The Association of Sleep Apnea and Cancer in Veterans

Sebastian M. Jara

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Amanda I. Phipps

Edward M. Weaver

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Abstract

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Sebastian M. Jara

Chair of the Supervisory Committee:

Amanda I. Phipps

Department of Epidemiology

OBJECTIVE: To test the association between pre-existing obstructive sleep apnea (OSA) and subsequent cancer in a large, long-term cohort of veteran patients.

METHODS: This retrospective matched cohort study included all veteran patients diagnosed with OSA 1993-2013 by ICD-9 codes in any Veterans Affairs facility and probability matched veteran patients without OSA. Cancer diagnoses were identified by ICD-9 codes at least two years after index OSA diagnosis in patients with OSA and matched inception year in patients without OSA. Treatment by continuous positive airway pressure (CPAP) prescription was identified by CPT and ICD-9 codes. We tested the association between OSA (diagnosis and treatment) and subsequent cancer using multivariate Cox regression with time since OSA diagnosis as the time axis, adjusting for potential confounders.

RESULTS: The cohort included 1,236,130 patients (593,429 with OSA and 642,701 without OSA) with mean age 58+/-13 years, predominantly male (94%), a minority obese (30%), and median follow up 3.9 years (range 2.0-24.1). The proportion of patients diagnosed with cancer was higher in those with vs. without OSA (6.2% vs. 3.0%, P<0.001). After adjusting for age, sex, year of diagnosis, smoking, alcohol use, obesity, and comorbidity, the hazard of developing cancer was more than double in patients with vs. without OSA (HR 2.02; 95% CI [1.98-2.05]; P<0.001). Adjusting for the same confounders, the hazard of developing cancer was 8% lower in patients prescribed CPAP vs. untreated patients, among OSA patients with a sleep test preceding their diagnosis (HR = 0.92, 95% CI: 0.88-0.97).

CONCLUSION: Pre-existing OSA was strongly associated with subsequent cancer diagnosis in this veteran cohort, independent of known cancer risk factors. Additionally, the provision of CPAP may be associated with a reduction in cancer incidence. Further analyses are ongoing, including analysis of specific cancer types, other OSA treatment modalities, and cancer-related mortality.

INTRODUCTION

Obstructive sleep apnea (OSA) is a prevalent disorder of symptomatic repeated episodes of upper airway collapse and obstruction during sleep.[1–3] OSA has been estimated to affect up to 15-30% of adult males and 5-15% of adult females in the US[4], with risk factors including increasing age, male sex, and obesity.[5] Untreated OSA has been associated with considerable morbidity including cardiovascular disease, cerebrovascular disease, metabolic disease, and neurocognitive dysfunction.[6–10] Through these (and other) mechanisms, untreated OSA appears to decrease long-term survival.[11–13] Treatment of OSA, by either continuous positive airway pressure (CPAP, first-line) or other modalities (surgery or oral appliance), appears to reduce these complications and may improve long-term survival, even in patients with only partial CPAP use.[6,12–15]

An emerging body of evidence has suggested that OSA is also associated with cancer.[16-36] A few studies have suggested that OSA may mechanistically promote the development of cancer through intermittent hypoxia and sleep fragmentation, leading to chronic oxidative stress and activation of factors which support tumor angiogenesis, cell survival, metastasis, and possibly more aggressive cancer behavior.[16–23] Several epidemiologic studies have further explored this association with mixed results.[24–36] A recent large-scale study of 5.6 million patients identified through a national health insurance database showed no increased cancer incidence overall, but did show positive associations between OSA and increased incidence of specific cancer types (kidney, pancreatic, and melanoma).[24] Two small studies showed a positive association between OSA severity and increased overall cancer incidence while another similar study showed no association.[25–27] A handful of studies have also shown positive associations between OSA and increased incidence and aggressiveness of specific cancer types.[31–36]

While several studies have evaluated the association between OSA and cancer, the results from these studies are not concordant and their study methodologies have differed.

Furthermore, many of these studies have either been limited by small sample sizes, relatively short patient follow-up, and/or limited confounder adjustment. Moreover, the effect of OSA treatment on cancer incidence has not been evaluated. The primary aim of this study was to test the hypothesis that pre-existing OSA is associated with an *increase* in subsequent cancer incidence in a large cohort of patients, with long-term follow-up and robust confounder adjustment. The second aim was to test the hypothesis that OSA treatment is associated with a *decrease* in subsequent cancer incidence among OSA patients.

