Title

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Journal

Annals of the American Thoracic Society, 19(5)

ISSN

2329-6933

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Publication Date

2022-05-01

DOI

10.1513/annalsats.202106-738oc

Peer reviewed

ORIGINAL RESEARCH

Polysomnographic Markers of Obstructive Sleep Apnea Severity and Cancer-related Mortality

A Large Retrospective Multicenter Clinical Cohort Study

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Abstract

Rationale: The evidence for an association between cancer survival and obstructive sleep apnea (OSA) remains underexplored.

Objectives: To evaluate an association between markers of OSA severity (respiratory disturbances, hypoxemia, and sleep fragmentation) and cancer-related mortality in individuals with previously diagnosed cancer.

Methods: We conducted a multicenter retrospective 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 Canadian academic hospitals and were previously diagnosed with cancer through the Ontario Cancer Registry. Multivariable cause-specific Cox regressions were used to address the research objective.

Results: We included 2,222 subjects. Over a median follow-up time of 5.6 years (interquartile range [IQR], 2.7–9.1 years), 261/2,222 (11.7%) individuals with prevalent cancer died from cancer-related causes, which accounted for 44.2% (261/590) of all-cause death. Controlling for age, sex, alcohol use disorder, prior heart failure, chronic obstructive pulmonary disease, hypertension, diabetes, treatment for OSA, clinic site, year of the sleep study, and time since the cancer diagnosis, measures of hypoxemia and sleep fragmentation, but not apnea–hypopnea index, were significantly associated with the cancer-specific mortality: percentage of time spent with arterial oxygen saturation (Sa_{O_2}) < 90% (hazard ratio [HR] per 5% increase, 1.05; 95% confidence interval, 1.01–1.09); mean Sa_{O_2} (HR per 3% increase, 0.79; 0.68–0.92); and percentage of stage 1 sleep (HR per 16% increase, 1.27; 1.07–1.51).

Conclusions: In a large clinical cohort of adults with suspected OSA and previously diagnosed cancer, measures of nocturnal hypoxemia and sleep fragmentation as markers of OSA severity were significantly associated with cancer-related mortality, suggesting the need for more targeted risk awareness.

Keywords: sleep apnea; obstructive; neoplasms; adult; mortality

(Received in original form June 23, 2021; accepted in final form November 16, 2021)

Supported by the ICES, which is funded by an annual grant from the Ontario Ministry of Health (MOH) and the Ministry of Long-Term Care (MLTC). This study also received funding from the Lung Health Foundation (also known as the Lung Association, Ontario), grant-in-aid; the American Thoracic Society Foundation Unrestricted Grant; 2020 CHEST Foundation Research Grant in Sleep Medicine; the Ottawa Hospital Sleep Walk; and the University of Ottawa Department of Medicine (DOM) Developmental Research Grant. Parts of this material are based on data and information compiled and provided by the Canadian Institute for Health Information, Cancer Care Ontario, and Immigration, Refugees, and Citizenship Canada's Permanent Resident Database. The analyses, conclusions, opinions, and statements expressed herein are solely those of the authors and do not reflect those of the funding or data sources; no endorsement is intended or should be inferred. M.P. was supported by the Academic Medical Association of Southwestern Ontario. A.M. reports income related to medical education from Livanova, Corvus, and Equillium. A.M. was supported by the National Heart, Lung, and Blood Institute. ResMed provided a philanthropic donation to University of California, San Diego. T.K. is supported by the 2020 PSI Graham Farquharson Knowledge Translation Fellowship Award and received a speaker honorarium from AstraZeneca Canada Inc., and is a clinical consultant at Pitolisant Medical Advisory Board (Paladin Labs Inc.).

Ann Am Thorac Soc Vol 19, No 5, pp 807–818, May 2022

DOI: 10.1513/AnnalsATS.202106-738OC
Internet address: www.atsjournals.org

Obstructive sleep apnea (OSA) is the most prevalent sleep disorder, affecting up to one billion people globally, including at least 6% of women and 13% of men (1–3). Although consistent evidence exists on the association between OSA and increased all-cause and cardiovascular mortality, data regarding the influence of OSA on other health outcomes (e.g., cancer, depression, and separate cardiovascular outcomes) remain limited (4).

Cancer poses a large and growing impact on the global population and healthcare system and remains the leading cause of death worldwide. Globally, an estimated number of new cases in 2020 was 19.3 million, and the number of cancer-related deaths was 10.0 million. A 47% increase in these numbers is expected by 2040 (5).

Previous studies have proposed OSA to be related to cancer development and progression through intermittent hypoxemia and/or sleep fragmentation (6–10). These mechanisms may alter sympathetic tone, and the inflammatory and immunoregulation pathways, which in turn may lead to maladaptive transcriptional regulation and to changes in the oncogenic properties of a tumor, thus rendering it more invasive and resistant to therapy (9–13).

The evidence of an association between markers of OSA severity and cancer development and progression is emerging but remains limited and inconsistent. Three longitudinal observational studies demonstrated a significant association between measures of nocturnal hypoxemia and cancer mortality in different populations: *1*) a clinical population of individuals with suspected OSA, among individuals aged less than 65 years (14) (for percent sleep time with arterial oxygen saturation [Sa_{O_2}] $< 90\%$); *2*) a clinical population of adults with moderate to severe OSA (15) (the hypoxemic groups identified by a latent class analysis); and *3*) a community-based sample (16) (for percent sleep time with $Sa_{O_2} < 90\%$]. Only one (16) of those three studies (14–16) showed that the apnea–hypopnea index (AHI) is independently associated with cancer mortality. Another community-based study showed the respiratory disturbance index was significantly associated with cancer mortality (17). Using the National Patient Registry, no association was found between inpatient sleep apnea and cancer mortality (18). Finally, although OSA has been reported repeatedly to be associated with all-cause mortality in general and clinical populations (17, 19–21), it remains unclear if the effect of OSA on all-cause mortality is different among those with or without cancer.

We conducted this multicenter retrospective cohort study to evaluate a potential association between markers of OSA severity (respiratory disturbances, nocturnal hypoxemia, and sleep fragmentation) and cancer-related mortality among individuals with previously diagnosed cancer, controlling for known risk factors for cancer progression. In addition, as an exploratory objective, we investigated whether the effect of severe OSA on all-cause mortality is greater in individuals with cancer than in those without cancer, among all individuals with suspected OSA.

The dataset from this study is held securely in coded form at ICES (formerly Institute for Clinical Evaluative Sciences). 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 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 on coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

Methods

Study Design

A retrospective multicenter cohort study was conducted through linkage of five large clinical sleep cohorts and provincial health administrative data housed at ICES (Ontario, Canada).

