Sleep disordered breathing and nocturnal hypoxemia are very prevalent in a lung cancer screening population and may condition lung cancer screening findings: Results of the prospective Sleep Apnea In Lung Cancer Screening (SAILS) study

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ARTICLE INFO

Article history:

Received

Received in revised form

Accepted

Published online

Keywords:

Sleep apnea

Sleep disordered breathing

Lung cancer

Screening

Emphysema

COPD

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ABSTRACT

Objective: Obstructive sleep apnea (OSA) can influence the appearance and proliferation of some tumors. The Sleep Apnea In Lung Cancer Screening (SAILS) study (NCT02764866) evaluated the prevalence of OSA and nocturnal hypoxemia in a high-risk population enrolled in a lung cancer screening program.

Methods: This was a prospective study of the prevalence of OSA in a lung cancer screening program. Subjects met the National Lung Screening Trial (NLST) age and smoking criteria (age 55–75 years; pack-years >30). Participants in the study were offered annual screening with low-dose computed tomography (LDCT) and pulmonary function testing, as well as home sleep apnea testing (HSAT) and a sleep-specific questionnaire. Sleep study–related variables, symptoms, and epidemiologic data were recorded.

Results: HSAT was offered to 279 subjects enrolled in our lung cancer screening program. HSAT results were available for 236 participants (mean age 63.6 years; mean tobacco exposure: 45 pack-years), of whom 59% were male and 53% were active smokers. Emphysema (74%) and chronic obstructive pulmonary disease (COPD) (62%) were common and in most cases mild in severity. OSA, including moderate to severe disease, was very common in this patient population. AHI distributions were as follows: AHI <5 (22.5%); 5–15 (36.4%); 15–30 (23.3%); and >30 (17.8%). Nocturnal hypoxemia (T90) ($p = 0.003$), diffusing capacity for carbon monoxide (DLCO) ($p = 0.01$), tobacco exposure ($p = 0.024$), and COPD ($p = 0.023$) were associated with OSA severity. Positive screening findings (nodules ≥6 mm) were associated with nocturnal hypoxemia on multivariate analysis adjusted for confounders (OR = 2.6, 95% CI = 1.12–6.09, $p = 0.027$).

Conclusion: Moderate to severe OSA is very prevalent in patients enrolled in a lung cancer screening program. Nocturnal hypoxemia more than doubles the risk of positive screening findings.

1. Introduction

Recent epidemiological evidence points to a link between obstructive sleep apnea (OSA) and cancer. Two large independent cohorts have reported an increased incidence of and mortality from cancer in subjects with sleep disordered breathing (SDB) [1–4]. Although the role of apnea or hypopnea events is unclear, existing evidence points to hypoxia as the presumptive common link between systemic inflammation and tumor progression and proliferation in the setting of SDB [5–7]. In particular, nocturnal hypoxemia, expressed as the percentage of sleep time spent with an oxyhemoglobin saturation < 90% (T90), has been postulated as a potential key variable in need of further study [1]. The association among sleep apnea, nocturnal hypoxemia, and cancer may be especially relevant for tobacco-related cancers, including lung cancer, in which hypoxia may play an instrumental role in carcinogenesis [8]. Existing animal data suggest that both intermittent and chronic hypoxemia may play a role in lung tumorigenesis and proliferation [9,10]. Because subjects enrolled in a lung cancer screening program are already at high risk for lung cancer due to their age and tobacco consumption, we sought to investigate the prevalence of SDB in the Fundación Jiménez Díaz (FJD) lung cancer screening program. A secondary objective of the study was to understand the potential role of SDB as a marker of risk and its impact on low-dose computed tomography (CT) scanning of the chest (LDCT) findings.

2. Methods

2.1. Study design

We conducted a prospective study, the Sleep Apnea In Lung Cancer Screening (SAILS) study, to evaluate the prevalence of OSA and nocturnal hypoxemia in subjects participating in the FJD's lung cancer screening program. Both the study protocol (EO99/2015_FJD) and the lung cancer screening protocol (PIC23/2014_FJD) were approved by the Clinical Research Ethics Committee of the Fundación Jiménez Díaz University Hospital. The SAILS study has been registered at ClinicalTrials.gov (NCT02764866).

