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Original Article

Obstructive sleep apnea and nocturnal hypoxemia are associated with an increased risk of lung cancer

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ABSTRACT

Study objectives: To identify a link between sleep disordered breathing, nocturnal hypoxemia, and lung cancer.

Methods: We conducted a cross-sectional study of a combined cohort of 302 individuals derived from the sleep apnea in lung cancer study (SAIL; NCT02764866) investigating the prevalence of sleep apnea in lung cancer, and the sleep apnea in lung cancer screening study (SAILS; NCT02764866) investigating the prevalence of sleep apnea in a lung cancer screening program. All subjects had spirometry and a chest CT, underwent home sleep apnea testing (HSAT), and completed a sleep related questionnaire. Subjects from the SAIL study underwent HSAT prior to initiating oncologic therapy or surgery. Subjects with an apnea-hypopnea index (AHI) > 15 were compared with a control group of individuals with an AHI < 15. Propensity score, near neighbor matching, and logistic regression adjusted for potential confounders, were used in order to evaluate the association between sleep apnea, the AHI, oxygen desaturation indices and lung cancer.

Results: The prevalence of sleep apnea and lung cancer in the combined cohort was 42% and 21%, respectively. Lung cancer was 8% more prevalent in patients with an AHI >15. The difference was statistically significant when assessed by propensity score matching ($p = 0.015$) and nearest neighbor matching ($p = 0.041$). Binary logistic regression adjusted for potential confounders revealed a statistically significant association between AHI ($p = 0.04$), nocturnal hypoxemia, including time spent below 90% oxyhemoglobin saturation (T90%; $p = 0.005$), 3% oxygen desaturation index (ODI3; $p = 0.02$) and lung cancer.

Conclusions: Sleep apnea and nocturnal hypoxemia are associated with an increased prevalence of lung cancer.

Clinical trial registration: SAIL study (NCT02764866) and SAILS study (NCT02764866)

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Abbreviations: OSA, Obstructive sleep apnea; PSM, propensity score matching; NNM, nearest neighbor matching; COPD, chronic obstructive pulmonary disease; AHI, apnea hypopnea index; ODI, oxygen desaturation index; T90, time spent below a 90% oxyhemoglobin saturation; SAIL, sleep apnea in lung cancer study; SAILS, sleep apnea in lung cancer screening study; HSAT, home sleep apnea testing; ATET, average treatment effect for the treated the; ATE, average treatment effect; NLST, national lung screening trial; SDB, sleep disordered breathing.

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1. Introduction

Obstructive Sleep Apnea (OSA) has been linked to a variety of cancers. Two large independent cohorts have reported an increased incidence and mortality from cancer in subjects with sleep disordered breathing (SDB) [1–4]. The association may be due to hypoxia fueling tumorigenesis, tumor progression and proliferation, and may be especially relevant for tobacco related tumors (eg, lung cancer) [5–8]. Nocturnal hypoxemia, a common finding in patients with OSA but also chronic obstructive pulmonary disease (COPD) and emphysema, has been identified as a key variable in need of further study [1]. We have conducted two separate studies investigating the prevalence of SDB in patients with newly diagnosed lung cancer (SAIL study; NCT02764866) and those participating in a lung cancer screening program (SAILS study; NCT02764866) using home sleep apnea testing (HSAT). The current analysis explores the association between moderate-severe OSA and lung cancer in a combined cohort derived from those studies.

2. Methods

We conducted a cross-sectional study including data derived from two prospectively recruited cohorts investigating the prevalence of sleep disordered breathing in patients with and at risk for lung cancer. Subjects with moderate-severe OSA defined as an AHI $\geq$15 were included in the study. Subjects with an AHI <15 were also included as controls. Lung cancer cases were derived from the SAIL study investigating the prevalence of SDB in patients with newly diagnosed lung cancer while patients at risk for lung cancer were selected from the SAILS study investigating the prevalence of SDB in a lung cancer screening program. Both studies were approved by The Clinical Research Ethics Committee of the Fundación Jiménez Díaz (FJD) University Hospital; (EO99/2015_FJD) and (EO 98/2015_FJD). Participants in the study signed an informed consent and were offered home sleep apnea testing (HSAT) and an epidemiologic and sleep related questionnaire.