The ethics committees of all institutions involved approved this study. 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, without consent, for health system evaluation and improvement. ICES is a prescribed entity under section 45 of Ontario's Personal Health Information Protection Act. 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. A confirming letter from the Research Ethics Board of Sunnybrook Health Sciences Centre is available upon request. As a prescribed entity, ICES must submit to triannual 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

Author Contributions: All co–authors were involved in the following: study conception and design, interpretation of data, revising the manuscript critically for the accuracy and important intellectual content, and final approval of the version to be published. M.P. is a custodian of the London Health Sciences Centre and Sleep Apnea Assessment Unit Polysomnography (PSG) Database. R.S.L. is a custodian of the St. Michael's Hospital Sleep Laboratory database. M.I.B. and B.J.M. are custodians of the Sunnybrook Health Sciences Centre sleep database. T.K. is a custodian of the Ottawa Hospital (TOH) Sleep Database. D.I.M. and G.L.B. are custodians of the Ottawa Hospital Surgical Sleep Database. T.K. was additionally involved in the literature search, dataset creation plan, data analyses, and drafting of the manuscript. T.K. and R.T. were additionally involved in data analyses. T.K. and R.T. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

by ICES's Privacy and Compliance Office. ICES was approved by the Commissioner for a fifth time in 2017.

Data Sources

1. Provincial health administrative data: ICES has housed high-quality individual-level databases on publicly funded services in Ontario since 1988 (22–24) (https://datadictionary.ices.on.ca). The databases 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 related mortality was derived from the Ontario Cancer Registry (OCR); this registry is based on multiple combined data sources to provide good quality incidence data since 1964 (25–28). The Registered Persons Database is a population-based registry maintained by the Ministry of Health and Long-Term Care in Ontario, Canada. It is particularly relevant for vital status information.
2. Clinical databases included clinical and polysomnographic data on consecutive adults referred for suspected OSA who underwent a diagnostic sleep study (level 1 polysomnography) and were described elsewhere (19, 29, 30): *1*) St. Michael's Hospital Sleep Laboratory database, 1994 (1996)–2010 (Toronto); *2*) Sunnybrook Health Sciences Centre sleep database, 2010–2015 (Toronto, NCT03383354); *3*) London Health Sciences Centre Sleep and Apnea Assessment Unit Polysomnography (PSG) Database, 2007–2015 (London); *4*) The Ottawa Hospital (TOH) Sleep Database, 2015–2017 (Ottawa, NCT03834792); and *5*) TOH Surgical Sleep Database, 2003–2011 (Ottawa). Details are also provided in Table E1 in the online supplement.

Populations of Interest

All consecutive adults who underwent a diagnostic sleep study (the index date) between 1994 and 2017 in four large academic hospitals (Ontario, Canada) were considered for inclusion. For the primary objective, we focused on individuals who were diagnosed with cancer before the index sleep study through the OCR. For the explanatory objective, we used the entire cohort of individuals who underwent a diagnostic sleep study within the study time frame independent of the cancer diagnosis. Details on the cohort creation are provided in Figure E1.

Exposures

As exposures, we considered markers of OSA severity, such as respiratory disturbances, nocturnal hypoxemia, and sleep fragmentation.

Given that the AHI is the conventional measure of OSA severity and this information was available in all five clinical cohorts, as the primary exposure, individuals were classified as not having OSA (AHI $<$ 5/h) or mild (AHI of 5–14.9/h), moderate (AHI of 15–30/h), or severe (AHI $>$ 30/h) OSA (31). Details on the AHI scoring criteria across sleep databases are presented in Table E1.

Other OSA severity markers derived from PSG were available in four of five clinical cohorts and were considered secondary exposures: *1*) an increase in AHI as a continuous variable (a measure of respiratory disturbances); *2*) a decrease in mean Sa_{O_2} in sleep and an increase in percentage of sleep time spent with Sa_{O_2} of less than 90% as continuous variables (measures of nocturnal hypoxemia) with severe nocturnal hypoxemia being defined as more than 30% of the sleep time with Sa_{O_2} of less than 90% (32, 33); *3*) a reduction in sleep efficiency (SE) and percentage of rapid eye movement (REM) sleep, and an increase in arousal index, the total number of awakenings in sleep and percentages of stage 1 (markers of sleep fragmentation).

Outcomes

The primary outcome was time from the date of the sleep study to cancer-related death defined from the OCR (cause-specific mortality was available until Dec 2017).

Given that attribution of cause of death is often problematic and can bias estimates (34, 35), we considered time from the index date to all-cause death defined from the Registered Persons Database (available until March 2019) as the secondary outcome. There is usually a 2- to 3-year lag to derived data on cause-specific mortality compared with all-cause mortality.

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

Confounders and Risk Factors

A large number of potential confounders and risk factors available from clinical and health administrative databases were considered, using a previously developed theoretical framework and definitions (29): *1*) from clinical databases at the date of the sleep study, age, sex, body mass index (BMI) (36–38), and self-reported smoking (39, 40); and *2*) from health administrative databases, separate prior comorbidities (chronic heart failure [CHF], chronic obstructive pulmonary disease [COPD], hypertension, diabetes, obesity, and alcohol use disorder), Charlson comorbidity index (to adjust for multimorbidity) (41), demographics (neighborhood income, rural, and immigrant status) at the date of the sleep study, prior healthcare exposure to adjust for a potential detection bias (number of primary care office visits within 1 year before the index date), the date of the initial cancer diagnosis, cancer type, stage, and OSA-related treatment in follow-up, such as initiation of positive airway pressure treatment or maxillomandibular advancement, uvulopalatopharyngoplasty, or bariatric surgical interventions (41–47) (*see* Table E2 for details). The number of individuals who underwent surgery to treat their underlying OSA was very small to consider separately from positive airway pressure therapy.

Analyses

Descriptive statistics were calculated to characterize the study population. We calculated crude mortality rates and 95% Wald confidence intervals (CIs) per 100 person-years for the entire sample and by exposure categories. Survival in exposure categories was estimated using the cumulative incidence function (48) for cancer-related mortality and the Kaplan-Meier method for all-cause mortality and compared between categories with the Gray's test (49) and the log-rank test, respectively.

