

# Obstructive Sleep Apnea and Incident Cancer: A Large Retrospective Multicenter Clinical Cohort Study

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## ABSTRACT

**Background:** To examine the association between the severity of obstructive sleep apnea (OSA) and nocturnal hypoxemia with incident cancer.

**Methods:** This was a multicenter retrospective clinical cohort study using linked clinical and provincial health administrative data on consecutive adults who underwent a diagnostic sleep study between 1994 and 2017 in four academic hospitals (Canada) who were free of cancer at baseline. Cancer status was derived from the Ontario Cancer Registry. Cox cause-specific regressions were utilized to address the objective and to calculate the 10-year absolute risk difference (ARD) in the marginal probability of incident cancer and the number needed to harm (NNH).

**Results:** Of 33,997 individuals considered, 33,711 with no missing OSA severity were included: median age, 50 years; 58% male; and 23% with severe OSA (apnea-hypopnea index >30). Of the

18,458 individuals with information on sleep time spent with oxygen saturation (SaO<sub>2</sub>) <90%, 5% spent >30% of sleep with SaO<sub>2</sub> <90% (severe nocturnal hypoxemia). Over a median of 7 years, 2,498 of 33,711 (7%) individuals developed cancer, with an incidence rate of 10.3 (10.0–10.8) per 1,000 person-years. Controlling for confounders, severe OSA was associated with a 15% increased hazard of developing cancer compared with no OSA (HR = 1.15, 1.02–1.30; ARD = 1.28%, 0.20–2.37; and NNH = 78). Severe hypoxemia was associated with about 30% increased hazard (HR = 1.32, 1.08–1.61; ARD = 2.38%, 0.47–4.31; and NNH = 42).

**Conclusions:** In a large cohort of individuals with suspected OSA free of cancer at baseline, the severity of OSA and nocturnal hypoxemia was independently associated with incident cancer.

**Impact:** These findings suggest the need for more targeted cancer risk awareness in individuals with OSA.

## Introduction

Obstructive sleep apnea (OSA) is a common sleep disorder, afflicting up to one billion people globally, including at least 6% of women and 13% of men (1, 2). OSA is characterized by repeated episodes of upper airway obstruction during sleep that may cause sleep fragmentation, sympathetic activation, and intermittent hypoxemia.

OSA has been postulated to be associated with cancer development and progression, possibly through intermittent hypoxemia and/or

sleep fragmentation (3–6). OSA-related intermittent hypoxia and sleep fragmentation may alter the sympathetic tone, angiogenesis, inflammatory pathways, and immunoregulatory cellular targets that, in turn, may lead to maladaptive transcriptional regulation and to changes in the oncogenic properties of the tumor rendering them more aggressive, invasive, and resistant to therapy (5–9).

Evidence linking OSA to cancer in humans is inconsistent (10, 11). While some studies have observed an association between OSA and cancer incidence (12–17), others have not (18–21), which have cast doubts on this association. In addition, it is undetermined whether this potential OSA/cancer association is relevant to all cancer types. Because of low cancer incidence, most studies to date have pooled all tumor subtypes to increase statistical power. This approach potentially dilutes observed associations with incident cancer, because specific types of malignant cells may have different responses to intermittent hypoxia and/or sleep fragmentation. Previous studies have also been limited by inadequate control of other potential cancer risk factors, such as obesity (22). Our previous study, based on a large, single-center cohort of adults with suspected OSA, did not find an association between the severity of OSA and either prevalent or incident cancer after controlling for risk factors (20). In subgroup analyses, we found that the level of oxygen desaturation was associated with smoking-related cancers; however, the results were limited by a relatively small sample size. Thus, there remains a need for robust and generalizable data regarding the association between OSA and cancer.

We conducted a multicenter clinical cohort study to examine the association between OSA severity and oxygen desaturation in sleep, and incident cancer (all and by subtypes), controlling for known risk factors, using five large clinical cohorts of patients with suspected OSA apparently free of any cancer at study entry. We hypothesized that through intermittent hypoxemia and/or sleep fragmentation, OSA

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**Note:** Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (<http://cebp.aacrjournals.org/>).

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would be associated with cancer development, including smoking-related cancers, as suggested by our previous single-center cohort study (20).

## Materials and Methods

### Study design

A retrospective multicenter clinical cohort study was conducted through the linkage of five large independent Ontario clinical sleep cohorts and provincial population-based health administrative data housed at ICES (formerly the Institute for Clinical Evaluative Sciences). The clinical cohorts contained clinical and polysomnographic data on consecutive adults referred for suspected OSA who underwent a diagnostic sleep study between 1994 and 2017.

### Data sources

#### Provincial health administrative data

ICES is an independent, nonprofit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data for health system evaluation and improvement. ICES has housed high-quality individual-level administrative databases on publicly funded services provided in Ontario since 1988 (refs. 23, 24; <https://datadictionary.ices.on.ca>). The datasets used for this study are held securely in a deidentified form at ICES and were linked using unique encoded identifiers at ICES. Information on cancer status and type was derived from the Ontario Cancer Registry (OCR), a computerized database of information on all Ontarians since 1964 who have been newly diagnosed with cancer or who have died of cancer, which is based on multiple combined sources of data to provide good quality incidence data (25–27).

#### Clinical data

Clinical data were obtained from: (i) St. Michael's Hospital Sleep Laboratory database, 1994 (1996)–2010 (Toronto, Ontario, Canada) is described elsewhere (28); (ii) Sunnybrook Health Sciences Centre sleep database, 2010–2015 (Toronto, Ontario, Canada, NCT03383354); (iii) London Health Sciences Centre Sleep and Apnea Assessment Unit PSG database, 2007–2015 (London, Ontario, Canada); (iv) the Ottawa Hospital (TOH) Sleep Database, 2015–2017 (Ottawa, Ontario, Canada, NCT03834792); and (v) TOH Surgical Sleep Database, 2003–2011 (Ottawa, Ontario, Canada) described elsewhere (ref. 29; Supplementary Table S1).

#### Populations of interest

All consecutive individuals who underwent a diagnostic sleep study between 1994 and 2017 in four large academic hospitals (Ontario, Canada) were considered for inclusion. We excluded uninsured individuals and those with prevalent cancer at the baseline as per the OCR. Details on cohort creation are provided in Supplementary Fig. S1.

#### Exposures

As exposures of interest, we considered two measures of OSA severity as categorical and continuous variables: apnea-hypopnea index (AHI), a conventional measure for defining OSA and its severity, and the degree of nocturnal oxygen desaturation. As the primary exposure, patients were classified as not having OSA (AHI < 5), or mild (AHI, 5–14.9), moderate (AHI, 15–30), or severe (AHI > 30/hour) OSA (30). Only information on primary exposure was available in all five clinical cohorts. As secondary exposures, we considered AHI

(evaluated as a continuous variable), and mean oxygen saturation (SaO<sub>2</sub>) in sleep and percent of sleep time spent with SaO<sub>2</sub> < 90% as continuous variables. Severe nocturnal hypoxemia was defined as >30% of sleep time with SaO<sub>2</sub> < 90% (31).

Details on AHI definitions in different clinical cohorts are presented in Supplementary Table S1.

### Outcomes

The primary outcome was time from the date of the diagnostic sleep study to incident cancer (any type) in patients free of any cancer at study entry. Similar to our previous study (20), and to validate findings from previous human and animal studies (5, 6), the following types and subgroups of cancers were considered in the secondary analyses: site specific (breast, colorectal, kidney, lung, melanoma, prostate, and urinary), etiology specific (smoking, alcohol, virus/immune, and hormone related), as well as detectable and nondetectable by screening (see Supplementary Table S2 for details on definition).

Each individual was followed forward from the date of the diagnostic sleep study to first of outcome, emigration from Ontario, death, or the end of the follow-up period (31 October 2017), whichever occurred first.

### Confounders and risk factors

A large number of potential confounders and risk factors available from clinical and health administrative data were considered: (i) from clinical data at the date of the sleep study: age, sex, body mass index (BMI), and self-reported smoking (current, ex-smoker, and never smokers) and (ii) from health administrative data: separate comorbidities at baseline, including obesity and alcohol use disorder, Charlson comorbidity index, neighborhood income, rural and immigrant status, and OSA-related treatment in follow-up, such as positive airway pressure (PAP) treatment initiation or bariatric, maxillomandibular advancement, and uvulopalatopharyngoplasty surgical interventions (32–36). Details on definitions are presented in Supplementary Table S3.