METHODS

STUDY DESIGN & SETTING

We conducted a retrospective matched cohort study of all veteran patients diagnosed with OSA through any Veterans Affairs (VA) medical facility, as well as veteran patients without OSA probability-matched 1-to-1 on age and year of index diagnosis, from October 1992 through September 2013 (defined as fiscal years 1993 to 2013). Within this cohort, we tested the association of pre-existing OSA with cancer incidence, and the association between OSA treatment and cancer incidence. This study and a waiver of informed consent were approved by the Institutional Review Boards at the VA Puget Sound Medical Center and the University of Washington.

STUDY SUBJECTS

Subjects included all adult veteran patients with a diagnosis of OSA, as well as a matched cohort of veteran patients without a diagnosis of OSA, for whom complete inpatient and outpatient administrative records were available (see Data Sources). Patients with OSA were identified based on the presence of *International Classification of Diseases* (ICD-9) codes for OSA in Inpatient and Outpatient Datasets in fiscal years 1993 to 2013 (see Data Sources). As a measure to reduce misclassification of OSA, we required OSA patients to have a diagnosis

code for OSA noted in at least 1 inpatient encounter or 2 outpatient encounters, according to a previously described algorithm for identifying OSA in administrative datasets.[37] The diagnosis from the first noted encounter was considered the index diagnosis of OSA. Veteran patients without OSA were identified by including veterans without a diagnosis code for OSA during this same timeframe, probability matched 1-to-1 on age and year of index diagnosis. We required all patients to have comorbidity data available for 2 years before index diagnosis or matched inception (see Outcome and Covariate Variables). All patients with a pre-existing diagnosis of cancer were excluded.

DATA SOURCES AND COLLECTION

The Veterans Health Administration (VHA) Inpatient and Outpatient Datasets are administrative databases of all inpatient, ambulatory, and ancillary service encounters provided at the 132 VA medical centers nationwide. The Inpatient Dataset includes diagnostic data, including the principal diagnosis of an inpatient encounter, as well up to 9 additional diagnoses (using ICD-9 diagnosis codes), starting from fiscal year 1991.[38] It also includes demographic data and data on inpatient procedures (using ICD-9 procedure codes). The Outpatient Dataset is managed analogously to the Inpatient Dataset and includes all ambulatory encounter diagnoses (ICD-9 diagnosis codes) starting from fiscal year 1997.[39] This dataset also includes demographic data and data on outpatient CPAP prescriptions and other outpatient surgical procedures (CPT codes). To determine CPAP prescription status, all inpatient and outpatient codes for CPAP prescription were identified and extracted, along with the date of CPAP prescription. Patients without a code for CPAP prescription in these VA administrative datasets were considered untreated. Additionally, patients with a diagnostic polysomnogram preceding their OSA diagnosis were identified using inpatient and outpatient codes for polysomnography.

To ascertain vital status, the VHA Vital Status File was used. Like the Inpatient and Outpatient Datasets, the Vital Status File is an administrative database with vital status

information collected and corroborated from numerous data sources including the Beneficiary Identification and Records Locator System (BIRLS) Death File database, data from the Centers for Medicare and Medicaid Services (CMS), and the Social Security Administration.[40] Vital status data extracted for the present study were current through February 1, 2017.

OUTCOME AND COVARIATE VARIABLES

The primary outcome was a diagnosis of cancer. Cancer diagnoses were identified by the presence of ICD-9 diagnosis codes for any malignant neoplasm in the Inpatient or Outpatient datasets in fiscal years 1993 to 2013. The ICD-9 code and the encounter date for the first cancer diagnosis were both extracted. Time to cancer diagnosis was calculated as the time from the date of index diagnosis in patients with OSA (or date of matched inception in patients without OSA) to the date of the first cancer diagnosis, or censoring by death or study conclusion (end of fiscal year 2015, September 30, 2015), whichever came first. To reduce the risk of reverse causality, only patients with their first cancer diagnosis at least two years after the date of index diagnosis of OSA (or date of matched inception) were included.

Covariates included age at index diagnosis for patients with OSA (or age of matched inception in patients without OSA), sex, race/ethnicity, smoking, alcohol use, obesity (body mass index ≥30 kg/m^2), and comorbidity (as described below). All demographic variables were identified from the VA databases. Data on smoking (current/former vs. none), alcohol use (abuse/dependence vs. none), and obesity (body mass index ≥ 30 kg/m^2 vs. < 30 kg/m^2) were obtained by identifying ICD-9 codes for these through encounters in the Inpatient and Outpatient datasets.

