Accepted Manuscript

Obstructive sleep apnea is associated with cancer mortality in younger patients

Miguel A. Martínez-García, Francisco Campos-Rodriguez, Joaquín Durán-Cantolla, Mónica de la Peña, María J. Masdeu, Mónica González, Félix del Campo, Pablo Catalán Serra, Irene Valero-Sánchez, M.J. Selma Ferrer, José M. Marín, Ferrán Barbé, M. Martínez, Ramón Farré, José M. Montserraton behalf of the Spanish Sleep Network

PII: S1389-9457(14)00094-X
DOI: http://dx.doi.org/10.1016/j.sleep.2014.01.020
Reference: SLEEP 2404

To appear in: *Sleep Medicine*

Received Date: 30 July 2013
Revised Date: 15 January 2014
Accepted Date: 17 January 2014

Please cite this article as: Martínez-García, M.A., Campos-Rodriguez, F., Durán-Cantolla, J., de la Peña, M., Masdeu, M.J., González, M., del Campo, F., Serra, P.C., Valero-Sánchez, I., Selma Ferrer, M.J., Marín, J.M., Barbé, F., Martínez, M., Farré, R., Montserrat, J.M., on behalf of the Spanish Sleep Network Obstructive sleep apnea is associated with cancer mortality in younger patients, *Sleep Medicine* (2014), doi: http://dx.doi.org/10.1016/j.sleep.2014.01.020

Original Article

Obstructive sleep apnea is associated with cancer mortality in younger patients

Miguel A. Martínez-García[a,p], Francisco Campos-Rodriguez[b], Joaquín Durán-Cantolla[c,p], Mónica de la Peña[d,p], María J. Masdeu[e,p], Mónica González[f], Félix del Campo[g,p], Pablo Catalán Serra[h], Irene Valero-Sánchez[a], M.J. Selma Ferrer[a], José M. Marín[i*], Ferrán Barbé[j,p], M. Martínez[k,p], Ramón Farré[m,p], José M. Montserrat[n,p], on behalf of the Spanish Sleep Network

[a]*Respiratory Department, La Fe University and Polytechnic Hospital, Valencia, Spain*

[b]*Respiratory Department, Valme University Hospital, Sevilla, Spain*

[c]*Alava University Hospital, Vitoria, Spain*

[d]*Respiratory Department, Son Espasses University Hospital, Palma de Mallorca, Spain*

[e]*Respiratory Department, Corporació Sanitaria Parc Tauli Hospital, Sabadell, Spain*

[f]*Respiratory Department, Marques de Valdecilla Hospital, Santander, Spain*

[g]*Respiratory Department, Rio Hortega Hospital, Valladolid, Spain*

[h]*Respiratory Unit, Requena General Hospital, Valencia, Spain*

[i]*Respiratory Department, Miguel Servet Hospital, Zaragoza, Spain*

[j]*Respiratory Department, Arnau de Vilanova Hospital, IRB, Lleida, Spain*

[k]*IRB Lleida, Lleida, Spain*

[m]*Facultat de Medicina, Universitat de Barcelona University, IDIBAPS, Spain*

[n]*Respiratory Department, Clinic Hospital–IDIBAPS, Barcelona, Spain*

[p]*CIBER de Enfermedades Respiratorias, Bunyola, Spain*

---

*Corresponding author. Address: Respiratory Department, La Fe University and Polytechnic Hospital, Bulevar Sur s/n, 46013 Valencia, Spain. Tel.: +34 609 86 59 34.

E-mail address: mianmartinezgarcia@gmail.com (M.A. Martínez-García).

ABSTRACT

Objective: The association between obstructive sleep apnea (OSA) and cancer mortality has scarcely been studied. The objective of this study was to investigate whether OSA is associated with increased cancer mortality in a large cohort of patients with OSA suspicion.

Methods: This was a multicenter study in consecutive patients investigated for suspected OSA. OSA severity was measured by the apnea–hypopnea index (AHI) and the hypoxemia index (% night-time spent with oxygen saturation <90%, $TSat_{90}$). The association between OSA severity and cancer mortality was assessed using Cox's proportional regression analyses after adjusting for relevant confounders.

Results: In all, 5427 patients with median follow-up of 4.5 years were included. Of these, 527 (9.7%) were diagnosed with cancer. Log-transformed $TSat_{90}$ was independently associated with increased cancer mortality in the entire cohort (hazard ratio [HR], 1.21; 95% confidence interval [CI], 1.03–1.42), as well as in the group of patients with cancer (HR, 1.19; 95% CI, 1.02–1.41). The closest association was shown in patients <65 years in both the AHI (continuous log-transformed AHI, HR, 1.87; 95% CI, 1.1–3.2; upper vs lower AHI tertile, HR, 3.98; 95% CI, 1.14–3.64) and the $TSat_{90}$ (continuous log-transformed $TSat_{90}$: HR, 1.73; 95% CI, 1.23–2.4; upper vs lower $TSat_{90}$ tertile: HR, 14.4; 95% CI, 1.85–111.6).
Conclusions: OSA severity was associated with increased cancer mortality, particularly in patients aged <65 years.