### Analyses

Descriptive statistics were used to characterize the study population: frequencies and proportions for dichotomous and categorical variables, means (SD) for normally distributed continuous data, and medians (interquartile ranges) for nonnormally distributed data. We calculated crude incidence rates for cancer per 1,000 person-years for the entire sample and by clinical cohort. Poisson regression was used to obtain 95% confidence intervals (CI; ref. 37). Given that in a frail population, all-cause death, termed a competing event, may preclude the occurrence of cancer and lead to overestimation of incidence by the Kaplan–Meier method (38), we estimated cancer incidence with the cumulative incidence function, which accounts for competing risks, and compared categories of OSA severity using Gray test (39).

Univariable and multivariable Cox cause-specific regressions to adjust for death as a competing event were used. The primary analyses used Cox cause-specific regressions to assess the relationship between OSA severity categories and the primary outcome, controlling for covariates. Covariates were entered into the statistical models sequentially, to assess the change in the estimated effect for exposure-related variables after each step: (i) univariate; (ii) age and sex; (iii) alcohol use disorder, chronic heart failure (CHF), chronic obstructive pulmonary disease (COPD), hypertension, and diabetes at baseline; and (iv) OSA treatment considered as a time-varying covariate. These covariates were considered as suggested previously (11, 20, 40) and were available in all clinical cohorts considered. A theoretical framework utilized for a

variable selection is presented in Supplementary Fig. S2. Analyses were performed on the clinical cohorts combined and each separately. To adjust for potential differences in scoring criteria between study sites and over time, all statistical models of the combined cohorts were additionally adjusted for the different sleep clinic sites involved and year of sleep study. We then used the final Cox regression model to calculate the absolute risk difference (ARD) in the 10-year marginal probability of incident cancer and the number needed to harm (NNH; ref. 41) associated with severe OSA.

In secondary analyses, applying the same analytic techniques, we investigated the relationship between different measures of exposure and types and subgroups of cancers listed above. The proportional hazards assumption for exposure variables were tested (42). We used restricted cubic-spline transformations for continuous variables if nonlinearity was observed. Given difficulty interpreting HRs from spline-transformed variables, we also categorized them into quartiles.

### Sensitivity analyses

To adjust for other potential confounders, we performed sensitivity analyses. First, we considered additional variables from provincial health administrative data, including obesity, additional demographic characteristics (neighborhood income, and rural and immigrant status), depression (43), and Charlson comorbidity index in our statistical model. Second, for four cohorts with detailed clinical and PSG information, we considered BMI (as a continuous variable) and total sleep time. We considered both obesity (from health administrative data) and BMI (from clinical data) in our statistical model given that OSA is more prevalent in obese individuals (44), and obesity has been shown to be independently associated with a higher risk of cancer development and progression (45, 46). Finally, because carcinogenic effects of some tobacco compounds may be exacerbated by intermittent hypoxemia or the inflamed upper airway environment associated with OSA (47, 48), in two cohorts with available information on smoking status, smoking was additionally considered in the statistical model.

We tested *a priori* determined interactions between exposure and age, sex, or BMI.

To adjust for the possible lag time between the diagnosis of OSA and cancer, incident cancers diagnosed within 1 year (lag period) from the date of the diagnostic sleep study were censored, and only cancers first diagnosed after that lag period were analyzed. To address the potential confounding by indication, variables reflecting the quality of care and prior health care exposure from health administrative data, such as receipt of blood glucose testing or chest X-ray within 3 years before the diagnostic sleep study and the number of the primary care office visit within 1 year before the diagnostic sleep study, were additionally considered in the statistical model. To assess how robust associations found in our study are to potential unmeasured or uncontrolled confounding, we utilized the E-value (49).

A complete case analysis was considered. Details on missing values per exposure and covariates are presented in Supplementary Fig. S1. All statistical analyses were performed in the secure environment at ICES following Ontario privacy standards using SAS Enterprise Guide 7.1. and SAS version 9.4 (SAS Institute Inc.).

### Research ethics and patient consent

The ethics committees of all institutions involved approved this study. The ICES is a prescribed entity under Section 45 of Ontario's Personal Health Information Protection Act (PHIPA). Section 45 is the provision that enables analysis and compilation of statistical

information related to the management, evaluation, and monitoring of, allocation of resources to, and planning for the health system. Section 45 authorizes health information custodians to disclose personal health information to a prescribed entity, like ICES, without consent for such purposes.

Projects conducted wholly under Section 45, by definition, do not require review by a research ethics board (REB). A confirming letter from the REB of Sunnybrook Health Sciences Centre (Toronto, Ontario, Canada), ICES' REB of Record, is available upon request.

As a prescribed entity, ICES must submit to tri-annual review and approval of its privacy and security policies, procedures, and practices by Ontario's Information and Privacy Commissioner. These include policies, practices, and procedures that require internal review and approval of every project by ICES' Privacy and Compliance Office. ICES was approved by the Commissioner for a fifth time in 2017.

### Data availability

The dataset from this study is held securely in coded form at ICES. While data sharing agreements prohibit ICES from making the dataset publicly available, access may be granted to those who meet prespecified criteria for confidential access, available at <https://www.ices.on.ca/DAS>. The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are, therefore, either inaccessible or may require modification.

## Results

### Study population characteristics

Of 33,997 individuals considered for inclusion in our study, 33,711 individuals with no missing OSA severity categories as measured by AHI were included: the median age was 50 years, 58% were male, and 32% had an AHI < 5, while 23% had an AHI > 30/hour. Of 18,458 individuals with available information on percent of sleep time spent with SaO<sub>2</sub> < 90%, 893 (5%) spent >30% of sleep time with SaO<sub>2</sub> < 90%.

Characteristics of the included individuals for the entire sample are presented in **Table 1** and per the sleep cohort in Supplementary Table S4. Individuals with severe OSA were more likely to be older men with higher BMI, reside in low neighborhood income, have more comorbidities, and were more likely to be treated for OSA.

### Outcome characteristics

Over a median follow-up time of 7 years, 2,498 of 33,711 (7.4%) individuals developed cancer with an incidence rate per 1,000 person-years of 10.3 (95% CI, 10.0–10.8). Details on the incident rate per sleep cohort are presented in Supplementary Table S4. The most frequent locations of cancer development were prostate ( $n = 460$ ), breast ( $n = 315$ ), colorectal ( $n = 268$ ), and lung ( $n = 241$ ; Supplementary Table S5). A total of 1,057 of 2,498 (42.3%) cancers were detectable by screening.

### The relationship between measures of OSA severity and incident cancer

In univariate analysis, cumulative cancer incidence increased across AHI ( $P < 0.0001$ ) and oxygen desaturations categories ( $P < 0.0001$ ; **Figs. 1** and **2**; Supplementary Fig. S3). Controlling for age, sex, alcohol use disorder, prior CHF, COPD, hypertension, and diabetes, treatment for OSA as a time-dependent covariate, clinic site, and year of sleep study, severe OSA was associated with a 15% increased hazard

**Table 1.** Characteristics of included individuals considered in the statistical models for the total population of interest, by OSA presence and severity<sup>a</sup>.

