

# Association between Obstructive Sleep Apnea and Cancer Incidence in a Large Multicenter Spanish Cohort

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**Rationale:** Obstructive sleep apnea (OSA) has been associated with increased cancer mortality, but whether it is also associated with cancer incidence is unknown.

**Objectives:** To investigate whether OSA is associated with increased cancer incidence in a large clinical cohort.

**Methods:** A multicenter, clinical cohort study including consecutive patients investigated for suspected OSA between 2003 and 2007 in seven Spanish teaching hospitals. Apnea-hypopnea index (AHI) and percent nighttime with oxygen saturation less than 90% (TSat<sub>90</sub>) were used as surrogates of OSA severity, both as continuous variables and categorized by tertiles. Cox proportional hazards regression analyses were used to calculate hazard ratio (HR) and 95% confidence interval (CI) for cancer incidence after adjusting for confounding variables.

**Measurements and Main Results:** A total of 4,910 patients were analyzed (median follow-up, 4.5 yr; interquartile range, 3.4–5.2). Compared with the lower TSat<sub>90</sub> category (<1.2%), the adjusted hazards (95% CI) of cancer incidence for increasing categories were 1.58 (1.07–2.34) for TSat<sub>90</sub> 1.2–12% and 2.33 (1.57–3.46) for TSat<sub>90</sub> greater than 12%. Continuous TSat<sub>90</sub> was also associated with cancer incidence (adjusted HR, 1.07 [1.02–1.13] per 10-unit increase in TSat<sub>90</sub>). In stratified analyses, TSat<sub>90</sub> was associated with cancer incidence in patients younger than 65 years (adjusted HR, 1.13 [95% CI, 1.06–1.21] per 10-unit increase in TSat<sub>90</sub>) and males (adjusted HR, 1.11 [95% CI, 1.04–1.17] per 10-unit increase in TSat<sub>90</sub>). AHI was not associated with cancer incidence in the adjusted analyses, except for patients younger than 65 years (adjusted HR for AHI >43 vs. <18.7, 1.66; 95% CI, 1.04–2.64).

**Conclusions:** Increased overnight hypoxia as a surrogate of OSA severity was associated with increased cancer incidence. This association seems to be limited to men and patients younger than 65 years of age.

**Keywords:** sleep apnea syndromes; intermittent hypoxia; cancer; sex; age

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## AT A GLANCE COMMENTARY

### Scientific Knowledge on the Subject

Recent research in animal models and human population cohorts has shown that sleep apnea and, specially, intermittent hypoxia may worsen the prognosis of cancer. To date, however, the relationship between sleep apnea and cancer incidence in humans has not yet been assessed.

### What This Study Adds to the Field

This study investigates the association between obstructive sleep apnea and cancer incidence in a large clinical cohort. Increased overnight hypoxia as a surrogate of obstructive sleep apnea severity was associated with increased incidence of cancer, and this association was stronger in patients younger than 65 years.

Obstructive sleep apnea (OSA) is a highly prevalent disorder characterized by repetitive upper airway obstructions during sleep that lead to intermittent hypoxia and sleep fragmentation. There is increasing evidence to implicate OSA as a risk factor for cardiovascular mortality and morbidity (1–4). Systemic mechanisms, such as intermittent hypoxia and oxidative stress, play an important intermediate role in these cardiovascular outcomes (5–7). Some of these pathophysiologic pathways seem, however, to also be decisively involved in the pathogenesis of other disorders, such as cancer. In this sense, chronic and intermittent hypoxia have been shown to play a key role in regulating the various stages of tumor formation and progression (8–10). Under intermittent hypoxia conditions, reactive oxygen species (ROS) are generated, and overexpression of the hypoxia-inducible factor-1 $\alpha$  leads to an up-regulation of proangiogenic mediators, such as vascular endothelial growth factor. These mediators are involved in carcinogenesis, increasing tumor vasculature, and accelerating tumor growth (11–13). Almendros and coworkers (14, 15) have recently shown in a mouse model of melanoma that intermittent hypoxia mimicking OSA enhances tumor growth and increases lung metastasis. Consistent with these experimental data, the Wisconsin cohort researchers have reported increased cancer mortality in patients with severe OSA (16). In addition to this poorer prognosis for cancer, it has been speculated that sleep apnea-related hypoxia may also increase the susceptibility to develop a new cancer (17), but this hypothesis has not yet been assessed and, therefore, research on this topic is needed. If it could be shown

that OSA predisposes to cancer, this would have a considerable impact on health policies for cancer prevention, because it would open up a way to intervene in the prevention of malignant neoplasms by early OSA diagnosis. In this study, we sought to investigate whether OSA was associated with increased incidence of cancer in a large cohort of patients studied for OSA suspicion.