Keywords:
Sleep apnea
Sleep-disordered breathing
Cancer
Mortality
Intermittent hypoxemia

1. Introduction

Obstructive sleep apnea (OSA) is characterized by repetitive episodes of partial or total obstruction of airflow, causing intermittent oxygen desaturation and sleep disruption [1–8]. Intermittent hypoxia (IH) is a hallmark of OSA severity and results in considerable injury at cell level [9]. IH has been associated with the overexpression of oxidative stress and inflammatory transcription factors, which are potentially involved in de-novo carcinogenesis, accelerated tumor growth, and increased resistance to treatments [9–14]. It is therefore biologically plausible to anticipate an association between OSA and cancer incidence and mortality [15,16]. Accordingly, Almendros et al. recently observed in an animal model of melanoma that mice subjected to an IH pattern mimicking OSA presented increased tumor growth rate [17] and metastasis to the lung [18], compared with normoxic controls. Along the same lines, our research group has recently reported greater cancer incidence in OSA patients with increased overnight hypoxia [19].

The only study that has previously addressed the association between OSA and cancer mortality in humans is based on the analysis of the Wisconsin Sleep Cohort – a community-based sample – which found a positive relationship between OSA and increased mortality from cancer [20]. Nevertheless, to the best of our knowledge, the association between OSA and cancer mortality in a large clinical cohort has so far not been analyzed. Given the potential clinical impact of such an association – both in terms of prognosis and therapy – the

aim of our study was to analyze the relationship between cancer mortality and the severity of OSA in a large sample of patients suspected of suffering from this sleep-disordered breathing.

2. Methods

2.1. Design and participants

This was a multicenter, longitudinal, retrospective cohort study in consecutive patients aged >18 years included in the databases of seven Spanish Sleep Units who had been assessed for suspected OSA between 2000 and 2007. We excluded patients with chronic respiratory failure (defined as chronic oxygen saturation <90% while breathing room air or prescribed domiciliary oxygen) or lack of available data on cancer, vital status or sleep study. The ethics committee of each center approved the study.

2.2. Data collection

All baseline variables were obtained from medical records and computerized databases in all the centers, and they were systematically recorded using a standardized protocol. The following baseline variables were assessed: age (years), body mass index (kg/m^2, BMI), sex, enrolment hospital, alcohol intake (g/day) and smoking habit (pack-years). The following variables related to the sleep study and treatment were also recorded: type of diagnostic sleep study – full polysomnography (PSG) or respiratory polygraphy (RP) – apnea–hypopnea index (AHI), hypoxemia index (night-time spent with oxygen saturation <90%, $TSat_{90}$) and continuous positive airway pressure (CPAP) prescription and compliance.

2.3. Sleep study and CPAP treatment

All patients underwent a diagnostic sleep study, either full standard PSG or RP, with a validated device, following the Spanish Society of Pneumology and Thoracic Surgery and standard guidelines for OSA diagnosis and treatment [21,22]. All the patients undergoing RP with recording artifacts, or presenting any discrepancy between the RP results and the clinical suspicion of OSA, a predominance of central events, or a subjective sleep time of <3 h, went on to have a full PSG. All the sleep test data were recorded manually by trained personnel. Apnea, hypopnea and AHI were defined following standard guidelines [21]; $TSat_{90}$ was defined as the percentage of night-time with arterial oxygen saturation (SaO_2) <90%. CPAP was titrated in the sleep laboratory on a second night by either full standard PSG or an autotitrating CPAP device. Adherence to CPAP was objectively assessed by the time counter on the device, from the start of treatment to the end of the follow-up.

2.4. Main endpoint of the study

The study's main endpoint was all-type cancer mortality. The follow-up finished on December 31, 2010. The presence of cancer and vital status was thoroughly assessed by using multiple concurrent approaches, which included: cancer and pathology registries, a review of

hospital and outpatient medical records, computerized databases and, when necessary, contact with the primary care physician in charge of the patient. When a participant died, information about the cause and date of death was obtained from the hospital medical records, if the patient died in the hospital, or from official death certificates in other cases.

2.5. Statistical analysis

The SPSS 19.0 package (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. Continuous variables are expressed as mean and standard deviation or median and interquartile range (IQR). Qualitative variables are indicated as absolute values and percentages. Normality in the distribution of variables was assessed by using the Kolmogorov–Smirnov test. Patients who did not die from cancer were censored at the date of death from any cause, date of last contact or end of follow-up, whichever occurred first. OSA severity was measured using $TSat_{90}$ and AHI, both as continuous variables and as tertiles, the lower category being the reference group. Moreover AHI was also measured as usual groups of severity (AHI <5, no OSA; AHI 5–14.9, mild OSA; AHI 15–29.9, moderate OSA; AHI ≥30, severe OSA). Since AHI and $TSat_{90}$ did not follow a normal distribution a log-transform method was used to analyse these variables as continuous. The baseline differences between the categorized groups were analyzed using the one-way analysis of variance test with Bonferroni correction in case of normal distribution, or the non-parametric Kruskal–Wallis test in that of non-normal distribution. The χ^2-test or Fisher exact test was used, as appropriate, to compare qualitative variables. Multiple imputation by chained equations was used in the case of missing values of BMI, $TSat_{90}$, alcohol intake or smoking habit as continuous variables, generating a high number of 50 imputations per missing value in order to minimize the inherent simulation error.