Primary analyses. We used Cox cause-specific regressions to assess the relationship between the primary exposure and outcome, controlling for covariates described above. Similar to our previous study (29), we entered covariates into the statistical models sequentially: model 1 adjusted for the clinic site and year of sleep study to control for potential differences in scoring criteria between sites and over time, and time since the cancer diagnosis; model 2 additionally adjusted for age and sex; model 3 additionally adjusted

Table 1. Characteristics of individuals diagnosed with cancer at any time before the diagnostic sleep study: the total population of interest and by outcome (cancer- and noncancer-specific mortality)

Variables of Interest	Censored (*n* = 1,632)	Cancer-Specific Death (*n* = 261)	Noncancer Death (*n* = 329)	Total (*N* = 2,222)
Demographics				
Age at the index date, mean ± SD	60.47 ± 12.44	66.14 ± 11.83	70.67 ± 11.10	62.65 ± 12.75
Sex, male	884 (54.2)	178 (68.2)	206 (62.6)	1,268 (57.1)
Neighborhood income quintile (Q)				
Q1	222 (13.6)	42 (16.1)	51 (15.5)	315 (14.2)
Q5	505 (30.9)	76 (29.1)	108 (32.8)	689 (31.0)
Leaving in rural area, yes	159 (9.7)	30 (11.5)	30 (9.1)	219 (9.9)
Being an immigrant, yes	102 (6.3)	6 (2.3)	8 (2.4)	116 (5.2)
Smoking history				
Current smokers,* yes, *n* (%)	68/705 (9.6)	19/106 (17.9)	16/161 (9.9)	103/972 (10.6)
Physical examination				
BMI, kg/m^2, mean ± SD	31.18 ± 7.26	31.56 ± 7.02	31.11 ± 7.35	31.21 ± 7.25
Polysomnographic indices				
OSA severity categories as measured by AHI				
Normal	413 (25.3)	56 (21.5)	61 (18.5)	530 (23.9)
Mild	454 (27.8)	64 (24.5)	74 (22.5)	592 (26.6)
Moderate	351 (21.5)	52 (19.9)	67 (20.4)	470 (21.2)
Severe	414 (25.4)	89 (34.1)	127 (38.6)	630 (28.4)
AHI, mean ± SD	22.24 ± 23.88	30.68 ± 28.53	32.32 ± 29.26	24.53 ± 25.52
Sa_{O_2}, mean ± SD	93.91 ± 2.57	92.46 ± 3.42	92.30 ± 3.51	93.52 ± 2.90
% of time spent with $Sa_{O_2} < 90\%$, mean ± SD	5.30 ± 14.30	14.87 ± 25.11	17.16 ± 27.18	8.11 ± 18.79
>30% of time spent with $Sa_{O_2} < 90\%$, yes	58 (3.6)	23 (8.8)	39 (11.9)	120 (5.4)
Sleep efficiency, mean ± SD	68.84 ± 21.98	60.45 ± 26.01	62.29 ± 20.42	67.05 ± 22.43
# Awakenings in sleep, mean ± SD	27.21 ± 15.39	31.22 ± 23.59	35.32 ± 30.28	28.81 ± 19.43
Arousal index, mean ± SD	32.49 ± 36.34	41.87 ± 42.77	44.97 ± 39.15	35.33 ± 37.79
% REM, mean ± SD	14.30 ± 8.17	13.42 ± 8.44	11.39 ± 7.74	13.77 ± 8.20
% Stage 1, mean ± SD	16.93 ± 14.74	22.66 ± 18.92	20.78 ± 19.38	18.09 ± 16.10
OSA-related treatment in follow-up				
PAP, or bariatric, MMA, or UPPP surgeries	612 (37.5)	76 (29.1)	98 (29.8)	786 (35.4)
Time from the index date to treatment initiation, yr, mean ± SD	1.31 ± 2.36	1.12 ± 1.74	1.31 ± 2.29	1.29 ± 2.30
Presence of prior comorbidities (from health administrative data)				
Alcohol use disorder	78 (4.8)	14 (5.4)	23 (7.0)	115 (5.2)
CHF	199 (12.2)	70 (26.8)	205 (62.3)	474 (21.3)
Diabetes	543 (33.3)	119 (45.6)	173 (52.6)	835 (37.6)
COPD	366 (22.4)	114 (43.7)	193 (58.7)	673 (30.3)
Hypertension	1,033 (63.3)	190 (72.8)	289 (87.8)	1,512 (68.0)
Obesity (hospitalization)	50 (3.1)	13 (5.0)	21 (6.4)	84 (3.8)
Charlson comorbidity index, mean ± SD	0.64 ± 1.51	1.58 ± 2.39	1.67 ± 2.32	0.90 ± 1.83
Primary healthcare exposure				
# Primary care office visits within 1 yr before the index date, mean ± SD	6.88 ± 6.26	8.63 ± 6.93	11.59 ± 12.90	7.78 ± 7.86
Prevalent cancer-related variables				
Years between cancer diagnosis and the index date, mean ± SD	8.81 ± 8.06	6.85 ± 7.01	9.46 ± 8.64	8.67 ± 8.06
Cancer type				
Prostate	346 (21.2)	60 (23.0)	94 (28.6)	500 (22.5)
Breast	294 (18.0)	26 (10.0)	44 (13.4)	364 (16.4)
Lung	31 (1.9)	26 (10.0)	11 (3.3)	68 (3.1)
Kidney	58 (3.6)	11 (4.2)	19 (5.8)	88 (4.0)
Urinary	40 (2.5)	13 (5.0)	15 (4.6)	68 (3.1)
Melanoma	106 (6.5)	11 (4.2)	12 (3.6)	129 (5.8)
Colorectal	119 (7.3)	25 (9.6)	43 (13.1)	187 (8.4)
Follow-up time, yr, mean ± SD	6.77 ± 4.34	4.85 ± 3.77	5.52 ± 4.15	6.36 ± 4.30

Definition of abbreviations: AHI = apnea–hypopnea index; BMI = body mass index; CHF = chronic heart failure; COPD = chronic obstructive pulmonary disease; MMA = maxillomandibular advancement surgery; OSA = obstructive sleep apnea; PAP = positive airway pressure treatment; Q = quartile; REM = rapid eye movement; Sa_{O_2} = oxygen saturation; SD = standard deviation; UPPP = uvulopalatopharyngoplasty.
Data are presented as *n* (%) per column, unless otherwise indicated. Numbers may not add to totals because of missing values.
*Percentage was calculated among those without missing values.

