SLEEP-DISORDERED BREATHING

Sleep Apnea and Cancer: Analysis of a Nationwide Population Sample

David Gozal, MD, MBA[1]; Sandra A. Ham, MS, MA[2]; Babak Mokhlesi, MD, MSc[3]

[1]Sections of Pediatric Sleep Medicine and Pulmonology, Department of Pediatrics, Prizkter School of Medicine, Biological Sciences Division, The University of Chicago, Chicago, IL; [2]Center for Health and the Social Sciences, The University of Chicago, Chicago, IL; [3]Sleep Disorders Center and the Section of Pulmonary and Critical Care Medicine, Department of Medicine, The University of Chicago, Chicago, IL

Study Objectives: Epidemiological evidence from relatively small cohorts suggests that obstructive sleep apnea (OSA) is associated with higher cancer incidence and mortality. Here we aimed to determine whether cancer incidence for major cancer types and risk of metastases or mortality from cancer are increased in the presence of OSA.

Methods: All OSA diagnoses included in an employee-sponsored health insurance database spanning the years 2003–2012 were identified and 1:1 matched demographically based on age, gender, and state of residence, or alternatively matched by comorbidities. The incidence of 12 types of cancer was assessed. In addition, another cohort of patients with a primary diagnosis of cancer was retrieved, and the risk of metastatic disease or cancer mortality was determined as a function of the presence or absence of OSA. Multivariate Cox proportional hazards regression models were fitted to assess the independent associations between OSA and outcomes of interest.

Results: Based on a cohort of ~5.6 million individuals, the incidence of all cancer diagnoses combined was similar in OSA and retrospectively matched cases. However, the adjusted risk of pancreatic and kidney cancer and melanoma were significantly higher in patients with OSA, while the risk of colorectal, breast, and prostate cancers appeared to be lower. Among individuals with a diagnosis of cancer, the presence of OSA was not associated with an increased risk for metastasis or death.

Conclusions: In a large nationally representative health insurance database, OSA appears to increase the risk for only a very selective number of cancer types, and does not appear to be associated with an increased risk of metastatic cancer or cancer-related deaths.

Keywords: cancer, sleep apnea, prevalence, melanoma, pancreatic cancer

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Significance

Sleep apnea has been recently implicated in higher prevalence and adverse outcomes among patients with solid tumor malignancies. However, whether the presence of apnea affects all types of oncological conditions or only selective types of tumors remains unclear. Using a health insurance database, we found that the adjusted risk of pancreatic and kidney cancer and melanoma was higher in apneic patients (over 1.7 million people), while risk for colorectal, breast, and prostate cancers appeared to be reduced. We conclude that the associations between sleep apnea and cancer appear to be selective and affect certain types of solid malignancies. These preliminary findings justify future prospective studies on the link between sleep apnea and cancer.

INTRODUCTION

Obstructive sleep apnea (OSA) is a highly prevalent condition throughout the lifespan, and has now been recognized as a major public health issue with potentially far reaching consequences, such as motor vehicle and work-related accidents, increased health morbidity, and cognitive and mood deficits impairing work efficiency and productivity.[1,2] The prevalence of OSA varies widely depending on gender and ethnicity, being higher in males and in some ethnic backgrounds.[3–8] OSA has been strongly associated with cardiovascular and metabolic morbidity and mortality, as well as behavioral and cognitive dysfunction.[9,10] In recent years, potential associations between obstructive sleep apnea (OSA) and solid tumor cancer prevalence and outcomes have emerged, suggesting that patients with OSA are at higher risk to develop solid tumor malignancies or to die from oncological complications.[11–18] However, not all of the studies have reached similar conclusions, possibly because most studies were underpowered.[19] Furthermore, the currently available studies examined either one type of cancer[16,17] or lumped all oncological malignancies together,[11–15] such that it remains unclear whether significant associations between OSA and cancer indeed exist, and whether such associations are particularly reflected in a specific subset of malignancies, rather than being all encompassing for solid tumors.

In a series of recent laboratory-based studies in murine models, the potential biological plausibility mechanistically linking sleep apnea, i.e., intermittent hypoxia and fragmented sleep, to cancer-related biological processes prompted us to hypothesize that some types of cancers, such as solid tumors, may be particularly susceptible to the concurrent presence of OSA, and therefore that their incidence or outcomes may be altered in OSA patients.[20–22] To examine these possibilities, we took advantage of an existing longitudinal nationwide-based health insurance database for working adults and retirees with employer-sponsored health insurance coverage.

METHODS

Data Source

The Truven Health MarketScan Research Databases are a collection of health insurance claims for working adults, retirees, and their dependents with employer-sponsored health insurance. For the current project, we used the MarketScan Commercial Claims and Encounters database, constructed from paid claims for employee-sponsored health insurance for 2003 to 2012, representing 17 million enrollees in 2003 to 57 million enrollees in 2012. For the purposes of this analysis we extracted data using inpatient services, outpatient services, inpatient admission, facility header, and enrollment tables.