Cumulative cancer mortality for each OSA category was calculated using the Kaplan–Meier method, and mortality curves were compared with the log-rank test. Association between cancer mortality and OSA severity was estimated using Cox proportional hazard regression models, with adjustment for the following potential confounders of clinical interest: age, sex, BMI, smoking status, alcohol intake, type of sleep study, and enrolment hospital (the latter included as a random effect). The results were expressed as hazard ratio (HR) and 95% confidence interval (CI).

To assess the effect of sex, CPAP treatment and age (dichotomized into <65 and ≥65 years) on the association of OSA with cancer mortality, additional subgroup analyses were performed. Moreover, given that, hypothetically, increased cancer mortality may be attributed to a greater cancer rate, a sensitivity analysis was performed with only patients diagnosed with cancer. The beginning of the time scale was the date of cancer diagnosis. A patient was

considered untreated if he/she did not receive active treatment or showed persistent bad compliance with CPAP (cumulative objective use <4 h/day or CPAP dropout). $P < 0.05$ was considered statistically significant.

3. Results

The initial analysis cohort included 5578 patients with clinical suspicion of OSA (Fig. 1). After applying the exclusion criteria, 5427 (97.5%) were included for analyses. Median age was 53.9 (13.1) years, and 22.2% were aged >65 years. Median (interquartile range [IQR]) AHI was 30 (14–52). CPAP was prescribed in 40.7% of patients. Data on $TSat_{90}$ were available in 5131 patients (94.5%); 65.9% of patients underwent RP and 34.1% full PSG.

Table 1 shows the main baseline characteristics between groups, divided into AHI tertiles. As expected, older age, male sex, and BMI were associated with increased OSA severity. Moreover, alcohol intake and smoking habit were also associated with increased OSA severity.

Median follow-up was 4.5 (IQR: 3.6–5.6) years (25,079.75 person-years). In all, 527 patients either received a diagnosis of cancer or had a prior history of cancer (9.7%). There were 369 all-cause deaths over the course of the study (6.8%) and 90 patients died from cancer (24.4% of deaths). The most frequent location sites of mortal cancers are shown in Table 2, according to sex and age.

Cumulative cancer mortality increased across $TSat_{90}$ categories (Fig. 2A) but no differences were found across AHI tertiles or severity categories (Fig. 2B). However, compared to the lower category, the fully adjusted HR (95% CI) of cancer mortality for the upper $TSat_{90}$ category ($TSat_{90}$ >13%) in the Cox regression analysis was 2.06 (1.72–4.58; P = 0.0001). A significant fully adjusted increase in mortality risk was also observed with increasing log-transformed $TSat_{90}$ as a quantitative variable (1.21 [1.03–1.42]; P = 0.019; Table 3). AHI categories were not associated with cancer mortality (Table 3).

3.1. Untreated patient analysis

When an additional analysis was run with only untreated patients, the association between cancer mortality and $TSat_{90}$ did not change significantly. AHI was not associated with cancer mortality in the adjusted analysis (Table 3).

3.2. Age and sex analyses

Statistically significant interactions were found between age (dichotomized into <65 and ≥65 years) and both AHI (P = 0.002) and $TSat_{90}$ (P = 0.031) and between sex and $TSat_{90}$ (P = 0.043). When stratified analyses were run, cancer mortality was associated in patients aged <65 years with both $TSat_{90}$ and AHI categories, as well as with $TSat_{90}$ and AHI

considered as log-transformed continuous variables (Table 4); and in men, $TSat_{90}$, categorized in tertiles as well as in linear terms, was associated with cancer mortality (Table 5).

3.3. Analysis of patients with a cancer diagnosis

When we analyzed the group of 527 patients with a diagnosis of cancer, only $TSat_{90}$ as a log-transformed continuous variable was significantly associated with cancer mortality after adjusting for confounders (HR, 1.19; 95% CI, 1.02–1.41; $P = 0.021$; Table 6). However, in patients aged <65 years, OSA severity measured by both AHI and $TSat_{90}$ was independently associated with increased mortality from cancer (Table 7).

4. Discussion

To our knowledge this is the first study in the literature to analyze the association between OSA and cancer mortality in a large clinical cohort. We have found that OSA severity measured by overnight hypoxia was associated with increased cancer mortality. The closest association was seen, however, in patients aged <65 years. These results were replicated in the group of patients with a diagnosis of cancer.

Intermittent hypoxia is one of the most specific landmarks of OSA and plays an important role in regulating tumor formation and progression. HIF-1 activates the transcription of genes that play critical roles in angiogenesis, stress oxidative response, genetic instability, immune evasion, metabolic reprogramming, invasion and metastasis, radiation resistance and stem-cell maintenance, as well as the faster spread of cancer [9–14,23–25]. Experimental studies in a mouse model of melanoma have shown that intermittent hypoxia similar to that found in OSA enhances tumor growth and metastasis and also worsens cancer outcome [17,18]. Only one previous study has addressed this topic in humans. Nieto et al. [20] analyzed 1522 subjects in a 22-year follow-up population-based study from the Wisconsin Sleep Cohort, reporting a significant increase in the probability of death from cancer in patients with severe OSA. Whether this finding reflects a more aggressive behavior of cancer in OSA patients can only be indirectly inferred, however, as the authors themselves and an editorial in this journal have acknowledged [20,25]. Since the study does not supply data on cancer diagnosis, it cannot be ruled out that this increase in cancer death was simply due to a higher cancer rate, as reported in a recent study [19].