Some of the results of this study have been previously reported in the form of an abstract (18, 19).

## METHODS

### Design and Patients

We performed a retrospective, multicenter, longitudinal cohort study. Consecutive patients older than 18 years included in the databases of seven Spanish teaching hospitals who had been assessed for suspected OSA between 2003 and 2007 were eligible. Patients were excluded if they had received a diagnosis of cancer at any time before the sleep study; if they had respiratory failure ( $\text{PaO}_2 < 60$  mm Hg,  $\text{O}_2$  saturation  $< 90\%$ , or long-term oxygen therapy) during OSA evaluation; or data about cancer or the sleep study were not available. The Ethics Committees of each hospital approved the study.

### Data Collection

All baseline variables were systematically recorded using a standardized protocol. Information was obtained from medical records and computerized databases. The following baseline variables were assessed: age (years); body mass index (BMI; kilograms per square meter); sex; hospital of enrollment; alcohol intake (grams per day); and smoking status (never, current, or former smoker) and use (pack-years).

### Sleep Study and Continuous Positive Airway Pressure Treatment

Every patient had a diagnostic sleep study, either full standard polysomnography (PSG) or validated respiratory polygraphy (RP), following the Spanish Society of Pneumology and Thoracic Surgery Guidelines for OSA diagnosis and treatment (20, 21). Sleep studies were manually scored according to standard criteria (22). PSG included the continuous recording of neurologic variables by electroencephalography, electrooculography, and electromyography; scoring of breathing variables on the basis of a flow tracing from an oronasal cannula and thermistor; measurement of thoracoabdominal motion by using thoracic and abdominal bands; recording of oxyhemoglobin saturation ( $\text{SO}_2$ ) with a finger pulse oximeter; and electrocardiography. RP included, at least, electrocardiography and recording of oronasal flow and pressure, respiratory movements, and  $\text{SO}_2$ . Apnea was defined as cessation of oronasal flow for more than 10 seconds and was classified either as obstructive or central based on the presence or absence of respiratory efforts. Hypopnea was defined as a discernible reduction in oronasal flow for more than 10 seconds followed by a greater than or equal to 4% decrease in  $\text{SO}_2$  or an arousal (23). The apnea-hypopnea index (AHI) was defined as the number of apneas plus hypopneas per hour of sleep (PSG) or recording (RP). Percent of nighttime spent with  $\text{SO}_2$  less than 90% ( $\text{TSat}_{90}$ ) was also recorded. Continuous positive airway pressure (CPAP) treatment was prescribed according to guidelines (20) and it was titrated with either full standard PSG or an autotitrating CPAP device (24).

### Endpoint

The endpoint of this study was cancer incidence, defined as the first occurrence of a malignant neoplasm at any time between the sleep study and the final follow-up date of December 31, 2010. The presence of cancer was thoroughly assessed by reviewing multiple concurrent sources of information, which included cancer and pathology registries, medical records and computerized databases, and when necessary by contacting the primary care physician in charge of the patient.

### Statistical Analysis

AHI and  $\text{TSat}_{90}$  were used as surrogates of OSA severity, both as continuous variables and categorized by tertiles. Continuous variables

are expressed as medians (interquartile range) and qualitative variables as absolute values (percentages). The baseline differences between OSA categories were compared using the nonparametric Kruskal-Wallis test for quantitative and the chi-square test for qualitative characteristics. Patients with incident cancer were analyzed until the date of cancer diagnosis. Patients who did not develop cancer were censored at the date of death, date of last contact, or the end of follow-up.

Cancer incidence density rates were calculated for each OSA category and compared using the incidence density ratio. Kaplan-Meier techniques were used to compare survival across OSA categories.

Multiple imputations by chained equations were used in case of missing values, generating a high number of 50 imputations per missing value to minimize the inherent simulation error.

