<br>Non-OSA: 40.3 (± 14.5)<br>Mild OSA: 49.2 (± 13.0)<br>Moderate OSA: 53.0 (± 11.7)<br>Severe OSA: 53.6 (± 12.3) | All: 74.5<br>No OSA: 65.4<br>Mild OSA: 69.2<br>Moderate OSA: 73.6<br>Severe OSA: 83.2 | Age, sex, BMI | PSG (AHI) | Breast (8), cervix (1), cholangiocarcinoma (0.8), colorectal (12.7), endometrium (1.3), upper gastrointestinal (1.7), head and neck (1.1), kidney (1.3), hematologic (6.5), lung (7.2), melanoma (4.0), meningioma (1.9), pancreaticobiliary (2.1), prostate (15.4), thyroid (1.14), urothelial (4.8), other (2.7) | 5.9 | 7 |
| Rodriguez Calle 2020[62] | Prospective community-based cohort | 1,050 | Spain | NR<br>Age range: 30–70 | 100 | NR (conference abstract) | RP (AHI, T90) | NR | 22.4 | 7 |
| Campos-Rodriguez 2013[21] | Retrospective clinic-based cohort | 4,910 | Spain | NR | NR | Age, sex, BMI, smoking use, alcohol intake | PSG or RP (AHI, T90) | Malignant neoplasm, including but not limited to colorectal (16.5), prostate (16.1), lung (9.2), breast (7.7) | 4.5 | 8 |
| Gislason 2016[45] | Retrospective administrative database cohort | 320,000 | Iceland | NR | NR | Age, sex | ICD | Malignant neoplasm, including but not limited to breast (2.7), prostate (3.2), melanoma (0.3) | 10 | 6 |
| Gozal 2016[22] | Retrospective administrative database matched cohort | 3,408,906 | United States | NR | 50.2 | Age, sex, morbid obesity, hypertension, type 2 diabetes, ischemic heart disease, coronary heart failure, stroke, cardiac arrhythmias, and depression | ICD | Bladder (5.9), breast (21.1), cervix (1.6), colorectal (11.0), kidney (6.0), liver (2.2), lung (11.1), melanoma (12.9), ovary (2.7), pancreas (2.9), prostate (23.3), rectum (0.09) | 3.5 | 8 |
| Huang 2021[55] | Prospective community-based cohort | 65,330 | United States | 73 | 0 | Race/ethnicity, family history of cancer, BMI, height, pack-years of smoking, alcohol | ICD | Smoking-related cancers (lung, colorectal, bladder, pancreas, kidney, oral cavity, | 8 | 5 |

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**Table 2**—Characteristics of included studies. (*Continued*)

| Study | Study Design | Sample Size | Country | Median Age (y) | % Male | Covariates | Measurement of OSA | Cancer Type(s) Included (%total cancers) | Median Follow-up Duration (y) | NOS Risk of Bias |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | drinking, physical activity, sleep duration, duration of hormonal therapy use by type, history of type 2 diabetes, aspirin use, and recent physical examination | | stomach, esophagus, liver, cervix uteri, pharynx, larynx, nasal cavities) (33.4)<br>Alcohol-related cancers (breast, colorectal, oral cavity, esophagus, liver, pharynx, larynx, nasal cavities) (46.3)<br>Obesity-related cancers (breast, colorectal, uterus, ovary, pancreas, kidney, thyroid, multiple myeloma, gallbladder, stomach, esophagus, liver) (65.0) | | |
| Jara 2020[37] | Retrospective administrative database matched cohort | 1,377,285 | United States | 55.2 | 94 | Age, sex, year of cohort entry, smoking status, alcohol use, obesity, and comorbidity | ICD | ICD-9 diagnosis codes for any malignant cancers excluding nonmelanomaSkin malignancies, including but not limited to kidney (6.8), pancreatic (2.8), melanoma (7.4), brain (1.3), colorectal (10.1), breast (1.2), bladder (8.7), cervical (0.1), liver (3.0), lung (17.9), ovarian (0.1), prostate (36.8), thyroid (1.8), uterine (0.2), pharyngeal (1.8) | 7.4 | 7 |
| Justeau 2020[29] | Prospective clinic-based cohort | 8,748 | France | 61 | 64.5 | Age, sex, BMI, smoking status, alcohol intake, diabetes, hypertension, medical history of cardiac disease and COPD, marital status, type of sleep study, and study site | RP or PSG (AHI, T90, ODI) | Malignant neoplasm including but not limited to lung (10.0), breast (9.3), colorectal (18.2), prostate (9.5) | 5.8 | 9 |
| Kendzerska 2021[56] | Retrospective clinic-based cohort | 33,711 | Canada | 50 | 58 | Age, sex, alcohol use disorder, heart failure, COPD, hypertension and diabetes at baseline, clinic site and year of sleep study, and treatment for OSA as a time-dependent covariate | PSG (AHI, T90) | NR | 7 | 7 |

