CHEST

Cancer and OSA
Current Evidence From Human Studies

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Despite the undeniable medical advances achieved in recent decades, cancer remains one of the main causes of mortality. It is thus extremely important to make every effort to discover new risk factors for this disease, particularly ones that can be treated or modified. Various pathophysiologic pathways have been postulated as possible causes of cancer or its increased aggressiveness, and also of greater resistance to antitumoral treatment, in the presence of both intermittent hypoxia and sleep fragmentation (both inherent to sleep apnea). Thus far, these biological hypotheses have been supported by various experimental studies in animals. Meanwhile, recent human studies drawing on preexisting databases have observed an increase in cancer incidence and mortality in patients with a greater severity of sleep-disordered breathing. However, the methodologic limitations of these studies (which are mostly retrospective and lack any measurement of direct markers of intermittent hypoxia or sleep fragmentation) highlight the need for controlled, prospective studies that would provide stronger scientific evidence regarding the existence of this association and its main characteristics, as well as explore its nature and origin in greater depth. The great epidemiologic impact of both cancer and sleep apnea and the potential for clinical treatment make this field of research an exciting challenge.

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Two of the cornerstone pathophysiologic characteristics of OSA are intermittent hypoxia and sleep fragmentation, which are produced by intermittent sleep-related respiratory events (particularly apnea and hypopnea) and their consequences. Both phenomena have been imputed, from a pathophysiologic standpoint, as having carcinogenic properties, as well as inducing more aggressive cancer and resistance to the treatment of a preexisting tumor.[1,2] Although the relationship between intermittent hypoxia (as well as chronic hypoxia) and the production of carcinogenic molecules has been well known for several decades,[3] other pathophysiologic routes (eg, those associated with the immune system and the sympathetic system) are still being investigated today. Excellent reviews of all these topics have recently been published.[4-6]

ABBREVIATIONS: AHI = apnea-hypopnea index; HR = hazard ratio; ODI = oxygen desaturation index; Tsat90% = nighttime spent with oxygen saturation < 90%

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In addition, there is growing interest in evaluating whether the current pathophysiologic hypotheses are reflected by any real clinical increase in the incidence of cancer or in cancer-related deaths. Many of the initial studies along these lines in animals did indeed show that the induction of sleep fragmentation and intermittent hypoxia (simulating OSA in humans) triggered increased tumoral growth and a higher probability of metastasis after the injection of tumoral cells.[7-11] These positive results, supporting the prevailing pathophysiologic hypotheses, encouraged the scientific community to continue research in this area. Accordingly, the last few years have seen a proliferation of both clinical and population-based studies in humans.[12-21] There has even been one meta-analysis of these studies,[22] along with obvious interest from the scientific community, as evident from various editorials published in high-impact journals.[23-28] This attention has occurred despite the fact that the methodology of the studies conducted to date was not ideal, as these were reviews of clinical databases or records of members of the general population initially created for other purposes.

The present review analyzes the studies published to date on humans with respect to the relationship between cancer and sleep-disordered breathing (Table 1), as well as their limitations (Table 2). It also explores ongoing studies that may shed light on the relationship, in addition to other challenges that need to be addressed by future studies on this topic.

Cancer in Patients With OSA

Cancer Incidence in Patients With OSA

The first study in humans to reveal a possible association between the presence of OSA and an increased incidence of cancer was published by the Spanish Sleep Network in 2013 (Fig 1).[12] This multicenter, retrospective study involved a clinical cohort of 4,910 participants with no history of cancer or respiratory failure. They were assessed for suspicion of OSA and followed up for an average of 4.5 years. OSA was diagnosed by using full polysomnography or respiratory polygraphy, following Spanish national guidelines. After adjusting for important confounding variables, a higher incidence of all types of cancers was associated with percent nighttime with oxygen saturation $< 90\%$ (Tsat90%) used as a surrogate of OSA severity; this association was not observed for the apnea-hypopnea index (AHI). Compared with the lower Tsat90% category ($< 1.2\%$), the adjusted hazard ratios (HRs) and 95% CIs of cancer incidence for increasing categories were 1.58 (95% CI, 1.07–2.34) for Tsat90% between 1.2% and 12% and 2.33 (95% CI, 1.57–3.46) for Tsat90% $\geq$ 12%. This association was limited to male patients aged < 65 years. Remarkably, in this subgroup of younger patients, not only Tsat90% but also AHI were independently associated with an increased incidence of cancer, suggesting that younger patients may be particularly susceptible to developing cancer in an OSA setting. Interestingly, an additional analysis including only 2,069 untreated patients replicated the results of the entire cohort, but the adjusted OR for the group with Tsat90% $\geq$ 12% was slightly higher (HR, 2.74 vs 2.33, respectively), prompting speculation that CPAP may confer some type of protection.