Associations between cancer incidence and OSA categories were estimated using Cox proportional hazards regression models, with adjustment for the following potential confounders: age, sex, BMI, smoking status and use, alcohol intake, type of diagnostic sleep study, and hospital of enrollment, the latter being included as random effects. The results were expressed as hazard ratios (HR) and 95% confidence intervals (CI). In addition, the association of continuous forms of  $\text{TSat}_{90}$  and AHI with cancer incidence was also examined.

To assess the differential effect of OSA severity on cancer incidence depending on sex, age at baseline ( $< 65$  vs.  $\geq 65$  yr), and obesity (BMI  $< 30$  vs.  $\geq 30$   $\text{kg/m}^2$ ), interactions between these variables were examined. Stratified models were then constructed for those interactions showing statistical significance. This approach may potentially decrease the power of the subanalyses, because of the smaller sample size. To exclude any potential treatment effect, an additional analysis was performed on untreated patients alone (no active treatment for OSA or CPAP adherence  $< 4$  h per day). Because the AHI may be influenced by the type of diagnostic sleep study, not only was this variable included as a confounder in the multivariate analyses but also the association between AHI categories and cancer incidence was separately assessed for each type of sleep study.

The R software package, version 2.15.1 (<http://www.r-project.org/>), was used, with a prespecified significance level of 0.05. Only *P* values less than the significance level were considered statistically significant.

## RESULTS

Of 5,320 eligible patients, 410 were excluded for the reasons previously detailed in the METHODS section. The number of individuals excluded for each specific reason can be seen in Figure 1. Data from 4,910 patients were finally analyzed. Four variables showed incomplete data. Multiple imputation was applied to BMI with 117 (2.4%),  $\text{TSat}_{90}$  with 276 (5.6%), alcohol intake with 417 (8.5%), and smoking use with 463 (9.4%) missing values. As expected, patients with increasing AHI severity had significantly higher age and BMI, and were more frequently male (Table 1). Sixty-eight percent of the sample underwent a RP, and the remaining 32% received a PSG.

Patients were followed-up for a median of 4.5 (interquartile range, 3.4–5.2) years. By the end of the study period, 261 patients (5.3%) had received a diagnosis of cancer. The most frequent locations were colorectal in 43 (16.5%) and prostate in 42 (16.1%) cases, followed by lung and breast cancer in 24 (9.2%) and 20 (7.7%) patients, respectively. Cancer incidence density rates increased with increasing AHI and  $\text{TSat}_{90}$  categories (Table 2). Compared with the lower categories, an increased cancer incidence density ratio was found for the upper AHI category (1.60; 95% CI, 1.16–2.14), and for the middle (1.90; 95% CI, 1.33–2.83) and upper (3.20; 95% CI, 2.28–4.62)  $\text{TSat}_{90}$  categories (Table 2). Cumulative cancer incidence increased across AHI (log-rank test,  $P = 0.014$ ) and  $\text{TSat}_{90}$  categories (log-rank test,  $P < 0.0005$ ) (Figure 2).

Compared with the lower severity category, the adjusted HR (95% CI) of cancer incidence for  $\text{TSat}_{90}$  categories in the Cox regression analysis were 1.58 (1.07–2.34) for  $\text{TSat}_{90}$  between 1.2% and 12%, and 2.33 (1.57–3.46) for  $\text{TSat}_{90}$  greater than 12% (Table 3). A significant increase in incidence risk with increasing

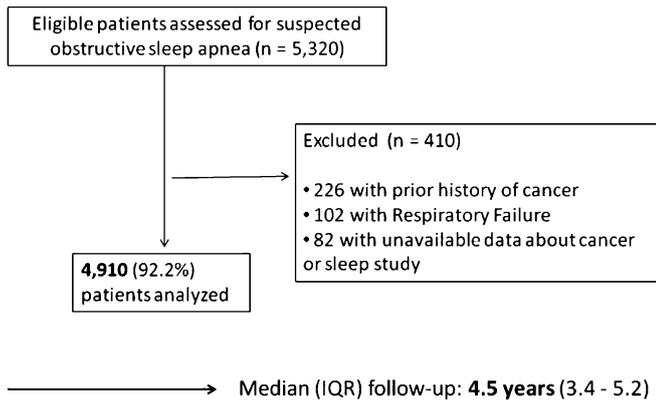


Figure 1. Study flowchart.