Variables N (number of individuals)	Total N = 33,711	No OSA n = 10,670	Mild OSA n = 8,964	Moderate OSA n = 6,483	Severe OSA n = 7,594
Demographics					
Age at the date of the diagnostic sleep study, mean (SD)	49.75 (14.10)	45.13 (14.43)	50.05 (13.36)	52.31 (13.11)	53.72 (13.46)
Sex, men	19,405 (57.6)	4,489 (42.1)	5,116 (57.1)	4,154 (64.1)	5,646 (74.3)
Neighborhood income quintile (Q)					
Q1 (poorest)	5,780 (17.1)	1,702 (16.0)	1,510 (16.8)	1,103 (17.0)	1,465 (19.3)
Q2	6,375 (18.9)	2,025 (19.0)	1,603 (17.9)	1,218 (18.8)	1,529 (20.1)
Q3	6,243 (18.5)	1,995 (18.7)	1,707 (19.0)	1,167 (18.0)	1,374 (18.1)
Q4	6,788 (20.1)	2,216 (20.8)	1,823 (20.3)	1,300 (20.1)	1,449 (19.1)
Q5 (wealthiest)	8,362 (24.8)	2,682 (25.1)	2,274 (25.4)	1,665 (25.7)	1,741 (22.9)
Living in rural area, yes	3,118 (9.2)	940 (8.8)	840 (9.4)	604 (9.3)	734 (9.7)
Being an immigrant, yes	3,203 (9.5)	1,023 (9.6)	878 (9.8)	600 (9.3)	702 (9.2)
Smoking history					
Current smokers, yes	2,651 (7.9)	773 (7.2)	779 (8.7)	507 (7.8)	592 (7.8)
Physical examination					
BMI, kg/m <sup>2</sup> , mean (SD)	31.46 (12.80)	28.66 (11.09)	31.24 (15.18)	32.11 (11.24)	34.83 (12.14)
Polysomnographic indices					
Total sleep time, hours, mean (SD)	5.35 (1.51)	5.57 (1.38)	5.60 (1.25)	5.44 (1.34)	4.69 (1.85)
Presence of prior comorbidities (as defined from health administrative data)					
Alcohol use disorder	1,848 (5.5)	546 (5.1)	483 (5.4)	366 (5.6)	453 (6.0)
CHF	3,135 (9.3)	559 (5.2)	704 (7.9)	632 (9.7)	1,240 (16.3)
Diabetes	9,161 (27.2)	1,839 (17.2)	2,270 (25.3)	1,912 (29.5)	3,140 (41.3)
COPD	6,135 (18.2)	1,519 (14.2)	1,609 (17.9)	1,255 (19.4)	1,752 (23.1)
Hypertension	16,602 (49.2)	3,755 (35.2)	4,225 (47.1)	3,601 (55.5)	5,021 (66.1)
Obesity (as one of the diagnoses identified at the hospitalization)	615 (1.8)	142 (1.3)	123 (1.4)	107 (1.7)	243 (3.2)
Depression (including anxiety for outpatient visits)	18,177 (53.9)	6,516 (61.1)	4,826 (53.8)	3,278 (50.6)	3,557 (46.8)
Charlson comorbidity index, mean (SD)	0.19 (0.72)	0.12 (0.56)	0.15 (0.63)	0.19 (0.72)	0.32 (0.97)
OSA-related treatment in follow-up					
PAP, or bariatric, MMA, or UPPP surgeries	11,583 (34.4)	1,176 (11.0)	2,147 (24.0)	3,123 (48.2)	5,137 (67.6)
Per clinical cohort (sleep database) <sup>b</sup>					
TOH surgical	3,804 (11.3)	1,719 (16.1)	750 (8.4)	596 (9.2)	739 (9.7)
London Health Sciences Centre	12,664 (37.6)	3,624 (34.0)	3,464 (38.6)	2,482 (38.3)	3,094 (40.7)
St. Michael's Hospital	9,424 (28.0)	2,024 (19.0)	2,557 (28.5)	2,090 (32.2)	2,753 (36.3)
Sunnybrook Health Sciences Centre	3,004 (8.9)	1,535 (14.4)	683 (7.6)	365 (5.6)	421 (5.5)
TOH Sleep Clinic	4,815 (14.3)	1,768 (16.6)	1,510 (16.8)	950 (14.7)	587 (7.7)
Per year of sleep study <sup>c</sup>					
1996	51 (0.6)	26 (0.4)	54 (0.5)	29 (0.4)	160 (0.5)
1997	56 (0.6)	33 (0.5)	145 (1.4)	46 (0.6)	280 (0.8)
1998	80 (0.9)	42 (0.6)	210 (2.0)	52 (0.7)	384 (1.1)
1999	113 (1.3)	67 (1.0)	216 (2.0)	77 (1.0)	473 (1.4)
2000	254 (2.8)	126 (1.9)	351 (3.3)	174 (2.3)	905 (2.7)
2001	298 (3.3)	180 (2.8)	338 (3.2)	217 (2.9)	1,033 (3.1)
2002	287 (3.2)	200 (3.1)	366 (3.4)	241 (3.2)	1,094 (3.2)
2003	275 (3.1)	204 (3.1)	303 (2.8)	256 (3.4)	1,038 (3.1)
2004	326 (3.6)	275 (4.2)	382 (3.6)	337 (4.4)	1,320 (3.9)
2005	333 (3.7)	247 (3.8)	354 (3.3)	297 (3.9)	1,231 (3.7)
2006	269 (3.0)	256 (3.9)	284 (2.7)	336 (4.4)	1,145 (3.4)
2007	698 (7.8)	628 (9.7)	651 (6.1)	685 (9.0)	2,662 (7.9)
2008	561 (6.3)	482 (7.4)	469 (4.4)	617 (8.1)	2,129 (6.3)
2009	593 (6.6)	529 (8.2)	498 (4.7)	744 (9.8)	2,364 (7.0)
2010	669 (7.5)	499 (7.7)	673 (6.3)	705 (9.3)	2,546 (7.6)
2011	508 (5.7)	362 (5.6)	717 (6.7)	479 (6.3)	2,066 (6.1)
2012	508 (5.7)	375 (5.8)	744 (7.0)	522 (6.9)	2,149 (6.4)
2013	574 (6.4)	400 (6.2)	753 (7.1)	485 (6.4)	2,212 (6.6)
2014	503 (5.6)	306 (4.7)	743 (7.0)	421 (5.5)	1,973 (5.9)
2015	1,042 (11.6)	602 (9.3)	1,351 (12.7)	483 (6.4)	3,478 (10.3)
2016	743 (8.3)	494 (7.6)	804 (7.5)	279 (3.7)	2,320 (6.9)
2017	222 (2.5)	149 (2.3)	264 (2.5)	107 (1.4)	742 (2.2)

Abbreviations: CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; MMA, maxillomandibular advancement surgery; OSA, obstructive sleep apnea; PAP, positive airway pressure treatment; SD, standard deviation; TOH, the Ottawa Hospital; UPPP, uvulopalatopharyngoplasty.

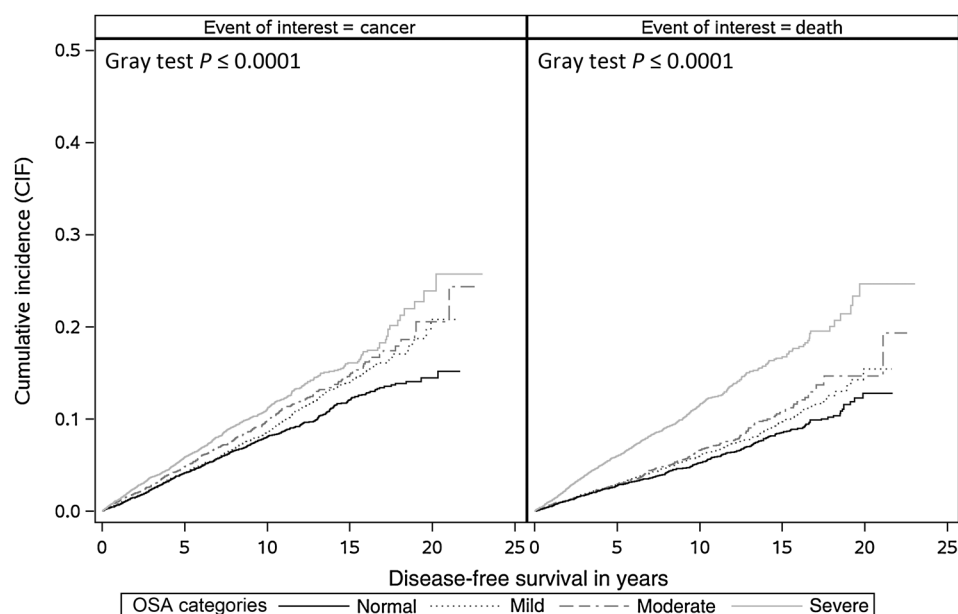
<sup>a</sup>Data are presented as number (% per column), unless otherwise indicated. Numbers may not add to totals because of missing values.

<sup>b</sup>Five clinical sleep cohorts in Ontario (Canada): (i) TOH surgical: TOH Surgical Sleep database, (ii) London Health Sciences Centre: London Health Sciences Centre Sleep and Apnea Assessment Unit PSG database, (iii) St. Michael's Hospital: St. Michael's Hospital Sleep Laboratory database, (iv) Sunnybrook Health Sciences Centre: Sunnybrook Health Sciences Centre Sleep database, and (v) TOH Sleep Clinic: TOH Sleep database.