These findings could not be replicated by Christensen et al[19] in a prospective study on the 8,783 members of the cohort of the Copenhagen City Heart Study. The investigators found no association between the incidence of cancer and the presence of symptoms related to OSA, on either an individual or overall level. When they analyzed different types of cancer (alcohol-, smoking-, virus/immune-, and hormone-related), only smoking-related cancer exhibited a greater incidence after adjustment for various confounders in patients with at least two OSA-related symptoms (HR, 1.73 [95% CI, 1.03-2.91]). Finally, the presence of excessive daytime sleepiness (defined as an Epworth Sleepiness Scale score > 16) was associated with a higher incidence of alcohol-related cancers (HR, 4.92 [95% CI, 1.45-16-76]) and virus/immune-related cancers (HR, 2.73 [95% CI, 1.2-5.91]) but not with smoking-related cancers. However, the number of patients analyzed in these subgroups was low, and hypersomnia cannot always be attributed to sleep-disordered breathing.

In the same lines, the Canadian Cohort Study[13] was conducted in 9,629 patients referred for suspicion of OSA between 1994 and 2010 to a single sleep center, with a follow-up of 7.8 years. OSA was diagnosed by using full polysomnography. As in the study by Christensen et al,[19] no associations were found between cancer incidence and various categories of AHI and Tsat90%. Although the Canadian and the Spanish studies share a retrospective, clinic-based design, there are significant differences that may explain some of the discrepancies. For example, the Canadian study was single-center whereas the Spanish study was multicenter. The former involved a bigger sample with a longer follow-up, but the patients seemed to be younger, less

TABLE 1] Summary of the Most Important Clinical Studies on the Association Between OSA and Cancer in Humans

Author	No. of Subjects	% Male Subjects	Design	OSA Diagnosis	Hypopnea Definition	Follow-up	Main Outcomes	Key Limitations	Main Findings
Cancer in patients with OSA: incidence studies									
Campos-Rodriguez, 2013[12] (Spanish Sleep Network cohort)	4,910 subjects with clinical suspicion of OSA	66.7	Multicenter retrospective clinical cohort study	Full PSG (31.9%) and RP (68.1%)	30%-90% reduction in oronasal flow for > 10 s associated with an oxygen desaturation ≥ 4% or an arousal	4.5 y	Cancer incidence (n = 261)	Retrospective Lack of control of some cancer risk factors Lack of direct measure of IH Lack of analysis of site-specific cancer mortality Majority use of RP	Severe OSA (Tsat90%) was associated with higher incidence of cancer, especially in patients aged < 65 y and men The association was slightly stronger in patients without CPAP treatment
Christensen et al, 2013[19] (Copenhagen City Heart Study Cohort)	8,783	45	Prospective cohort study	OSA symptoms		13 y	Cancer incidence (n = 1,985)	OSA diagnosis based on symptoms	No relationship between OSA symptoms and higher cancer incidence except for patients with ESS score ≥ 16 in participants aged < 50 y and smoking-related cancers
Kendzerska et al, 2014[13] (Canadian cohort)	10,149 subjects with clinical suspicion of OSA	61.9	Multicenter retrospective clinical cohort study	Full PSG	Decrease > 50% in the baseline amplitude of breathing for > 10 s or a clear but smaller decrease in amplitude for > 10 s associated with either an oxygen saturation ≥ 3% or an arousal	7.8 y	Cancer incidence (n = 627) and prevalence (n = 520)	Single-center and retrospective study No direct measure of intermittent hypoxia Lack of analysis of common cancer subtypes	The relationship between AHI/Tsat90% and cancer prevalence and incidence became nonsignificant after adjusting by sex, age, BMI, and smoking status Tsat90% was associated with the development of smoking-related cancers