TSat<sub>90</sub> score was also observed (adjusted HR, 1.07 [95% CI, 1.02–1.13] per 10-unit increase in TSat<sub>90</sub>). AHI was not associated with cancer incidence in the adjusted analysis, neither as a categorical nor as a continuous variable (Table 3). This lack of association between AHI and cancer incidence persisted, even when we separately analyzed patients who received a PSG (upper vs. lower AHI category, HR 1.30; 95% CI, 0.69–2.43) and a RP (upper vs. lower AHI category, HR 1.10; 95% CI, 0.71–1.69). When an additional analysis was run on untreated patients alone, the results did not significantly change (Table 3).

Statistically significant interactions were found between age and both AHI ( $P = 0.003$ ) and TSat<sub>90</sub> ( $P = 0.036$ ) and between sex and TSat<sub>90</sub> ( $P = 0.049$ ), but not between obesity (BMI  $\geq 30$ ) and AHI or TSat<sub>90</sub> ( $P > 0.1$  for both). When stratified analyses by age and sex were run, in patients younger than 65 years, cancer incidence was associated with both TSat<sub>90</sub> and AHI categories (Table 4), and with continuous TSat<sub>90</sub> (adjusted HR, 1.13 [95% CI, 1.06–1.21] per 10-unit increase in TSat<sub>90</sub>). In men, TSat<sub>90</sub>, both categorized in tertiles and as a linear term (adjusted HR, 1.11 [95% CI, 1.04–1.17] per 10-unit increase in TSat<sub>90</sub>), but not AHI, was associated with cancer incidence (Table 5). No association between TSat<sub>90</sub> or AHI and cancer was found in women and patients greater than or equal to 65 years (Tables 4 and 5).

## DISCUSSION

The findings of this study show that OSA severity based on TSat<sub>90</sub> was independently associated with increased risk of incident cancer. A relationship was also found between cancer incidence and the upper AHI category, but this disappeared after adjusting for confounders, except in the case of patients younger than 65 years. The association between OSA and incident cancer seems to be limited to patients younger than 65 years and male sex.

The relationship between OSA and cancer has scarcely been investigated, and to the best of our knowledge this is the first study to address the association between OSA and cancer incidence in humans. In a mouse model of melanoma, Almendros and coworkers (14, 15) have recently reported that intermittent hypoxia similar to that found in severe OSA increases tumor growth, tumor necrosis, and lung metastasis compared with mice subjected to normoxia. These findings are consistent with the first human evidence on the relationship between OSA and excessive mortality from cancer provided by the Wisconsin Sleep Cohort (16). In this population-based cohort, individuals with an AHI greater than or equal to 30 had an adjusted hazard of cancer mortality of 4.8 (95% CI, 1.7–13.2), compared with non-sleep apnea (AHI < 5) participants, and this association was even stronger when percent of sleep time with SO<sub>2</sub> less than 90% was analyzed (adjusted hazard, 8.6; 95% CI, 2.6–28.7).

Our findings suggest that hypoxia may also be the pathologic link between OSA and cancer incidence. We have found that patients who spent more than 12% of nighttime with SO<sub>2</sub> below 90% had a more than twofold greater adjusted risk of incident cancer, and even those who spent more than 1.2% of nighttime in this situation were at increased risk of cancer, compared with individuals who spent less than 1.2% of the time with saturation below 90%. Increasing continuous TSat<sub>90</sub> was associated with increasing cancer incidence with an adjusted HR of 1.07 (95% CI, 1.02–1.13, per 10-unit increase in TSat<sub>90</sub>).