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**Table 2**—Characteristics of included studies. (*Continued*)

| Study | Study Design | Sample Size | Country | Median Age (y) | % Male | Covariates | Measurement of OSA | Cancer Type(s) Included (%total cancers) | Median Follow-up Duration (y) | NOS Risk of Bias |
|---|---|---|---|---|---|---|---|---|---|---|
| Kendzerska 2014[23] | Retrospective clinic-based cohort | 9,629 | Canada | 48 | 62 | Age, sex, BMI, and smoking status | PSG (AHI) | NR | 7.8 | 7 |
| Labarca 2019[61] | Prospective clinic-based cohort | 889 | Chile | 49.6 | 57.6 | Age, sex, alcohol use disorder, chronic heart failure, COPD, hypertension, diabetes at baseline; OSA treatment (time-varying) | HSAT (T90) | NR | 4.7 | 5 |
| Marshall 2014[20] | Prospective community-based cohort | 389 | Australia | AHI < 5 events/h: 52.8<br>AHI 5–14 events/h: 54.7<br>AHI > 15 events/h: 55.1 | AHI < 5 events/h: 73.1<br>AHI 5–14 events/h: 76.5<br>Moderate–severe AHI > 15 events/h: 72.2 | Age, sex, BMI (normal, overweight, obese), waist circumference (small, medium, or large), smoking status (never, ex, current), and excluding people with cancer history | HSAT (AHI) | ICD-9 diagnosis codes for any malignant cancers (% not reported) | 20 | 7 |
| Martínez-García 2014[57] | Retrospective clinic-based cohort | 5,427 | Spain | NR | NR | Age, sex, BMI, smoking status, alcohol intake, type of sleep study, and enrollment hospital | PSG or RP (AHI, T90) | All types of cancer, including but not limited to respiratory tract, gastrointestinal tract, urinary tract, breast, prostate, hepatobiliary, brain, pancreatic, genital tract, thyroid, skin melanoma, hematologic (% not reported) | 4.5 | 9 |
| Nieto 2012[19] | Prospective community-based cohort | 1,522 | United States | 47.5 | 55.1 | Age (time scale), sex, BMI, BMI squared, smoking | PSG (AHI, T90) | ICD-9 diagnosis codes for any malignant cancers (% not reported) | 22 | 7 |
| Polonis 2019[59] | Prospective clinic-based cohort | 161 | United States | Non-OSA: 35.6<br>OSA: 47.3 | Non-OSA: 67<br>OSA: 87 | Telomere length, age, BP, heart rate, BMI, sex, DM, dyslipidemia, hypertension, smoking, race | PSG (AHI) | NR | 12.7 | 7 |
| Sillah 2019a[58] | Retrospective clinic-based cohort | 328 | United States | NR | NR | Age, sex, BMI, and smoking | PSG or HSAT (AHI, T90) | All cancers, including breast, colorectal, uterus, kidney, lung, lymphoma, melanoma, prostate, thyroid (% not reported) | 5.3 | 7 |
| Sillah 2019b[30] | Retrospective clinic-based case-cohort | 1,466 | United States | 51.8 | 57.1 | Age, sex, BMI, race, smoking status | PSG or HSAT (AHI, T90) | NR | 5.07 | 5 |

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**Table 2**—Characteristics of included studies. (*Continued*)

| Study | Study Design | Sample Size | Country | Median Age (y) | % Male | Covariates | Measurement of OSA | Cancer Type(s) Included (%total cancers) | Median Follow-up Duration (y) | NOS Risk of Bias |
|---|---|---|---|---|---|---|---|---|---|---|
| Sillah 2018[44] | Retrospective clinic-based cohort | 34,402 | United States | 51.6 | 57.4 | Age, sex | ICD | ICD-3 diagnosis codes for any malignant cancers or metastatic disease, including but not limited to prostate (13), pancreas (2.5), melanoma (8.2), lung and bronchus (7.3), kidney (6.3), female breast (14.4), uterus (5.3), colorectal (5), other sites (37.8) | 5.3 | 6 |
| Singh 2018[60] and Singh 2019[63] | Retrospective clinic-based cohort | 23,571 | Australia | NR | NR | Age, sex, BMI, smoking, socioeconomic status, and blood pressure | PSG (AHI) | NR | 11.9 | 7 |

AHI = apnea-hypopnea index, BMI = body mass index, COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus, HSAT = home sleep apnea test, ICD = *International Classification of Diseases*, NOS = Newcastle-Ottawa scale, NR = not reported, OSA = obstructive sleep apnea, PSG = polysomnography, RP = validated respiratory polygraphy; T90 = sleep duration with arterial oxygen saturation < 90%.

study that used the respiratory disturbance index rather than the AHI to measure OSA did not change our meta-analysis findings.[20]

### *Nocturnal hypoxemia in OSA, as measured by T90*

Patients with OSA who had moderate (T90 1.2–12%, HR 1.28, 95% CI 1.07–1.54, $I^2$ = 0%) and severe (T90 > 12%, HR 1.43, 95% CI 1.16–1.76, $I^2$ = 69%) nocturnal hypoxemia had significantly higher pooled hazards of incident cancer (**Figure 2**), compared with those with no/mild nocturnal hypoxemia (T90 < 1.2%). Five of 6 included studies[21,23,29–31] had adjusted for age, sex, and BMI; 4[21,23,29,30] also adjusted for smoking, and 2 studies[29,31] further adjusted for race, alcohol, hypertension, diabetes, cardiac disease, and COPD. One conference abstract did not provide information on covariates.[62] For the meta-analysis on severe nocturnal hypoxemia, which had substantial heterogeneity ($I^2$ = 69%, n = 6), the association remained significant in all prespecified sensitivity analyses (**Table S4**; studies with a median duration of follow-up ≥ 5 years, adjustment for ≥ 1 covariate, adjustment for obesity, and a moderate or low risk of bias). Heterogeneity was lower ($I^2$ = 0%, n = 5) in the subgroup of studies with ≥ 5 years of follow-up.