Comorbidity was assessed using the Deyo modification of the Charlson Comorbidity Index.[41,42] The Charlson Comorbidity Index consists of 19 specific comorbid medical conditions that have each been shown to predict mortality.[41] Each condition is assigned a point value, weighted based on the severity of the comorbidity. The sum of all present comorbid conditions

yields an overall index score, which provides a summary of baseline health. The Deyo modification extracts and weights the same conditions from administrative databases using the corresponding ICD-9 codes.[42] The Deyo-modified Charlson Comorbidity Index was created for each patient from all inpatient and outpatient diagnoses in the two years preceding the date of index diagnosis (or date of matched inception). Because patients with a pre-existing diagnosis of cancer were excluded, the Charlson Comorbidity Index score for each patient reflects the sum presence of each comorbid condition aside the cancer-specific comorbidities.

DATA ANALYSIS

Descriptive data are reported as mean +/- standard deviation or percentage frequency. Bivariate comparisons were carried out using the Student's t-test for continuous data and the chi-square test for categorical data. Differences in the proportion of patients with a cancer diagnosis were compared using the chi-square test. Cox proportional hazard regression was used to compare the hazards for developing cancer between patients with vs. without a diagnosis of OSA, using time since OSA diagnosis (or time since matched inception) as the time axis. Multivariate Cox regression was performed adjusting for age at OSA diagnosis (or matched inception), sex, diagnosis year (or year of matched inception), smoking, alcohol use, obesity, and comorbidity. Cox proportional hazard regression was also used to compare the hazards for developing cancer between OSA patients prescribed CPAP vs. untreated OSA patients, using time since OSA diagnosis as the time axis; CPAP prescription was modeled as a time-dependent exposure, based on the date of CPAP prescription. Multivariate Cox regression was also performed for analyses of CPAP treatment, adjusting for the same previously mentioned confounding variables. A P-value < 0.05 was considered statistically significant. All analyses were performed with Stata/SE 14 (Stata Inc., College Station, TX).

RESULTS

The cohort included 1,236,130 patients consisting of 593,429 patients with an OSA diagnosis and 642,701 patients without an OSA diagnosis. The cohort had a mean age of 58 +/- 13 years, was predominantly male, and predominantly White (Table 1). There were significant differences in several characteristics between patients with vs. without diagnosed OSA. Notably, patients with diagnosed OSA were more predominantly obese and had more comorbidities than the comparison group. Although significant differences in other characteristics were noted, the magnitude of these differences were small. There was no significant difference in follow-up time between comparison groups (Table 1).

The proportion of patients diagnosed with cancer by the end of the study period was higher in patients with an OSA diagnosis compared to patients without (6.2% vs. 3.0%, $P < 0.001$). This significant difference persisted throughout the follow-up period (Figure 1).

After multivariable adjustment, patients with an OSA diagnosis had more than double the hazard of developing cancer during the study period than the comparison group (Table 2, HR = 2.02, 95% CI: 1.98-2.05). All confounding variables assessed had a significant, independent association with cancer. Specifically, as expected, increasing age, smoking, alcohol use, obesity, and increasing comorbidity were all associated with a higher hazard of cancer diagnosis; increasing year of diagnosis (or matched inception) was associated with a lower hazard of developing cancer. In analyses restricted only to OSA patients with a documented diagnostic polysomnogram preceding their diagnosis (n=145,228), patients with OSA still had more than double the hazard of developing cancer than patients without an OSA diagnosis, after adjusting for the same potential confounding variables (Table 3). In this model, male sex (vs. female sex) no longer had a significant, independent association with developing cancer. However, associations between the other potential confounding variables and cancer were comparable to those in the primary model.

Of the 593,429 patients with an OSA diagnosis, 164,426 (28%) were prescribed CPAP while the remaining 429,003 (72%) patients were untreated. OSA patients with a CPAP prescription were more predominantly obese and had a slightly shorter follow up than untreated OSA patients (Table 4). Differences in other characteristics were statistically significant but small in magnitude. The proportion of patients diagnosed with cancer by the end of the study period was lower in OSA patients prescribed CPAP compared to untreated OSA patients (5.0% vs. 6.7%, $P < 0.001$).

After adjustment for the same potential confounding variables as in the previous model, patients prescribed CPAP had an 8% lower adjusted hazard of developing cancer than untreated patients, among OSA patients with a documented diagnostic polysomnogram preceding their diagnosis (Table 5, HR = 0.92, 95% CI: 0.88-0.97). All potential confounding variables in this model had a significant, independent association with cancer, except for male sex and obesity. When this same analysis was performed among all OSA patients, regardless of whether patients had a preceding polysomnogram, the difference in the hazard of developing cancer, between patients prescribed CPAP and untreated patients, was no longer signicant (Table 6, HR = 0.99, 95% CI: 0.96-1.01). Like with previous models, most confounding variables (except for obesity) had a significant, independent association with cancer.