(Continued)

TABLE 1] *(Continued)*

Author	No. of Subjects	% Male Subjects	Design	OSA Diagnosis	Hypopnea Definition	Follow-up	Main Outcomes	Key Limitations	Main Findings
Chang et al, 2014[14] (Taiwanese cohort)	846 women with OSA codes and 4,230 control subjects paired according to age	Women	National Health Insurance Database–based population study	Full PSG OSA (ICD-9-CM codes 780.57 780.53 327.23 780.51)	NA	5 y	Breast cancer incidence. (n = 44; 12 in patients with OSA)	Use of administrative claims database Lack of information of some breast cancer risk factors, OSA severity, level of hypoxemia, and CPAP treatment	Higher adjusted breast cancer incidence in OSA patients compared with control subjects without OSA Nonsignificant tendency to stronger association in women > 30 y
Chen and Hwang, 2014[15] (Taiwanese cohort)	23,055 patients with OSA and 69,165 control subjects paired according to age and sex	66.8	National Health Insurance Database–based population study	Full PSG OSA (ICD-9-CM codes 780.57 780.53 327.23 780.51)	NA	10 y	CNS cancer incidence (n = 124; 38 in patients with OSA)	Use of administrative claims database Some cases based on symptoms Lack of some cancer risk factors, OSA severity, level of hypoxemia, and CPAP treatment False-positive findings and negative OSA diagnosis	Higher CNS cancer incidence (especially brain cancer) in patients with OSA compared with the control group without OSA More evident in the subgroup of insomnia/OSA and hypersomnia/OSA subgroups Higher risk of CNS cancer in the OSA group without surgical treatment
Marshall et al, 2014[16] (Busselton Health Study Cohort)	390	73.6	Population-based study	MESAM IV	No direct measure of hypopnea	20 y	Cancer incidence (n = 125; 100 nonskin cancers)	No direct mea sure of respiratory events (apnea and hypopnea) Only 18 people with moderate to severe OSA Lack of control for some cancer risk factors No data about OSA treatment	Moderate to severe OSA was associated with an adjusted incidence of cancer (even when skin cancers were excluded)

(Continued)

TABLE 1] *(Continued)*

Author	No. of Subjects	% Male Subjects	Design	OSA Diagnosis	Hypopnea Definition	Follow-up	Main Outcomes	Key Limitations	Main Findings
Cancer in patients with OSA: mortality studies									
Nieto et al, 2012[17] (Wisconsin Sleep Cohort Study)	1,522	55.1	Population-based study	Full PSG	Discernible reduction in breathing (sum of chest and abdominal excursions) with a reduction in oxyhemoglobin saturation of ≥ 4%	22 y	Cancer mortality (n = 50)	Lack of data on cancer incidence Small number of fatal cancers (n = 50) Lack of a measure of IH Lack of analysis of site-specific cancer mortality	Severe SDB was associated with increased cancer mortality Cancer mortality increased linearly with increasing SDB severity, especially Tsat<90% More evident in association with individuals without daytime sleepiness or obesity The association was slightly stronger in patients not treated with CPAP
Marshall, 2014[16] (Busselton Health Study Cohort)	390	73.6	Population-based study	MESAM IV	No direct measure of hypopnea	20 y	Cancer mortality (n = 39)	No direct measure of respiratory events (apnea and hypopnea) Only 18 people with moderate to severe OSA Lack of control for some cancer risk factors No data about OSA treatment	Moderate to severe OSA was associated with adjusted cancer mortality (even when skin cancers were excluded)

(Continued)