Patient Selection

We queried inpatient service tables for all hospitalizations for adults aged 30 to 94 years (77 million enrollees) with International Classification of Diseases, Ninth Edition – Clinical Manifestations (ICD-9-CM) diagnosis codes for OSA or 12 cancers (Table S1 in the supplemental material). We constructed three analytic samples: OSA with a demographically matched cohort (DMC), OSA with comorbidity matched cohort (CMC), and identified patients with cancer with a subgroup who also had OSA. Cohorts with control groups were used for assessing incidence. Outcomes (i.e., metastases and mortality) were assessed using the cancer cohort. For the OSA samples, the first date of service in the database with an OSA diagnosis and CPAP was classified as the index diagnosis. Patients with Healthcare Common Procedure Coding System (HCPCS) codes for continuous positive airway pressure (CPAP) in the year prior to first OSA diagnosis and those with any diagnosis of cancer or metastasis at any time up to six months after index OSA or with multiple cancers were excluded. Those with less than 365 days of enrollment either prior to or following the index diagnosis were also excluded.

Two control groups were selected from among 28.6 million adult enrollees aged 30–94 years who had at least 2 years of enrollment with no OSA, sleep study, or CPAP codes for the entire duration in Marketscan, and no cancer or metastasis codes during the first 18 months of enrollment. Those with diagnoses for multiple cancers during Marketscan enrollment were not eligible for retrospective matching. The demographically matched cohort (DMC) was selected from eligible enrollees of the same sex within the same 5-year age group and state. Age at OSA index diagnosis for cases was matched with age at one year into enrollment for matched cases. We selected one DMC control for every OSA case. The OSA cases and the DMC comprised the DMC analytic sample.

The second group was a comorbidity matched cohort (CMC) selected from the same pool of potential matching sample as for the DMC. OSA case data for the 6 months prior to index diagnosis and data from months 6 to 12 of enrollment for potential CMC cases were used for assessing comorbidities for matching. We queried the inpatient and outpatient service, facility header, and inpatient admission tables for all diagnosis data in billing claims over the respective 6-month interval. Using comorbidity classifications for morbid obesity, hypertension, type 2 diabetes, ischemic heart disease, coronary heart failure, stroke, cardiac arrhythmias, and depression (Table S1), patients were considered to have had a given comorbidity if an associated ICD-9 code was found at least once in the data tables. The 7 dichotomous comorbidity variables (without obesity) were concatenated together with 5-year age group and gender to create an index variable for matching cases to CMC cases by exact combinations of age group, gender, and comorbidities. Age at OSA index diagnosis for cases was matched with age at one year into enrollment for CMC. Using this index, we selected one CMC control for every OSA case. All of the CMC cases were assigned an index date as the date of the one-year anniversary of enrollment. The CMC analytic sample included the OSA cases and CMC cases.

The third and final sample consisted of all cases of any of 12 cancers (Table S1) who had at least 365 days of enrollment prior to and following the initial diagnosis of cancer (index date) and no metastasis codes prior to the index date. Those who were also OSA cases from the OSA sample comprised a subgroup of the cancer sample; those with cancer and any sleep study or CPAP codes but not an OSA diagnosis were excluded.

Follow-up Data

For the DMC and CMC samples, we examined details of all subsequent diagnoses in available tables from the index date until the earlier of the last date of patient enrollment or the end of the records in December 2012. To determine the end of follow-up, we used the enrollment table to obtain the final month of insurance enrollment for each patient. End of follow-up was the last day of the final month of enrollment, typically because of change in annual election of health insurance plan, change of employment, or the date of death. The earliest date of diagnosis for each of the 12 cancers was considered the date of cancer diagnosis event. For each person in the cancer analytic sample, we queried the same data tables for diagnosis codes for metastasis. The first date of diagnosis for metastasis was considered the date of metastasis. We captured discharge status from the inpatient tables in the final year of enrollment and coded patients as having died or been alive at the end of enrollment.

Covariates

Age in years on the respective index date for each sample and gender were reported in the inpatient and outpatient service tables. Age was classified into 5-year age groups for matching and analytical models and 10-year age groups for descriptive analyses. We assessed the same comorbidities as for the CMC matching based on ICD-9 diagnosis codes for the 6 months prior to the date of the respective index diagnosis or index date for all 3 analytic samples (Table S1). Using data from the OSA index date to the end of follow up, quartiles of mean number of OSA diagnoses per year were computed for the OSA sample. The OSA sample had categories of < 0.5 dx/y, 0.5–0.99, 1.0–2.49, and ≥ 2.5 diagnoses per year, and the cancer subsample had cut-points of 0.3, 0.7, and 2.3 diagnoses per year. The lowest quartiles were treated as reference groups. The occurrence of any CPAP codes during the entire duration of Marketscan enrollment was used to classify OSA cases as having CPAP or not having received CPAP.