DISCUSSION

The results of this study support the hypothesis that pre-existing OSA is associated with increased cancer incidence. In particular, we observed a two-fold higher hazard of developing cancer in patients with diagnosed OSA compared to patients without an OSA diagnosis, both in unadjusted models and after robust adjustment for important confounders. This effect persisted in analyses restricted to OSA patients with a documented polysomnogram preceding their diagnosis. Additionally, although results were mixed, this study also provides evidence to support the hypothesis that OSA treatment, as assessed by CPAP prescription, may be

associated with a decreased cancer incidence. In analyses restricted only to OSA patients with a documented polysomnogram before diagnosis, the adjusted hazard of developing cancer was 8% lower in OSA patients prescribed CPAP compared to untreated OSA patients. However, this association was no longer observed in analyses that included all OSA patients, regardless of whether they had a preceding polysomnogram. While further investigation is needed, this finding is encouraging and suggests that OSA treatment may be associated with decreased cancer incidence.

Several past studies have evaluated the association between OSA and cancer incidence with mixed results.[24–26,28,30] In the largest study to date, Gozal et al. studied 5.6 million patients, including 1.7 million patients with an OSA diagnosis, identified from an administrative national health insurance database, and found no association between OSA and cancer incidence after adjustment for age, sex, and eight comorbidities.[24] Interestingly, subgroup analysis revealed that OSA was associated with an increased incidence of certain cancers (kidney, pancreatic, and melanoma) and a decreased incidence of other cancers (colorectal, breast, and prostate). Similarly, in another large study of ~10,000 patients identified through a single academic medical center, Kendzerska et al. found no association between OSA and cancer incidence after adjustment for age, sex, smoking, and obesity.[25] In contrast, in a smaller study of ~400 patients with 20 years of follow up, Marshall et al. found that moderate-severe OSA was associated with both increased cancer incidence and cancer-related mortality, after adjustment for similar confounders.[26] A multicenter cohort study of ~5000 patients by Campos-Rodriguez et al. found that increasing OSA severity was associated with an increased cancer incidence in male patients and patients under age 65 years, but not in the overall cohort, after confounder adjustment.[28] Studies of specific cancer types have suggested an association between OSA and increased incidence and aggressiveness of kidney cancer[31], pancreatic cancer[32], melanoma[33], colorectal cancer[34], breast cancer[35], and central nervous system cancers.[36]

The discrepancy in the results reported from past studies likely stems from the logistical challenges in performing a well-controlled study of the association between OSA and cancer. Because of the natural course of cancer development after risk factor exposure, long-term patient follow-up is needed to detect new cancers that arise. Yet, most past studies on OSA and cancer have reported a relatively short patient follow-up. While the largest study to date includes an impressive 5.6 million patients, mean follow-up after OSA diagnosis was only 3.2 years.[24] In contrast, the studies with longer patient follow-up had smaller samples sizes, inherently limiting their statistical power to detect differences in cancer incidences, evaluate OSA treatment, or perform subsequent adjusted analyses.[25,26,28] Adjustment for confounding in these studies was often limited and inconsistent. Several known potential confounders (such as age, sex, and obesity) were frequently included in adjusted models; however, comorbidity was seldom included. One study included robust adjustment for eight comorbidities, but did not adjust for smoking[24], an important cancer risk factor and a factor previously associated with OSA.[43]

Several unique features in this study help to mitigate the challenges inherent in previous studies. This study includes patients diagnosed over a 20-year period, with some patients having up to 24 years of follow-up from their OSA diagnosis date. Additionally, this study includes a large sample size of OSA patients from all VA medical centers across the United States. Thus, this cohort draws from a broad and heterogeneous geographic sample, which strengthens the generalizability of the findings. Furthermore, this study includes robust adjustment for potential confounders. On average, the patients with an OSA diagnosis differed from the matched comparison group on several characteristics, notably with a higher frequency of obesity and a higher burden of comorbidity. A direct comparison of cancer incidence between these two groups would have been biased by these differences. Indeed, all confounders included in the model had a significant, independent association with cancer, even if small, further highlighting the need for adjustment. Comorbidity is especially important to adjust for, as both OSA and cancer are associated with multiple comorbid conditions. This study included the