In our large cohort investigated for suspicion of OSA, we found that overnight hypoxia was independently associated with increased cancer mortality. These findings concur with those of the Wisconsin study [20], where the association between cancer mortality and OSA severity was stronger when the time spent with oxygen saturation <90% (the same oximetric parameter used in our study) was used as a surrogate of OSA severity.

The most especially relevant finding of our study, however, was that the association between OSA and mortality from cancer seems to be limited to younger patients. In our study, patients aged <65 years with an AHI >44.5 had a four-fold greater adjusted risk of cancer mortality, compared with those with an AHI <19.1, and this risk was greater when oximetric parameters were considered. The significant association between both continuous AHI and $TSat_{90}$ and mortality suggests that cancer mortality increases with OSA severity.

Given that in our study we knew which patients had had a prior history of cancer or had developed an incident cancer during the follow-up, we had the unique opportunity to assess cancer mortality in this subgroup of 527 patients. This sensitivity analysis replicated the results of the entire cohort. These data suggest that in our study increased cancer mortality in younger patients with OSA cannot be attributed only to higher cancer incidence but also probably to more aggressive tumor behaviour.

The reasons why OSA may increase mortality from cancer in younger, but not in elderly, patients are unclear. Although this lack of association found in our study should be interpreted cautiously because of its methodological limitations, this result concurs to a certain extent with a very recent study by Christensen et al. using the Copenhagen City Heart study, comprising more than 8000 patients with a follow-up of 13 years. They found that daytime hypersomnia was associated with a nearly five-fold cancer risk only among younger individuals (aged <50 years) although caution should be taken in the comparison between these studies because the different average age [27]. One possible explanation for the presence of this association only in younger patients is the ischemic preconditioning hypothesis, which was pre-established in a cardiovascular context but could also play a role in older patients suffering from cancer [28]. Accordingly, older survivors with a long-term intermittent hypoxia challenge could develop some compensatory mechanisms to counteract intermittent tissue hypoxia, resulting in a lower mortality from cancer, although this hypothesis has yet to be proved. Another explanation might be that, at older ages, relative risks observed for risk factors and outcomes are almost universally smaller that at younger ages by the effect of aging itself.

It is worth noting that when patients with good adherence to CPAP treatment were excluded from the analysis, the association between OSA severity and cancer mortality became more intense, opening up the possibility of a protective effect derived from CPAP. A similar finding was reported by Nieto et al. [20] in their analysis of the Wisconsin Sleep Cohort. Nevertheless, this parameter was not the main outcome in either of these studies; accordingly, the results related to CPAP treatment must be interpreted with caution and investigated by specific research.

The main strengths of our study include the fact that it is the first in the literature to investigate the association between OSA and cancer mortality in a large, clinical multicenter cohort comprising more than 5000 patients. In this respect, almost no data on cancer were lost since both cancer diagnosis and causes of mortality were thoroughly investigated by means of several concurrent approaches. Furthermore, as the presence of either a history of prior cancer or the occurrence of a new cancer during the follow-up were thoroughly traced, we had the possibility to investigate cancer mortality in a subgroup of patients with cancer, in order to exclude the bias of increased mortality being simply due to a higher cancer rate. This clinical series has the advantage of their clinical application since the patients included in this study are representative of the type of patients usually referred to a sleep laboratory.

It is important, however, to mention the limitations of the study. First, the retrospective design of our study means that some relevant variables in cancer mortality (e.g. lifestyle, hours of sleep, nutrition, physical activity, cancer treatments or cancer stages) were not collected, so we cannot rule out their influence on the conclusions of the study. Nevertheless, the most relevant confounders with respect to cancer mortality, such as tobacco use, alcohol intake, obesity, sex, and age, were used in the analyses. Second, we did not use a direct measure of intermittent hypoxia, such as the desaturation index, but rather used a marker of hypoxia (both intermittent and chronic), night-time spent with 90% desaturation. To minimize this potential bias, however, all patients with respiratory failure (room-air oxygen saturation <90%) were excluded from the study. Third, some of our patients were diagnosed by RP and this could have influenced the analyses with respect to AHI categories, especially in mild OSA. To overcome this limitation, we included the type of study as an adjusted variable and conducted a sensitivity analysis by separately assessing the association between AHI and cancer mortality in patients who underwent RP or PSG. AHI, either as categorized or as a continuous variable, was not associated with increased mortality of cancer in the adjusted models in either of these subsets (data not shown). Fourth, because of the retrospective nature of the study and the inclusion of both prevalent and incident cancers over the time of sleep study in the analysis of the subgroup of patients with cancer, we did not know the number and severity of sleep-disordered breathing at the time of cancer diagnosis. Finally, since the present study refers to a clinical series, its conclusions may not apply to the general population.

In conclusion, the results of this study on our clinical series suggest a positive association between OSA severity and increased cancer mortality limited to patients aged <65 years, whereas no association was shown in women and elderly patients. Further prospective studies are needed, not only to confirm our results but also to establish the role of other

confounders not recorded in the present study. It is also important to investigate the role of the histological classification and organ location of the malignant tumors, as well as the potential effect of CPAP treatment on this association.