Statistical Analysis

We summarized the distribution of patient demographics and comorbidities for each of the 3 samples using descriptive analyses. We performed χ^2 tests for bivariate analyses of categorical variables. Multivariate Cox proportional hazards regression was used to examine factors associated with incidence of each cancer separately in the DMC and CMC samples, and with cancer outcomes in the cancer sample. For each cohort and outcome, 2 models were constructed: controlling for age, gender, and state of residence; and controlling for age, gender, state of residence, and the 8 comorbidities. The association of study group, age group, gender, comorbidities with survival until event in each sample for respective outcomes was quantified using hazard ratios. We used 2-sided tests, with P values < 0.05

Table 1—Demographics and comorbidities of OSA cases and comparison groups.

	Incidence Samples						Outcomes Sample					
	OSA		CMC		DMC		OSA		No OSA		Outcomes Total	
	n	%	n	%	n	%	n	%	n	%	n	%
Total	1,704,417	100.0	1,704,489	100.0	1,704,905	100.0	28,838	100.0	670,610	100.0	699,448	100.0
Gender												
Men	855,321	50.2	855,138	50.2	855,441	50.2	15,328	53.2	315,015	47	330,343	47.2
Women	849,096	49.8	849,351	49.8	849,464	49.8	13,510	46.8	355,595	53	369,105	52.8
Gender by age group, y												
Men												
30–39	137,109	8.0	137,081	8.0	137,109	8.0	203	0.7	5,840	0.9	6,043	0.9
40–49	237,421	13.9	237,386	13.9	237,421	13.9	973	3.4	22,066	3.3	23,039	3.3
50–59	276,659	16.2	276,528	16.2	276,659	16.2	4,091	14.2	77,086	11.5	81,177	11.6
60–69	141,296	8.3	141,200	8.3	141,296	8.3	5,487	19.0	98,023	14.6	103,510	14.8
70–79	46,400	2.7	46,393	2.7	46,400	2.7	3,198	11.1	70,499	10.5	73,697	10.5
> 79	16,436	1.0	16,550	1.0	16,556	1.0	1,376	4.8	41,501	6.2	42,877	6.1
Women												
30–39	135,896	8.0	135,884	8.0	135,896	8.0	459	1.6	18,811	2.8	19,270	2.8
40–49	232,535	13.6	232,518	13.6	232,535	13.6	2,004	6.9	57,598	8.6	59,602	8.5
50–59	283,513	16.6	283,492	16.6	283,513	16.6	4,398	15.3	102,399	15.3	106,797	15.3
60–69	126,532	7.4	126,472	7.4	126,532	7.4	3,735	13.0	83,748	12.5	87,483	12.5
70–79	46,682	2.7	46,682	2.7	46,682	2.7	1,916	6.6	54,538	8.1	56,454	8.1
> 79	23,938	1.4	24,303	1.4	24,306	1.4	998	3.5	38,501	5.7	39,499	5.6
Follow-up, y, mean (SD)	3.20 (1.87)		3.75 (2.32)		3.91 (2.39)		2.80 (1.51)		3.32 (2.03)		3.30 (2.01)	
Comorbidities												
Morbid obesity	55,224	3.2	7,044	0.4	3,802	0.2	665	2.3	2,555	0.4	3,220	0.5
Hypertension	299,557	17.6	299,390	17.6	155,851	9.1	6,207	21.5	114,272	17.0	120,479	17.2
Type 2 diabetes	236,288	13.9	236,068	13.8	113,640	6.7	6,337	22.0	85,242	12.7	91,579	13.1
Ischemic heart disease	136,584	8.0	136,495	8.0	59,720	3.5	4,215	14.6	62,902	9.4	67,117	9.6
Congestive heart failure	47,002	2.8	46,771	2.7	11,591	0.7	1,410	4.9	16,527	2.5	17,937	2.6
Stroke	24,191	1.4	24,094	1.4	7,022	0.4	556	1.9	8,357	1.2	8,913	1.3
Arrhythmia	51,389	3.0	51,192	3.0	16,835	1.0	1,786	6.2	23,369	3.5	25,155	3.6
Depression	92,157	5.4	91,864	5.4	19,456	1.1	1,153	4.0	9,943	1.5	11,096	1.6

OSA, obstructive sleep apnea group; CMC, comorbidity-matched control group, matched with OSA by age, gender, and all comorbidities; DMC, demographically matched control group, matched with OSA by age, gender, and state.

considered to be statistically significant. All statistical analyses were performed with SAS 9.3 (SAS Institute, Cary, NC).