Deyo modification of the Charlson Comorbidity Index, which allows for adjustment of up to 19 specific comorbid medical conditions, and thus provides comprehensive adjustment for this multifaceted confounder.[41,42]

Of note, this is the first study to assess the association between OSA treatment, by CPAP prescription, and cancer incidence. In analyses restricted to OSA patients with a preceding polysomnogram, OSA patients prescribed CPAP had an 8% lower adjusted hazard of developing cancer compared to untreated OSA patients. However, no association was observed when this analysis was performed among all OSA patients. There are several potential explanations for these mixed findings. OSA is a chronic disorder that often goes undiagnosed for several years. Thus, it is possible that the OSA patients in our cohort may have been experiencing intermittent hypoxia and sleep fragmentation, as well as other deleterious consequences of OSA, for several years prior to formal diagnosis and treatment. This delay may diminish the potential observed beneficial effects of OSA treatment on subsequent cancer incidence in the period of follow up. In addition, this study encompasses a 20-year period of time in which substantial changes in OSA practice patterns have occurred at the VA. In 2004, OSA became a service-connected condition with disability benefits, gradually implemented over a 10-year period, which provided veterans with a financial incentive to receive an OSA diagnosis.[44,45] As such, the frequency of OSA diagnoses increased dramatically during this period. In this study, 76% of the OSA cohort was diagnosed in 2010 or after. As such, patients receiving a diagnosis later in the study timeframe had a shorter follow up period and may have had milder OSA, both of which could potentially weaken the noted association between CPAP prescription and cancer.

Importantly, this study also assessed CPAP prescription, not CPAP treatment. Because adherence to CPAP has historically been variable and poor, data on CPAP prescription is an imperfect proxy for effective CPAP treatment. Thus, while patients were prescribed CPAP, they may not have actually received effective treatment, which may partially explain the results

observed. Despite having data on CPAP prescription, an important limitation of this study was lack of data on CPAP usage and compliance among OSA patients. Additionally, although the VA system is thought to be self-contained, some veteran patients in this study may have received care outside of the VA system. Thus, it is possible that some OSA patients may have been misclassified as untreated when, in fact, they received treatment by a provider outside of the VA. While data on care received outside the VA system are not available, restricting analyses to OSA patients with a documented polysomnogram through the VA may reduce this source of misclassification by selecting for patients that received their care more exclusively through the VA. The preceding polysomnogram is also a marker of involvement of a sleep medicine program that might provide more thorough CPAP care (titration polysomnogram, CPAP education, and support) than CPAP prescribed by other providers not part of a sleep medicine program. Thus, the analyses among patients with a preceding polysomnogram, which demonstrated an 8% lower adjusted hazard of developing cancer in CPAP prescribed patients compared to untreated patients, may more accurately reflect the potential impact of CPAP on subsequent cancer in OSA patients.

There are several other important limitations to this study. In addition to lacking data on CPAP usage and compliance among OSA patients, data on polysomnogram results, and thus OSA severity, were not available. A few studies have suggested an association between OSA severity and cancer outcomes, which could not be evaluated in this study. However, OSA severity is often evaluated because of its association with subsequent comorbidity. Thus, adjusting for comorbidity in this study may have partially accounted for differences in OSA severity, particularly in analyses assessing OSA treatment. Additionally, because OSA was identified by ICD-9 diagnosis codes, and not by polysomnogram results, there is potential for misclassification of OSA in this study. Indeed, inherent to the use of large administrative databases are potential biases and errors in coding. Also possible is the presence of undiagnosed OSA in the comparison group of patients without an OSA diagnosis, which could

also potentially weaken the association between OSA and cancer. In an effort to reduce the misclassification of OSA in this study, we employed a validated algorithm that has been shown to identify OSA in administrative databases with high specificity and positive predictive value.[37] Furthermore, analyses restricted only to OSA patients with a preceding polysomnogram, as a marker of definitive diagnostic testing, further helped to reduce misclassification of OSA. Because this misclassification is non-differential, it presents a conservative bias (i.e. towards the null hypothesis of no association), it is reassuring that significant associations were observed between OSA (both diagnosis and treatment) and cancer incidence. While it is theoretically possible that cancer diagnoses were also misclassified in this dataset, this is less likely given the implications of a cancer diagnosis and the necessary work up often required for diagnosis. Another limitation is generalizability. Our cohort consisted solely of veterans with treatment data from VA medical facilities. Because veterans carry a greater risk of OSA, cancer, and comorbidity, the results of this study may not generalize to the entire US population. However, because this study includes data across all VA medical centers nationwide, it provides broad geographic and practice-pattern representation, both of which enhance generalizability. Lastly, as an observational study, this study was inherently subject to confounding, both from known and unknown potential confounders. We attempted to mitigate this, albeit imperfectly, through robust adjustment for demographics, cancer risk factors, and comorbidity.