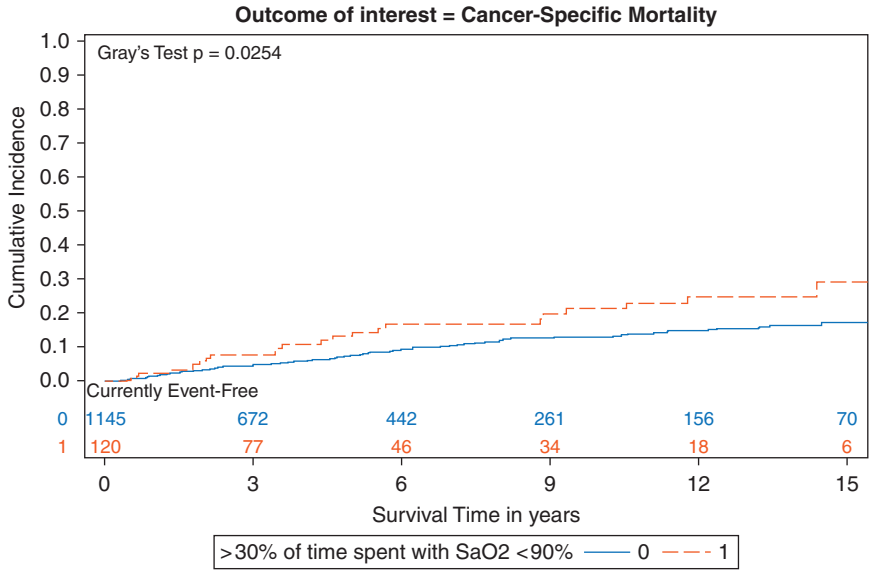

Figure 1. Estimated cumulative incidence of cancer-related mortality by nocturnal hypoxemia severity: >30% of time spent with Sa_{O_2} < 90% (1) versus not (0). Sa_{O_2} = oxygen saturation.

for separate comorbidities; and model 4 additionally adjusted for OSA treatment considered as a time-varying covariate. These covariates were available in all clinical cohorts and were considered as previously noted (29, 50, 51).

We then used the final adjusted Cox regression model (model 4) to derive 5-year marginal probabilities of mortality and calculate absolute risk difference (ARD) and the number needed to harm (NNH) (52) associated with severe OSA (versus normal) and severe nocturnal hypoxemia (versus not).

Secondary analyses. ***Secondary exposures.*** Applying the same analytic techniques described above, we investigated the relationship between secondary exposures and the primary outcome. Each exposure was entered separately into the model. To adjust for OSA severity, we additionally included AHI in model 4, but the estimates remained similar (Table E3); thus, AHI was not considered in the presented models to prevent excess multicollinearity.

The proportional hazards assumption was evaluated for the primary exposures by plotting the Scaled Schoenfeld residuals versus time and the natural log of time. After applying locally estimated scatterplot smoothing, no major departures from proportionality were observed. All exposures were modeled as linear and converted to quartiles to evaluate potential dose–response relationships across the distributions.

Secondary outcome. Using conventional Cox regression modeling and the same modeling approaches described above, we assessed the relationship between primary and secondary exposures and the secondary outcome.

Sensitivity analyses. To adjust for other potential confounders and risk factors, we performed several sensitivity analyses. First, on all five databases, we considered additional variables before the index date from health administrative data, including obesity (model 5), additional demographics (neighborhood income, rural, and immigrant status), Charlson comorbidity index, and prior healthcare exposure in our statistical model (model 6). Second, for databases with detailed clinical and PSG information, we additionally considered BMI (available in four cohorts) (models 7 and 8) and smoking status (available in two cohorts) (model 9) (Table E3). We tested *a priori* determined interactions between exposures and age, sex, or BMI.

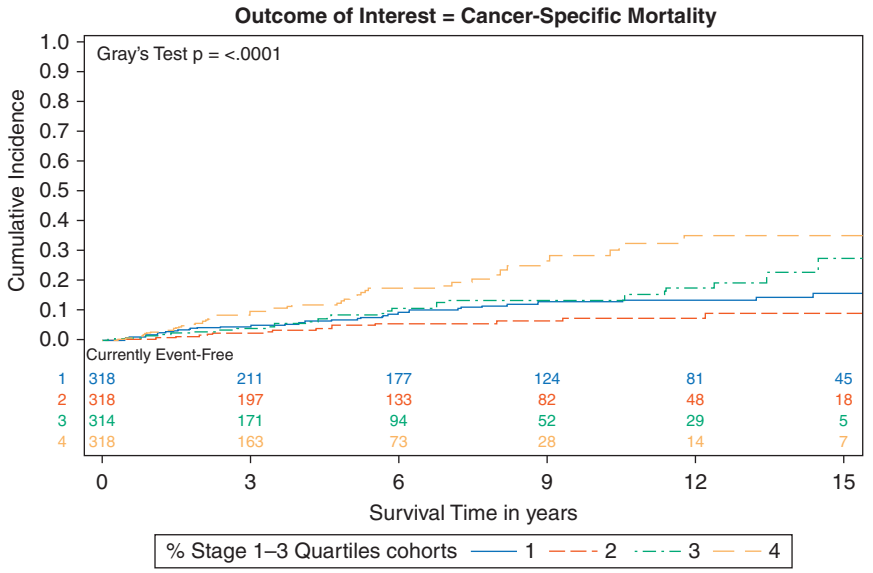

Figure 2. Estimated cumulative incidence of cancer-related mortality, per quartile (Q) increase in the percentage of stage 1 of sleep: Q1 (<7.1%), Q2 (7.1–13.1%), Q3 (13.1–23.5%), and Q4 (≥23.5%).

Table 2. Results from multivariable Cox cause-specific regressions on the associations between cancer-related mortality and polysomnography indices, including measures of the presence and severity of obstructive sleep apnea