One additional large retrospective study of 33,711 Canadian participants,[56] which was not included in the meta-analysis as it used a unique T90 cutoff of > 30%, found an association (HR 1.32, 95% CI 1.08–1.61; absolute risk difference 2.38%, 95% CI 0.47–4.31; number needed to harm = 42) with all-cancer incidence after adjusting for 11 covariates (**Table 2**). The authors additionally reported a small increase in the hazard of incident cancer (HR 1.02, 95% CI 1.01–1.04) per 5% increase in T90 after similar adjustment. In contrast, another retrospective cohort study of 19,327 Australian participants reported no increased hazards (HR 1.01, 95% CI 0.94–1.08) of incident cancer among patients with nocturnal hypoxemia measured by T90, although their cutoff used for T90 was unspecified.[63]

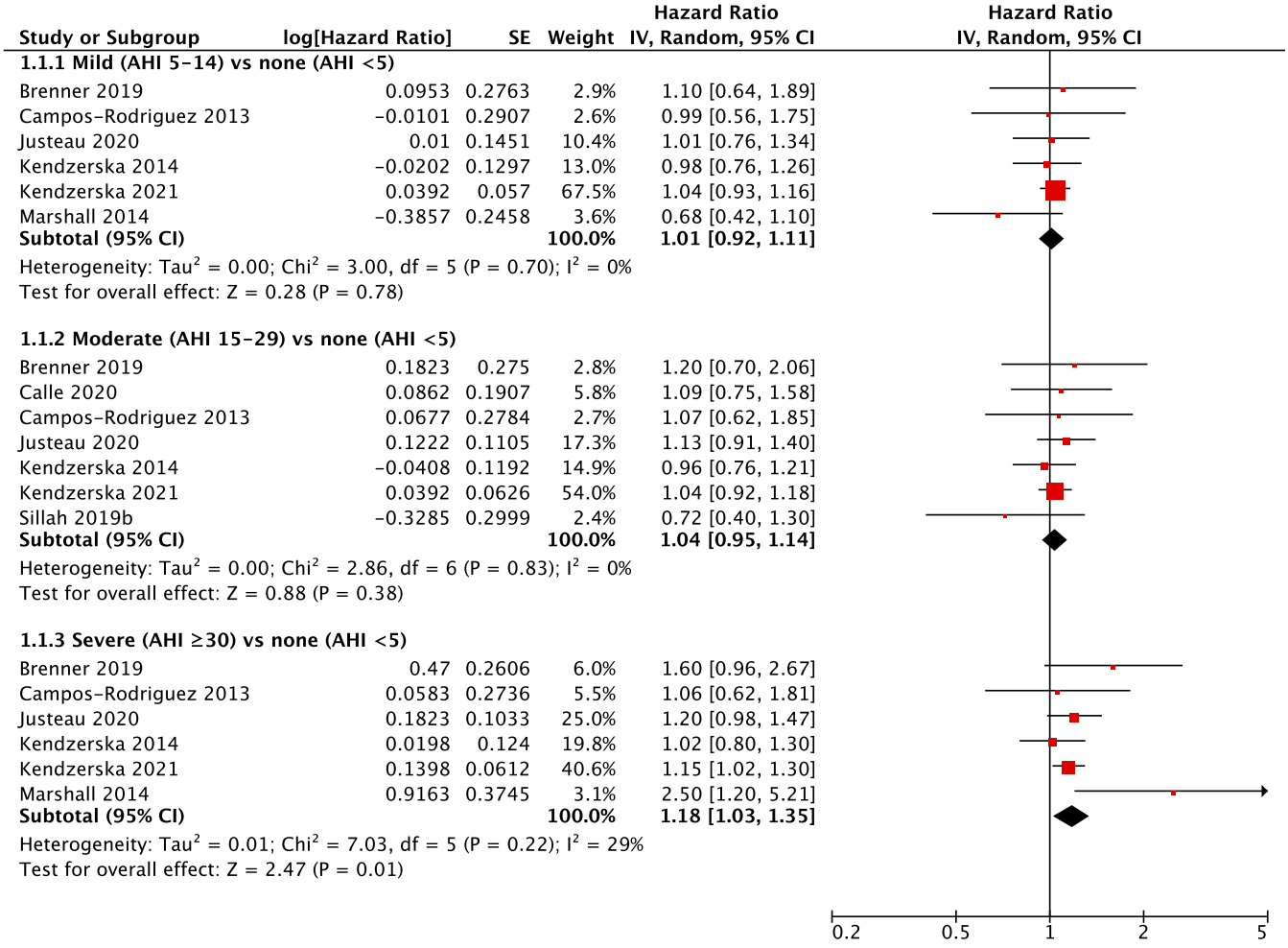
### *OSA measured by ICD*

Five studies reported ICD diagnosis of OSA,[22,37,44,45,55] of which 3[22,37,44] specifically indicated ICD-9 diagnosis. Among the 5 studies, 2 studies adjusted only for age and sex. The 3 other studies[22,37,55] all adjusted for age, sex, and BMI; 2 studies[37,55] further adjusted for smoking and alcohol, and 2 studies[22,55] further adjusted for hypertension, diabetes, and cardiac disease. Compared with patients without OSA, patients with a diagnosis of OSA (**Figure S2** in the supplemental material) were not at increased pooled hazards of incident cancer (HR 1.26, 95% CI 0.86–1.85). Heterogeneity in this analysis was considerable ($I^2$ = 100%). The association did not achieve statistical significance and heterogeneity remained considerable ($I^2$ = 100%) in all prespecified sensitivity analyses (**Table S4**), although meta-analysis of the 4 studies with a median duration of follow-up ≥ 5 years showed an equivocal relationship (pooled HR 1.34, 95% CI 0.97–1.85, $I^2$ = 99%).

### *OSA measured by ODI, lowest $SaO_2$, and arousal index*

Two studies investigated OSA diagnosed by the ODI 3% (either as a continuous or categorical variable) and found no association with cancer incidence,[29,30] after multiple adjustment for age, sex,

**Figure 1**—Longitudinal associations between mild (n = 62,630), moderate (n = 64,757), and severe (n = 62,630) OSA, diagnosed based on the AHI, with all-cancer incidence.




Black diamonds are the estimated pooled HR for each random-effects meta-analysis; red box sizes reflect the relative weight apportioned to studies in the meta-analysis. AHI = apnea-hypopnea index, CI = confidence interval, HR = hazard ratio, IV, inverse variance, OSA = obstructive sleep apnea.

BMI, smoking status and other covariates. Meta-analysis could not be performed as ODI severity was stratified according to quartiles[29] and tertiles,[30] respectively. One of these studies further investigated the utility of lowest $SaO_2$ and the arousal index as continuous and categorical variables and found no associations with cancer incidence after multiple adjustment.[30]

## Cancer mortality

### *OSA measured by AHI*

Patients with severe OSA, moderate OSA, and mild OSA based on AHI were not at increased pooled hazards of cancer mortality (**Figure 3**) compared with those without OSA, after adjustment for age, sex, and BMI.[19,20,57,58]

### *Nocturnal hypoxemia in OSA, as measured by T90*

Patients with OSA who had severe nocturnal hypoxemia (T90 > 12%) were at an increased pooled hazard of cancer mortality (HR 2.66, 95% CI 1.21–5.85, $I^2$ = 64%) compared with patients with no/mild nocturnal hypoxemia (T90 < 1.2%) after adjustment for age, sex, BMI, and smoking.[19,57,58] One of these studies further adjusted for alcohol intake, type of sleep study, and enrollment hospital.[57] Compared with patients without OSA, patients with moderate OSA were not at an increased risk of cancer mortality (**Figure 4**). Sensitivity analyses were not performed as there were only 3 studies.