Conflicts of interest

None declared.

Funding source

(058/2011) Spanish Respiratory Society (SEPAR).

References

1. Shamsuzzaman AS, Gersh BJ, Somers VK. Obstructive sleep apnea: implications for cardiac and vascular disease. JAMA 2003;290:1906–14.
2. Barbé F, Durán-Cantolla J, Sánchez de la Torre M, Martínez-Alonso M, Carmona C, Barceló A, et al. Effect of continuous positive airway pressure on the incidence of hypertension and cardiovascular events in nonsleepy patients with obstructive sleep apnea: a randomized controlled trial. JAMA 2012;307:2161–8.
3. Marín JM, Carrizo SJ, Vicente E, Agustí AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea–hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet 2005;365:1046–53.
4. Durán-Cantolla J, Aizpuru F, Montserrat JM, Ballester E, Terán-Santos J, Aguirregomoscorta JI, et al. Continuous positive airway pressure as a treatment for systemic hypertension in subjects with obstructive sleep apnoea: randomised controlled trial. BMJ 2010;341:c5991.
5. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993;328:1230–6.
6. Durán J, Esnaola S, Rubio R, Iztueta A. Obstructive sleep apnea–hypopnea and related clinical features in a population-base sample of subjects aged 30 to 70 yr. Am J Respir Crit Care Med 2001;163:685–9.
7. Tufik S, Santos-Silva R, Taddei JA, Bittencourt LR. Obstructive sleep apnea syndrome in the Sao Paulo Epidemiologic Sleep Study. Sleep Med 2010;11:441–6.
8. Phillipson EA. Sleep apnea – a major public health problem. N Engl J Med 1993;328:1271–3.
9. Levy P, Pépin JL, Arnau C, Tamisier R, Borel JC, Dematteis M, et al. Intermittent hypoxia and sleep-disordered breathing: current concepts and perspectives. Eur Respir J 2008;32:1082–95.
10. Toffoli S, Michiels C. Intermittent hypoxia is a key regulator of cancer cell and endothelial cell interplay in tumours. FEBS J 2008;275:2991–3002.

11. Semenza GL. Oxygen sensing, homeostasis and disease. N Engl J Med 2011;365:537–47.
12. Reuter S, Gupta SC, Chaturvedi MM. Oxidative stress, inflammation, and cancer: how are they linked? Free Rad Biol Med 2010;49:1603–16.
13. Hursting SD, Hursting MJ. Growth signals, inflammation, and vascular perturbations. Mechanistic links between obesity, metabolic syndrome and cancer. Arterioscler Thromb Vasc Biol 2012;32:1766–70.
14. Dewhirst MW. Intermittent hypoxia furthers the rationale for hypoxia-inducible factor-1 targeting. Cancer Res 2007;67:854–5.
15. Nozoe KT, Tufik S, Andersen ML. Is sleep related to cancer in murine models of obstructive sleep disorder? Eur Respir J 2012;39:1051.
16. Martínez-García MA, Campos-Rodriguez F, Farré F. Sleep apnoea and cancer: current insights and future perspectives. Eur Resp J 2012;40:1315–17.
17. Almendros I, Montserrat JM, Ramírez J, Torres M, Duran-Cantolla J, Navajas D, Farré R. Intermittent hypoxia enhances cancer progression in a mouse model of sleep apnea. Eur Respir J 2012;39:215–17.
18. Almendros I, Montserrat JM, Torres M, et al. Intermittent hypoxia increases melanoma metastasis to the lung in a mouse model of sleep apnea. Respir Physiol Neurobiol 2013;186:303–7.
19. Campos-Rodríguez F, Martínez-García MA, Martínez M, Duran-Cantolla J, Peña Mde L, Masdeu MJ, et al. Association between obstructive sleep apnea and cancer incidence in a large multicenter Spanish cohort. Am Respir J Crit Care Med 2013;1:99–105.
20. Nieto FJ, Peppard PE, Young T, Finn L, Hla KM, Farré R. Sleep-disordered breathing and cancer mortality: results from the Wisconsin Sleep Cohort Study. Am J Respir Crit Care Med 2012;186:190–4.
21. Montserrat JM, Amilibia J, Barbé F, Capote F, Durán J, Mangado NG, et al. Treatment of sleep apnea–hypoapnea syndrome. Arch Bronconeumol 1998;34:204–6.
22. Rechtschaffen A, Kales A. A manual of standardized terminology and scoring system for sleep stages of human subjects. Los Angeles: Brain Information Service/Brain Research Institute, University of California at Los Angeles; 1968.
23. Rofstad EK, Gaustad JV, Egeland TAM, Mathiesen B, Galappathi K. Tumors exposed to acute cyclic hypoxic stress show enhanced angiogenesis, perfusion and metastatic dissemination. Int J Cancer 2010;127:1535–46.
24. Carmeliet P, Dor Y, Herbert JM, Fukumura D, Brusselmans K, Dewerchin M, et al. Role of HIF-1alpha in hypoxia-mediated apoptosis, cell proliferation and tumour angiogenesis. Nature 1998;394:485–90.