TABLE 1] *(Continued)*

Author	No. of Subjects	% Male Subjects	Design	OSA Diagnosis	Hypopnea Definition	Follow-up	Main Outcomes	Key Limitations	Main Findings
Martínez-García, 2014[18] (Spanish Sleep Network Cohort)	5,427 subjects with clinical suspicion of OSA	65.1	Multicenter retrospective clinical cohort study	Full PSG (34.5%) and RP (65.5%)	30%-90% reduction in oronasal flow for > 10 s associated with an oxygen desaturation ≥ 4% or an arousal	4.5 y	Cancer mortality (n = 90)	Retrospective Lack of control of some cancer risk factors No direct measure of IH Lack of analysis of site-specific cancer mortality Majority use of RP	Severe OSA (Tsat90%) was associated with higher cancer mortality, especially in patients aged < 65 y and men The association was slightly stronger in patients without CPAP treatment AHI was associated with cancer mortality in 527 patients previously diagnosed with cancer
OSA in patients with cancer									
Martínez-García, 2014[21]	56 patients with cutaneous melanoma	60.7	Multicenter pilot study	RP	30%-90% reduction in oronasal flow for > 10 s associated with an oxygen desaturation ≥ 4%	No	Association between OSA and markers of aggressiveness of melanoma	No follow-up Small number of patients included Retrospective regarding the diagnosis of melanoma RP use	High prevalence of OSA in patients with melanoma AHI and Tsat90% were predictors of fast-growing melanoma Significant correlation between AHI/ODI and Breslow index

AHI = apnea-hypopnea index; ESS = Epworth Sleepiness Scale; ICD-9-CM = *International Classification of Diseases, Ninth Revision, Clinical Modification*; IH = intermittent hypoxia; NA = not available; PSG = full polysomnography; RP = respiratory polygraphy; SDB = sleep-disordered breathing; Tsat90% = nocturnal time spent with an oxygen saturation < 90%.

TABLE 2] Limitations of the Human Studies Addressing the Association Between OSA and Cancer Incidence and Mortality

Studies not originally designed to address the association between OSA and cancer
Intermittent hypoxia was not adequately assessed
Small number of events (both incident cancers and cancer-related deaths) may lead to lack of statistical power in subgroup analyses
Most studies did not investigate specific cancer sites
Important confounding variables such as sleep duration, sleep fragmentation, and shift work were not taken into account. Excessive daytime sleepiness and insomnia were only superficially investigated
The role of OSA treatment was not adequately assessed

obese, and with lower OSA severity than in the Spanish study. Nevertheless, both the Canadian cohort and the Copenhagen City Heart Study revealed a significant association between Tsat90% and smoking-related cancers, suggesting that the carcinogenic effects of tobacco may be exacerbated by intermittent hypoxia associated with OSA. Although this association was not assessed in the Spanish study, the Canadian study did report a higher proportion of current smokers, which may also help explain these disparate findings.

Conversely, two Taiwanese, retrospective clinic-based studies published in 2014 analyzed the association between OSA and specific cancer sites. Chang et al[14] used the National Health Insurance Database to identify 846 women with a diagnosis of OSA by using full polysomnography (when AHI was ≥ 5), based on *International Classification of Diseases, Ninth Revision, Clinical Modification,* codes and 4,230 age-matched control subjects who were followed up for 5 years. The adjusted HR of breast cancer in patients with OSA was higher than that of the control group (HR, 2.09 [95% CI, 1.06-4.12]). Stratified analysis revealed no significant age-related differences in the risk of breast cancer. With a similar design, Chen and Hwang[15] used the medical claims database of Taiwan's National Health Institute to identify 23,055 incident cases with newly diagnosed *International Classification of Diseases, Ninth Revision, Clinical Modification,* OSA codes (diagnosed by full polysomnography when AHI was ≥ 5), who were matched according to age and sex to patients without OSA. After a 10-year follow-up period, participants with