<sup>c</sup>Fewer than five individuals in 1994–1995 per each category

**Figure 1.**

Estimated cumulative incidence of incident cancer and all-cause mortality by OSA severity categories as measured by the AHI: no OSA (AHI < 5), mild ( $5 \leq \text{AHI} < 15$ ), moderate ( $15 \leq \text{AHI} \leq 30$ ), and severe ( $\text{AHI} > 30$ ). At 10 years, the cumulative incidence of cancer was 11.1% (95% CI, 10.2%–12.0%) among individuals with severe OSA, 9.7% (95% CI, 8.8%–10.7%) among individuals with moderate OSA, 8.6% (95% CI, 7.8%–9.4%) among individuals with mild OSA, and 8.1% (95% CI, 7.4%–8.8%) among those with no OSA. The corresponding rates at 15 years were 16.1% (95% CI, 14.7%–17.5%), 14.8% (95% CI, 13.3%–16.4%), 14.0 (95% CI, 12.7%–15.3%), and 12.1% (95% CI, 11.1%–13.2%), respectively.



of developing cancer as compared with those with no OSA (HR, 1.15; 95% CI, 1.02–1.30; ARD, 1.28%; 95% CI, 0.20%–2.37%; and NNH = 78). Severe nocturnal hypoxemia (>30% of sleep spent with  $\text{SaO}_2 < 90\%$ ) was associated with about 30% increased hazard (HR, 1.32; 95% CI, 1.08–1.61; ARD, 2.38%; 95% CI, 0.47–4.31; and NNH = 42; **Table 2**). Using different definitions of exposures, we confirmed our main results and a dose–response relationship between OSA severity and incident cancer controlling for confounders (**Table 2**; Supplementary Fig. S4). Results per sleep cohort are presented in Supplementary Table S6.

Limited by a relatively small sample size and multiple comparisons, we found in secondary analyses, colorectal, kidney, lung, and smoking-related cancer subtypes to be directionally consistently associated with primary and secondary sleep apnea-related exposures (all HRs > 1),

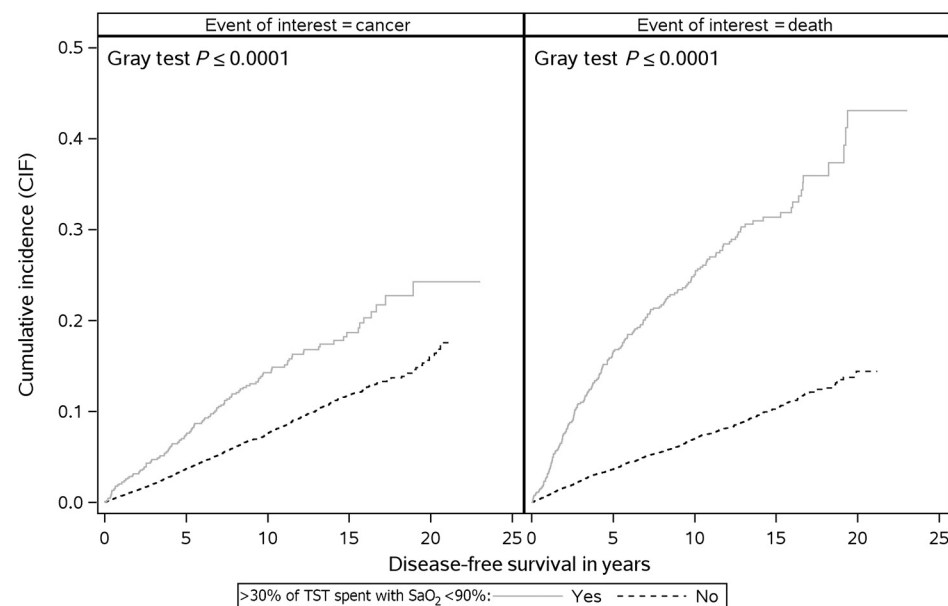
adjusting for age, sex, alcohol use disorder, prior CHF, COPD, hypertension, and diabetes, and treatment for OSA as time-dependent covariate, clinic site, and year of sleep study (**Table 3**).

**Sensitivity analyses**

For the primary outcome, these results remained similar when additionally controlling for (i) obesity, neighborhood, income, rural and immigrant status, and Charlson comorbidity index (as defined from health administrative data) and (ii) BMI and sleep time (as defined from clinical data), on a smaller sample with no missing values for the BMI (**Table 4**). The observed associations were attenuated when additionally controlling for smoking; however, smoking status was available for only a small proportion of individuals in two clinical cohorts only. When we refitted our final model, which included a

**Figure 2.**

Estimated cumulative incidence of incident cancer and all-cause mortality by the degree of nocturnal oxygen desaturation as measured by percent of sleep time spent with  $\text{SaO}_2$  below 90%: >30% versus  $\leq 30\%$ . At 10 years, the cumulative incidence of cancer was 14.2% (95% CI, 11.7%–17.0%) among individuals who spent more than 30% of sleep time with  $\text{SaO}_2 < 90\%$  and 7.6% (95% CI, 7.1%–8.1%) among individuals who spent  $\leq 30\%$  of sleep time with  $\text{SaO}_2 < 90\%$ . The corresponding rates at 15 years were 18.7% (95% CI, 15.5%–22.1%) and 11.7% (95% CI, 11.0%–12.5%), respectively. TST, total sleep time.



**Table 2.** Results from multivariable Cox cause-specific regressions on the associations between incident cancer (primary outcome) and the presence and severity of OSA as defined by the AHI or the degree of nocturnal oxygen desaturation.

Exposures	Model 1	Model 2	Model 3	Model 4
Primary exposure				
OSA severity by categories as defined by AHI ( <i>N</i> = 33,711)				
Severe OSA: yes vs. no	1.43 (1.31-1.56)	1.12 (1.02-1.22)	1.09 (1.00-1.20)	1.11 (1.01-1.22)
Severity vs. normal (reference group)				
Mild	1.30 (1.16-1.46)	1.05 (0.94-1.17)	1.04 (0.93-1.16)	1.04 (0.93-1.17)
Moderate	1.45 (1.29-1.63)	1.04 (0.92-1.17)	1.03 (0.91-1.16)	1.04 (0.92-1.18)
Severe	1.73 (1.55-1.93)	1.15 (1.03-1.29)	1.12 (1.00-1.25)	1.15 (1.02-1.30)
Secondary exposures				
OSA severity by AHI as a continuous variable ( <i>n</i> = 29,907)				
AHI quartiles				
Q2 (AHI 4-12) vs. Q1 (AHI < 4)	1.55 (1.32-1.81)	1.20 (1.03-1.41)	1.20 (1.02-1.40)	1.20 (1.02-1.41)
Q3 (AHI 12-28) vs. Q1 (AHI < 4)	1.90 (1.62-2.21)	1.26 (1.08-1.48)	1.25 (1.07-1.46)	1.27 (1.08-1.48)
Q4 (AHI ≥ 28) vs. Q1 (AHI < 4)	2.27 (1.95-2.64)	1.33 (1.14-1.56)	1.29 (1.10-1.51)	1.32 (1.12-1.56)
OSA severity by the degree of nocturnal oxygen desaturation: mean SaO <sub>2</sub> as a continuous variable ( <i>n</i> = 18,767)				
Mean SaO <sub>2</sub> quartiles				
Q3 (SaO <sub>2</sub> 94.9%-96%) vs. Q4 (SaO <sub>2</sub> ≥ 96%)	1.44 (1.19-1.75)	1.13 (0.93-1.38)	1.13 (0.93-1.38)	1.13 (0.93-1.38)
Q2 (SaO <sub>2</sub> 93.4%-94.9%) vs. Q4 (SaO <sub>2</sub> ≥ 96%)	1.87 (1.55-2.24)	1.23 (1.02-1.48)	1.19 (0.99-1.44)	1.19 (0.99-1.44)
Q1 (SaO <sub>2</sub> < 93.4%) vs. Q4 (SaO <sub>2</sub> ≥ 96%)	2.65 (2.21-3.17)	1.23 (1.02-1.48)	1.29 (1.06-1.56)	1.28 (1.06-1.55)
OSA severity by the degree of nocturnal oxygen desaturation: percent of sleep time spent with SaO <sub>2</sub> < 90% ( <i>n</i> = 18,458)				
↑ in 5% of TST spent with SaO <sub>2</sub> < 90%	1.07 (1.06-1.08)	1.03 (1.02-1.05)	1.02 (1.01-1.04)	1.02 (1.01-1.04)
>30% of TST spent with SaO <sub>2</sub> < 90%: yes vs. no	2.16 (1.79-2.6)	1.47 (1.21-1.78)	1.32 (1.09-1.61)	1.32 (1.08-1.61)

Note: Estimates are presented as adjusted HRs and 95% CIs. Model 1: exposure + year of study + sleep clinic site; model 2: model 1 + age + sex; model 3: model 2 + alcohol use disorder + prior CHF + COPD + hypertension + diabetes; model 4: model 3 + OSA treatment as time varying covariate.