RESULTS

Cohort

Of 30.3 million enrollees who met the criteria for either OSA or eligibility to be a control, 5.62% had OSA. Thirty-two percent of those with any OSA diagnosis met all of the study inclusion criteria; 65% of the initial sample was excluded for insufficient enrollment duration. Of the 5,596,888 enrollees who were included in at least one of the three analytic samples, 3,706,690 (66.2%; mostly matching cohort cases or cancer cases) were in one sample; 1,858,296 (33.2%; mostly OSA cases) were in two samples; and 31,902 (0.6%; mostly cancer cases with OSA) were in all three samples. Of the OSA cases, 1,676,235 (98.3%) were in two samples and the remaining 28,838 (1.7%) were in all three samples. The OSA sample for incidence analyses had mean (SD) 3.20 (1.87) years of follow-up and the CMC and DMC had 3.75 (2.32) and 3.91 (2.39) years, respectively. The demographic and comorbidity characteristics of each of the cohort samples are shown in Table 1.

Cancer Incidence in OSA Patients

The incidence of any type of cancer was similar among OSA patients and DMC (Figure 1), as well as among CMC (Figure 1). However, the overall incidence of 7 types of cancer, namely melanoma (HR = 1.14, CI = 1.10–1.18), bladder (HR = 1.07, CI = 1.02–1.13), lung (HR = 1.09, CI = 1.05–1.13), liver (HR = 1.19, CI = 1.10–1.30), cervix (HR = 1.17, CI = 1.06–1.29) and kidney (HR = 1.41, CI = 1.34–1.49), and pancreas (HR = 1.24, CI = 1.15–1.34) was significantly higher among OSA patients when compared to the DMC cohort while controlling for age and gender. After adjustment for comorbidities, only the incidence of kidney (HR = 1.30, CI = 1.23–1.37) and pancreatic (HR = 1.14, CI = 1.06–1.23) cancer and melanoma (HR = 1.13, CI = 1.09–1.18) remained significantly elevated, and such findings were corroborated by similar analyses using the CMC sample (Figure 1). Conversely, the incidence of colon (HR = 0.87, CI = 0.83–0.91 in both), breast (HR = 0.95–0.97, CI = 0.93–0.99), rectum (0.77, CI = 0.72–0.82 in both), and prostate (HR = 0.93, CI = 0.90–0.96 in both) cancers was significantly lower in OSA patients when compared to either DMC or CMC control cohorts (Figure 1). The incidence rates of each cancer in the CMC group and OSA group are further