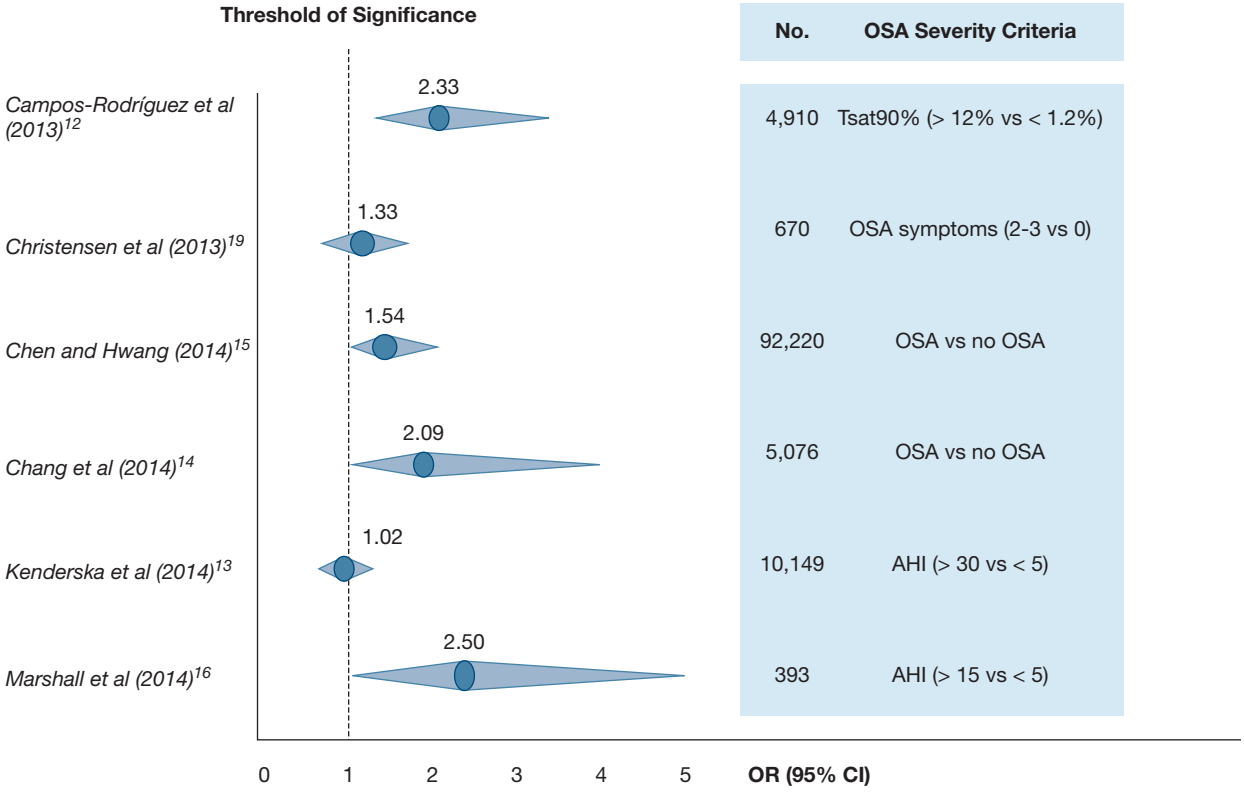

Figure 1 – *Cancer incidence in patients with OSA according to various criteria of severity. Blue circles indicate OR and triangles indicate 95% CIs. [a]Chang et al[14] and Chen and Hwang[15] do not specify OSA severity criteria. AHI = apnea-hypopnea index; Tsat90% = nighttime spent with oxygen saturation < 90%.*

OSA had a significantly higher risk of developing primary CNS cancers than the control group (adjusted HR, 1.54 [95% CI, 1.01-2.37]). A significantly higher risk of primary CNS cancers was observed in a subgroup of patients with OSA and insomnia, compared with those without insomnia (adjusted HR, 2.20 [95% CI, 1.39-3.49]). Further studies are required to ascertain whether this additive effect of OSA and insomnia on cancer incidence is exclusive to brain cancers or may be extrapolated to other associations. Remarkably, the risk of primary CNS cancers was reduced to a level similar to that of the control group in one subgroup of patients who underwent surgical treatment for OSA (adjusted HR, 0.98 [95% CI, 0.31-3.09]); the OSA group that did not undergo surgical treatment presented with an increased incidence of cancer (adjusted HR, 1.83 [95% CI, 1.23-2.74]). This outcome suggests that treatment intervention in OSA may be useful to reduce the risk of cancer incidence, at least in CNS tumors.

The Busselton cohort,[16] consisting of 390 participants aged < 65 years who were followed up for 20 years, provides the basis for the only population-based study analyzing the association between OSA and cancer. Moderate to severe OSA (diagnosed by using MESAM IV, a device with no recording of oronasal flow or pressure) was associated with an increased incidence of all-type and non–skin cancer in this study, compared with non-OSA participants (adjusted HRs of 2.5 [95% CI, 1.2-5.0] and 2.9 [95% CI, 1.4-6.1], respectively).