25. Wouters A, Pauwels B, Lardon F, Vermorken JB. Review: Implications of in vitro research on the effect of radiotherapy and chemotherapy under hypoxic conditions. Oncologist 2007;12:690–712.
26. Redline S, Quan SF. Sleep apnea: a common mechanism for the deadly triad – cardiovascular disease, diabetes, and cancer? Am J Respir Crit Care Med 2012;186:123–4.
27. Christensen AS, Clark A, Salo P, Nymann P, Lange P, Prescott E, Rod NH. Symptoms of sleep-disordered breathing and risk of cancer: a prospective cohort study. Sleep 2013;36:1429–35.
28. Lavie L, Lavie P. Ischemic preconditioning as a possible explanation for the age decline relative mortality in sleep apnea. Med Hypoth 2006;66:1069–73.

Table 1

Baseline characteristics of the sample, according to AHI categories.

Variables	AHI <19.1 (n = 1830)	AHI 19.1–44.5 (n = 1807)	AHI >44.5 (n = 1790)
Age (years)*	51.4 (13.4)	56.5 (12.5)	57.7 (12.6)
Age >65 years*	333 (18.2)	523 (28.9)	613 (34.2)
Male sex*	1018 (55.3)	1243 (68.4)	1274 (70.5)
BMI (kg/m^2)*	30.8 (6.1)	32.1 (5.9)	34.8 (6.6)
Obesity (BMI ≥30)*	1066 (57.9)	1249 (68.7)	1500 (83.1)
Smoking (pack-years)*	12.8 (20.4)	15.2 (21.9)	18.7 (26.1)
Alcohol intake (g/day)*	7.1 (19.8)	8.7 (21.6)	11.5 (24.2)
AHI*	9 (4.6–14.1)	30.3 (24.6–36.9)	63.9 (53–78)
$TSat_{90}$*	0.5 (0–4)	5 (1–14)	19 (7–42.9)
PSG study*	792 (43)	594 (32.7)	485 (23.8)

AHI, apnea–hypopnea index; BMI, body mass index; $TSat_{90}$, night-time spent with an oxygen saturation of hemoglobin <90%; PSG, polysomnography study.

Continuous variables presented as mean (standard deviation) except for AHI and $TSat_{90}$ as median (interquartile range) and qualitative as absolute number (percentage).

Median values for alcohol intake and smoking are presented for those patients who drank alcohol and smoked.

*P < 0.005 for comparison of age, age >65 years, sex, BMI, BMI >30, smoking use, alcohol intake, AHI, $TSat_{90}$ (night-time spent with oxygen saturation <90%), male sex, polysomnography, and obesity across groups.

Table 2

Location of mortal cancers in the whole group, and according to the different subgroups studied.

Location	Total deaths from cancer	Deaths from cancer in subgroups studied			
		Age <65 years		Age ≥65 years	
		Men	Women	Men	Women
Respiratory tract	24	9	15	23	1
Gastrointestinal tract	20	6	14	12	8
Urinary tract	6	0	6	4	2
Breast	6	2	4	0	6
Prostate	6	1	5	6	0
Hepatobiliar	5	2	3	4	1
Brain	4	1	3	5	1
Pancreatic	3	0	3	2	1
Genital tract	3	1	2	0	3
Thyroid	3	0	3	2	0
Skin melanoma	2	0	2	2	0
Hematological	1	1	0	1	0
Others	7	2	5	6	1
Total	90	25	65	66	24

Gastrointestinal tract includes esophageal, stomach and colorectal; respiratory tract includes lungs and airway; hepatobiliar includes liver and gallbladder; hematological includes one leukemia; skin includes melanoma; urinary includes kidney, ureter and bladder; genital tract includes testicles, ovary and endometrium.

Table 3

Association between cancer mortality and AHI and hypoxemia index categories.[a]

Obstructive sleep apnea categories	Entire cohort (n = 5427) (90 deaths)		Untreated patients (n = 3219) (51 deaths)	
	Adjusted HR (95% CI)[b]	P-value	Adjusted HR (95% CI)[b]	P-value
AHI (events/h)				
Log_{10} AHI (continuous)	0.98 (0.77–1.26)	0.87	0.98 (0.70–1.31)	0.87
AHI categories (tertiles)				
<19.1	1	–	1	–
19.1–44.5	0.84 (0.46–1.54)	0.58	0.62 (0.29–1.37)	0.23
>44.5	0.97 (0.55–1.73)	0.92	0.96 (0.46–2.00)	0.96
AHI categories				
<5	1	–	1	–
5–14.9	0.71 (0.21–1.87)	0.54	0.48 (0.13–1.53)	0.33
15–29.9	0.77 (0.35–1.74)	0.63	0.51 (0.16–1.44)	0.34
≥30	0.99 (0.43–1.9)	0.77	0.98 (0.41–2.21)	0.88
Hypoxemia index, $TSat_{90}$				
Log_{10} $TSat_{90}$ (continuous)	1.21 (1.03–1.42)	0.019	1.27 (1.02–1.51)	0.03
$TSat_{90}$ categories				
<1.2%	1	–	1	–
1.2%–13%	1.61 (0.79–3.25)	0.19	1.77 (0.72–4.37)	0.22
>13%	2.06 (1.72–4.58)	0.001	2.53 (1.03–6.20)	0.043

AHI, apnea–hypopnea index; HR, hazard ratio; CI, confidence interval; $TSat_{90}$, % time <90% saturation.