Patients enrolled in the screening program meet the National Lung Screening Trial (NLST) age and smoking criteria (age 55–75 years and tobacco consumption ≥30 pack-years). Study subjects were recruited between February 2016 and April 2017. Participants in the study signed an informed consent form and were offered annual LDCT and pulmonary function testing, including spirometry and diffusing capacity for carbon monoxide (DLCO), as part of the lung cancer screening program. In addition, volunteers signing an additional study-related informed consent form were offered home sleep apnea testing (HSAT) and an epidemiologic and sleep-related questionnaire detailing sleep habits and symptoms. The following variables were collected; sex, age, body mass index (BMI), neck and waist circumference, percentage of visceral fat, comorbidities, tobacco exposure, pulmonary function, and radiological findings, including the presence of lung nodules and their size, as well as emphysema, its severity, and distribution. Visceral fat was measured using bioelectrical impedance analysis. Sleep parameters including the apnea–hypopnea index, snoring detected in each sleep position (prone, lateral, or supine), oxygen saturation, including baseline and mean sleep 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.

2.2. SDB evaluation

The HSAT device used in all patients was the NOX-T3 portable sleep monitor (T3; Nox Medical, Reykjavik, Iceland). The device includes a nasal cannula for oronasal flow and pressure recordings, thoracic and abdominal bands capable of measuring respiratory movements, a pulse oximeter, and a microphone to document snoring. Apneas were defined as a 90% or greater reduction in oronasal flow lasting more than 10 seconds. Hypopneas were defined as a 30–60% decrease in airflow lasting more than 10 seconds associated with an oxygen saturation drop of at least 3%. The apnea–hypopnea index (AHI) was defined as the number of apneas plus hypopneas per hour of recording. A sleep technician systematically scored the results of the HSAT manually after the automatic analysis performed by the software.

Based on the AHI, the severity of OSA was classified as follows: mild OSA (AHI ≥ 5–14.9/h), moderate OSA (AHI ≥ 15–29.9/h), and severe OSA (AHI ≥ 30/h). Continuous positive airway pressure (CPAP) treatment was offered to patients with either severe OSA in the absence of cardiovascular risk factors or moderate OSA with excessive daytime somnolence and/or cardiovascular risk factors.

2.3. Screening protocol

Patients underwent initial baseline LDCT scanning to detect noncalcified solid nodules

and emphysema. Annual screening was performed unless a nodule ≥6 mm was found at baseline. Details of the screening protocol are available at www.ielcap.org.

2.4. COPD and emphysema assessment

COPD was defined as a forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ratio less than 70% on spirometric testing. Specialized chest radiologists qualitatively assessed emphysema on LDCT.

2.5. Statistical analysis

Statistical analysis was performed using R software version 3.1.2. Qualitative variables are reported with frequencies and percentages. Quantitative variables are reported with mean values and standard deviations and with medians and interquartile range in cases of nonnormal distribution.

Univariate analysis for IAH, 3% ODI and 4% ODI were performed using the Student *t* test to compare between two groups and analysis of variance (ANOVA) when comparing more than two groups. The Pearson correlation coefficient was used to evaluate the relationship between quantitative variables and IAH, 3% ODI, and 4% ODI values, respectively.

Univariate analysis of T90 was performed differently because of its nonnormal distribution. Mann–Whitney test was used when comparing two groups, and the Kruskal–Wallis test was used when comparing more than two groups. The Spearman correlation coefficient was used to evaluate the relationship between quantitative

variables and the T90.

To evaluate the relationship between AHI grouped in ranges and qualitative variables we used the χ^2 test or Fisher exact test. Comparisons between groups were performed using ANOVA.

Multivariate analyses of IAH, T90, 3% and 4% ODI, and AHI categories were performed using a multivariate linear regression model.

p Values ≤0.05 were considered statistically significant.