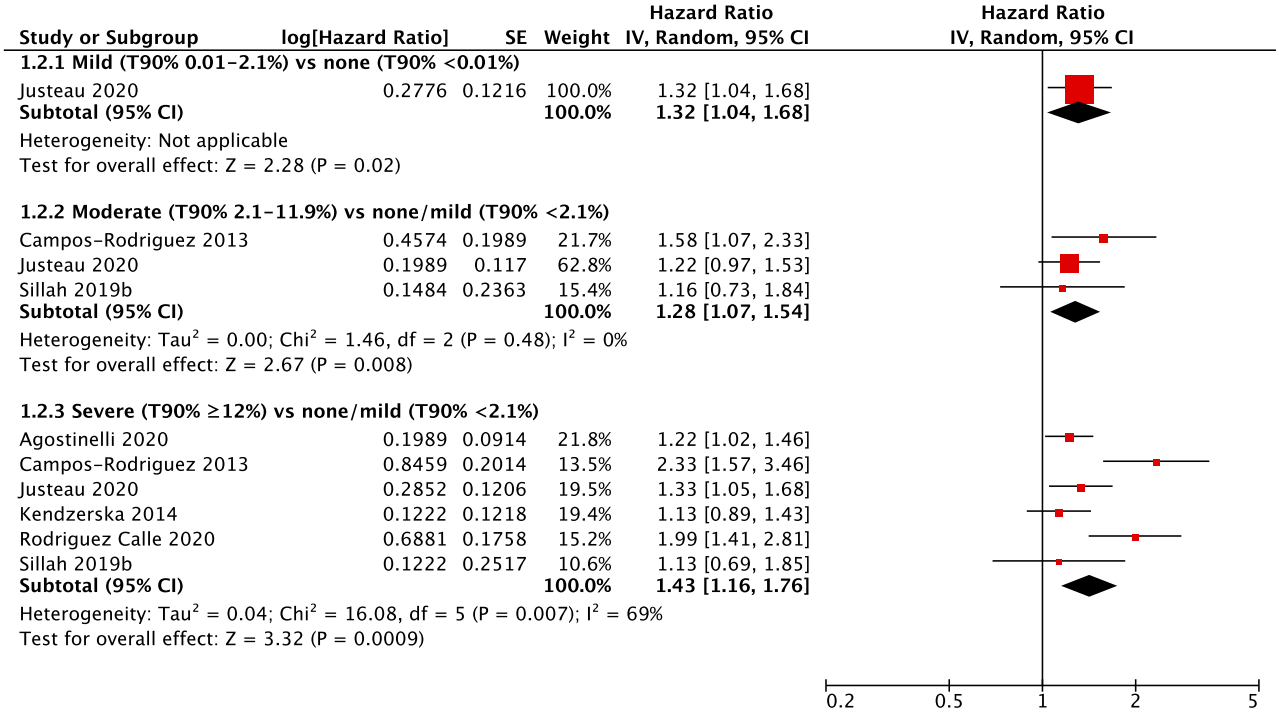
### *OSA measured by ICD*

One study with a median follow-up of 3.5 years found no association between an ICD diagnosis of OSA with the overall risk of cancer metastases or risk of cancer mortality.[22] This nationwide population sample also found no increased cancer mortality for 12 individual types of cancer among patients with an ICD diagnosis of OSA.

### *OSA measured by ODI, lowest $SaO_2$, and arousal index*

No studies in the existing literature explored other measures of OSA (such as the ODI, lowest $SaO_2$, and arousal index)

**Figure 2**—Longitudinal associations between moderate (n = 15,124) and severe (n = 63,801) OSA, diagnosed based on percentage T90, with all-cancer incidence.




Black diamonds are the estimated pooled HR for each random-effects meta-analysis; red box sizes reflect the relative weight apportioned to studies in the meta-analysis. An estimate from a single study for mild OSA (n = 8,748) based on T90 is