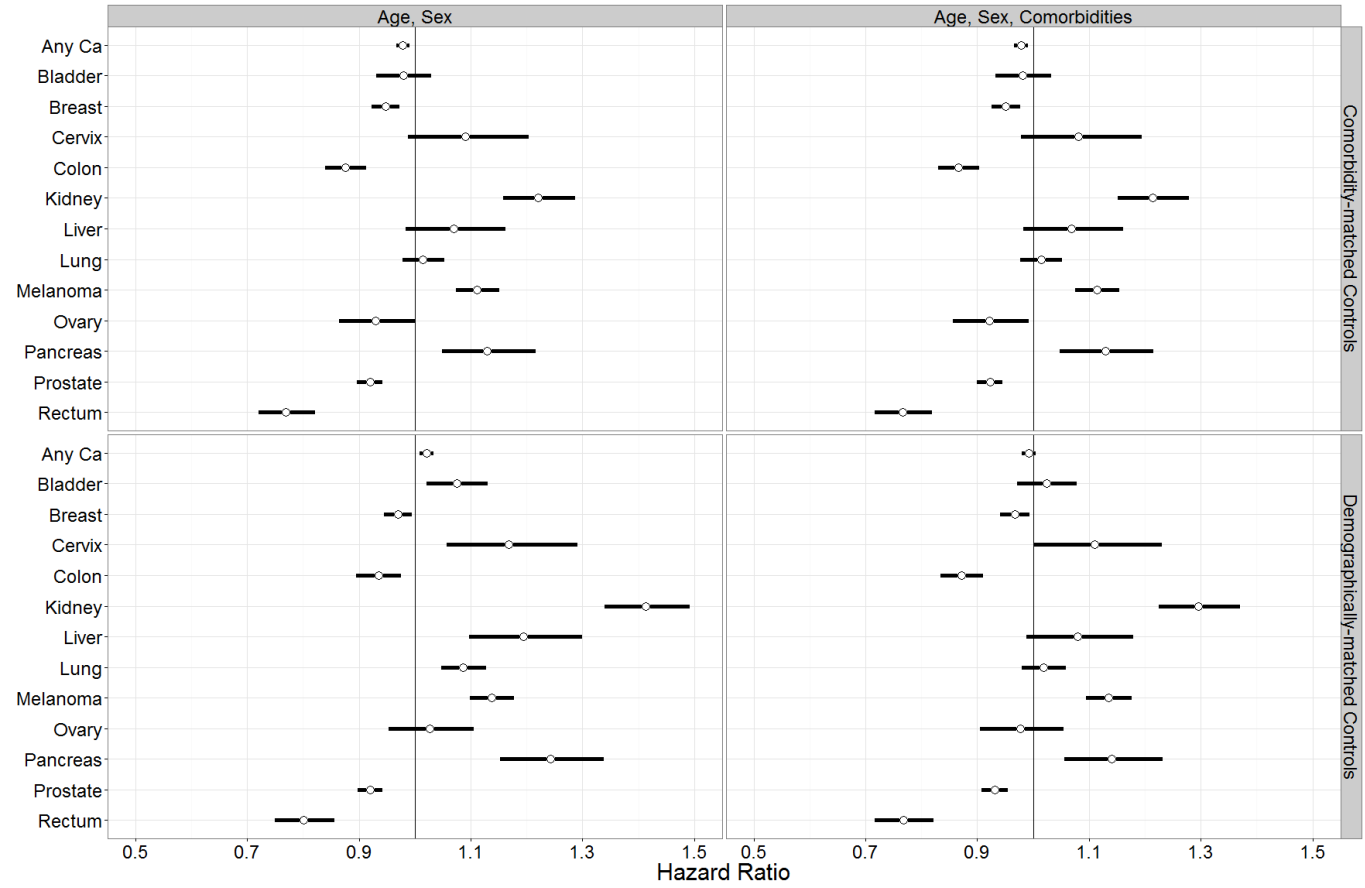

Figure 1—Hazard ratios of incident cancer in OSA versus demographically matched and comorbidity matched cohort groups. Bar = 95% CI. Demographically matched control group-matched with OSA by age, gender, and state. Comorbidity-matched control group-matched with OSA by age, gender, and all comorbidities.

illustrated according to age and gender in Figure 2, and for all cancers in Figure S1 in the supplemental material.

Risk of Cancer Metastasis and Death in OSA Patients

To examine the potential clinical course altering effect of OSA in cancer patients, we identified those patients in the database who had a diagnosis of one of the 12 cancer types selected for the present study who had no evidence of metastatic disease, and assessed the incidence of metastasis or death according to the presence or absence of OSA, while adjusting for concurrent comorbidities (Table 2). The overall demographic and cancer subgroup characteristics of this cohort are shown in Tables 1 and 2, respectively. As illustrated in Figure 3, the hazard ratios for metastasis for all cancers and for most cancer types were significantly lower among OSA patients compared to those patients with cancer but without OSA, with the exception of breast and liver cancers, which showed no significant differences in metastatic risk (Figure 3). Similarly, mortality rates for any cancer type were significantly lower in the OSA cohort, with 5 cancer types showing no significant differences (Figure 3). Adjustments of the data based on the frequency of OSA diagnosis showed persistent reductions in metastatic rates and mortality, except when CPAP therapy was prescribed, in which case no significant differences in metastatic rates or mortality emerged (Figure S2 in the supplemental material).

DISCUSSION

The present study shows that globally speaking the incidence of cancer is not different among patients with OSA when compared to either a demographically matched or comorbidity-matched cohort. However, our study also indicates that there are differences in the association of concurrent presence of OSA regarding selective cancers, with some (i.e., kidney and melanoma) exhibiting increased incidence, and others (i.e., colon, rectal, lung) showing reduced incidence. Furthermore, we found no evidence supporting the presence of deleterious effects of OSA on cancer outcomes. Thus, notwithstanding the preliminary murine-based reports implicating constitutive components of OSA, namely intermittent hypoxia and sleep fragmentation, as being mechanistically involved in the increased proliferation, invasion, and metastatic potential in a restricted number of tumor models,[20–22] the epidemiological data analyzed herein suggests that the laboratory-based observations may be applicable to only a selected repertoire of human cancers.

Before we discuss the potential implications of our study, there are several limitations that deserve comment. First, we

should point out that most of these limitations are primarily inherent to the analysis of large administrative databases. For example, the presence of OSA and metastasis are entirely dependent on physician billing practices, such that we cannot exclude the possibility of coding errors or reporting biases. However, the inclusion of data on CPAP use as an additional corroborative measure in this study provides additional assurance, given that billing for CPAP is dependent on durable medical equipment providers. Of note, issues have arisen as to the validity of OSA diagnosis when using electronic databases. In a study by McIsaac and colleagues,[23] the combination of a polysomnogram followed by receipt of a PAP device, as used in our approach herein, exhibited high specificity for a true diagnosis of OSA as well as the highest positive likelihood ratio of all algorithms, even if a note of caution needs to be exercised when dealing with such databases. Furthermore, there is no reason to infer that such errors or biases are specifically restricted to one of the cohorts included in this study. Indeed, we approached the control cohorts using two separate and distinct matching strategies, namely using demographic criteria (DMC cohort), or matching for comorbidities in addition to demographic criteria (CMC cohort). Both approaches yielded