3. Results

Study participation was offered to 279 individuals enrolled in the lung cancer screening program, with 236 individuals completing HSAT. No significant differences were found between subects completing testing after signing informed consent forms and those not adherent to the study protocol. The study design is shown in Fig. 1. Among the 236 individuals who completed the HSAT, 232 had pulmonary function tests and at least one baseline LDCT, and 215 provided answers to the sleep questionnaire. Salient participant characteristics and comorbidities are shown in Table 1 and Table 2, respectively. Lung cancer prevalence at baseline was 2%. Seventeen individuals (7.2%) had undergone sleep testing prior to enrollment in the study for suspected SDB, and gave consent to include their baseline sleep data in the study. Sleep testing in this group was performed on average 1.4 ± 1.9 years prior to enrollment.

Sleep apnea (AHI <5) was ruled out in 53 individuals but was present in 183 (77.5%), including 86 subjects (36.4%) with mild, 55 (23.3%) with moderate, and 42 (17.8%) with severe OSA. Mean AHI was 16.60 ± 16.0/h. Key sleep-related parameters are

summarized in Table 3.

Multivariate analysis was performed to identify key variables related to the prevalence of SDB and nocturnal hypoxemia in the study population demonstrating a correlation between the AHI, baseline SpO_2 ($p = 0.003$) and snoring ($p = 0.008$). The AHI had no impact on screening findings (nodules ≥ 6 mm at baseline LDCT).

Statistically significant associations with the AHI stratified by OSA severity are shown in Table 4. Multivariate ordinal logistic regression was performed with stratification of the AHI by OSA severity showing a correlation with snoring (odds ratio [OR] = 5.78, 95% confidence interval [CI] = 2.05–16.26, $p = 0.001$).

Nocturnal hypoxemia (T90) was correlated on univariate analysis with the presence of arrhythmias ($p = 0.043$) and positive screening findings ($p = 0.003$). Subjects with significant nocturnal hypoxemia defined as a T90 > 12% were more likely to have positive screening findings at baseline on multivariate analysis adjusted for possible confounders (OR = 2.6, 95%CI = 1.12–6.09, $p = 0.027$).

Screening findings were not conditioned by either the ODI 3% or the ODI 4% in both univariate and multivariate analyses.

4. Discussion

Our study sheds new light on the putative links between lung cancer risk, nocturnal hypoxemia, and sleep apnea. Significant OSA and nocturnal hypoxemia were very prevalent in a cohort of asymptomatic patients meeting current screening guideline

recommendations. Furthermore, positive screening findings, defined as the presence at baseline of at least one nodule measuring 6 mm or more in diameter, were almost three times more likely in subjects with significant nocturnal hypoxemia.

As expected, lung cancer prevalence was low at the time of the inclusion of patients. Our intention was to look at the prevalence of OSA among patients at risk for lung cancer but not among patients with diagnosed lung cancer. Sleep-disordered breathing has not been previously studied in the context of lung cancer screening. The FJD screening program offers low-dose CT screening to patients attending a pulmonary specialty clinic at a single hospital in Madrid meeting NLST age and tobacco exposure criteria, including heavy smokers, and those attending a smoking cessation program. Although our patients did not seek evaluation or treatment for sleep-related disorders although and most of them denied excessive daytime sleepiness (mean Epworth Sleepiness Scale score, 5.73), a sleep-related questionnaire revealed that 15.2% reported witnessed apneas and 41% were usual snorers. Many study participants had emphysema, COPD, or both, as is often the case in lung cancer cohorts, but generally mild in severity with a median FEV_1 and DLCO of 77.6% and 84.9%, respectively.

The prevalence of SDB in patients with COPD, a key risk factor for lung cancer, has been a matter of ongoing study. A high prevalence of OSA in COPD patients (85%) has been reported, although the findings in one small study were probably biased by the inclusion of symptomatic patients [11]. Larger prospective studies have reported a wide range of prevalence of OSA in COPD, ranging from 11% to 65.9% [12–14]. Recent cohort-based studies, including the Sleep Heart Health study, have found no difference in the prevalence of OSA when comparing COPD patients with the general population [15–17]. That notwithstanding, patients sharing both pathologies appear to have worse outcomes, including an increased risk of hospitalization and death. Furthermore, CPAP

treatment may improve survival and decrease hospital admissions in this population [18–20]. One of the salient findings of the study, a high prevalence of moderate to severe OSA (41.1%), suggests that the intersection of COPD and sleep disordered breathing in this setting may have wide-ranging implications for preventive efforts and early detection [21].