The data from these five studies addressing cancer incidence (excluding the study by Christensen et al[19] because it lacked sleep studies) were pooled in a recent meta-analysis.[22] Data from 34,848 patients with OSA and 77,380 without OSA were compared. Patients with OSA exhibited an increased risk of cancer incidence (relative risk, 1.53 [95% CI, 1.31-1.79]). This association was attenuated after adjustment for traditional cancer risk factors (relative risk, 1.40 [95% CI, 1.01-1.95]), but it remained significant. However, despite the large number of patients included in the meta-analysis, it proves difficult to infer any independent association, largely due to several major limitations such as the studies' different designs and their great heterogeneity.

Finally, shortly after the meta-analysis study,[22] Fang et al[20] published a nested case–control study of 68,422 patients with incident cancer and 136,844 without cancer matched for age and sex from the National Health Insurance Database of Taiwan. Within these two groups, sleep apnea was diagnosed in 4,843 and 10,226 patients, respectively. Patients with sleep apnea had an adjusted (age, sex, economic variables, geographical variables, and Charlson comorbidity index) increased risk of breast cancer (HR, 2.10 [95% CI, 1.16-3.80]), nasal cancer (HR, 5.96 [95% CI, 2.96-11.99]), and prostate cancer (HR, 3.69 [95% CI, 1.98-6.89]).

Cancer Mortality and Progression in Patients With OSA

One study published in 2012 with the aim of evaluating the role of OSA and the effect of treatment with CPAP on cardiovascular mortality in a large number of elderly patients produced an unexpected finding (Fig 2).[29] In addition to the increase in cardiovascular mortality, there was also a trend toward an increase in mortality from cancer (OR, 3.01 [95% CI, 0.81-11.1]), but this finding was less marked in patients who had been prescribed treatment with CPAP (OR, 1.5 [95% CI, 0.44-5.66]). Although these results did not prove a significant association, probably due to the low number of patients who died of cancer (n = 38), they were sufficient to alert the scientific community to a possible relationship between OSA and increased cancer mortality (along the lines of previous animal studies) and also suggest some relevant pathophysiologic routes.

In 2012, the Wisconsin population-based cohort was the first to report a significant association between OSA and poorer cancer prognosis.[17] The authors used 22-year mortality follow-up data from 1,522 participants and observed that survival-free cancer mortality progressively decreased over time in a dose–response fashion with increasing levels of OSA severity. Severe OSA (measured by using an AHI ≥ 30) was an independent predictor of cancer mortality (adjusted HR, 4.8 [95% CI, 1.7-13.2]). Remarkably, this association was stronger when Tsat90% was used as a surrogate of OSA severity, instead of the AHI (percentile > 97 [> 11.2% of the time] vs percentile < 73 [< 0.8% of the time]; adjusted HR, 8.6 [95% CI, 2.6-28.7]). Stratifications according to sex and age did not modify this association, but obesity and sleepiness did. A dose–response association between OSA and cancer mortality was more clearly statistically significant in nonobese participants compared with obese subjects and in nonsleepy participants compared with sleepy subjects. These findings concur with those obtained in an animal model of melanoma in which intermittent hypoxia mimicking OSA promoted cancer progression in lean rodents but not in obese rodents.[9] Finally, when the 151 patients