AHI and $TSat_{90}$ as continuous variables were log-transformed (log_{10} AHI and log_{10} $TSat_{90}$).

[a]Multivariate Cox regression analyses.

[b]Adjusted for: age, sex, body mass index, smoking status and use, alcohol intake, type of sleep study, and enrolment hospital.

Table 4

Association between cancer mortality and AHI and hypoxemia index categories, stratified by age.[a]

Obstructive sleep apnea categories	Age ≥65 years (n = 1469) (64 deaths)		Age <65 years (n = 3958) (26 deaths)	
	Adjusted HR (95% CI)[b]	*P*-value	Adjusted HR (95% CI)[b]	*P*-value
AHI (events/h)				
Log_{10} AHI (continuous)	0.81 (0.63–1.06)	0.13	1.87 (1.1–3.2)	0.02
AHI categories				
<19.1	1		1	
19.1–44.5	0.62 (0.85–3.10)	0.15	2.75 (0.73–10.4)	0.14
>44.5	0.94 (0.50–1.78)	0.86	3.98 (1.14–3.64)	0.033
Hypoxemia index, $TSat_{90}$				
Log_{10} $TSat_{90}$ (continuous)	1.06 (0.87–1.29)	0.57	1.73 (1.23–2.4)	0.002
$TSat_{90}$ categories				
<1.2%	1		1	
1.2–13%	0.99 (0.46–5.15)	0.99	7.63 (1.02–61.4)	0.04
>13%	1.08 (0.51–2.30)	0.83	14.4 (1.86–111.6)	0.01

AHI, apnea–hypopnea index; HR, hazard ratio; CI, confidence interval; $TSat_{90}$, % time <90% saturation.

[a]Multivariate Cox regression analyses.

[a]Adjusted for: age, sex, body mass index, smoking status and use and alcohol intake.

Table 5

Association between cancer mortality and AHI and hypoxemia index categories, stratified by sex.[a]

AHI, apnea–hypopnea index; HR, hazard ratio; CI, confidence interval; $TSat_{90}$, % time <90% saturation.

Obstructive sleep apnea categories	Men (n = 3525) (66 deaths)		Women (n = 1902) (24 deaths)	
	Adjusted HR (95% CI)[b]	*P*-value	Adjusted HR (95% CI)[b]	*P*-value
AHI (events/h)				
Log_{10} AHI (continuous)	0.95 (0.71–1.27)	0.75	0.98 (0.61–1.56)	0.95
AHI categories				
<19.1	1		1	
19.1–44.5	0.75 (0.89–1.79)	0.74	0.60 (0.17–2.08)	0.60
>44.5	0.87 (0.44–1.73)	0.69	1.23 (0.43–3.50)	0.70
Hypoxemia index, $TSat_{90}$				
Log_{10} $TSat_{90}$ (continuous)	1.27 (1.02–1.57)	0.03	1.07 (0.78–1.48)	0.7
$TSat_{90}$ categories				
<1.2%	1		1	
1.2–13%	1.20 (0.54–2.71)	0.65	3.25 (0.68–15.7)	0.14
>13%	1.92 (1.05–4.07)	0.023	2.00 (0.36–11.00)	0.43

[a]Multivariate Cox regression analyses.

[b]Adjusted for: age, body mass index, smoking status and alcohol intake.

Table 6

Association between cancer mortality and AHI and hypoxemia index categories in patients diagnosed with cancer.[a]

Obstructive sleep apnea severity measures	Patients diagnosed by cancer (n = 527) (90 deaths)	
	Adjusted HR (95% CI)[b]	P-value
Log_{10} AHI (continuous)	0.95 (0.75–1.20)	0.69
AHI categories (tertiles)		
<19.1	1	
19.1–44.5	0.77 (0.42–1.43)	0.41
>44.5	0.82 (0.45–1.48)	0.51
AHI categories		
<5	1	
5–14.9	0.71 (0.38–1.76)	0.36
15–29.9	0.79 (0.44–1.56)	0.44
≥30	0.81 (0.44–1.57)	0.63
Log_{10} $TSat_{90}$ (continuous)	1.19 (1.02–1.4)	0.021
$TSat_{90}$ categories		
<1.2%	1	
1.2–13%	1.68 (0.8–3.5)	0.17
>13%	1.67 (0.28–3.57)	0.19

AHI, apnea–hypopnea index; HR, hazard ratio; CI, confidence interval; $TSat_{90}$, % time <90% saturation.

Adjusted for: age, sex, body mass index, smoking status and use, alcohol intake, type of sleep study and enrolment hospital.

[a]Multivariate Cox regression analysis.