Exposures	Model 1	Model 2	Model 3	Model 4
Primary exposure				
OSA severity by categories as defined by AHI (n = 2,222): none (AHI < 5/h), mild (AHI = 5–14.9/h), moderate (AHI = 15–30/h), or severe (AHI > 30/h)				
Severe OSA, yes vs. no	**1.42 (1.10–1.85)**	1.23 (0.95–1.61)	1.21 (0.93–1.59)	1.27 (0.96–1.70)
Mild vs. normal	1.17 (0.82–1.69)	1.04 (0.73–1.50)	1.06 (0.73–1.52)	1.08 (0.74–1.55)
Moderate vs. normal	1.21 (0.82–1.78)	0.96 (0.65–1.42)	0.99 (0.67–1.46)	1.04 (0.69–1.55)
Severe vs. normal	**1.61 (1.13–2.28)**	1.24 (0.87–1.77)	1.23 (0.86–1.77)	1.33 (0.90–1.96)
Secondary exposures				
OSA severity by AHI as a continuous variable* (n = 1,964)				
AHI: ↑ in 29	**1.26 (1.09–1.44)**	**1.16 (1.00–1.34)**	1.12 (0.97–1.30)	1.14 (0.97–1.34)
Degree of nocturnal oxygen desaturation (n = 1,265)				
Mean Sa_{O_2}: ↑ in 3%	**0.74 (0.65–0.83)**	**0.77 (0.67–0.88)**	**0.79 (0.68–0.92)**	**0.79 (0.68–0.92)**
↑ in 5% of TST spent with Sa_{O_2} < 90%	**1.07 (1.04–1.11)**	**1.06 (1.02–1.09)**	**1.05 (1.01–1.09)**	**1.05 (1.01–1.09)**
>30% of TST spent with Sa_{O_2} < 90%, yes vs. no	**2.07 (1.30–3.27)**	**1.78 (1.12–2.83)**	1.55 (0.95–2.52)	1.55 (0.95–2.54)
Other markers of OSA severity derived from PSG (n missing: from 276 to 954)				
Sleep efficiency, quartiles				
Q1 (<57.4%) vs. Q4 (⩾89.6%)	**2.44 (1.64–3.61)**	1.46 (0.96–2.23)	1.48 (0.97–2.26)	1.48 (0.97–2.26)
Q2 (57.4–72.4%) vs. Q4 (⩾89.6%)	1.28 (0.84–1.98)	0.85 (0.55–1.34)	0.85 (0.54–1.34)	0.85 (0.54–1.33)
Q3 (72.4–83.5%) vs. Q4 (⩾89.6%)	1.10 (0.71–1.71)	0.82 (0.52–1.28)	0.88 (0.56–1.39)	0.88 (0.56–1.39)
Number of awakenings in total sleep time, quartiles				
Q2 (18–25) vs. Q1 (<18)	1.01 (0.65–1.57)	1.08 (0.69–1.68)	1.18 (0.76–1.86)	1.18 (0.75–1.86)
Q3 (25–36) vs. Q1 (<18)	0.97 (0.62–1.49)	0.97 (0.63–1.50)	1.03 (0.66–1.59)	1.02 (0.66–1.59)
Q4 (⩾36) vs. Q1 (<18)	1.40 (0.91–2.14)	1.17 (0.76–1.80)	1.21 (0.78–1.85)	1.20 (0.78–1.85)
Arousal index, quartiles				
Q2 (11-23.9) vs. Q1 (<11)	1.26 (0.78–2.01)	1.18 (0.73–1.90	1.18 (0.73–1.90)	1.18 (0.73–1.91)
Q3 (23.9-45.6) vs. Q1 (<11)	1.44 (0.90–2.29)	1.20 (0.74–1.92)	1.18 (0.73–1.89)	1.18 (0.73–1.89)
Q4 (⩾45.6) vs. Q1 (<11)	**1.76 (1.10–2.81)**	1.32 (0.82–2.13)	1.28 (0.79–2.06)	1.27 (0.78–2.06)
% Stage 1 sleep, quartiles				
Q2 (7.1–13.1) vs. Q1 (<7.1)	0.58 (0.32–1.05)	0.55 (0.30–1.00)	0.52 (0.29–0.96)	0.52 (0.29–0.96)
Q3 (13.1–23.5) vs. Q1 (<7.1)	1.34 (0.80–2.24)	1.11 (0.66–1.88)	1.06 (0.63–1.81)	1.07 (0.63–1.81)
Q4 (⩾23.5) vs. Q1 (<7.1)	**2.69 (1.68–4.33)**	**1.88 (1.14–3.11)**	**1.79 (1.07–2.98)**	**1.80 (1.07–3.00)**
% REM sleep, quartiles				
Q1 (<8.3) vs. Q4 (⩾19.5)	1.41 (0.88–2.26)	1.12 (0.69–1.80)	1.08 (0.66–1.75)	1.07 (0.66–1.75)
Q2 (8.3–14.0) vs. Q4 (⩾19.5)	0.93 (0.56–1.53)	0.81 (0.49–1.34)	0.81 (0.49–1.34)	0.81 (0.48–1.34)
Q3 (14.0–19.5) vs. Q4 (⩾19.5)	0.88 (0.54–1.43)	0.79 (0.48–1.29)	0.78 (0.48–1.28)	0.78 (0.48–1.27)

Definition of abbreviations: AHI = apnea–hypopnea index; CHF = chronic heart failure; COPD = chronic obstructive pulmonary disease; OSA = obstructive sleep apnea; PSG = polysomnography; Q = quartile; REM = rapid eye movement; Sa_{O_2} = oxygen saturation; TST = total sleep time.

Estimates are presented as adjusted hazard ratios and 95% confidence intervals. Estimates in bold indicate significantly associated ($P < 0.05$). Model 1: exposure + year of study + sleep clinic site + years since the cancer diagnosis. 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.

*For continuous variables, to standardized, the estimates were reported per interquartile range.

Finally, we redefined the outcome as time from the cancer diagnostic date from the OCR to cancer-related mortality and refitted models 1–4. However, this approach is limited by the immortal time bias, as our study population is only those who survived long enough after the cancer diagnosis to have a sleep study.

Explanatory analysis. To determine if the combined presence of severe OSA and cancer is associated with worse survival, we used a cross-sectional approach to avoid bias associated with the timing of the cancer diagnosis. Specifically, using logistic regressions and controlling for confounders available at baseline (model 3), we compared odds ratios for all-cause death between four groups: *1*) cancer (prevalent or incident) with AHI higher than 30 per hour; *2*) cancer with AHI of 30 or less per hour; *3*) AHI of more than 30 per hour without cancer; and *4*) AHI of 30 or less per hour without cancer (reference group). A similar approach was used for severe hypoxemia. Relative excess risk owing to interaction (RERI), a recommended measure of biological interaction (53), was calculated to quantify synergy (54). A RERI of zero indicated no interaction, a RERI greater than zero indicated a positive interaction, and a RERI less than zero indicated a negative interaction; a 95% CI that crossed zero indicated insignificance of the interaction (*see* the online supplement for details).

Complete case analysis was considered. All statistical analyses were performed in the secure environment at ICES following Ontario privacy standards using SAS Enterprise Guide 7.1, SAS Version 9.4 (SAS Institute Inc.).