The present study was also limited to an analysis of cancer overall. Indeed, previous work has shown potential associations between OSA and increased incidence of several specific cancers.[24,31–36] Given that differential associations with specific cancer sites are likely to be obscured in analyses of all cancers combined, it will be important to assess if these associations exist, and to what extent they exist, in this cohort of veteran patients. Additionally, future analyses will include several potential proxies for CPAP usage and compliance, such as the frequency of CPAP supply refills. Further analyses incorporating these proxies for usage may provide a better assessment of CPAP treatment effect on cancer outcomes. Lastly, there is

evidence to suggest that OSA may be associated with cancer-related mortality.[26,27,29] Future studies will test the association between OSA, and OSA treatment, on cancer-related mortality.

CONCLUSION

Pre-existing OSA is strongly associated with subsequent cancer diagnosis, independent of known cancer risk factors. Additionally, the provision of CPAP may also be associated with a reduction in cancer incidence, but further study in patients adherent to CPAP is needed to better test the association between CPAP treatment and cancer.

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TABLES

Table 1. Cohort Description

Characteristic	**All Patients** N=1,236,130	**With OSA** All N=593,429	**With OSA** Preceding PSG N=145,228	**Without OSA** N=642,701	***P*-Value**
Age, mean +/- SD (years)	58 +/- 13	58 +/- 13	58 +/- 12	58 +/- 14	< 0.001
Men (%)	94%	95%	96%	93%	< 0.001
White‡ (%)	79%	78%	75%	80%	< 0.001
Smoking (%)	21%	22%	24%	20%	< 0.001
Alcohol Use (%)	10%	10%	11%	9%	< 0.001
Obesity (%)	30%	46%	52%	14%	< 0.001
Comorbidity Index, mean +/- SD	0.9 +/- 1.3	1.2 +/- 1.5	1.2 +/- 1.6	0.6 +/- 1.0	< 0.001
Follow Up (years)					0.33
Mean +/- SD	5.2 +/- 3.0	5.2 +/- 2.8	4.9 +/- 2.5	5.2 +/- 3.1	
Median (Range)	3.9 (2.0-24.1)	4.1 (2.0-24.1)	4.0 (2.0-24.0)	3.8 (2.0-24.1)	
% with Cancer Diagnosis	4.5%	6.2%	5.9%	3.0%	< 0.001

**P*-value comparing patients with and without OSA.

‡Calculated from proportion of cohort with known race/ethnicity. Data on race/ethnicity missing for 32% of cohort (28% of patients with OSA and 37% in patient of patients without OSA).

Abbreviations: OSA, obstructive sleep apnea; PSG, polysomnogram; SD, standard deviation.

Table 2. Hazard of Cancer: Patients with vs. without OSA (Cox Regression)

Variable	Reference Group	Unadjusted HR (95% CI)	*Adjusted HR (95% CI)	‡*P*-Value
With OSA	Without OSA	2.14 (2.10-2.18)	2.02 (1.98-2.05)	< 0.001
Age (years)	One Year Younger	1.03 (1.03-1.03)	1.03 (1.03-1.03)	< 0.001
Male Sex	Female Sex	1.46 (1.40-1.52)	0.95 (0.91-0.99)	0.016
Year of Diagnosis	One Year Prior	0.92 (0.92-0.92)	0.91 (0.91-0.91)	< 0.001
Smoking	No Smoking	1.37 (1.34-1.39)	1.49 (1.46-1.52)	< 0.001
Alcohol Use	No Alcohol Use	1.25 (1.22-1.29)	1.28 (1.25-1.31)	< 0.001
Obesity	No Obesity	1.24 (1.22-1.26)	1.03 (1.01-1.05)	0.001
Comorbidity Index	One Less Index Score	1.23 (1.23-1.24)	1.10 (1.10-1.10)	< 0.001

*Adjusted for age at diagnosis (or matched inception), sex, year of diagnosis (or matched inception), smoking, alcohol use, obesity, and comorbidity.
‡Adjusted model.
Abbreviations: OSA, obstructive sleep apnea; HR, hazard ratio; CI, confidence interval.