Variables collected for all subjects included; sex, age, body mass index (BMI), neck and waist circumference, % of visceral fat, comorbidities, tobacco exposure, pulmonary function and radiological findings. Sleep parameters including the apnea-hypopnea index, oxygen saturation, desaturation indices (both 3% and 4% oxygen desaturation indexes, ODI), and time spent below 90% saturation expressed as a percentage of total sleep time (T90) were also recorded. Daytime sleepiness, evidence of snoring and witnessed apneas, sedative use, Epworth Sleepiness Scale scores, and details of sleep habits and timing as well as the presence or absence of insomnia were addressed in the sleep questionnaire. Among patients with lung cancer, tumor histology; tumor, node, metastasis (TNM) and stage at diagnosis were collected as recommended by the seventh edition of the International Association for the Study of Lung Cancer (IASLC) TNM classification [9].

2.1. SDB evaluation

The HSAT device used in all patients was the NOX-T3 portable sleep monitor (T3; Nox Medical, Reykjavik, Iceland), which has been validated for the detection of OSA [10]. The device includes a nasal cannula for oronasal flow and pressure recordings, thoracic and abdominal bands, a pulse oximeter, and a microphone. Apneas were defined as a 90% or greater reduction in oronasal flow lasting more than 10 s. Hypopneas were defined as a 30–90% decrease in airflow lasting more than 10 s associated with an oxygen saturation drop of at least 3%. The apnea-hypopnea index (AHI) was defined as the sum of apneas and hypopneas per hour of recording.

2.2. Screening protocol

Patients enrolled in the FJD lung cancer screening program meet the National Lung Screening Trial (NLST) age and smoking criteria (Age 55–75 and tobacco consumption $\geq$ 30 pack-years). Testing includes periodic LDCT scanning and pulmonary function studies. Details of the screening protocol are available at www.ielcap.org.

2.3. Statistical analysis

Propensity score matching (PSM) was used in order to avoid selection and confusion bias to evaluate the association between sleep apnea defined as an AHI $\geq$ 15 (independent variable) and lung cancer (dependent variable) [11,12]. We assigned patients to two groups based on SDB severity. Control subjects had an AHI ranging from 0–14 events/hour of sleep (Group B) and OSA subjects had an AHI $\geq$ 15 events/hour of sleep (Group A). We selected the subjects for each matched group using PSM and nearest neighbor matching (NNM) taking into account potential confounders such as variables known to cause or worsen OSA (eg, BMI, age, sex, neck circumference, sedative consumption, smoking history, and COPD) and lung cancer (eg, age, sex, smoking history, and COPD), while excluding variables known to be affected by the presence of OSA (eg, respiratory event indices, hypertension, ictus, diabetes, hyperlipidemia, coronary heart disease, heart failure, insomnia, cardiac arrhythmias) [13]. The variables used to calculate the propensity score were age, sex, BMI, neck circumference, sedative consumption, smoking history defined as pack-years, and COPD. We determined the region of common support between patients with and without OSA using the predict score to plot the distribution of probabilities in the exposed (group A; AHI $\geq$ 15) and un-exposed (group B; AHI < 15) in order to minimize disparities in patient characteristics and ensure having an adequate number of controls [11,12]. Thereafter we matched subjects with a ratio of OSA vs no OSA of 1:5 and compared the balance pre and post matching using the standardized differences and the Rubin index to ensure a good balance of the OSA and control groups [11,13]. In order to evaluate the association of an AHI $\geq$15 with lung cancer, we considered subjects with an AHI $\geq$15 as treated subjects and those with an AHI 0–14 as controls and calculated the average treatment effect for the treated (ATET) and the average treatment effect (ATE) with their corresponding 95% confidence intervals (95% CI) estimated by the Robust Method. We also estimated the ATE using the inverse probability weighting method to adjust for selection bias, using weighted means instead of simple means to evaluate the association of OSA with lung cancer [14]. In order to investigate the association of respiratory event indices as continuous variables (AHI, ODI3%, ODI4%, T90%) with lung cancer we used a multivariate binary logistic regression model adjusting for potential confounders, which were those variables that are associated with the exposure (OSA) and the outcome (lung cancer) and were not lying in the causal path from the exposure to the outcome according to directed acyclic graphs (DAG). Variable selection was based on existing evidence, biological plausibility, and statistical association (variables associated with the exposure and the outcome with a $P < 0.20$ were included in the model). Statistical significance was set at a $P < 0.05$ at two tails for all tests. We performed all statistical analysis using Stata 14 (StataCorp, LLC, College Station, Texas, USA).