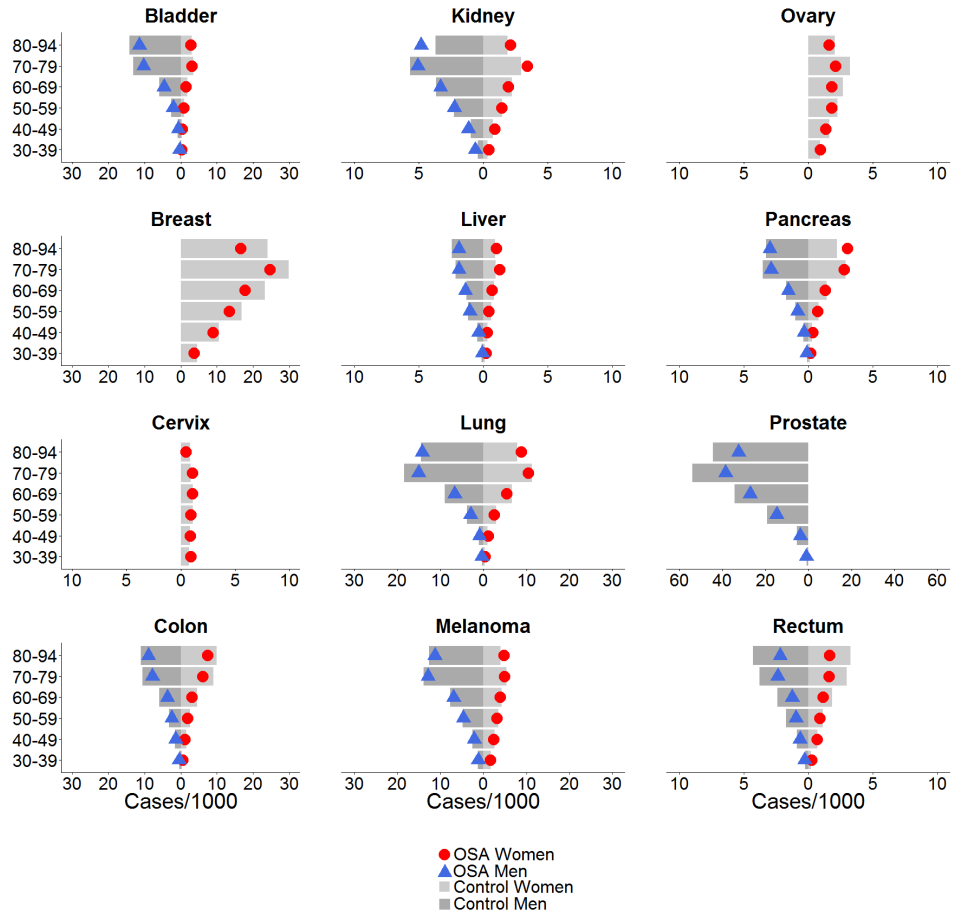

Figure 2—Rates of cancer in the comorbidity-matched cohort and OSA group, by age group and gender.

Table 2—Number of cancer types among the various cohorts.

	Incidence Samples						Outcomes Sample					
	OSA		CMC		DMC		OSA		No OSA		Outcomes Total	
Organ	n cases	cases/1,000	n cases	cases/1,000	n cases	cases/1,000	n	%	n		n	%
Any cancer	48,015	28.17	59,232	34.75	59,775	35.06	28,838	4.1	670,610	95.9	699,448	100
Bladder	2,832	1.66	3,501	2.05	3,398	1.99	1,763	4.6	36,702	95.4	38,465	100
Breast	10,143	5.95	12,763	7.49	13,036	7.65	6,502	3.4	184,491	96.6	190,993	100
Cervix	771	0.45	837	0.49	816	0.48	458	3.5	12,627	96.5	13,085	100
Colon	3,810	2.24	5,242	3.08	5,192	3.05	2,250	3.7	58,150	96.3	60,400	100
Kidney	2,877	1.69	2,854	1.67	2,595	1.52	1,715	5.8	27,950	94.2	29,665	100
Liver	1,070	0.63	1,221	0.72	1,166	0.68	432	5.2	7,866	94.8	8,298	100
Lung	5,328	3.13	6,416	3.76	6,401	3.75	2,389	5.0	45,266	95.0	47,655	100
Melanoma	6,188	3.63	6,794	3.99	6,945	4.07	3,860	4.4	84,591	95.6	88,451	100
Ovary	1,311	0.77	1,682	0.99	1,593	0.93	832	3.6	22,324	96.4	23,156	100
Pancreas	1,388	0.81	1,531	0.90	1,472	0.86	571	5.7	9,383	94.3	9,954	100
Prostate	11,201	6.57	14,694	8.62	15,410	9.04	7,361	4.4	160,793	95.6	168,154	100
Rectum	1,469	0.86	2,265	1.33	2,308	1.35	933	3.4	26,193	96.6	27,126	100

OSA, obstructive sleep apnea group; CMC, comorbidity-matched control group, matched with OSA by age, gender, and all comorbidities; DMC, demographically matched control group, matched with OSA by age, gender, and state.