included for visual comparison. CI = confidence interval, HR = hazard ratio, IV, inverse variance, OSA = obstructive sleep apnea, T90 = sleep duration with arterial oxygen saturation < 90%.

individually in relation to cancer mortality in the existing literature. However, 1 additional study, excluded from meta-analysis, used latent class analysis incorporating 4 variables (T90, ODI 3%, lowest $SaO_2$, and median $SaO_2$) to derive a "hypoxemic cluster."[61] They reported that severe hypoxemia (HR 5.75, 95% CI 1.03–32.17) but not moderate hypoxemia (HR 1.11, 95% CI 0.91–13.61) was associated with all-cancer mortality.

### Quality of evidence

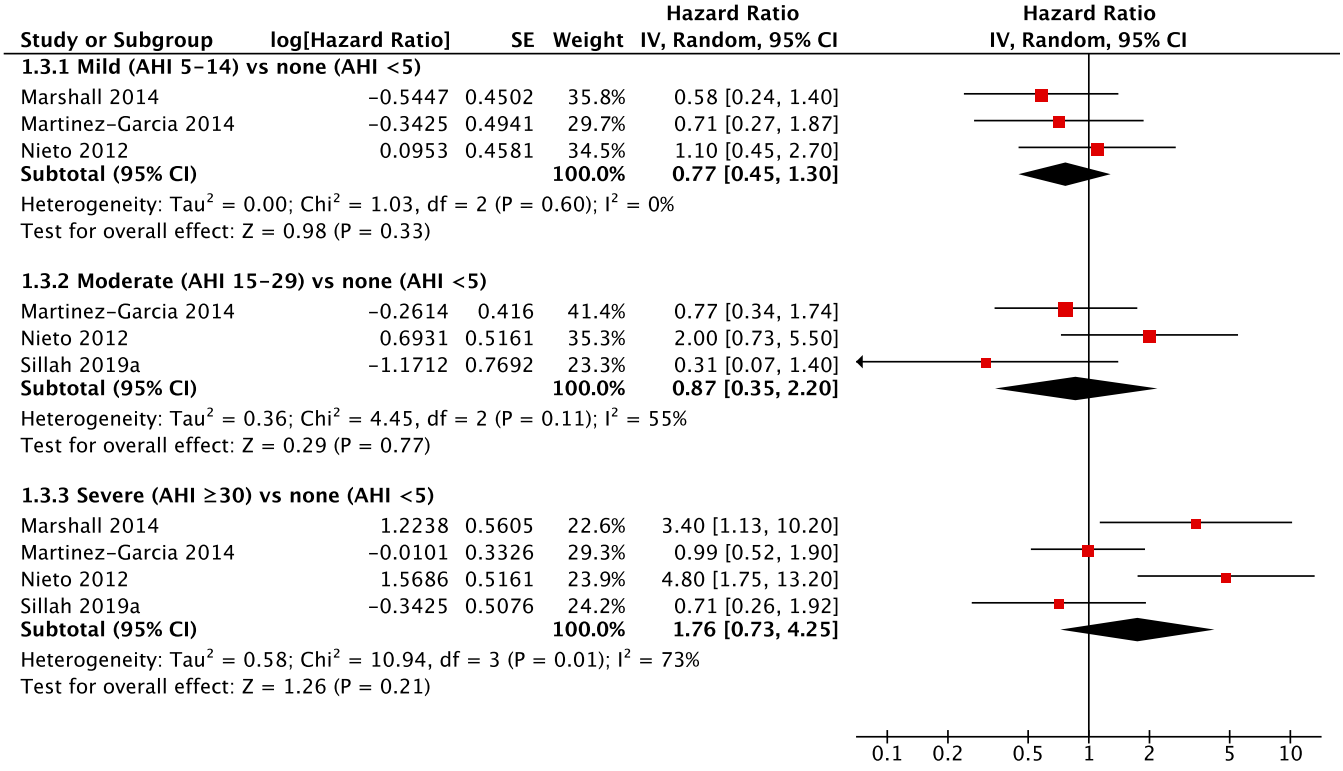
The quality of evidence at the outcome level is summarized in **Table S3.** Most outcomes had low to moderate quality, mainly limited by heterogeneity. In a number of subgroups (eg, ≥ 5 years of follow-up), quality increased as heterogeneity decreased. Evidence based on the ICD was of very low quality.