Current evidence supports that patients with COPD and emphysema are ideal candidates for lung cancer screening, as they are at high risk for the development of lung cancer [22–24]. Emphysema is a powerful predictor of lung cancer risk and has been included in risk scores determining eligibility for lung cancer screening [25]. Given the fact that the prevalence of OSA in our study was high among subjects meeting NLST inclusion criteria, we believe that HSAT may be useful in patients enrolled in lung cancer screening and smoking cessation programs.

The finding that significant nocturnal hypoxemia almost triples the risk of positive screening findings in our screening cohort is provocative, and may be considered an intermediate endpoint linking OSA and lung cancer. Although intermittent hypoxemia and oxidative stress play an important role in well-documented cardiovascular outcomes in the setting of sleep disordered breathing [26–28], some of these pathophysiologic pathways may also be involved in oncogenesis. Nocturnal hypoxemia has been described as a key variable predicting lung cancer incidence and progression in experimental and animal models [29–32]. A murine model of melanoma revealed that intermittent hypoxemia mimicking OSA enhanced tumor growth and promoted lung metastases [33,34] whereas an in vitro lung cancer study showed that tumor hypoxia led to a phenotypic change in macrophages that favored metastasis [35]. Another animal study also found an association between hypoxia and increased risk of metastases as well as resistance to radiation therapy and chemotherapy [36].

The Wisconsin Sleep Cohort Study investigated the association between SDB and cancer in a human cohort. It found a strong dose–response relationship between SDB and cancer mortality [2]. Similarly, a large Spanish epidemiological cohort reported an increased cancer incidence in patients with nocturnal hypoxemia. Individuals with T90 scores greater than 12% were at high risk [1]. Although the 2% prevalence of lung cancer in our patient population is not high enough for a relatively small sample to find associations between nocturnal hypoxemia and lung cancer prevalence or incidence, the intermediate endpoint of positive screening findings and its association with a T90 > 12% may have clinical significance for the ongoing worldwide implementation of lung cancer screening. In particular, the coexistence in our cohort of sleep disordered breathing, lung function abnormalities, and emphysema, and its implications for lung cancer screening, is a matter of ongoing study. We believe that our findings suggest a link among all three pathologies linked to cancer, and may condition lung cancer screening inclusion criteria and prevention strategies.

Our study is the first to prospectively investigate sleep disordered breathing in a high-risk population of asymptomatic subjects enrolled in a lung cancer screening program. Study generalizability is limited to the lung cancer screening setting. In addition, there is a potential selection bias because our population is based on smokers or former smokers more than 55 years of age. However, because our screened patients meet NLST age and tobacco-specific inclusion criteria that are the basis of current guidelines, our findings have implications for ongoing screening programs.

Although the prospective design of the study has obvious advantages, it also has several limitations. First of all, the study was conducted in a single center and does not have a control group. Although this may limit its external validation, it is important to keep in mind that the FJD participates in a larger international cohort and follows ERS

recommendations regarding the establishment of lung cancer screening programs [37]. Furthermore, the FJD's sleep center has been accredited by the Spanish Society of Pneumology and Thoracic Surgery (SEPAR) and participates in the well-established Spanish Sleep Network [38].

Our study relied on HSAT, which may underestimate the apnea–hypopnea events when compared to conventional polysomnography, because the latter allows detection of arousals seen on the electroencephalogram. Nevertheless, a recent multicenter prospective study has shown that HSAT is comparable to polysomnography, with the additional benefit of a substantially lower cost [39]. In any case, a hypothetical underestimation of OSA prevalence by HSAT would only support our conclusion that sleep disordered breathing is very common in a lung cancer screening setting. The HSAT portable monitor that we used for this study is potentially superior to other similar devices such as the ApneaLink (ResMed Corporation, Poway, CA), because in addition to the nasal cannula, it includes a pulse oximeter, thoracic and abdominal bands capable of measuring respiratory movements, and a microphone, all of which increase the device's sensibility for apneas, hypopneas, and oxygen saturation changes.