Results

An Association between Markers of OSA Severity and Cancer-related Mortality in Individuals with Previously Diagnosed Cancer

Of 2,222 subjects with previously diagnosed cancer at baseline included (mean age, 62.7 years, 57.1% men, and mean BMI, 31.2 kg/m^2), 23.9% had AHI of less than 5 per hour, 28.4% had AHI of more than 30 per hour, and 5.4% spent more than 30% of time spent sleeping with Sa_{O_2} of less than 90% (Table 1). The most frequent cancer locations were prostate, breast, colorectal, and melanoma. For those with available information on the tumor stage ($n = 475$), most individuals (~75%) had stage 1 (184/475 [38.7%]) or 2 (174/475 [36.6%]); 70/475 (14.7%) individuals had stage 3, and 47/475 (9.9%) stage 4. Over a median follow-up time of 5.6 years (interquartile range [IQR], 2.7–9.1 years), 261/2,222 (11.7%) individuals died from cancer-related causes, which accounts for 44.2% (261/590) of all-cause death (Table E4). Other frequent causes of death were cardiometabolic (169/590 [28.6%]), respiratory (38/590 [6.4%]), and nervous system (36/590 [6.1%]) disorders.

The cancer-related mortality rates per 100 person-years ranged between 5.04 (95% CI, 4.35–5.84) in no OSA and 8.77 (95% CI, 7.89–9.75) in the severe OSA category, and between 6.32 (95% CI, 5.74–6.95) and 14.07 (95% CI, 11.58–17.10) for those without and with severe hypoxemia, respectively (Table E5). In univariate analyses, the cancer-related mortality rates significantly increased across oxygen desaturation categories and some measures of sleep fragmentation, such as a decrease in sleep efficiency and an increase in percentage of stage 1 of sleep ($P < 0.03$) (Figures 1 and 2), but not AHI categories ($P > 0.08$). Controlling for age, sex, alcohol use disorder, prior CHF, COPD, hypertension, diabetes, treatment for OSA, clinic site, year of the sleep study, and time since the cancer diagnosis, the following measures of hypoxemia and sleep fragmentation, but not AHI, were significantly associated with cancer-specific mortality: percent time spent with Sa_{O_2} of less than 90% (hazard ratio [HR] per 5% increase, 1.05; 95% CI, 1.01–1.09), mean Sa_{O_2} (HR per 3% increase, 0.79; 0.68–0.92), and percentage of stage 1 sleep (HR per 16% increase, 1.27; 1.07–1.51) (Table 2 and Table E3). These associations remained similar and significant when additionally controlling for BMI, smoking status, and supplementary demographic characteristics, multimorbidity, and prior primary care exposure (Table E3). The results also remained similar in the different population subsets with available data. The ARD for severe OSA versus normal was 2% (95% CI, 0 to 8) with NNH of 40; the ARD for severe hypoxemia versus not was 5% (95% CI, −1 to 9) with NNH of 21; and the ARD for quartile 1 versus quartile 4 of mean Sa_{O_2} was 7% (95% CI, 3 to 15) with NNH of 14. All prespecified statistical interactions tested were not significant (all P values > 0.1). OSA-related treatment was not significantly associated with cancer-related mortality (Table E6). Finally, when we redefined the outcome as the time since the cancer diagnostic date to cancer-related mortality, AHI of more than 30 per hour (vs. AHI < 5/h) became significantly associated with an approximately 60% increased hazard of cancer-related mortality: HR of 1.61 (95% CI, 1.10–2.37).

The Relationship between Markers of OSA and All-Cause Mortality in Adults with Previously Diagnosed Cancer

Over a median follow-up time of 6.4 years (IQR, 3.7–10.1), 663/2,222 (29.8%) individuals died from any causes with the mortality rate per 100 person-years of 4.1 (95% CI, 3.8–4.5). Characteristics of individuals by all-cause death are presented in Table E7.

The all-cause mortality rates per 100 person-years ranged between 3.2 (95% CI, 3.8–2.7) in individuals with no OSA and 5.6 (95% CI, 5.0–6.4) in the severe OSA category, and between 3.8 (95% CI, 3.4–4.3) and 8.6 (95% CI, 6.7–10.9) for those without and with severe hypoxemia, respectively (Table E7). In univariate analysis, the all-cause mortality rates increased across AHI ($P < 0.0001$) and oxygen desaturations categories ($P < 0.0001$), and measures of sleep fragmentation, such as reduced sleep efficiency and percentage of REM sleep, and increased number of awakenings in sleep, arousal index, and percentage of stage 1 of sleep ($P < 0.0001$) (Figures E2–E5). Controlling for age, sex, alcohol use disorder, prior CHF, COPD, hypertension, and diabetes, treatment for OSA, clinic site, year of the sleep study, and time since the cancer diagnosis, all markers of OSA severity were significantly associated with all-cause mortality (Table E8). In addition, when controlling for BMI, smoking status, and supplementary demographic characteristics, multimorbidity, and prior primary care exposure, these associations were attenuated but remained significant for the majority of markers (Table E9).

Explanatory Analyses: Testing Synergetic Interaction between the Presence of OSA and Cancer

Of 39,044 individuals considered, 35,922 individuals with no missing OSA severity categories as measured by AHI were included (Figure E1): the median age was 51 years, 20,669 (57.5%) were men, 1,254 (6.4%) had prevalent cancer, and 2,498 (7.0%) had incident cancer (Table 3). Of 35,922, 1,346 (3.7%) individuals had both cancer and severe OSA, 3,363 (9.4%) had cancer without severe OSA, 6,875 (19.1%) had severe OSA only, and 24,338 (67.8%) individuals had neither cancer nor severe OSA. Characteristics of individuals with available information on the percentage of sleep time spent with Sa_{O_2} of less than 90% ($n = 19,645$) for the total sample and by subgroups are presented in Table E10. Over a median of 8.1 years (4.4–11.8 years), 4,019/35,922 (11.2%) died from any cause.

Controlling for age, sex, alcohol use disorder, prior CHF, COPD, hypertension, or diabetes, year of study, sleep clinic site, and years since the cancer diagnosis, the highest odds (about fourfold) of all-cause mortality were associated with the combined presence of severe OSA or hypoxemia and cancer compared with the reference group. However, the synergistic effect was not confirmed (Table 4). In those diagnosed with cancer, the odds of death were 1.17 times higher (95% CI, 1.00–1.38) in individuals with severe OSA compared with those with nonsevere OSA. At the same time, in those without diagnosed cancer, the odds of death associated with severe OSA were 1.31 times higher (95% CI, 1.18–1.46) compared with those with nonsevere OSA. This finding did not confirm our hypothesis of the greater effect of severe OSA on all-cause mortality in individuals with cancer than in those without cancer.