3. Results

We selected 302 patients using PSM from a total of 365 subjects enrolled in the aforementioned studies. The resulting cohort was predominantly male (58.6%) and overweight (mean BMI of 28.5 $\pm$ 5.2 kg/m^2), with a mean age of 64.7 $\pm$ 7.7 years. Almost half of the

subjects had moderate to severe OSA (129 or 42%). The overall prevalence of lung cancer was 21%. General characteristics of the cohort are summarized in Table 1.

The region of common support was wide enough to assure the stability of estimates obtained by the matching method and select an adequate number of controls (See Fig. 1). Before matching, the distribution of sex, neck circumference, smoking history, and COPD was unbalanced between the groups. These differences became negligible (<10%) after balancing by propensity score (Table 2). The Rubin index decreased from 91.9 before matching to 11.6 after matching, confirming an adequate bias reduction.

Propensity score matching and NNM were performed using five controls with an AHI <15 for every subject having an AHI ≥15. Lung cancer was 6.3–8.9% more likely depending on the statistical method used in group A subjects with OSA when compared to group B subjects with an AHI <15 (lowest prevalence for the ATE method using propensity score matching [0.063] and highest for the ATET method using nearest neighbor matching [0.089]). The difference reached statistical significance when measured by PSM and NNM using the ATET (P = 0.015 and 0.041 respectively) and approached statistical significance when measured using the ATE by PSM, NNM and inverse probability weighting (Table 3).

The association of AHI and desaturation indices as continuous variables with lung cancer was explored using binary logistic regression adjusted for age, sex, smoking, alcohol consumption, emphysema, BMI, neck circumference and sedative consumption. We found a statistically significant association between AHI, nocturnal hypoxemia and lung cancer, including the AHI (0.040), ODI3% (p = 0.022), and the T90% (p = 0.005). The association between the ODI4% (p = 0.068), OSA, and lung cancer did not reach statistical significance, although a trend was seen including a dose-response gradient in the O.R. according to OSA severity (Table 4).

Table 1
General characteristics of the cohort.

Characteristic	
N	302
Age, mean (SD)	64.7 (7.7)
Sex	
Female, n (%)	125 (41%)
Male, n (%)	177 (59%)
BMI, mean (SD)	28.5 (5.2)
Neck Circumference in cm, mean (SD)	39 (5.1)
Visceral fat, median (IQR)	12 (8–17)
T90%, median (IQR)	5.5 (0.8–30.2)
Lung cancer, n (%)	64 (21)
Obstructive sleep apnea	
Normal AHI < 5, n (%)	65 (21.5)
Mild AHI 5–14, n (%)	108 (35.8)
Moderate AHI 15–30, n (%)	70 (23.2)
Severe AHI > 30, n (%)	59 (19.5)
Comorbidities	
Emphysema, n (%)	211 (69.9)
COPD, n (%)	152 (50.3)
High blood pressure, n (%)	125 (41.4)
Hyperlipidemia, n (%)	102 (33.8)
Diabetes Mellitus, n (%)	44 (14.6)
Depression/Anxiety, n (%)	39 (12.9)
Coronary heart disease, n (%)	27 (8.9)
Heart failure, n (%)	22 (7.3)
Stroke, n (%)	20 (6.6)
Cardiac arrhythmia, n (%)	19 (6.3)
Insomnia, n (%)	10 (3.3)
History of smoking, n (%)	255 (98)
Pack-year index, median (IQR)	47 (35–60)
Alcohol consumption, n (%)	7 (2.3)