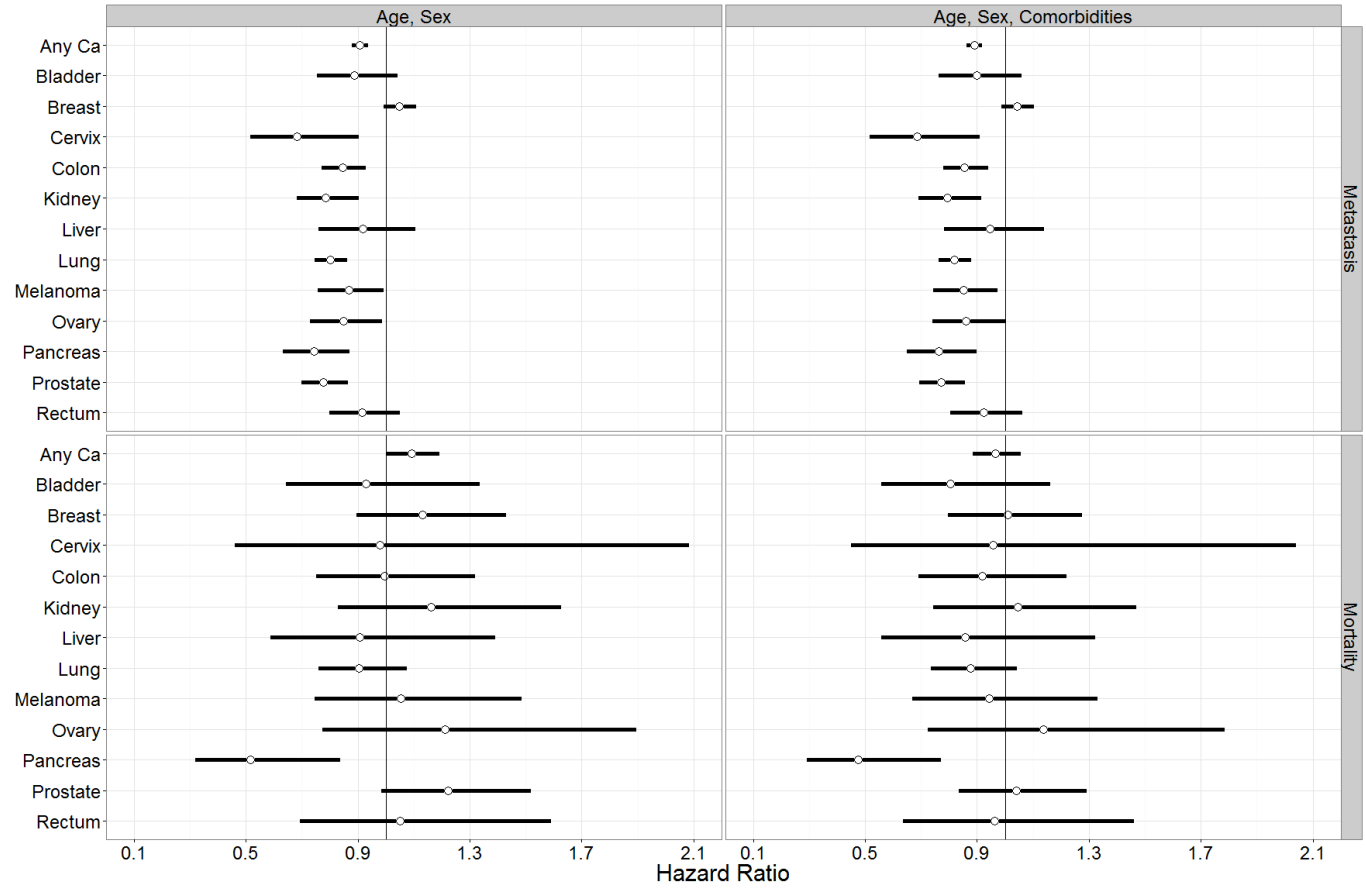

Figure 3—Hazard ratios of metastasis and mortality for patients with OSA versus those with no OSA for any cancer overall and 12 cancer subsamples. Bar = 95% CI.

essentially analogous conclusions. As mentioned earlier, the Truven MarketScan database does not provide information regarding the race/ethnicity of patients. Low wage and part-time workers are underrepresented, and the database does not include unemployed individuals. The racial disparities regarding health care utilization are very relevant to OSA and to cancer outcomes.[24,25] In addition, information on weight or body mass index could not be controlled for in this cohort, as they are not reported in the database. However, since OSA is particularly prevalent in obese subjects, and obesity is a risk factor for cancer,[26–30] one would have anticipated that a higher risk of incident cancer or worse cancer outcomes in the OSA cohort would occur, and might be explained at least in part by the concurrent higher prevalence of obesity in OSA.[31,32] This putative assumption was not corroborated by the current findings. Similarly, both OSA and obesity exhibit increased markers of oxidative stress, which have been implicated in tumorigenesis.[33,34] Nonetheless, we acknowledge that race and obesity are important confounding variables and the lack of both race and obesity status constitutes an important limitation, particularly in matched cases selection. We however posit that the CMC cohort should minimize if not annul such concerns. In spite of these limitations, we believe that in matching a geographical location to the level of state of residence should also serve to minimize any potential discrepancies between the groups. We should also remark that information on mortality in the database is restricted to in-hospital deaths, and all deaths that could have occurred outside the hospital would not be captured. In addition, the cause of death is not specifically available, such that all-cause mortality and not cancer-specific mortality can be derived from the database.