Table 3. Hazard of Cancer: OSA Patients with Preceding Polysomnogram (Cox Regression)

Variable	Reference Group	Unadjusted HR (95% CI)	*Adjusted HR (95% CI)	‡*P*-Value
With OSA & PSG§	Without OSA	2.23 (2.17-2.29)	2.03 (1.97-2.09)	< 0.001
Age (years)	One Year Younger	–	1.03 (1.03-1.03)	< 0.001
Male Sex	Female Sex	–	1.03 (0.98-1.10)	0.255
Year of Diagnosis	One Year Prior	–	0.91 (0.90-0.91)	< 0.001
Smoking	No Smoking	–	1.66 (1.61-1.71)	< 0.001
Alcohol Use	No Alcohol Use	–	1.42 (1.37-1.47)	< 0.001
Obesity	No Obesity	–	1.09 (1.06-1.13)	0.001
Comorbidity Index	One Less Index Score	–	1.15 (1.14-1.16)	< 0.001

*Adjusted for age at diagnosis (or matched inception), sex, year of diagnosis (or matched inception), smoking, alcohol use, obesity, and comorbidity.
‡Adjusted model.
§Compares patients OSA and a preceding polysomnogram (n=145,228) to patients without OSA (N=642,701).
Abbreviations: OSA, obstructive sleep apnea; HR, hazard ratio; CI, confidence interval; PSG, polysomnogram.

Table 4. Description of OSA Patients by OSA Treatment Status (N=593,429)

Characteristic	CPAP (N=164,426)	Untreated (N=429,003)	*P-Value
Age, mean +/- SD (years)	57 +/- 12	58 +/- 13	< 0.001
Men (%)	95%	96%	< 0.001
White‡ (%)	76%	79%	< 0.001
Smoking (%)	23%	22%	< 0.001
Alcohol Use (%)	10%	10%	< 0.001
Obesity (%)	51%	44%	< 0.001
Comorbidity Index, mean +/- SD	1.2 +/- 1.5	1.2 +/- 1.5	< 0.001
Follow Up (years)			< 0.001
Mean +/- SD	4.6 +/- 2.1	5.4 +/- 3.0	
Median (Range)	3.9 (2.0-24.0)	4.3 (2.0-24.1)	
% with Cancer Diagnosis	5.0%	6.7%	< 0.001

**P*-value comparing OSA patients prescribed CPAP and untreated OSA patients.
‡Calculated from proportion of cohort with known race/ethnicity. Data on race/ethnicity missing for 30% of OSA patients prescribed CPAP and 17% of untreated OSA patients.
Abbreviations: OSA, obstructive sleep apnea; CPAP, continuous positive airway pressure; SD, standard deviation.

Table 5. Hazard of Cancer by OSA Treatment: Preceding Polysomnogram (Cox Regression)

Variable	Reference Group	Unadjusted HR (95% CI)	*Adjusted HR (95% CI)	‡P-Value
CPAP	Untreated	0.78 (0.74-0.82)	0.92 (0.88-0.97)	0.002
Age (years)	One Year Younger	–	1.04 (1.03-1.04)	< 0.001
Male Sex	Female Sex	–	0.91 (0.81-1.02)	0.094
Year of Diagnosis	One Year Prior	–	0.91 (0.91-0.92)	< 0.001
Smoking	No Smoking	–	1.27 (1.21-1.34)	< 0.001
Alcohol Use	No Alcohol Use	–	1.10 (1.02-1.18)	0.009
Obesity	No Obesity	–	1.01 (0.96-1.05)	0.826
Comorbidity Index	One Less Index Score	–	1.05 (1.03-1.06)	< 0.001

*Adjusted for age at diagnosis (or matched inception), sex, year of diagnosis (or matched inception), smoking, alcohol use, obesity, and comorbidity.
‡Adjusted model.
Abbreviations: OSA, obstructive sleep apnea; HR, hazard ratio; CI, confidence interval; CPAP, continuous positive airway pressure.