## DISCUSSION

In this meta-analysis of 20 multiple-adjusted observational studies, patients with OSA who had moderate or severe nocturnal hypoxemia, defined using T90, had a 30%–40% higher all-cancer risk than those with no/mild nocturnal hypoxemia. In addition, severe nocturnal hypoxemia was associated with a 2.5-fold higher all-cancer mortality. When OSA severity was measured by the AHI, only patients with severe OSA, but not patients with moderate OSA, had a significantly higher all-cancer risk than patients without OSA. Overall, evidence was of low to moderate quality.

To the best of our knowledge, this is the first and most comprehensive meta-analysis that elucidates the association between OSA and cancer through separate consideration of different measures of OSA, such as the AHI, T90, and ICD. Two previous meta-analyses on this topic,[24,25] published in 2015, came to conflicting conclusions despite using nearly identical primary studies. Furthermore, they investigated only the AHI but not other indices, likely due to limitations of the primary literature at that time. More recently, a meta-analysis published in August 2021 sought to describe the all-cancer and type-specific cancer incidence in patients with OSA.[64] While the descriptive incidence is potentially useful in policy-making, this study did not perform any statistical comparisons between patients with OSA and those without OSA, instead relying on simple numerical comparisons with known worldwide cancer incidence rates. Their raw incidence rates are unadjusted and subject to confounding, including by age and sex. In addition, they did not investigate cancer mortality. Therefore, our study provides a more reliable measure of the covariate-adjusted association between OSA, measured via various indices, with all-cancer incidence and mortality.

**Figure 3—**Longitudinal associations between mild (n = 7,338), moderate (n = 7,277), and severe (n = 7,666) OSA, diagnosed based on the AHI, with all-cancer mortality.



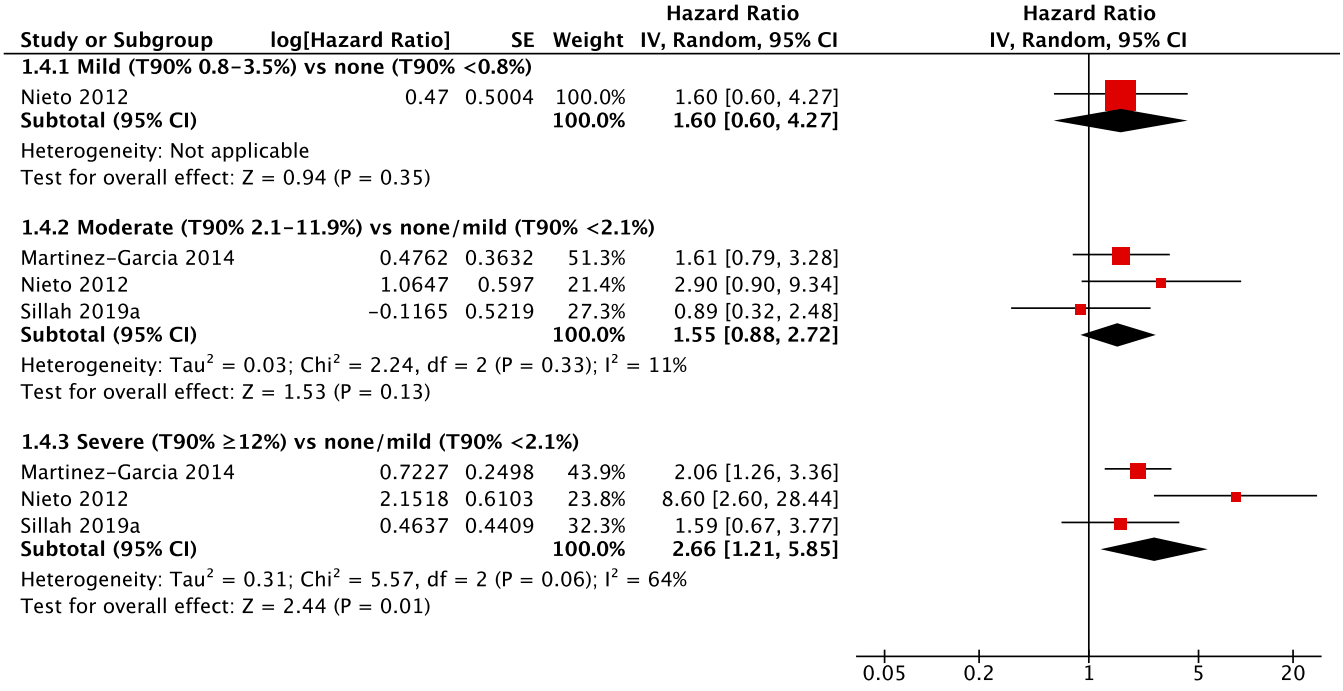

Black diamonds are the estimated pooled HR for each random-effects meta-analysis; red box sizes reflect the relative weight apportioned to studies in the meta-analysis. AHI = apnea-hypopnea index, CI = confidence interval, HR = hazard ratio, IV, inverse variance, OSA = obstructive sleep apnea.