Table 7

Association between cancer mortality and AHI and hypoxemia index categories, stratified by sex and sex in patients diagnosed with cancer.[a]

Obstructive sleep apnea severity measures	Age ≥65 years (*n* = 264) 28 deaths		Age <65 years (*n* = 263) 62 deaths		Men (*n* = 358) 63 deaths		Women (*n* = 169) 27 deaths	
	Adjusted HR (95% CI)[b]	*P*-value	Adjusted HR (95% CI)[b]	*P*-value	Adjusted HR (95% CI)[b]	*P*-value	Adjusted HR (95% CI)[b]	*P*-value
Log_{10} AHI (continuous)	0.78 (0.59–1.02)	0.12	1.62 (1.08–2.4)	0.021	0.98 (0.7–1.3)	0.86	1.13 (0.78–1.01)	0.52
AHI categories								
<19.1	1	–	1	–	1	–	1	–
19.1–44.5	0.68 (0.3–1.39)	0.28	2.02 (0.5–8.01)	0.32	0.82 (0.4–1.7)	0.59	0.75 (0.2–2.9)	0.68
44.5	0.59 (0.3–1.17)	0.13	3.7 (1.05–13.2)	0.019	0.73 (0.36–1.46)	0.37	1.29 (0.99–1.77)	0.11
Log_{10} $TSat_{90}$ (continuous)	1.03 (0.84–1.28)	0.75	1.79 (1.05–3.35)	0.019	1.15 (0.96–1.37)	0.13	1.29 (0.99–1.77)	0.11
$TSat_{90}$ categories								
<1.2%	1	–	1	–	1	–	1	–
1.2–13%	1.12 (0.5–2.5)	0.78	8.59 (1.1–68.8)	0.043	1.45 (0.6–3.4)	0.4	2.71 (0.46–15.8)	0.27
>13%	0.99 (0.45–2.2)	0.99	12.8 (1.6–104.8)	0.017	1.78 (0.77–4.12)	0.18	1.43 (0.19–10.47)	0.22

AHI, apnea–hypopnea index; HR, hazard ratio; CI, confidence interval; $TSat_{90}$, % time <90% saturation.

[a]Multivariate Cox regression analyses.

[b]Adjusted for: age, sex, body mass index, smoking status and alcohol intake.

Fig. 1. Flow chart of the study. OSA, obstructive sleep apnea; IQR, interquartile range.

Fig. 2. Kaplan–Meier curves. Cumulative cancer mortality, with respect to (A) hypoxemia index (% time <90% saturation, $TSat_{90}$; log-rank test, 22.27; $P < 0.0001$) and (B) and apnea–hypopnea index (AHI; log-rank test, 3.16; $P = 0.12$).

[Fig. 2: Typesetter, please transpose labelling of panels A and B.]

Author queries

1. Table 1 footnote, 'and qualitative as absolute number (percentage)': please clarify which values are numbers (percentages) in table – the wording currently does not seem clear.
2. Please check column subheadings for Table 2 (cf. original).
3. References 14–28 have been renumbered – please check (9 and 14 duplicated in original document).

Figure 1

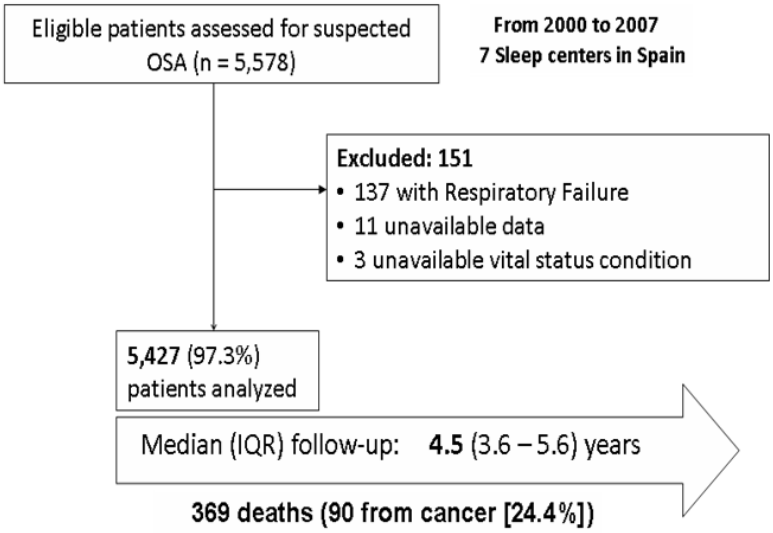

Figure 2A

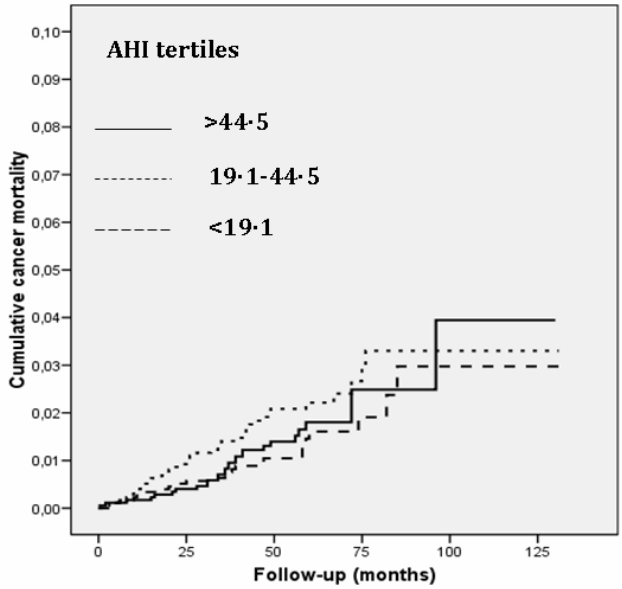

Figure 2B