Table 6. Hazard of Cancer by OSA Treatment: All OSA Patients (Cox Regression)

Variable	Reference Group	Unadjusted HR (95% CI)	*Adjusted HR (95% CI)	‡*P*-Value
CPAP	Untreated	0.80 (0.78-0.82)	0.99 (0.96-1.01)	0.329
Age (years)	One Year Younger	–	1.03 (1.03-1.03)	< 0.001
Male Sex	Female Sex	–	0.87 (0.82-0.91)	< 0.001
Year of Diagnosis	One Year Prior	–	0.91 (0.91-0.92)	< 0.001
Smoking	No Smoking	–	1.33 (1.29-1.36)	< 0.001
Alcohol Use	No Alcohol Use	–	1.12 (1.08-1.16)	< 0.001
Obesity	No Obesity	–	1.00 (0.98-1.03)	0.706
Comorbidity Index	One Less Index Score	–	1.06 (1.05-1.06)	< 0.001

*Adjusted for age at diagnosis (or matched inception), sex, year of diagnosis (or matched inception), smoking, alcohol use, obesity, and comorbidity.
‡Adjusted model.
Abbreviations: OSA, obstructive sleep apnea; HR, hazard ratio; CI, confidence interval; CPAP, continuous positive airway pressure.

FIGURES

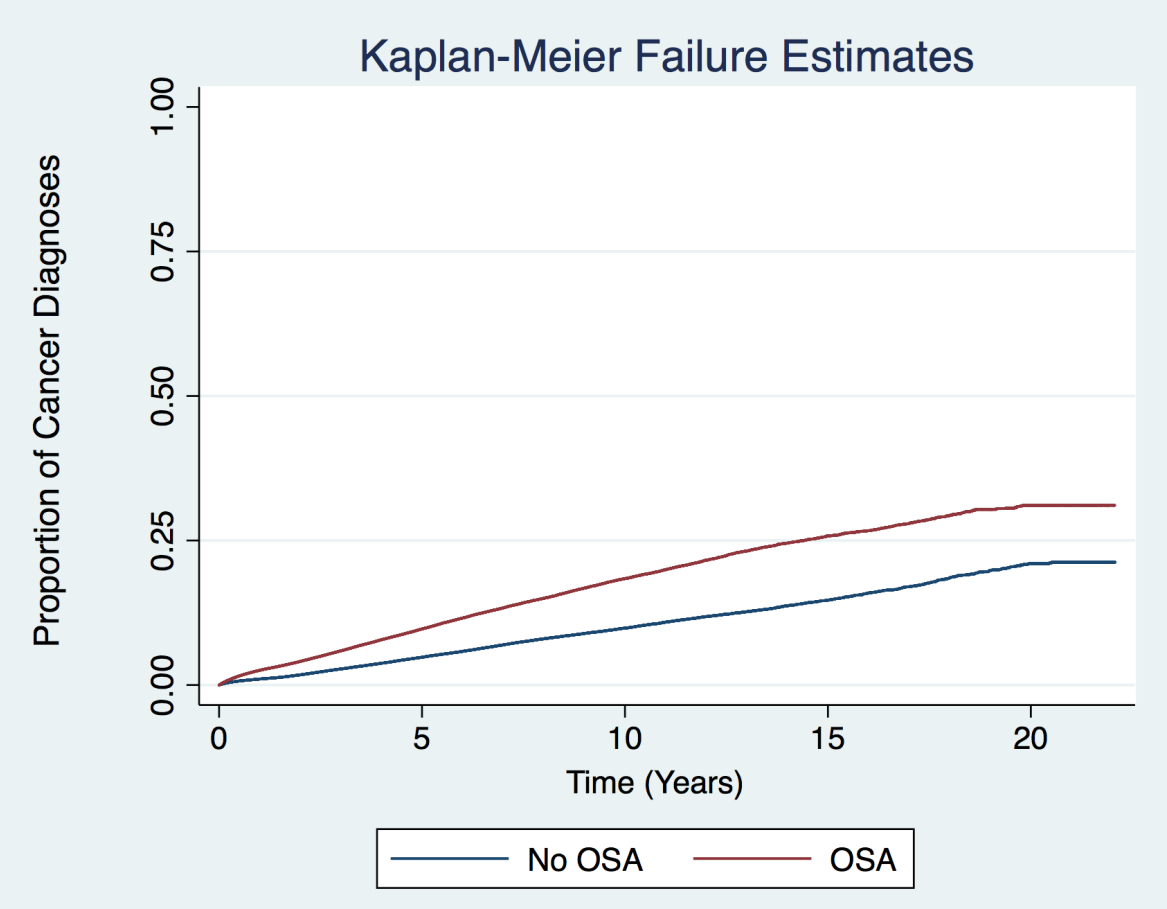

Figure 1. Proportion of patients with and without obstructive sleep apnea (OSA) that obtain a cancer diagnosis after time (years), with time 0 defined as two years after the initial OSA diagnosis or inception into the cohort. Patients with OSA had a significantly higher proportion of cancer diagnoses throughout the follow-up period than patients without OSA (Log-rank P < 0.0001).