In comparing the different indices of diagnosing OSA, we identified a strong advantage of T90 in demonstrating the associations of OSA with all-cancer incidence and mortality, as compared with AHI- and ICD-diagnosed OSA. Through multiple prespecified sensitivity analyses, we demonstrated that the association of T90-defined nocturnal hypoxemia and all-cancer incidence remained significant, while the association between AHI-defined severe OSA and all-cancer risk lost significance. Furthermore, T90 was the only indicator that demonstrated a significant association between OSA and all-cancer mortality. ICD-diagnosed OSA was not associated with all-cancer incidence, regardless of sensitivity analyses.

The relative superiority of T90 in predicting cancer incidence and mortality may suggest that arterial desaturation events may need to cross a severity threshold in order to deplete tissue or interstitial oxygen reserves, and achieve a minimum hypoxic burden to drive carcinogenesis.[9,65] In intermittent hypoxia alone, T90 would measure the burden of only severe desaturation events with desaturations of > 10%, while the AHI/respiratory disturbance index would additionally measure shallow desaturation (ie, $SpO_2$ > 90%), hypopnea, and arousal events that may obscure the association between hypoxia and cancer risk.[66,67] However, the T90 does not differentiate intermittent hypoxia in OSA from persistent hypoxia in diseases such as COPD, cardiac failure, or obesity hypoventilation,[29] which makes it difficult to attribute the observed effect entirely to OSA. While 2 studies found a positive association of T90 with cancer risk even after adjusting for cardiac disease and COPD,[29,31] residual confounding cannot be excluded. Additionally, the T90 severity thresholds of 1.2% and 12%–13%, while defined based on tertiles from previous studies[19,21,57] and widely used subsequently,[23,30,31,62] are somewhat artificial and vary marginally between studies.

Stronger evidence to support an association between intermittent hypoxia and cancer would require the use of indices like the ODI, which quantifies the number of desaturation events above a given magnitude (eg, 3%).[30] In our systematic review, only 2 studies investigated the ODI 3% and found no association with all-cancer risk after multiple adjustment; thus, further studies are required. We suggest studies to consider analyzing the ODI using a range of desaturation cutoffs, including > 10%,[68] to explore the desaturation severity threshold hypothesis. This is observed similarly in cardiovascular events,[66] where a doubling of desaturation-associated events was associated with hypertension prevalence, while events with a lower magnitude of oxygen desaturation were not.[69] Comprehensive animal models and experimental data are required to verify this "threshold" hypothesis,[9] and may guide the development of more sensitive and specific indices of nocturnal hypoxemia for predicting cancer risk. Regardless, our findings add to the

**Figure 4**—Longitudinal associations between moderate (n = 7,277) and severe (n = 7,277) OSA, diagnosed based on percentage T90, with all-cancer mortality.




Black diamonds are the estimated pooled HR for each random-effects meta-analysis; red box sizes reflect the relative weight apportioned to studies in the meta-analysis. An estimate from a single study for mild OSA (n = 1,522) based on T90 is included for visual comparison. CI = confidence interval, HR = hazard ratio, IV, inverse variance, OSA = obstructive sleep apnea, T90 = sleep duration with arterial oxygen saturation < 90%.

literature calling for more comprehensive ways to characterize OSA apart from the traditional AHI, and emphasize that the use of a single index is inadequate in clinical practice.[66] In line with other authors,[21,29] we propose that T90 be used in combination with the AHI in clinical practice to better identify patients at risk of cancer incidence and mortality.

The advantage of T90 over the AHI may also provide mechanistic insights into the likely causal relationship between OSA and cancer. In brief, OSA is hypothesized to cause cancer by means of intermittent hypoxia and sleep fragmentation, which have been studied in cellular and murine models of melanoma, myeloma, and lung, breast, colon, and kidney cancer.[9,70] Intermittent hypoxia upregulates hypoxia-inducible factors (HIF), causes DNA mutations via reactive oxygen species (ROS), enhances proinflammatory nuclear factor κB (NFκB), promotes angiogenesis via vascular endothelial growth factor (VEGF), and causes immune dysregulation.[12–15] Sleep fragmentation in the form of repetitive microarousals provokes the sympathetic nervous system and similarly promotes inflammation, oxidative stress, and immune deregulation.[5,12,16] These biological consequences are, in fact, the hallmarks of cancer.[17] Apart from the compelling translational evidence, a recent Mendelian randomization study, which used genetic variants as an instrument variable for the exposure, also provides causal evidence for the relationship between OSA and breast cancer in 2 populations.[71] While the T90 measures only deep desaturation events (whether intermittent or continuous), the AHI incorporates both arousals and intermittent desaturation events, thus acting as a crude measure of both sleep fragmentation and intermittent hypoxia. Although the advantage of T90 over AHI in our study does not exclude sleep fragmentation as a mediator of cancer risk, it may suggest a larger role for nocturnal hypoxemia. Future studies may thus consider comparing measures of nocturnal hypoxemia (eg, T90, ODI) with measures of sleep fragmentation (microarousals, sleep fragmentation index,[72] movement distribution[73]) in predicting cancer risk and mortality.