Notes: SD: standard deviation; n: number; BMI: body mass index in kg/m^2.

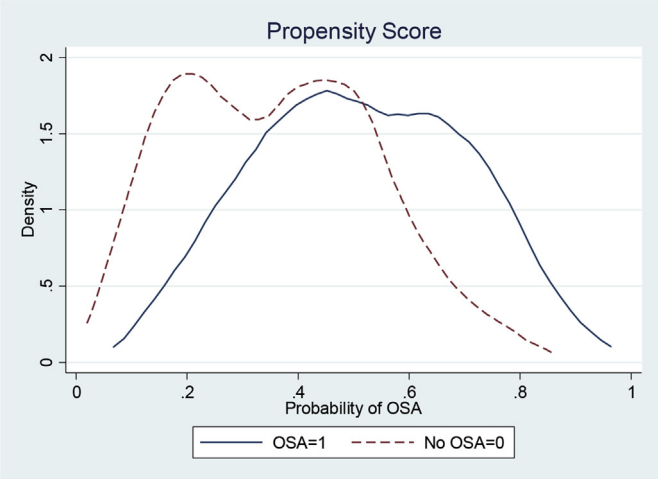

Fig. 1. Region of common support between patients with and without obstructive sleep apnea. **Notes**: This figure shows a good region of common support in the probability of developing OSA, which is required to obtain stable estimates from the matching methods. OSA: obstructive sleep apnea.

4. Discussion

We found an association between nocturnal hypoxemia, the AHI, and lung cancer on multivariate analysis adjusted for potential confounders, as well as a modest increase in the prevalence of lung cancer in patients with moderate to severe sleep apnea. Numerous epidemiologic studies in humans have reported an elevated cancer prevalence in patients with OSA [1,2,8,15]. However, few studies have investigated the prevalence of OSA in specific cancers. Animal models have also investigated the potential influence of OSA in lung cancer incidence and progression, but to our knowledge this is the first study in humans that can affirm that the AHI and nocturnal hypoxemia are indeed associated with an increased prevalence of lung cancer.

Evidence in favor of a link between OSA and cancer includes mostly retrospective cohort studies. In a study of 1522 patients investigating cancer related mortality in patients with OSA, a dose-response relationship was found between OSA severity as measured by AHI and T90 and cancer mortality after 22 years of follow up [2]. In that retrospective study, hypoxemia (T90) was a better predictor of cancer deaths than the AHI (HR 8,6; 95%CI: 2,6–28,7). A prospective cohort study found that moderate to severe OSA (AHI ≥ 15) was an independent predictor of cancer incidence and mortality [4]. The T90 was also a strong predictor of cancer incidence in a study of 4910 patients undergoing sleep studies for suspected OSA. Those with a T90 > 12% were twice as likely to develop cancer [1]. Similar results were reported by Martinez-Garcia et al., in their retrospective study of 5427 patients investigating cancer related mortality [3]. In that study, an association between cancer mortality and a T90 > 13% was found. Their finding was especially relevant for patients under 65 years of age, and both the AHI and T90 were independent predictors of mortality [3]. Alternately, other studies have found no association between the AHI and a greater cancer prevalence. In a retrospective study of 10,000 subjects, cancer incidence was not associated with severe OSA [8].