Discussion

In this multicenter cohort study using clinical and health administrative data from more than 2,000 individuals who had suspected sleep apnea and previously

Table 3. Characteristics of individuals who underwent a diagnostic sleep study between 1994 and 2017 in four academic centers (Ontario, Canada): the total population of interest and by obstructive sleep apnea severity status (apnea–hypopnea index > 30 vs. ⩽30) and being diagnosed with cancer (before or after the sleep study) (*N* total = 35,992)

Variables	Nonsevere OSA and No Cancer (*n* = *24,338*)	Nonsevere OSA and Cancer (*n* = *3,363*)	Severe OSA and No Cancer (*n* = *6,875*)	Severe OSA and Cancer (*n* = *1,346*)	Total (*N* = *35,922*)
Outcome: all-cause death in follow-up	1,505 (6.2)	1,061 (31.5)	880 (12.8)	573 (42.6)	4,019 (11.2)
Cancer status at index date					
Incident cancer	0 (0.0)	1,779 (52.9)	0 (0.0)	719 (53.4)	2,498 (7.0)
Prevalent cancer	0 (0.0)	1,584 (47.1)	0 (0.0)	627 (46.6)	2,211 (6.2)
Demographics					
Age at the date of the diagnostic sleep study, median (IQR)	48.0 (38.0–58.0)	59.0 (51.0–68.0)	53.0 (44.0–62.0)	63.0 (55.0–72.0)	51.0 (41.0–61.0)
Sex, male	12,769 (52.5)	1,809 (53.8)	5,103 (74.2)	988 (73.4)	20,669 (57.5)
Neighborhood income quintile (Q), *n* (%)					
Q1	4,015 (16.5)	522 (15.5)	1,337 (19.4)	219 (16.3)	6,093 (17.0)
Q2	4,524 (18.6)	593 (17.6)	1,373 (20.0)	251 (18.6)	6,741 (18.8)
Q3	4,542 (18.7)	587 (17.5)	1,254 (18.2)	244 (18.1)	6,627 (18.4)
Q4	5,001 (20.5)	650 (19.3)	1,337 (19.4)	252 (18.7)	7,240 (20.2)
Q5	6,137 (25.2)	997 (29.6)	1,540 (22.4)	373 (27.7)	9,047 (25.2)
Leaving in rural area, yes	2,215 (9.1)	315 (9.4)	668 (9.7)	139 (10.3)	3,337 (9.3)
Being an immigrant, yes	2,413 (9.9)	176 (5.2)	662 (9.6)	68 (5.1)	3,319 (9.2)
Presence of prior comorbidities					
Chronic obstructive pulmonary disease	3,804 (15.6)	1,025 (30.5)	1,481 (21.5)	493 (36.6)	6,803 (18.9)
Diabetes	5,397 (22.2)	1,147 (34.1)	2,780 (40.4)	667 (49.6)	9,991 (27.8)
Hypertension	10,387 (42.7)	2,201 (65.4)	4,439 (64.6)	1,083 (80.5)	18,110 (50.4)
Chronic heart failure	1,580 (6.5)	589 (17.5)	1,036 (15.1)	402 (29.9)	3,607 (10.0)
Alcohol use disorder	1,279 (5.3)	190 (5.6)	410 (6.0)	83 (6.2)	1,962 (5.5)
Obesity (hospitalization)	340 (1.4)	79 (2.3)	209 (3.0)	71 (5.3)	699 (1.9)
Primary health care exposure					
# Primary care office visits within 1 yr before the index date, median (IQR)	5.0 (2.0–9.0)	6.0 (3.0–10.0)	5.0 (2.0–9.0)	6.0 (4.0–10.0)	5.0 (3.0–9.0)

Definition of abbreviations: IQR = interquartile range; OSA = obstructive sleep apnea; Q = quartile.
Data are presented as *n* (%) per column, unless otherwise indicated. Numbers may not add to totals because of missing values.

diagnosed cancer, measures of nocturnal hypoxemia and sleep fragmentation as markers of OSA severity, but not AHI, were significantly associated with cancer-related mortality independent of known risk factors. These findings support an association between OSA and reduced survival in individuals with cancer through both intermittent hypoxemia and sleep fragmentation, suggesting the need for more targeted risk awareness in individuals with combined OSA and cancer. We confirmed these findings for all-cause mortality as the secondary outcome. The association found for an increase in AHI and reduction in REM sleep with all-cause but not cancer-related mortality can be explained by different physiological pathways involved in OSA and cancer, versus other mortality causes, such as cardiovascular, or increased statistical power owing to longer follow-up time, and a large number of events for all-cause mortality as an outcome. Confirming this assumption, when we redefined the outcome as the time since the cancer diagnostic date to cancer-related mortality, the effect of AHI became significant. Compared with other published studies that investigated this association, we considered other markers of OSA severity than measures of respiratory disturbances and nocturnal hypoxemia; we also first implemented a biological measure of interaction to understand whether the effect of severe OSA on all-cause mortality is greater in individuals with cancer than in those without cancer.

Controlling for known risk factors, the highest odds (about fourfold) of all-cause mortality were associated with the combined presence of severe OSA or hypoxemia and cancer when compared with individuals without OSA or cancer. Although the RERI of more than zero found in our study indicates a potential synergetic effect, it was not significant statistically. Given these results, we cannot completely exclude that the excess mortality risk related to markers of severe OSA is independent of cancer. However, owing to our study design, individuals with cancer had to be healthier than average cancer patients to get sleep testing, which may bias our results toward the null.

We confirmed results from other studies suggesting that OSA and hypoxemia severity are potential contributing factors to mortality in individuals with cancer (14, 16, 17). There are several potential explanations for the

Table 4. Effect of the presence of severe obstructive sleep apnea or hypoxemia on all-cause mortality compared to a reference group of those with neither cancer (prevalent or incident) nor severe obstructive sleep apnea or hypoxemia controlling for confounders* (effect expressed as odds ratios and 95% confidence intervals)