As previously mentioned, the current epidemiological evidence on the incidence and outcomes of cancer in patients with OSA has primarily consisted of relatively small population-based cohorts or clinical cohorts and has been somewhat contradictory. For example, Christensen et al. studied 8,783 subjects and found no significant relationships between self-reported sleep abnormalities and cancer.[12] Similarly, a study on nearly 10,000 patients with OSA revealed no evidence of increased risk for either prevalent or incident cancer when compared to a general population-based database.[19] In contrast, in a study of 847 women with sleep-study diagnosed OSA, the odds of developing breast cancer were 2-fold those of a matched cohort of > 4,000 women.[18] In 3 epidemiological studies that included a total of ~7,000 patients, the presence of OSA was significantly associated with cancer incidence or outcomes.[11,13–15] Furthermore, a significant association emerged between measures of cutaneous malignant melanoma aggressiveness and the severity of OSA,[17] and treatment with CPAP detected reductions in cancer-related gene expression in circulating leukocytes.[35]

The increased propensity for cancer incidence was recently corroborated by a systematic review and meta-analysis.[36] Our current findings attempt to reconcile the differences among all aforementioned studies, and further point to the presence of 3 divergent relationships between various cancer types and OSA, specifically increased, decreased, or unchanged incidence of specific cancer types. Indeed, an increased incidence of kidney cancer and melanoma emerged among patients with OSA, and is putatively reflective of the unique role of hypoxia and hypoxia-inducible factors (HIFs) in the pathogenesis and outcomes of these tumors.[37–41] Conversely, the incidence of colorectal and lung cancers was reduced in OSA patients. The explanation for these findings is unclear, considering the wide array of effects that hypoxemia exerts on solid tumor properties,[42–44] and the more prominent impact of intermittent hypoxemia, as occurs in OSA, in inducing a more aggressive cancer cell subtype.[45] It is, however, possible that human cancer cells originating from various organs and cell types recruit HIF-related pathways in very different ways, and that the fate of such cancer cells is also markedly and divergently regulated by the presence and activity of HIFs, thereby accounting for the discrepant incidence findings in the current study.[46,47] It is noteworthy that the hazard ratios for cancer incidence found herein are such that they would account for only a small, albeit significant portion of the variance to be explained by the presence of OSA. Nonetheless, it is unlikely that a well-controlled prospective longitudinal study of a very large cohort of OSA patients will take place in the near future, such that the field will have to rely on existing cohorts to better refine the attributable risk of cancer in OSA patients.

To further examine the potential impact of OSA on cancer outcomes, we assessed a separate cohort of nearly 700,000 cancer patients, of whom slightly less than 30,000 had OSA. The presence of OSA was not associated with increased incidence of metastases or mortality, and in fact may suggest the opposite for some of the cancer types, namely a potential reduction in risk of such cancer-related complications. These results differ a priori from the findings reported by others,[11,14] and may reflect the marked differences in cohort size, the fact that all of the patients in the current database were medically insured with improved access to medical care, or that differences in the types of cancers that emerged in smaller cohorts may reflect intermittent-hypoxemia sensitive cancers. In addition, it is possible, albeit unlikely, that the published retrospective cohort studies showing increased mortality may have included less biases in individual exposures and selection, or in reported outcomes.

In summary, using a longitudinal database that included > 1.7 million patients with OSA over a decade spanning period revealed markedly discrepant risks for incident cancer, when compared to 1-to-1 demographically or comorbidity-matched cohorts. Furthermore, in a separate cancer patient cohort, the presence of OSA was not only not associated with increased metastatic risk or mortality, but could even be associated with small reductions in such risks. Although early diagnosis and treatment of OSA appears justified due to the multifaceted end-organ morbidity burden imposed by this condition, the present study does not provide compelling evidence that would warrant, at least for now, enumerating OSA as a general risk factor for incident cancer and for adverse cancer outcomes, except in a very restricted set of malignancies such as pancreatic and renal cancer and melanoma.

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Address correspondence to: David Gozal, MD, MBA, Section of Pediatric Sleep Medicine, Department of Pediatrics, Pritzker School of Medicine, The University of Chicago, Knapp Center for Biomedical Discovery, Room 4100, 900 E. 57th Street, Mailbox 4, Chicago, IL 60637-1470. Tel: (773) 702-3360; Fax: (773) 834-1444; Email: dgozal@uchicago.edu

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