Putative mechanisms linking OSA and cancer include systemic inflammation and oxidative stress, hypoxemia, sleep fragmentation, increased sympathetic drive, and alterations in immune function produced or augmented by SDB [16]. Nocturnal hypoxemia has been described as a key variable predicting lung cancer

Table 2
Balance of selected variables before and after matching.

Variable	Before matching			After matching		
	Group A	Group B	Standardized differences (%)	Group A	Group B	Standardized differences (%)
Age	65.3	64.4	11.8	65.5	65.4	1.4
Sex	1.26	1.53	−55.6	1.32	1.33	−0.8
BMI (kg/m2)	30.4	27.2	64.5	28.7	28.8	−2.5
Neck circumference (cm)	41.0	37.7	67.8	39.6	39.9	−7.0
Sedative consumption	0.23	0.19	10.2	0.21	0.19	5.2
Smoking (pack-year index)	54.4	51.4	11.4	51.1	51.9	−3.0
COPD	0.48	0.52	−7.5	0.50	0.51	−1.5

Notes: Group A: patients with an apnea-hypopnea index ≥15; Group B: patients with an apnea-hypopnea index <15; BMI: body mass index in kg/m^2.

incidence and progression in experimental and animal models [5,17–19]. Intermittent hypoxemia leads to faster tumor growth in mice [20]. It also leads to greater invasiveness and an increase in circulating DNA [21]. A recent study found that exosomes from patients with sleep apnea enhance proliferation and migration of human adenocarcinoma cells [22]. Hypoxemia can also lead to phenotypic changes in tumor associated macrophages when cultured alongside lung cancer cells [23]. Intermittent hypoxemia in this setting leads to faster growth and migration of tumor cells suggesting that hypoxemia plays an obvious role enabling a permissive tumor stroma.

Many lung cancer patients suffer from emphysema and/or COPD. Both conditions may further amplify the deleterious influence of nocturnal hypoxemia on lung cancer tumorigenesis and progression. A study investigating oxidative stress in a heterogeneous group of healthy controls, patients with OSA, lung cancer, or COPD, found that oxidative damage was common, and that antioxidant mechanisms were also active in response to oxidative stress in all three diseases [24]. An animal model investigating the link between COPD and lung cancer found that chronic hypoxemia was associated with over-expression of HIF-2α which favors angiogenesis and cellular proliferation [25]. Chronic hypoxemia in that model also stimulated pro-inflammatory cytokines, growth factors, and the epithelial–mesenchymal transition. Both emphysema and COPD were very prevalent in our cohort, affecting 70 and 50% of the patients respectively. Since moderate-severe OSA was also very prevalent (42%), it is likely that a combination of parenchymal abnormalities, alterations in lung function, and sleep disordered breathing may coexist in many patients leading to a hypoxemia related susceptibility to lung cancer.

Martínez-García et al., reported that both the AHI and ODI3% are related to greater tumor growth and advanced stage measured by the Breslow index in their cohort of patients with melanoma [26]. The prevalence of OSA defined as an AHI >5 in 50 patients with melanoma was high (61%), but still inferior to the prevalence detected in our original cohort of lung cancer patients (80% with an AHI > 5) [26]. The higher prevalence of SDB in lung cancer, a tobacco related malignancy, agrees with epidemiologic evidence suggesting hypoxia plays an instrumental role in carcinogenesis in this setting [8]. Nocturnal hypoxemia and oxygen desaturation were more common and intense in our cohort when compared to melanoma patients, a finding that may reflect OSA severity, and/or underlying lung disease such as COPD and emphysema.

Table 4
Effect of key respiratory event variables on lung cancer prevalence.