Effect of Exposures	Odds Ratio Estimate	Lower 95% Confidence Limit for Odds Ratio	Upper 95% Confidence Limit for Odds Ratio
Interaction between the presence of cancer (prevalent or incident) and severe OSA as defined by AHI > 30 events/hour (yes/no)			
Reference group: neither severe OSA nor cancer	1	1	1
Cancer with no severe OSA vs. reference	3.38	3.04	3.77
Severe OSA with no cancer vs. reference	1.31	1.18	1.46
Combined severe OSA and cancer vs. reference	3.98	3.44	4.60
RERI (95% CI)†	0.29 (−0.33 to 0.90)		
Severe OSA and cancer vs. no severe OSA and cancer	1.17	1.00	1.38
Interaction between the presence of cancer (prevalent or incident) and severe nocturnal hypoxemia (yes/no)			
Reference group: neither severe hypoxemia nor cancer	–	–	–
Cancer with no severe hypoxemia vs. reference	2.89	2.53	3.30
Severe hypoxemia with no cancer vs. reference	2.31	1.88	2.84
Combined severe hypoxemia and cancer vs. reference	4.05	2.92	5.61
RERI (95% CI)	−0.15 (−1.54 to 1.25)		

Definition of abbreviations: AHI = apnea–hypopnea index CHF = chronic heart failure; CI = confidence interval; COPD = chronic obstructive pulmonary disease; HR = hazard ratio; OSA = obstructive sleep apnea; RERI = relative excess risk owing to interaction.
*Controlling for age, sex, alcohol use disorder, prior CHF, COPD, hypertension, diabetes, year of study, sleep clinic site, and years since the cancer diagnosis.
†RERI = HR11 (severe OSA and cancer) − HR10 (severe OSA with no cancer) − HR01 (cancer with no severe OSA) + 1.

observed association between increased all-cause mortality and severe OSA or hypoxemia in individuals with cancer. Certainly, OSA would be expected to cause increased mortality in patients with cancer by increasing cardiovascular and metabolic risk in a manner previously described in individuals without cancer (19, 55, 56). However, OSA has also been postulated to be linked to cancer development and progression through its adverse downstream physiological consequences such as systemic intermittent hypoxia, oxidative stress, increased sympathetic nervous system activity, altered immune response, systemic inflammation, endothelial dysfunction and disrupted circadian rhythm (9–13). There is evidence that intermittent hypoxia may affect the entire carcinogenesis process from initial tumor formation to growth and metastasis (13). Disruption of circadian rhythm through sleep fragmentation may also influence tumor cell behavior (13). Finally, an increase in sympathetic nervous system activity may affect tumors and their microenvironments (13). Despite the potential importance of the arousals in an understanding of the sleep process, controlling for confounders, the association with cancer-related mortality was found for an increase in percentage of stage 1 sleep, but not arousal index, which could be explained by high variability in the scoring of arousals (57), which likely biases our results toward the null and requires further investigations.

Strengths and Limitations

Our study had many strengths, including *1*) long follow-up through health administrative data with a relatively large number of events for cancer-related and all-cause mortality; *2*) a wide range of OSA severity derived from PSG recording from different sleep centers across Ontario, contributing to generalizability of our results; *3*) access to a high-quality validated cancer registry; *4*) reasonably robust adjustment for confounders; and *5*) presentation of both relative and absolute risks.

Our study was limited by its observational and historical design using data from clinical academic centers over the different time periods, hindering its generalizability and increasing the potential for unmeasured confounding (e.g., information on cancer staging was not available for approximately 80% of the cohort), referral bias, and age-period-cohort effects despite multiple sensitivity analyses. Although our study population is limited to individuals who were referred for sleep disorder assessment and underwent PSG, thus lacking for a truly non-OSA comparison group compared with community-based studies, we have a much higher proportion and spectrum of severe sleep apnea compared with community-based studies, which facilitates addressing our main research aim of investigating an association between markers of OSA severity and cancer-related mortality. Importantly, our results on the association between sleep time spent with Sa_{O_2} of less than 90% and cancer mortality are consistent with a community-based study (16). In addition, the generalizability of our findings is limited by including long-term cancer survivors. Assessment of sleep disorders may not be a

priority for individuals with short cancer-related prognoses. Misclassification bias may be associated with identifying a cause of death, which was addressed by considering all-cause mortality as a secondary outcome. The number of cancer-related deaths still was not large enough to focus on different cancer subtypes. Differences in cancer treatment between individuals with and without OSA (data not available in our study) may also contribute to increased cancer-related mortality. Individuals with OSA often have other comorbid conditions, such as cardiovascular conditions, which may influence clinical decisions. We have addressed this limitation partly by controlling for separate conditions and multimorbidity in our statistical model. In addition, cancer outcomes have changed over time owing to improvement in cancer care (58, 59), but we do not think there is any bias in OSA severity over time that should coincide that has not been considered by covariates in our model. Although we were not able to properly adjust for other sleep disorders, our main results remained similar, additionally controlling for periodic leg movements in sleep as derived by PSG and self-reported restless legs, excessive daytime sleepiness and insomnia (results are not shown). Further, despite adjustment for sleep center and study year in the statistical models, differences in the definition of hypopnea over time and across clinical cohorts may be an important limitation (60, 61). Still, it reflects the real-world variability in the definition of AHI across different sleep centers and countries and over time (62), which likely biases the results toward the null owing to randomness in variability but improves the generalizability of our findings. In four out of five sleep cohorts under the study, the definitions of hypopnea had not changed over the time frame when data were extracted. Importantly, measures of nocturnal hypoxemia found in our study to be associated with cancer-related mortality is more comparable between centers and more stable over time. Finally, although our results were limited by multiple comparisons, reassuringly, they were consistent across multiple statistical models, suggesting the robustness of our findings.

Future research should determine the relative importance of different pathways to OSA, hypoxemia and/or sleep fragmentation-related mortality risk. Subsequent trials should test whether improvements in OSA care and sleep quality, through a holistic sleep intervention, including cognitive behavioral therapy for insomnia (63), reduce long-term mortality among individuals diagnosed with cancer. More research is also needed to investigate the association between other causes of sleep fragmentation, such as insomnia, restless legs, and circadian rhythm disorders, including shiftwork, and cancer development or progression.

Conclusions

In a large clinical cohort of adults with suspected OSA and prevalent cancer, measures of nocturnal hypoxemia and sleep fragmentation as markers of OSA severity, but not AHI, were significantly associated with cancer-related mortality. In adults with suspected OSA, regardless of the cancer status, the highest all-cause mortality risk was found in individuals with severe OSA and cancer. However, the effect of these factors together does not exceed the effect of each factor considered individually. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors thank Dr. Victor Hoffstein for creating and maintaining the St. Michael's Hospital Sleep Laboratory database. The authors also thank the research assistants at the London Health Sciences Centre, Nariko Kuwahara and Sherry Coulson, and at the Ottawa Hospital Research Institute (OHRI), Moussa Meteb, Aseel Ahmad, and Randa Ahmad for their role in databases preparation, as well as Cayden Peixoto (OHRI research assistant) for his role in the manuscript preparation.

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