Abbreviations: AHI, apnea-hypopnea index; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; OSA, obstructive sleep apnea; Q, quartile (1-4); SaO<sub>2</sub>, oxygen saturation; TST, total sleep time.

smoking status for smoking-related cancer as an outcome, the same trend was noted. Specifically, the association was attenuated and became nonsignificant for the severity of OSA as defined by AHI (HR for severe vs. no OSA, 1.10; 95% CI, 0.72-1.69). The association remained significant for severe nocturnal hypoxemia (>30% of sleep spent with SaO<sub>2</sub> < 90%; HR, 1.54; 95% CI, 1.02-2.33).

All the predefined interactions were nonsignificant (*P* values for interaction term > 0.1).

The adjusted effect of OSA-related treatment in follow-up was not significant (HR, 0.92; 95% CI, 0.82-1.04; Supplementary Table S7). Factors significantly associated with the increased risk of incident cancer were older age, male sex, an increase in BMI, and the presence of

**Table 3.** Results from multivariable Cox cause-specific regressions on the associations between incident cancer subtypes (secondary outcomes) and the presence and severity of OSA as defined by the AHI or the degree of nocturnal oxygen desaturation controlling for age, sex, alcohol use disorder, prior CHF, COPD, hypertension, and diabetes, and treatment for OSA as time-dependent covariate, clinic site, and year of sleep study (model 4)<sup>a</sup>.

Cancer type	Severe OSA vs. others	Severe vs. no OSA	AHI: Q4 vs. Q1	Mean SaO <sub>2</sub> : Q1 vs. Q4	↑ in 5% in TST spent with SaO <sub>2</sub> < 90%	>30% of TST spent with SaO <sub>2</sub> < 90% vs. no
Site specific						
Colorectal	1.30 (0.98-1.72)	<b>1.63 (1.12-2.38)</b>	<b>2.69 (1.48-4.90)</b>	1.69 (0.90-3.18)	<b>1.05 (1.01-1.09)</b>	1.68 (0.95-2.96)
Kidney	1.28 (0.83-1.98)	1.01 (0.59-1.75)	1.04 (0.50-2.18)	<b>3.02 (0.97-9.43)</b>	1.06 (0.99-1.13)	1.87 (0.79-4.40)
Lung	<b>1.34 (1.00-1.80)</b>	1.38 (0.94-2.04)	<b>1.78 (1.03-3.10)</b>	<b>2.05 (1.01-4.15)</b>	<b>1.04 (1.01-1.08)</b>	<b>1.77 (1.08-2.91)</b>
Melanoma	1.03 (0.68-1.58)	1.52 (0.85-2.71)	<b>2.49 (1.03-6.05)</b>	1.63 (0.49-5.48)	0.99 (0.90-1.09)	1.37 (0.47-4.01)
Prostate	0.99 (0.80-1.22)	1.07 (0.80-1.42)	<b>1.63 (1.06-2.51)</b>	1.08 (0.68-1.73)	0.99 (0.95-1.04)	0.86 (0.50-1.47)
Urinary	<b>1.72 (1.08-2.75)</b>	1.59 (0.85-2.95)	1.00 (0.43-2.32)	1.06 (0.33-3.36)	1.05 (0.99-1.13)	1.62 (0.65-4.03)
Etiology specific						
Alcohol	0.88 (0.57-1.34)	0.83 (0.48-1.42)	1.06 (0.48-2.33)	<b>4.28 (1.27-14.44)</b>	1.07 (1.01-1.12)	1.97 (0.99-3.94)
Hormone	1.03 (0.88-1.22)	1.10 (0.89-1.35)	<b>1.35 (1.01-1.81)</b>	1.02 (0.75-1.41)	0.99 (0.95-1.02)	0.83 (0.54-1.27)
Smoking	<b>1.20 (1.00-1.46)</b>	1.16 (0.91-1.49)	1.32 (0.95-1.85)	<b>2.01 (1.28-3.16)</b>	<b>1.04 (1.02-1.07)</b>	<b>1.62 (1.15-2.3)</b>
Detectable by screening	1.06 (0.91-1.23)	1.10 (0.91-1.33)	<b>1.35 (1.04-1.76)</b>	1.06 (0.79-1.41)	1.00 (0.97-1.03)	1.00 (0.70-1.41)

Note: Estimates are presented as adjusted HRs and 95% CIs.

Abbreviations: CI, confidence interval; HR, hazard ratio; OSA, obstructive sleep apnea; Q, quartile (1 to 4); SaO<sub>2</sub>, oxygen saturation; TST, total sleep time.

<sup>a</sup>Presented only for cancer subtypes with at least one statistically significant association (in bold).

**Table 4.** Sensitivity analyses: results from multivariable Cox cause-specific regressions on the associations between incident cancer (primary outcome) and the presence and severity of OSA as defined by the AHI or the degree of nocturnal oxygen desaturation controlling for additional covariates with missing values<sup>a</sup>.

Exposure	Model 5	Model 6	Model 7	Model 8	Model 9	Model 10
Primary exposure						
OSA severity by categories as defined by AHI						
Severe OSA: yes vs. no	<b>1.11 (1.01-1.22)</b>	<b>1.11 (1.01-1.22)</b>	1.08 (0.97-1.22)	1.07 (0.95-1.20)	1.08 (0.96-1.21)	1.05 (0.90-1.22)
Severity vs. normal (reference group)						
Mild	1.04 (0.93-1.17)	1.04 (0.93-1.17)	1.09 (0.95-1.26)	1.10 (0.95-1.27)	1.11 (0.96-1.28)	1.01 (0.83-1.23)
Moderate	1.04 (0.92-1.18)	1.04 (0.92-1.18)	1.13 (0.96-1.32)	1.13 (0.97-1.33)	1.14 (0.98-1.34)	1.03 (0.84-1.27)
Severe	<b>1.14 (1.01-1.29)</b>	<b>1.15 (1.01-1.30)</b>	<b>1.18 (1.01-1.39)</b>	<b>1.17 (1.00-1.38)</b>	<b>1.19 (1.01-1.39)</b>	1.07 (0.86-1.32)
Secondary exposures						
OSA severity by AHI as a continuous variable						
AHI quartiles						
Q4 (≥28) vs. Q1 (<4)	<b>1.20 (1.02-1.41)</b>	<b>1.21 (1.03-1.42)</b>	<b>1.21 (1.03-1.42)</b>	<b>1.22 (1.04-1.43)</b>	<b>1.23 (1.04-1.44)</b>	1.14 (0.92-1.41)
Q3 (12-28) vs. Q1 (<4)	<b>1.27 (1.08-1.48)</b>	<b>1.27 (1.08-1.49)</b>	<b>1.26 (1.08-1.48)</b>	<b>1.27 (1.08-1.49)</b>	<b>1.28 (1.09-1.50)</b>	1.10 (0.89-1.37)
Q2 (4-12) vs. Q1 (<4)	<b>1.32 (1.12-1.55)</b>	<b>1.33 (1.12-1.57)</b>	<b>1.30 (1.10-1.53)</b>	<b>1.28 (1.09-1.52)</b>	<b>1.29 (1.09-1.53)</b>	1.16 (0.93-1.45)
OSA severity by the degree of nocturnal oxygen desaturation: mean SaO <sub>2</sub>						
Mean SaO <sub>2</sub> quartiles						
Q1 (<93.4%) vs. Q4 (≥96%)	<b>1.27 (1.05-1.54)</b>	<b>1.25 (1.03-1.51)</b>	1.21 (0.99-1.48)	<b>1.22 (1.00-1.48)</b>	1.20 (0.98-1.46)	1.18 (0.96-1.46)
Q2 (93.4-94.9%) vs. Q4 (≥96%)	1.19 (0.99-1.43)	1.17 (0.97-1.41)	1.14 (0.95-1.38)	1.15 (0.95-1.40)	1.14 (0.94-1.38)	1.13 (0.92-1.39)
Q3 (94.9-96%) vs. Q4 (≥96%)	1.13 (0.93-1.38)	1.11 (0.91-1.35)	1.11 (0.91-1.35)	1.12 (0.92-1.37)	1.10 (0.90-1.35)	1.07 (0.86-1.32)
OSA severity by the degree of nocturnal oxygen desaturation: percent of sleep time spent with SaO <sub>2</sub> < 90%						
>30% of TST spent with SaO <sub>2</sub> < 90%: yes vs. no	<b>1.30 (1.07-1.58)</b>	<b>1.31 (1.08-1.60)</b>	<b>1.25 (1.02-1.53)</b>	<b>1.23 (1.00-1.50)</b>	<b>1.23 (1.00-1.51)</b>	<b>1.26 (1.00-1.57)</b>

Note: Model 4, exposure + year of study + sleep clinic site + age + sex + alcohol use disorder + prior CHF + COPD + hypertension + diabetes + OSA treatment as time-varying covariate; model 5: model 4 + obesity (as defined from HAD); model 6: model 5 + other variables from HAD: (i) other demographics (neighborhood income and rural and immigrant status) and (ii) other comorbidities including depression and Charlson comorbidity index; model 7: model 4 + BMI (as a continuous variable); model 8: model 7 + TST; model 9: model 8 + other variables from HAD including obesity (please see above for details); and model 10: model 9 + current smoking (yes/no). Boldface indicates statistical significance.