The likelihood that OSA is causally related to cancer incidence and mortality has one other intriguing implication. In recent years, obesity has gained acceptance, including by international task forces,[74,75] as a causal risk factor for numerous cancers. However, the majority of studies examining the obesity–cancer relationship did not consider the likelihood of OSA,[70] which exists in 40%–70% of obese patients.[76,77] Therefore, it is possible that at least some of the cancer risk attributed to obesity could, in fact, be due to underlying OSA.[70] Conversely, in both our meta-analyses of T90 with cancer incidence and cancer mortality, all of the included studies had adjusted for BMI. While BMI is not a perfect measure of adiposity,[70] our findings nonetheless increase the likelihood that OSA imposes a risk of cancer that is independent of obesity. Future studies may thus wish to explore the association of obesity and cancer, independent of OSA.

## Strengths and limitations

The strengths of this study lie in the large number of systematically included studies with appropriate adjustment for key

confounders and sound methodological decisions, such as separate consideration of different OSA indices and the exclusion of estimates for specific cancer types in this analysis of all-cancer risk. All 20 included studies also achieved a Newcastle-Ottawa scale of at least 5, indicating moderate to low risk of bias. Nonetheless, our findings should be interpreted with due consideration of their limitations. First, there exists some heterogeneity in our findings. While heterogeneity decreased among the studies with ≥ 5 years of follow-up for T90, the heterogeneity remained significant in our findings for ICD. The high heterogeneity for the ICD meta-analysis may be explained by the insufficient sensitivity and specificity of ICD in OSA,[78,79] which results in varying degrees of selection bias across different studies. Heterogeneity may also be due to differences in the clinical populations, such as women with OSA potentially being more susceptible to adverse cardiometabolic outcomes than men with OSA,[80] although it was not possible to evaluate these differences in the current meta-analysis and should be considered for future studies. Second, most epidemiological studies to date evaluated cancer as a single outcome variable,[9] and there exists a need to identify if the association holds true for the incidence, mortality, aggressiveness, and progression of individual cancers. At present, numerous cancer types (melanoma,[22,37,44,45] thyroid,[37,55] kidney,[22,37,44] urinary tract,[35,37,55] breast,[35,37,44,81] lung,[37,55] colorectal,[37,82] pancreatic,[22,55] prostate,[35,37] non-Hodgkin lymphoma,[83] central nervous system,[37,84] ovarian,[37] uterine,[37] nasal,[35] and pharyngeal[37]) have been associated with a diagnosis of OSA, although there is substantial disagreement, particularly from a nationwide analysis of 5.6 million individuals.[22] Only 1 published article[56] and 1 unpublished study in abstract form[31] had investigated the associations of specific OSA indices (AHI and T90) with different cancer types. Furthermore, there is very limited evidence on associations with cancer aggressiveness, only for breast cancer and melanoma.[85,86] Since different cancer types may exhibit varied behaviors under intermittent or sustained hypoxia and sleep fragmentation, it is essential to investigate individual associations. Third, this observational meta-analysis is consistent with biological evidence but cannot prove a causal relationship between OSA and cancer, as there may be residual unadjusted confounding. In the absence of randomized trials showing a benefit of OSA treatment on cancer risk, our multiple-adjusted observational conclusions may represent the best clinical evidence currently available. Fourth, 13 included studies were clinic-based and 3 were administrative database studies, which may have introduced selection bias, although the 4 prospective community-based cohorts all reported positive associations of OSA measures with cancer outcomes. Fifth, due to insufficient studies, we could not evaluate potential publication bias. This meta-analysis may be updated in the next decade when new studies are available.

## CONCLUSIONS

In a meta-analysis of 20 multiple-adjusted observational studies with low–moderate quality of evidence overall, T90-defined moderate and severe nocturnal hypoxemia among patients with OSA was associated with a 30%–40% higher all-cancer risk, while AHI-defined severe (but not moderate) OSA was associated with an 18% higher all-cancer risk that was attenuated on sensitivity analyses. Additionally, T90-defined severe nocturnal hypoxemia was associated with a 2.5-fold higher all-cancer mortality, while AHI-stratified OSA severities were not associated with all-cancer mortality. The relative advantage of T90 over AHI in predicting cancer risk emphasizes the importance of using a variety of indices in combination to characterize OSA in clinical practice, and may provide mechanistic insights on a possible causal relationship. Well-designed prospective clinical studies are now needed to explore whether OSA influences the aggressiveness and progression of cancer. The differential risk of OSA for individual cancer types and their varying mechanisms should also be comprehensively reviewed in order to recommend appropriate screening and treatment strategies. Randomized trials are further required to confirm if adequate treatment of OSA can mitigate this risk. Our findings provide a comprehensive, novel, and timely clarification of this important epidemiological relationship, amid the rising global disease burdens of OSA and cancer.

## ABBREVIATIONS

AHI, apnea-hypopnea index
BMI, body mass index
CI, confidence interval
COPD, chronic obstructive pulmonary disease
HR, hazard ratio
ICD, *International Classification of Diseases*
ODI, oxygen desaturation index
OSA, obstructive sleep apnea
$SaO_2$, arterial oxygen saturation
T90, sleep duration with arterial oxygen saturation < 90%

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