In this study we have measured the percent of nighttime spent with SO<sub>2</sub> less than 90%, a marker of overnight hypoxia. Unfortunately, the best marker of intermittent hypoxia, the oxygen desaturation index, was not available in most patients and could not be used. Nevertheless, provided that patients with respiratory failure or long-term oxygen therapy had been excluded from the study and, given that OSA is associated with intermittent,

TABLE 1. BASELINE CHARACTERISTICS OF THE COHORT, ACCORDING TO AHI CATEGORIES

Variables	AHI < 18.7 (n = 1,637)	AHI 18.7–43 (n = 1,643)	AHI > 43 (n = 1,630)
Continuous variables, median (interquartile range)			
Age, yr	51 (41–60)	56 (47–65)	57 (48–66)
Body mass index, kg/m <sup>2</sup>	29.7 (26.5–33.5)	30.9 (27.9–34.6)	33.2 (30–37.6)
Smoking use, pack-year *	21.5 (12–34.9)	24.7 (14.8–40)	29.9 (15–45.1)
Alcohol intake, g/d*	30 (16–40)	30 (20–50)	30 (20–57)
AHI	9 (4.5–14.1)	30.1 (24.3–36.7)	63.9 (53.2–78)
TSat <sub>90</sub>	0.4 (0–4)	4.2 (1–13)	17.6 (6–40.7)
Categorical variables, n (%)			
Male sex	935 (57.1)	1,139 (69.3)	1,202 (73.7)
Smoking status			
Never smokers	862 (52.6)	814 (49.5)	766 (46.9)
Former smokers	419 (25.6)	404 (24.5)	444 (27.2)
Current smokers	356 (21.7)	426 (25.9)	420 (25.7)
Polysomnography	675 (41.2)	508 (30.9)	384 (23.6)
Obesity (BMI $\geq 30$ kg/m <sup>2</sup> )	758 (46.3)	923 (56.1)	1,228 (75.3)

Definition of abbreviations: AHI = apnea-hypopnea index; BMI = body mass index; TSat<sub>90</sub> = percent of nighttime spent with oxygen saturation < 90%.

$P < 0.0005$  for comparison of age, sex, BMI, AHI, TSat<sub>90</sub>, male sex, polysomnography, and obesity across groups.  $P = 0.004$  for comparison of smoking status,  $P < 0.023$  for comparison of pack-year of smoking use, and  $P > 0.1$  for comparison of alcohol intake across groups.

\* The median values for alcohol intake and pack-years are given for those patients who smoked and drank alcohol.

TABLE 2. CANCER INCIDENCE DENSITY RATES FOR OSA CATEGORIES

OSA Categories	Cancer Incidence, n	Person-Years of Follow-up	Cancer Incidence Density Rates*	Incidence Density Ratio (95% CI)
<b>AHI categories</b>				
<18.7	67	7,181.9	9.33	1
18.7–43	89	7,002.7	12.71	1.40 (0.99–1.87)
>43	105	7,155.5	14.67	1.60 (1.16–2.14) <sup>†</sup>
<b>TSat<sub>90</sub> categories</b>				
<1.2%	43	7,190.5	5.97	1
1.2–12%	83	7,182.4	11.58	1.90 (1.33–2.83) <sup>‡</sup>
>12%	135	6,967.1	19.36	3.20 (2.28–4.62) <sup>§</sup>

Definition of abbreviations: AHI = apnea-hypopnea index; CI = confidence interval; OSA = obstructive sleep apnea; TSat<sub>90</sub> = percent of night time spent with oxygen saturation < 90%.

\* Rates per 1,000 person-years.

<sup>†</sup>  $P = 0.003$ , compared with the reference group (AHI < 18.7).

<sup>‡</sup>  $P = 0.0006$  compared with the reference group (TSat<sub>90</sub> < 1.2%).

<sup>§</sup>  $P < 0.0005$  compared with the reference group (TSat<sub>90</sub> < 1.2%).

rather than with chronic hypoxia, we think that in this study TSat<sub>90</sub> may indirectly reflect intermittent hypoxia.

Remarkably, in our study TSat<sub>90</sub> was a stronger predictor of cancer incidence than AHI, both as a linear term and as a categorical variable. One possible explanation for this finding may be that a proportion of respiratory events were accompanied by small drops in oxygen saturation or even by no desaturation at all (those hypopneas scored by arousals) and, therefore, AHI would be a less adequate surrogate of intermittent hypoxia than TSat<sub>90</sub>. These results suggest that TSat<sub>90</sub> would be a better marker of cancer risk than AHI among individuals with OSA, although this issue needs to be replicated in future studies.