Variable	OR	95%CI		P
AHI (ln)	1.382	1.015	1.882	0.040
ODI3% (ln)	1.452	1.056	1.997	0.022
ODI4% (ln)	1.355	0.977	1.880	0.068
T90% (ln)	1.467	1.121	1.920	0.005
OSA mild	1.107	0.471	2.599	0.815
OSA moderate	1.583	0.619	4.052	0.338
OSA severe	2.574	0.950	6.973	0.063
OSA moderate-severe	1.806	0.957	3.408	0.068

Notes: Measures of association obtained from the most parsimonious binary logistic regression multivariate model after adjusting for age, sex, smoking, alcohol consumption, emphysema, body mass index, neck circumference, basal oxygen saturation by pulse oximetry and sedative consumption.
AHI (ln): logarithmically transformed apnea-hypopnea index in number of events per hour of sleep; ODI3% (ln): logarithmically transformed oxygen desaturation index 3%; ODI4% (ln): logarithmically transformed oxygen desaturation index 4%; T90% (ln): logarithmically transformed time percentage with SpO2 < 90%. These variables were logarithmically transformed because they didn't have a normal distribution by Kolmogorov–Smirnov test.
OSA mild: obstructive sleep apnea with AHI 5–14; OSA moderate: obstructive sleep apnea with AHI 15–30; OSA mild: obstructive sleep apnea with AHI >30.

We performed propensity score matching (PSM) using five controls (AHI < 15) for each case of moderate to severe OSA (AHI ≥ 15) mimicking randomization with minimal differences after balancing. We used two different outcomes: the ATET and the ATE, which measure the effect of a treatment exposure (in this case moderate-severe OSA) on an outcome (ie, lung cancer). Analysis using the ATET method which allows redundancy in the control group revealed a significant association between AHI and lung cancer. The absence of statistical significance using the ATE is probably due to sample size. Propensity score matching has been gaining support ever since it was first published in the 1980's and is widely accepted in clinical journals today [13]. It generates the

Table 3
Effect of moderate or severe OSA on lung cancer.

METHOD	ATET	95%CI		P	ATE	95%CI		P
Propensity Score matching	0.065	0.013	0.117	0.015	0.063	−0.031	0.156	0.190
Nearest Neighbor matching	0.089	0.003	0.174	0.041	0.073	−0.027	0.173	0.153
Inverse Probability Weighting	NA	NA	NA	NA	0.088	−0.130	0.188	0.088

Notes: Propensity Score matching and Nearest Neighbor matching performed using five controls per subject with moderate or severe OSA (apnea-hypopnea index ≥ 15); ATET: average treatment effects (treatment effects = moderate to severe obstructive sleep apnea effects) among treated subjects (treated subjects = moderate to severe obstructive sleep apnea patients); ATE: average treatment effects (moderate to severe obstructive sleep apnea effects comparing subjects with apnea-hypopnea index ≥ 15 vs apnea-hypopnea index < 15). 95%CI: 95% Confidence Interval, obtained by the Robust Method. NA: does not apply. An ATET or ATE of 0.065 means that OSA subjects have 6.5% more probability of developing lung cancer as compared with subjects without OSA.

statistical power that was initially lacking due to our relatively small sample size.

Our study has several limitations. Sample size is an obvious one, although we were able to correct for this limitation with the ATET method; albeit at the potential expense of bias from an unidentified confounder. The cross sectional design of the study does not distinguish whether lung cancer is the cause or the effect of OSA. It simply points to an association between the two. Furthermore, some studies have shown no correlation and most of those in agreement with our findings share a retrospective design. Finally, many of the positive correlations are derived from animal studies which may not necessary be applicable to humans.

5. Conclusion

We found an increased prevalence of lung cancer in patients with OSA and an association between AHI, nocturnal hypoxemia and lung cancer on multivariate analysis adjusted for possible confounders. Larger prospective longitudinal studies are needed to confirm our findings, investigate the molecular mechanisms behind the association, and determine whether treatment of SDB with CPAP has any role in the setting of lung cancer.

Disclosure statement

Dr. Seijo reports funding from Menarini supporting the lung cancer screening program, during the conduct of the study; and has received personal fees from Roche, as well as personal fees from Chiesi, outside the submitted work, for scientific presentations related to lung cancer. The rest of the authors had no potential conflict of interest to report.

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Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2019.05.011.

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