5. Conclusion

In conclusion, we found a high prevalence of unsuspected OSA in a lung cancer screening population meeting NLST inclusion criteria and therefore compliant with current screening guidelines. Many of these subjects had mild emphysema and/or COPD, suggesting that the overlap syndrome may be especially relevant in this context. More importantly, nocturnal hypoxemia was a robust predictor of positive screening

findings after adjusting for potential confounders, a finding with potentially far-reaching implications for the future of lung cancer screening.

Conflict of interest

The authors declare that they have no conflicts of interest.

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Fig. 1. Study design. CT, computed tomography; HSAT, home sleep apnea test; PFT, pulmonary function test.

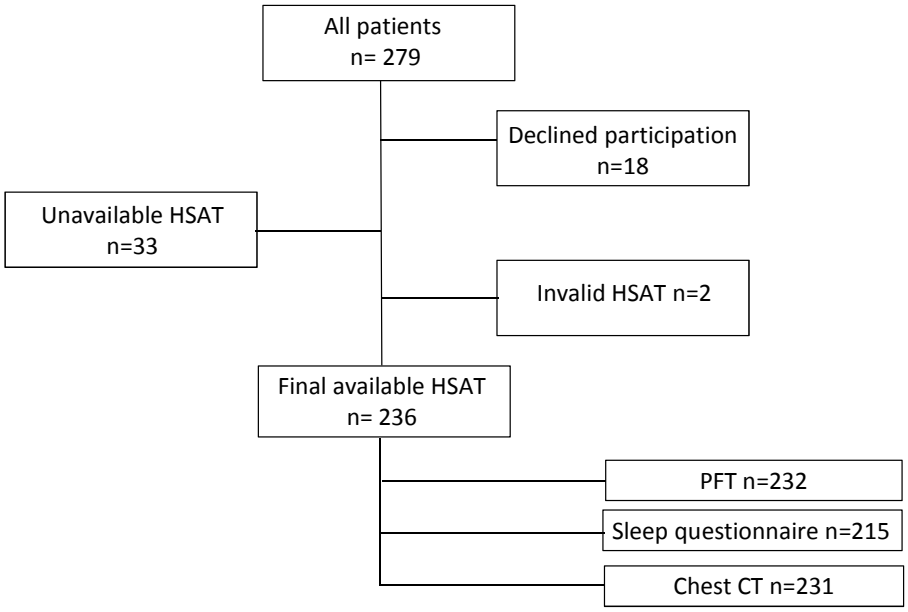

Table 1

Baseline characteristics of study subjects.

Variables	**Mean ± SD / median (IQR) / n (%)**
Sex (n = 236) Men Women	 140 (59.3%) 96 (40.7%)
Age, yr (n = 236)	63.6 ± 8.8
BMI, kg/m^2 (n = 236)	28.6 ± 5.21
Pack-yr (n = 229)	45 (38-60)
COPD (n = 232)	144 (62.1%)
Emphysema (n = 232)	172 (74.2%)
Nodules ≥6 mm (n = 232)	35 (15.1%)
FEV_1% (n = 232)	77.6 ± 20.1
DLCO% (n = 226)	84.9 ± 21.5
ESS (n = 215)	5.73 ± 3.45
Visceral fat % (n = 232)	13.1 ± 5.98

BMI, body mass index; COPD, Chronic Obstructive Pulmonary Disease; ESS, Epworth Sleepiness Scale; FEV_1, forced expiratory volume in 1 second; DLCO, carbon monoxide diffusing capacity.

Table 2

Comorbidities in study subjects (n = 235)

Variables	n (%)
Hypertension	96 (40.8%)
Diabetes	36 (15.3%)
Dyslipidemia	81 (34.5%)
Lung cancer	3 (1.3%)
Stroke	14 (6%)
Ischemic heart disease	18 (7.7%)
Arrhythmia	14 (6%)
Smoking status Former smoker Active smoker	 111 (47.2%) 124 (52.8%)
Anxiety/depression	30 (12.8%)
Sedative use	47 (20%)
Daily alcohol consumption	3 (1.3%)

Table 3

Main sleep variables in study subjects.