With regards to the mechanisms likely to be involved in the development of cancer in patients with OSA, we hypothesize that various pathways triggered by hypoxia may play a key role. Although we have measured overnight hypoxia, and not specifically intermittent hypoxia, recent research has found that elevation of ROS levels during the reoxygenation periods of intermittent hypoxia can modify gene expression through the regulation of the activity of some transcription factors and signaling pathways involved in tumorigenesis (10, 13), and increased oxidative stress has been reported as a risk factor for developing some solid and hematologic cancers (25–27). OSA has been recognized as an oxidative stress disorder (5, 28–30), and various parameters of OSA severity including several oximetric parameters have been shown to be correlated with oxidative stress (5, 31). In addition, both chronic and intermittent hypoxia and ROS can activate transcription factors, such as hypoxia-inducible factor-1, which are known to promote angiogenesis and enhance tumor progression.

Our study has an observational design and many patients received CPAP treatment based on the presence of symptomatic or severe OSA. The decision to analyze the entire cohort irrespective of treatment was based on the assumption that OSA is a chronic disorder and, therefore, patients would have been suffering from intermittent hypoxia and other related consequences of OSA for many years before starting treatment. Nevertheless, because a treatment effect may have hidden a possible association between OSA and cancer, we conducted an additional analysis including only untreated patients. In this subset of patients, the analyses replicated the results of the entire cohort. This finding should not be interpreted as a lack of efficacy of CPAP treatment in preventing the appearance of cancer associated with OSA but simply reflects the fact that our study was not designed to address this question.

The association between OSA and cancer incidence differed according to sex and age. However, these results should be interpreted cautiously, because the smaller number of individuals in each age and sex subgroup may have decreased the power to detect relevant associations. When the results were stratified by

age, we found a strong relationship between OSA severity, measured by AHI and TSat<sub>90</sub>, and cancer incidence in patients younger than 65 years, but not in older patients. These data are consistent with the lack of cardiovascular consequences found in elderly patients with OSA in some reports (3, 32,

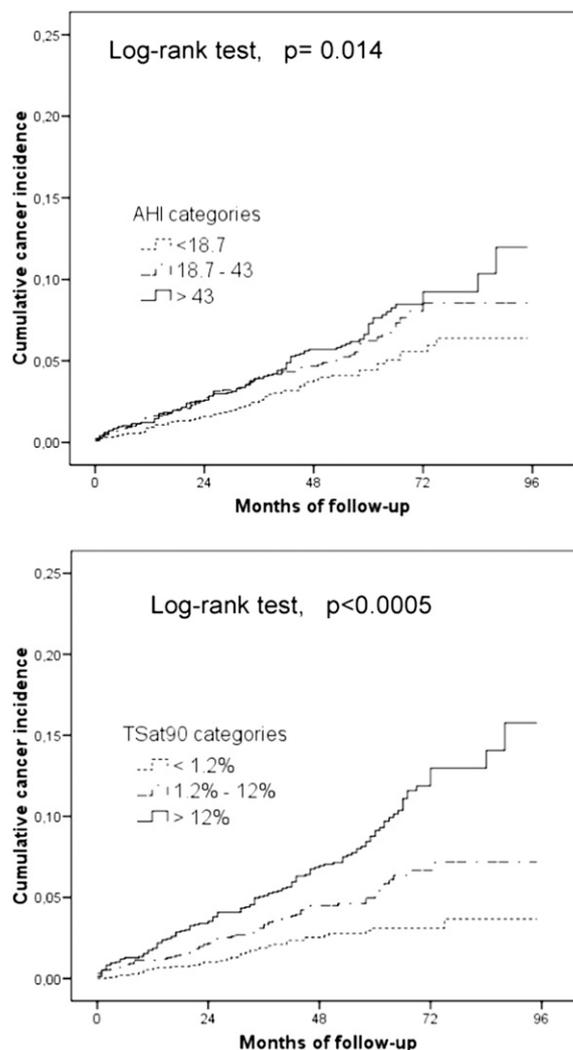


Figure 2. Kaplan-Meier curves showing cumulative cancer incidence, according to AHI (upper panel) and TSat<sub>90</sub> (lower panel) categories. AHI = apnea-hypopnea index; TSat<sub>90</sub> = percent of nighttime spent with oxygen saturation less than 90%.