Abbreviations: AHI, apnea-hypopnea index; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease; HAD, health administrative data; OSA, obstructive sleep apnea; Q, quartile (1-4); SaO<sub>2</sub>, oxygen saturation; TST, total sleep time.

<sup>a</sup>Number of missing values for each secondary covariate: BMI, *n* missing = 4,276; TST, *n* missing = 3,989; current smoking, *n* missing = 18,417; income status, *n* missing = 163; and rural status, *n* missing = 40.

COPD and hypertension. Being an immigrant was associated with a decreased risk of incident cancer.

Our results on the effect of severe OSA and hypoxemia remained similar, additionally adjusting for the possible lag time between OSA and cancer diagnoses and for variables reflecting the quality of care and prior health care exposure (Supplementary Table S8).

## Discussion

In a multicenter cohort study using clinical and health administrative data from more than 30,000 individuals who had suspected sleep apnea, we found that the severity of OSA, expressed by AHI or nocturnal oxygen desaturations, was associated in a dose-dependent manner with cancer incidence independent of known cancer-related risk factors with the greatest risk noted for individuals with severe hypoxemia. Although the ARD associated with severe OSA was modest, given the estimated global prevalence of moderate to severe OSA (AHI ≥ 15/hour) of 425 million in adults ages 30-69 years globally (2), the NNH of 78 could not be ignored. Crudely, that would suggest about 2.5 million additional cancer cases per 10 years globally if the NNH is 78 and about 200 million individuals have severe OSA. The ARD and NNH were even more clinically relevant for severe hypoxemia. These findings support the hypothesis on the association between OSA and cancer incidence through intermittent hypoxemia and/or sleep fragmentation, suggesting the need for more targeted cancer risk awareness

in individuals with OSA. It prompts additional research on how cancer biology interfaces with sleep apnea pathophysiology, including the role of OSA treatment in decreasing cancer risk. Our findings also assist in advocating for better care and research into new therapies for OSA by adding to the known consequences of OSA.

The incidence rate for all cancers combined in Ontario, Canada in 2018 was projected to range from 61.1 per 100,000 in those ages 39 years and under to 2,716.8 per 100,000 in people ages 80 years and older with 524.3 per 100,000 in those between ages 40 and 59 years old (www.cancercareontario.ca), suggesting a higher cancer incident rate in our study population with suspected sleep apnea of similar age (1,030/100,000). Furthermore, controlling for the competing risk of all-cause death and multiple potential risk factors, including BMI, our results support findings from other studies that reported an association between OSA and incident cancer (12-17, 50). Inconsistencies with previous studies (18-21) can be explained by possible misclassification of exposure, with health administrative diagnostic codes (18) or self-reported symptoms (19) being utilized instead of polysomnographic recording to define OSA, or being underpowered (21).

OSA has been postulated to be linked to cancer development and progression through its adverse downstream physiologic and biochemical consequences, such as systemic intermittent hypoxia, oxidative stress, systemic inflammation, increased sympathetic nervous system activity, endothelial dysfunction, altered immune response,

and disrupted circadian rhythm (5–9). Through transcription factors and their regulation, intermittent hypoxia has been suggested to affect the entire carcinogenesis process from initial tumor formation and growth to cell migration from the tumor to the remote sites in the body (9). Intermittent hypoxia may also affect tumors by acting on endothelial cells in the tumor microenvironment through vascular remodeling and angiogenesis (9, 51). Immune cells of the tumor microenvironment are another target for intermittent hypoxemia to influence cancer progression along with systemic or local inflammatory responses and increased levels of reactive oxygen species associated with OSA (9). Among observational studies that evaluated the association between incident cancer and measures of nocturnal hypoxemia (13, 20, 21), two clinical cohort studies (13, 20) reported an association with the percent sleep time with  $\text{SaO}_2 < 90\%$ ; although the finding was specific to smoking-related cancer only in one study (20). The remaining study (21) did not confirm an association between measures of nocturnal hypoxemia and incident cancer. Concerning cancer mortality, two observational studies demonstrated a significant association between sleep time spent with  $\text{SaO}_2 < 90\%$  and cancer mortality; one in a clinical population (52) and another in a community-based sample (53).

Disruption of circadian rhythm through sleep fragmentation and/or intermittent hypoxia associated with OSA may also influence tumor cell behavior, including DNA repair, regulation of the cell cycle, and apoptosis (9). Finally, an increase in sympathetic nervous system activity associated with the acute and long-term carotid body response to intermittent hypoxia may affect tumors and their microenvironments, causing progression and metastatic activity (9, 54).

Although our findings support the association of OSA with cancer incidence of any type, there is conflicting evidence of whether OSA is associated with an increased incidence of specific cancer types. Similar to other studies (13), we found prostate, breast, colorectal, and lungs to be the most frequent locations in individuals with suspected OSA. We also found that OSA severity was associated with the incidence of colorectal (13, 55), prostate (13, 16), lung (13), melanoma (18, 50), and kidney (18, 50) cancers, associations which were suggested in animal studies (4, 8). In contrast, we did not find evidence suggesting an association between OSA and breast cancer in women (12, 13, 16, 50), or a lower risk of certain cancer types for individuals with OSA (18, 50). Many prior studies were not designed to assess the association between OSA and cancer types and were often of small sample size. Thus, their results needed to be interpreted with caution.

Consistent with a recently published meta-analysis (40), we did not find that a shorter total sleep time was associated with incident cancer. It has been suggested that the upregulation of the programmed death cell receptor in patients with OSA appears to be preferentially mediated by intermittent hypoxia, rather than sleep fragmentation (56). Furthermore, we confirmed the effect of other potential risk factors for cancer development, such as being overweight (46), older age (10), hypertension (57), and the presence of other respiratory diseases associated with low systemic oxygen levels, such as COPD (58). We also confirmed a healthy immigrant effect for cancer in Canada (59). We did not find a significant statistical interaction between BMI and OSA severity for cancer risk, confirming results from the animal study where intermittent hypoxia and obesity independently increased tumor growth in mice without a synergistic effect (3).

Next, a possible positive effect of continuous PAP treatment on gene pathways related to tumorigenesis has been suggested (60, 61). Although we did not find a statistically significant effect of OSA-

related treatment in follow-up on incident cancer using the cutoff of 0.05, the results do not rule out an 18% hazard reduction associated with treatment given, (95% CI, 0.82–1.04). If the effect is indeed this large, the results could not be ignored. Whether OSA, in fact, promotes carcinogenesis and whether treatment of OSA might prevent cancer, it would be another piece of the puzzle to understand the origins of cancer, as well as a possible treatment avenue to prevent malignancy.

Our study has many strengths, including (i) long follow-up through the provincial administrative data with a relatively large number of events, (ii) a wide range of OSA severity defined using polysomnographic recording from different sleep centers across Ontario, which represented diverse populations (Supplementary Table S4) contributing to generalizability of our findings, (iii) access to comprehensive validated high-quality cancer registry to define outcomes, (iv) reasonably robust confounder control data, and (v) presentation of both absolute risks and RRs.

The main limitation of our study was its observational and retrospective design utilizing data from clinical academic centers only, over the differing time periods, which limits its generalizability and increases the potential for unmeasured confounding, age-period cohort effects, and indication and surveillance bias despite multiple sensitivity analyses.

For example, information on occupational risk and family history of cancer was not available. The observed HR of 1.15 for the effect of severe OSA could be explained away by an unmeasured confounder that was associated with both the severe OSA and incident cancer by a risk ratio of 1.6-fold each (CI, 1.2), above and beyond the measured confounders, but weaker confounding could not do so. Given the magnitude, it does not seem implausible. However, we believe it to be unlikely given that this means that an unmeasured confounder would have to be associated with both incident cancer and measures of OSA severity by a risk ratio of 1.6-fold each, through pathways independent of age, sex, alcohol use disorder, prior CHF, COPD, hypertension, diabetes, and OSA treatment as a time-varying covariate. It seems less plausible for severe nocturnal hypoxemia:  $E = 2$  (CI, 1.4; Supplementary Fig. S5). Furthermore, information on smoking status was available for only a small proportion of individuals in two clinical cohorts only. However, when controlling additionally for smoking status, the association remained significant for severe nocturnal hypoxemia, confirming our research hypothesis. We also lack data on adherence with PAP treatment and OSA control on PAP and following surgery. However, given that all individuals were considered as treated following the date of PAP claim or surgery, lack of this information would bias our results toward the null.