Variable	Mean ± SD / median (IQR)	Minimum value	Maximum value
AHI	16.60 ± 16.0	0.20	86.40
T90	4.60 (0.72–25.10)	0.00	99.10
3% ODI	16.40 ± 15.4	0.10	80.60
4% ODI	10.30 ± 12.60	0.00	80.10
Supine AHI	27.80 ± 25.80	0.00	103.00
Snore index	23.50 ± 21.50	0.00	86.20
Baseline SpO_2	93.30 ± 2.79	80.00	98.00
Initial sleep SpO_2	91.40 ± 6.31	3.90	97.40
Median sleep SpO_2	91.60 ± 2.70	77.40	97.40
Minimum sleep SpO_2	82.70 ± 6.43	51.00	93.00

AHI, apnea–hypopnea index; IQR: Interquartile range; SD, standard deviation; SpO2, oxygen saturation; T90, percentage of sleep time with oxygen saturation <90%.

Table 4

AHI relationships categorized by severity of OSA.

Variable	No OSA	Mild OSA	Moderate OSA	Severe OSA	*p*
Sex, n (%)					<0.001
Men	21 (15)	46 (32.9)	41 (29.3)	32 (22.9)	
Women	32 (33.3)	40 (41.7)	14 (14.6)	10 (10.4)	
Tobacco status, n (%)					0.018
Former	19 (17.1)	35 (31.5)	31 (27.9)	26 (23.4)	
Active	34 (27.4)	51 (41.1)	23 (18.5)	16 (12.9)	
Snore, n (%)					<0.001
No	8 (47.1)	6 (35.3)	3 (17.6)	0 (0%)	
Usual	7 (7.2)	32 (33)	30 (30.9)	28 (28.9)	
Ocasional	19 (37.3)	17 (33.3)	11 (21.6)	4 (7.8)	
Unknown	14 (26.9)	26 (50)	7 (13.5)	5 (9.6)	
Witnessed apneas, n (%)					0.009
No	31 (33.7)	32 (34.8)	19 (20.7)	10 (10.9)	
Yes	2 (5.6)	12 (33.3)	13 (36.1)	9 (25)	
Unknown	15 (16.9)	37 (42.6)	19 (21.3)	18 (20.2)	
DLCO, mean ± SD	77.2 ± 20	84.6 ± 23	90 ± 19.8	88.6 ± 20.8	0.012
Weight, mean ± SD	69.1 ± 14.6	75 ± 15.6	82.9 ± 16.6	88.2 ± 18.7	<0.001
Neck, mean ± SD	36 ± 4.74	39 ± 5.18	40.6 ± 4.06	42.4 ± 5.14	<0.001

Waist, mean ± SD	98.1 ± 12.6	103 ± 13.4	109 ± 15.6	112 ± 12.3	<0.001
BMI, mean ± SD	26 ± 4.07	27.9 ± 4.51	29.8 ± 5.49	31.8 ± 5.25	<0.001
% Visceral fat, mean ± SD	9.8 ± 4.48	12.1 ± 5.11	14.5 ± 6.22	17.3 ± 6.04	<0.001

AHI, apnea–hypopnea index: No OSA, AHI <5; Mild OSA, AHI 5–14.9; Moderate OSA, AHI 15–30; Severe OSA, AHI ≥30.

Highlights

Obstructive sleep apnea was very prevalent in a lung cancer screening population meeting National Lung Screening Trial criteria.

Lung nodules were more likely in subjects with nocturnal hypoxemia.

Nocturnal hypoxemia more than doubles the risk of positive screening findings.

ICMJE Uniform Disclosure Form

Dear Sirs:

In the article entitle:

"Sleep disordered breathing and nocturnal hypoxemia are very prevalent in a lung cancer screening population and may condition lung cancer screening findings. Results of the prospective SAILS (Sleep Apnea In Lung Cancer Screening) study":

There are no conflict of interest to report by authors:

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