**TABLE 3. MULTIVARIATE COX REGRESSION ANALYSIS: ASSOCIATION BETWEEN CANCER INCIDENCE AND OSA CATEGORIES**

OSA Categories	Entire Cohort ( <i>n</i> = 4,910)		Untreated Patients ( <i>n</i> = 2,069)	
	Adjusted HR (95% CI)*	<i>P</i> Value	Adjusted HR (95% CI)*	<i>P</i> Value
AHI, events/h				
AHI (continuous)	1.00 (0.99–1)	0.61	1.00 (0.99–1)	0.99
AHI categories (tertiles)				
<18.7	1	—	1	—
18.7–43	1.10 (0.79–1.53)	0.54	1.08 (0.72–1.61)	0.69
>43	1.17 (0.84–1.65)	0.33	1.06 (0.65–1.73)	0.79
AHI categories				
<5	1	—	1	—
5–14.9	0.99 (0.56–1.77)	0.98	1.01 (0.56–1.82)	0.97
15–29.9	1.07 (0.62–1.85)	0.82	1.15 (0.64–2.06)	0.64
≥30	1.06 (0.62–1.80)	0.83	1.02 (0.55–1.86)	0.96
TSat <sub>90</sub>				
TSat <sub>90</sub> (continuous)	1.00 (1–1.01)	0.003	1.00 (1–1.01)	0.023
TSat <sub>90</sub> categories				
<1.2%	1	—	1	—
1.2–12%	1.58 (1.07–2.34)	0.021	1.88 (1.16–3.04)	0.010
>12%	2.33 (1.57–3.46)	<0.0005	2.74 (1.62–4.60)	<0.0005

*Definition of abbreviations:* AHI = apnea-hypopnea index; CI = confidence interval; HR = hazard ratio; OSA = obstructive sleep apnea; TSat<sub>90</sub> = percent of nighttime spent with oxygen saturation < 90%.

\*Adjusted for age, sex, body mass index, smoking status and use, alcohol intake, type of sleep study, and hospital of enrollment (as random effects).

33). Although these age differences may simply reflect a survival bias or the aforementioned loss of power in a smaller sample, some authors have proposed the so-called “ischemic preconditioning hypothesis” to explain this paradox (34). This hypothesis argues that age decline in cardiovascular effects of OSA could be explained by the activation of protective and adaptive mechanisms against intermittent hypoxia (35). Should this hypothesis be true, a similar defense mechanism against the effects of intermittent hypoxia on cancer development cannot be ruled out as an explanation of these age-related differences. The association of cancer with male sex is more intriguing. A different response to intermittent hypoxia may be present in women as compared with men. However, because male sex accounted for 66.7% of the entire cohort and some of the most common cancers were sex-dependent, it cannot be excluded that these sex differences in cancer incidence simply reflect a lack of statistical power for women, selection bias, or the particular profile of our cohort.

The strengths of this work include being the very first study to investigate the association between OSA and cancer incidence and its large, multicenter cohort comprising nearly 5,000 patients. Our study also has limitations, however, the most important being the retrospective design, which precluded the assessment of such variables as lifestyle, hours of sleep, nutrition, and physical activity. Nevertheless, the most relevant confounders regarding cancer incidence, such as tobacco, alcohol, obesity, sex, or age, have been adjusted for, and the presence of a new cancer was thoroughly investigated by using multiple concurrent approaches. Because of this retrospective design, we lacked information about oxygen desaturation index in many patients, which precluded the use of this marker of intermittent hypoxia. Nevertheless, to avoid the bias of chronic hypoxia, patients with respiratory failure or long-term oxygen therapy were excluded from the study. Although we cannot rule out that some patients had mild-to-moderate chronic hypoxia caused by obesity or other diseases,

**TABLE 4. MULTIVARIATE COX REGRESSION ANALYSIS: ASSOCIATION BETWEEN CANCER INCIDENCE AND OSA CATEGORIES, STRATIFIED BY AGE**