Variations in the definition of hypopnea across clinical cohorts and over time may be an important limitation (62, 63), despite adjustment for a sleep center and study year in the statistical analyses. However, it reflects the real-world variability in the AHI definition across different sites, countries, and over time (64), which likely biases our results toward the null due to randomness in variability, but increases the generalizability of our findings. Furthermore, in one of the sleep cohorts, which utilized uniform criteria over time (65) with the largest sample size and the longest follow-up, we confirmed our main results on the relationship between AHI and incident cancer controlling for confounders. In addition, Ho and colleagues (62), utilizing the Sleep Heart Health Study data, compared three different definitions of AHI and suggested little reclassification of disease status in individuals with high AHI levels. Importantly, the degree of nocturnal hypoxemia, which is more comparable between centers and more stable over time, was associated with about 30% increased hazard of developing cancer. Other measures of OSA severity and treatment



responsiveness have been proposed and may better predict consequences, such as cancer risk, but are yet to be adopted widely (66). Finally, although our sample size was robust, we recognize that we still were underpowered for some subgroups, for example, specific tumor types. Thus, we acknowledge that further work will be required to advance knowledge further. Nonetheless, we believe that our findings represent an important advance despite these acknowledged limitations.

## Conclusion

In a large multicenter clinical cohort free of cancer at baseline with varying degrees of OSA, the severity of OSA was independently associated with incident cancer. Our findings suggest the need for more targeted cancer risk awareness in individuals diagnosed with OSA. Additional research is warranted into the relationship between cancer biology and OSA pathophysiology, including the role of OSA treatment in decreasing cancer risk. If confirmed, cancer risk should be discussed and addressed in individuals newly diagnosed with OSA and over the course of their disease with the stronger support for OSA treatment as an avenue toward cancer prevention.

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## Authors' Contributions

**T. Kendzerska:** Conceptualization, data curation, formal analysis, funding acquisition, validation, investigation, visualization, methodology, writing—original draft, project administration, writing—review and editing. **M. Povitz:** Conceptualization, data curation, funding acquisition, validation, investigation, methodology, writing—review and editing. **R.S. Leung:** Conceptualization, data curation, funding acquisition, validation, investigation, writing—review and editing. **M.I. Boulos:** Conceptualization, data curation, funding acquisition, validation, investigation, writing—review and editing. **D.I. McIsaac:** Data curation, funding acquisition, validation, investigation, writing—review and editing. **B.J. Murray:** Conceptualization, data curation, funding acquisition, validation, investigation, writing—review and editing. **G.L. Bryson:** Data curation, funding acquisition, validation, investigation, writing—review and editing. **R. Talarico:** Data curation, formal analysis, methodology, writing—review and editing. **J.F. Hilton:** Conceptualization, funding acquisition, validation, investigation, writing—review and editing. **A. Malhotra:** Conceptualization, validation, investigation, visualization, writing—review and editing. **A.S. Gershon:** Conceptualization, data curation, supervision, validation, investigation, project administration, writing—review and editing.

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## References

- Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol* 2013;177:1006–14.
- Benjafield AV, Ayas NT, Eastwood PR, Heinzer R, Ip MSM, Morrell MJ, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *Lancet Respir Med* 2019;7:687–98.
- Almendros I, Montserrat JM, Torres M, Bonsignore MR, Chimenti L, Navajas D, et al. Obesity and intermittent hypoxia increase tumor growth in a mouse model of sleep apnea. *Sleep Med* 2012;13:1254–60.
- Almendros I, Khalyfa A, Trzepizur W, Gileles-Hillel A, Huang L, Akbarpour M, et al. Tumor cell malignant properties are enhanced by circulating exosomes in sleep apnea. *Chest* 2016;150:1030–41.
- Gozal D, Farre R, Nieto FJ. Obstructive sleep apnea and cancer: epidemiologic links and theoretical biological constructs. *Sleep Med Rev* 2016;27:43–55.
- Gozal D, Farre R, Nieto FJ. Putative links between sleep apnea and cancer: from hypotheses to evolving evidence. *Chest* 2015;148:1140–7.
- Liu Y, Song X, Wang X, Wei L, Liu X, Yuan S, et al. Effect of chronic intermittent hypoxia on biological behavior and hypoxia-associated gene expression in lung cancer cells. *J Cell Biochem* 2010;111:554–63.
- Martinez-Garcia MA, Campos-Rodriguez F, Almendros I, Garcia-Rio F, Sanchez-de-la-Torre M, Farre R, et al. Cancer and sleep apnea: cutaneous melanoma as a case study. *Am J Respir Crit Care Med* 2019;200:1345–53.
- Hunyor I, Cook KM. Models of intermittent hypoxia and obstructive sleep apnea: molecular pathways and their contribution to cancer. *Am J Physiol Regul Integr Comp Physiol* 2018;315:R669–87.
- Martinez-Garcia MA, Campos-Rodriguez F, Barbe F. Cancer and OSA: current evidence from human studies. *Chest* 2016;150:451–63.
- Palamaner Subash Shantha G, Kumar AA, Cheskin LJ, Panholty SB. Association between sleep-disordered breathing, obstructive sleep apnea, and cancer incidence: a systematic review and meta-analysis. *Sleep Med* 2015;16:1289–94.
- Chang W-P, Liu Mu-En, Chang W-C, Yang AC, Ku Y-C, Pai J-T, et al. Sleep apnea and the subsequent risk of breast cancer in women: a nationwide population-based cohort study. *Sleep Med* 2014;15:1016–20.
- Campos-Rodriguez F, Martinez-Garcia MA, Martinez M, Duran-Cantolla J, Peña MDeLa, Masdeu MJ, et al. Association between obstructive sleep apnea and cancer incidence in a large multicenter Spanish cohort. *Am J Respir Crit Care Med* 2013;187:99–105.
- Marshall NS, Wong KK, Cullen SR, Knuiman MW, Grunstein RR. Sleep apnea and 20-year follow-up for all-cause mortality, stroke, and cancer incidence and mortality in the Busselton Health Study Cohort. *J Clin Sleep Med* 2014;10:355–62.
- Chen JC, Hwang JH. Sleep apnea increased incidence of primary central nervous system cancers: a nationwide cohort study. *Sleep Med* 2014;15:749–54.
- Fang HF, Miao NF, Chen CD, Sithole T, Chung MH. Risk of cancer in patients with insomnia, parasomnia, and obstructive sleep apnea: a nationwide nested case-control study. *J Cancer* 2015;6:1140–7.
- Brenner R, Kivity S, Peker M, Reinhorn D, Keinan-Boker L, Silverman B, et al. Increased risk for cancer in young patients with severe obstructive sleep apnea. *Respiration* 2019;97:15–23.
- Gozal D, Ham SA, Mokhlesi B. Sleep apnea and cancer: analysis of a nationwide population sample. *Sleep* 2016;39:1493–500.