OSA Categories	≥65 yr ( <i>n</i> = 1,203)		<65 yr ( <i>n</i> = 3,707)	
	Adjusted HR (95% CI)*	<i>P</i> Value	Adjusted HR (95% CI)*	<i>P</i> Value
AHI, events/h				
AHI (continuous)	0.99 (0.98–1)	0.07	1 (1–1.01)	0.053
AHI categories				
<18.7	1	—	1	—
18.7–43	0.87 (0.55–1.38)	0.57	1.26 (0.79–2.01)	0.32
>43	0.72 (0.44–1.18)	0.202	1.66 (1.04–2.64)	0.032
TSat <sub>90</sub>				
TSat <sub>90</sub> (continuous)	1 (0.99–1.01)	0.35	1.01 (1–1.01)	<0.0005
TSat <sub>90</sub> categories				
<1.2%	1	—	1	—
1.2–12%	1.06 (0.59–1.90)	0.83	1.95 (1.14–3.33)	0.014
>12%	1.60 (0.92–2.78)	0.092	2.95 (1.71–5.09)	<0.0005

*Definition of abbreviations:* AHI = apnea-hypopnea index; CI = confidence interval; HR = hazard ratio; OSA = obstructive sleep apnea; TSat<sub>90</sub> = percent of nighttime spent with oxygen saturation < 90%.

\*Adjusted for age, sex, body mass index, smoking status and use, alcohol intake, type of sleep study, and hospital of enrollment (as random effects).

**TABLE 5. MULTIVARIATE COX REGRESSION ANALYSIS: ASSOCIATION BETWEEN CANCER INCIDENCE AND OSA CATEGORIES, STRATIFIED BY SEX**

OSA Categories	Men (n = 3,276)		Women (n = 1,634)	
	Adjusted HR (95% CI)*	P Value	Adjusted HR (95% CI)*	P Value
AHI, events/h				
AHI (continuous)	1 (0.99–1.01)	0.22	0.99 (0.98–1)	0.25
AHI categories				
<18.7	1	—	1	—
18.7–43	1.25 (0.83–1.90)	0.27	0.89 (0.50–1.57)	0.68
>43	1.45 (0.96–2.20)	0.072	0.67 (0.35–1.30)	0.24
TSat <sub>90</sub>				
TSat <sub>90</sub> (continuous)	1.01 (1–1.01)	<0.0005	0.99 (0.98–1)	0.75
TSat <sub>90</sub> categories				
<1.2%	1	—	1	—
1.2–12%	1.75 (1.08–2.82)	0.022	1.32 (0.66–2.63)	0.42
>12%	2.60 (1.61–4.20)	<0.0005	1.84 (0.88–3.82)	0.101

Definition of abbreviations: AHI = apnea-hypopnea index; CI = confidence interval; HR = hazard ratio; OSA = obstructive sleep apnea; TSat<sub>90</sub> = percent of nighttime spent with oxygen saturation < 90%.

\*Adjusted for age, body mass index, smoking status and use, alcohol intake, type of sleep study, and hospital of enrollment (as random effects).

we believe that most of the overnight hypoxia measured by TSat<sub>90</sub> in our study indirectly reflects intermittent hypoxia derived from OSA. Unfortunately, our study did not have sufficient statistical power for an analysis of OSA with site-specific cancer incidence, because the most common cancer location accounted for only 43 patients. Given that our patients had been studied by means of two different diagnostic methods, this could have influenced the analyses with respect to AHI categories. However, continuous AHI was not associated with cancer incidence, and when we separately assessed the association between AHI and cancer incidence in patients who received RP and PSG, AHI was not associated with increased incidence of cancer in either subsets. Finally, it cannot be ruled out that the lack of association between OSA and cancer incidence in females and patients greater than or equal to 65 years may be attributed to a lack of power to detect these associations, because both subsets included smaller sample sizes compared with the subgroups of males and younger patients, in which this relationship was shown.

In summary, this study suggests an association between OSA severity measured by TSat<sub>90</sub> and incidence of cancer, independently of several known confounding factors, particularly in patients younger than 65 years. Given the characteristics of our study, prospective studies should confirm this association and investigate whether a specific cancer location or cancer subtype is more prone to be associated with this sleep disorder and the potential role of CPAP treatment in this relationship. Future research should also identify which polysomnographic indices (including different oximetric parameters and measures of intermittent hypoxia) best describe this association, and the threshold values associated with an increased risk of cancer. These studies should also assess other potential confounders, such as physical activity, diet and caloric intake, hours of sleep, and others that have not been analyzed in this study because of its retrospective design. Finally, whether women and elderly are really protected against this association should be specifically assessed in studies adequately powered for these subgroups.

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