19. Christensen AS, Clark A, Salo P, Nymann P, Lange P, Prescott E, et al. Symptoms of sleep disordered breathing and risk of cancer: a prospective cohort study. *Sleep* 2013;36:1429–35.
20. Kendzerska T, Leung RS, Hawker G, Tomlinson G, Gershon AS. Obstructive sleep apnea and the prevalence and incidence of cancer. *CMAJ* 2014;186:985–92.
21. Sillah A, Watson NF, Gozal D, Phipps AI. Obstructive sleep apnea severity and subsequent risk for cancer incidence. *Prev Med Rep* 2019;15:100886.
22. Bhaskaran K, Douglas I, Forbes H, dos-Santos-Silva I, Leon DA, Smeeth L. Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5.24 million UK adults. *Lancet* 2014;384:755–65.
23. Institute for Clinical Evaluative Sciences. Improving health care data in Ontario. ICES investigative report. Available from: <https://www.ices.on.ca/Publications/Atlases-and-Reports/2005/Improving-health-care-data-in-Ontario>.
24. Juurlink D, Preyra C, Croxford R, Chong A, Austin P, Tu J, et al. Canadian Institute for Health Information Discharge Abstract Database: A Validation Study. Toronto: Institute for Clinical Evaluative Sciences; 2006. Available from: <https://www.ices.on.ca/Publications/Atlases-and-Reports/2006/Canadian-Institute-for-Health-Information>.
25. Robles SC, Marrett LD, Clarke EA, Risch HA. An application of capture-recapture methods to the estimation of completeness of cancer registration. *J Clin Epidemiol* 1988;41:495–501.
26. Hall S, Schulze K, Groome P, Mackillop W, Holowaty E. Using cancer registry data for survival studies: the example of the Ontario Cancer Registry. *J Clin Epidemiol* 2006;59:67–76.
27. Brenner DR, Tammemagi MC, Bull SB, Pinnaduwa D, Andrulis IL. Using cancer registry data: agreement in cause-of-death data between the Ontario Cancer Registry and a longitudinal study of breast cancer patients. *Chronic Dis Can* 2009;30:16–9.
28. Kendzerska T, Gershon AS, Hawker G, Leung RS, Tomlinson G. Obstructive sleep apnea and risk of cardiovascular events and all-cause mortality: a decade-long historical cohort study. *PLoS Med* 2014;11:e1001599.
29. McIsaac DI, Gershon A, Wijeyesundera D, Bryson GL, Badner N, van Walraven C. Identifying obstructive sleep apnea in administrative data: a study of diagnostic accuracy. *Anesthesiology* 2015;123:253–63.
30. Fleetham J, Ayas N, Bradley D, Ferguson K, Fitzpatrick M, George C, et al. Canadian Thoracic Society guidelines: diagnosis and treatment of sleep disordered breathing in adults. *Can Respir J* 2006;13:387–92.
31. Lewis CA, Fergusson W, Eaton T, Zeng I, Kolbe J. Isolated nocturnal desaturation in COPD: prevalence and impact on quality of life and sleep. *Thorax* 2009;64:133–8.
32. North CM, Christiani DC. Women and lung cancer: what is new? *Semin Thorac Cardiovasc Surg* 2013;25:87–94.
33. Stephenson GD, Rose DP. Breast cancer and obesity: an update. *Nutr Cancer* 2003;45:1–16.
34. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med*. 2003;348:1625–38.
35. Sogaard M, Thomsen RW, Bossen KS, Sorensen HT, Norgaard M. The impact of comorbidity on cancer survival: a review. *Clin Epidemiol* 2013;5:3–29.
36. Hystad P, Carpiano RM, Demers PA, Johnson KC, Brauer M. Neighbourhood socioeconomic status and individual lung cancer risk: evaluating long-term exposure measures and mediating mechanisms. *Soc Sci Med* 2013;97:95–103.
37. Rothman KJ, Greenland S, Lash TL. *Modern epidemiology*. 3rd ed. Philadelphia, PA: Wolters Kluwer/Lippincott Williams & Wilkins; 2008.
38. Wolbers M, Koller MT, Wittman JC, Steyerberg EW. Prognostic models with competing risks: methods and application to coronary risk prediction. *Epidemiology* 2009;20:555–61.
39. Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. *Circulation* 2016;133:601–9.
40. Chen Y, Tan F, Wei L, Li X, Lyu Z, Feng X, et al. Sleep duration and the risk of cancer: a systematic review and meta-analysis including dose-response relationship. *BMC Cancer* 2018;18:1149.
41. Austin PC. Absolute risk reductions and numbers needed to treat can be obtained from adjusted survival models for time-to-event outcomes. *J Clin Epidemiol* 2010;63:46–55.
42. Harrell FE. *Regression modeling strategies: with applications to linear models, logistic regression, and survival analysis*. New York, NY: Springer; 2001.
43. Pitman A, Suleman S, Hyde N, Hodgkiss A. Depression and anxiety in patients with cancer. *BMJ* 2018;361:k1415.
44. Lam JC, Mak JC, Ip MS. Obesity, obstructive sleep apnoea and metabolic syndrome. *Respirology* 2012;17:223–36.
45. Park J, Morley TS, Kim M, Clegg DJ, Scherer PE. Obesity and cancer-mechanisms underlying tumour progression and recurrence. *Nat Rev Endocrinol* 2014;10:455–65.
46. Stone TW, McPherson M, Gail Darlington L. Obesity and cancer: existing and new hypotheses for a causal connection. *EBioMedicine* 2018;30:14–28.
47. Abrams JA, Lee PC, Port JL, Altorki NK, Neugut AI. Cigarette smoking and risk of lung metastasis from esophageal cancer. *Cancer Epidemiol Biomarkers Prev* 2008;17:2707–13.
48. Zhang Q, Tang X, Zhang ZF, Velikina R, Shi S, Le AD. Nicotine induces hypoxia-inducible factor-1 $\alpha$  expression in human lung cancer cells via nicotinic acetylcholine receptor-mediated signaling pathways. *Clin Cancer Res* 2007;13:4686–94.
49. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. *Ann Intern Med* 2017;167:268–74.
50. Sillah A, Watson NF, Schwartz SM, Gozal D, Phipps AI. Sleep apnea and subsequent cancer incidence. *Cancer Causes Control* 2018;29:987–94.
51. Dudley AC. Tumor endothelial cells. *Cold Spring Harb Perspect Med* 2012;2:a006536.
52. Martínez-García MA, Campos-Rodríguez F, Durán-Cantolla J, de la Peña M, Masdeu MJ, González M, et al. Obstructive sleep apnea is associated with cancer mortality in younger patients. *Sleep Med* 2014;15:742–8.
53. Nieto FJ, Peppard PE, Young T, Finn L, Hla KM, Farre R. Sleep-disordered breathing and cancer mortality: results from the Wisconsin Sleep Cohort Study. *Am J Respir Crit Care Med* 2012;186:190–4.
54. Cole SW, Nagaraja AS, Lutgendorf SK, Green PA, Sood AK. Sympathetic nervous system regulation of the tumour microenvironment. *Nat Rev Cancer* 2015;15:563–72.
55. Chen C-Y, Hu J-M, Shen C-J, Chou Yu-C, Tian Yu-F, Chen Y-C, et al. Increased incidence of colorectal cancer with obstructive sleep apnea: a nationwide population-based cohort study. *Sleep Med* 2019;66:15–20.
56. Cubillos-Zapata C, Almendros I, Diaz-Garcia E, Toledano V, Casitas R, Galera R, et al. Differential effect of intermittent hypoxia and sleep fragmentation on PD-1/PD-L1 upregulation. *Sleep* 2020;43:zs285.
57. Han H, Guo W, Shi W, Yu Y, Zhang Y, Ye X, et al. Hypertension and breast cancer risk: a systematic review and meta-analysis. *Sci Rep* 2017;7:44877.
58. Marhuenda E, Campillo N, Gabasa M, Martínez-García MA, Campos-Rodríguez F, Gozal D, et al. Effects of sustained and intermittent hypoxia on human lung cancer cells. *Am J Respir Cell Mol Biol* 2019;61:540–4.
59. McDonald JT, Farnworth M, Liu Z. Cancer and the healthy immigrant effect: a statistical analysis of cancer diagnosis using a linked census-cancer registry administrative database. *BMC Public Health* 2017;17:296.
60. Hernández-Jiménez E, Cubillos-Zapata C, Toledano V, Pérez de Diego R, Fernández-Navarro I, Casitas R, et al. Monocytes inhibit NK activity via TGF- $\beta$  in patients with obstructive sleep apnoea. *Eur Respir J* 2017;49:1602456.
61. Gharib SA, Seiger AN, Hayes AL, Mehra R, Patel SR. Treatment of obstructive sleep apnea alters cancer-associated transcriptional signatures in circulating leukocytes. *Sleep* 2014;37:709–14.
62. Ho V, Crainiceanu CM, Punjabi NM, Redline S, Gottlieb DJ. Calibration model for apnea-hypopnea indices: impact of alternative criteria for hypopneas. *Sleep* 2015;38:1887–92.
63. Punjabi NM, Newman AB, Young TB, Resnick HE, Sanders MH. Sleep-disordered breathing and cardiovascular disease: an outcome-based definition of hypopneas. *Am J Respir Crit Care Med* 2008;177:1150–5.
64. Malhotra A, Younes M, Kuna ST, Benca R, Kushida CA, Walsh J, et al. Performance of an automated polysomnography scoring system versus computer-assisted manual scoring. *Sleep* 2013;36:573–82.
65. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The report of an American Academy of Sleep Medicine Task Force. *Sleep* 1999;22:667–89.
66. Randerath W, Bassetti CL, Bonsignore MR, Farre R, Ferini-Strambi L, Grote L, et al. Challenges and perspectives in obstructive sleep apnoea: report by an *ad hoc* working group of the Sleep Disordered Breathing Group of the European Respiratory Society and the European Sleep Research Society. *Eur Respir J* 2018;52:1702616.