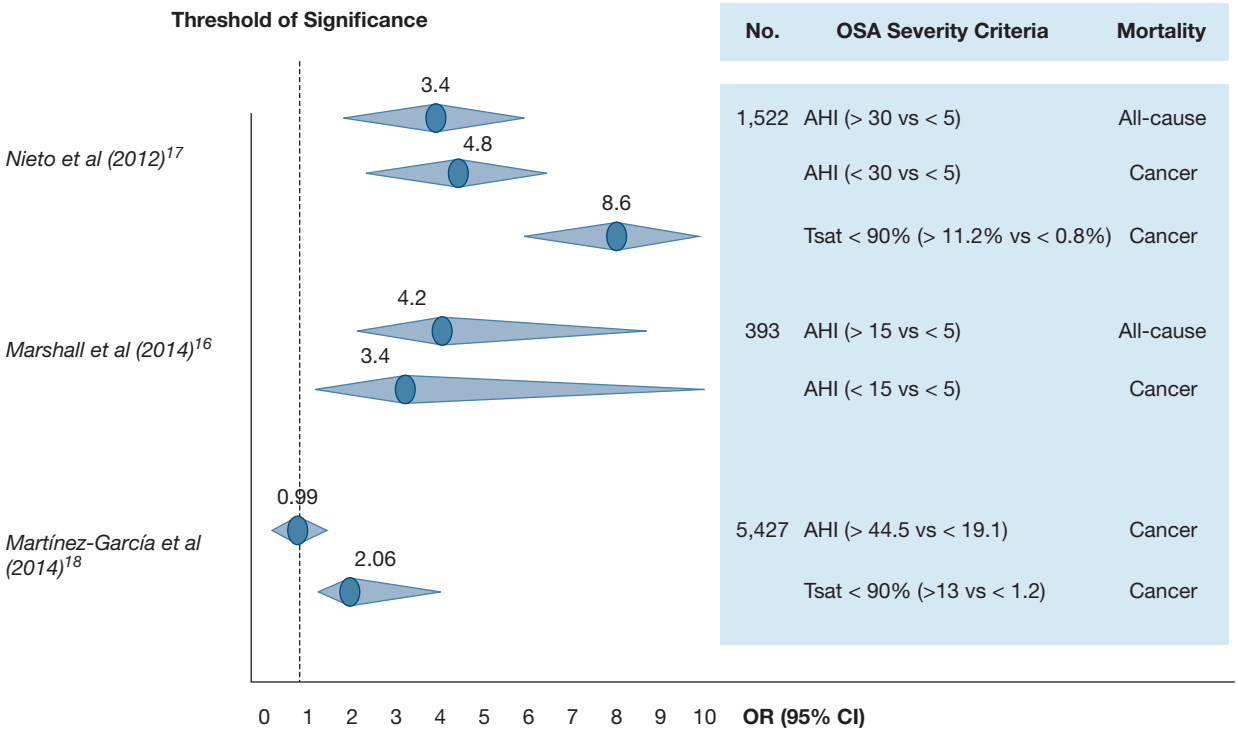

Figure 2 – *All-cause and cancer mortality in patients with OSA according to different criteria of severity. Blue circles indicate OR and triangles indicate 95% CIs.*

treated with CPAP were excluded, there was a slightly stronger association between OSA and cancer mortality. These findings concur with those of the Spanish[12] and Taiwanese[14,15] studies of incident cancer, suggesting that treatment of OSA may reduce poorer cancer outcomes.

The Busselton[16] cohort also provided data about mortality. Thirty-nine cancer deaths were observed over a 20-year follow-up period. After controlling for several confounders, an AHI ≥ 15 was associated with a 3.4-fold increase in cancer mortality (95% CI, 1.1-10.2) compared with non-OSA participants.

The Spanish clinical cohort[18] also analyzed this outcome and obtained similar findings to those reported for cancer incidence. Tsat90% as a surrogate for OSA severity was independently associated with increased cancer mortality (HR, 1.21 [95% CI, 1.03-1.42]), but AHI was not. Again, this association was strongly modified by age: it was absent among participants ≥ 65 years of age but very strong in patients aged < 65 years (adjusted HRs comparing highest vs lowest tertiles were 4.0 [95% CI, 1.1-3.6] for AHI and 14.4 [95% CI, 1.9-111.6] for Tsat90%). In keeping with the results of the Wisconsin study,[17] when patients with good adherence to CPAP treatment were excluded from the analysis, the association between OSA and cancer mortality became more intense, opening up the possibility of a protective effect derived from CPAP.

One important question raised by these three studies is whether the association between OSA and cancer mortality is due to more aggressive cancer behavior or simply to the higher incidence rate previously reported. Only the Spanish study tried to address this topic by analyzing a group of 527 patients with an established diagnosis of cancer.[18] It found that OSA severity measured by using both AHI and Tsat90% was independently associated with increased cancer mortality only in the group of younger patients (aged < 65 years) (adjusted HRs comparing highest vs lowest tertiles were 3.7 [95% CI, 1.05-13.2] for AHI and 12.8 [95% CI, 1.6-104.8] for Tsat90%). These findings suggest that, at least in younger patients, OSA severity increases cancer aggressiveness and progression, leading to greater cancer mortality. Table 3 describes the subgroup of patients found in these studies to have a possibly greater incidence of cancer or risk of mortality from cancer.

OSA in Patients With Cancer

Beyond the proven association between a higher prevalence of OSA in patients with head and neck tumors, due to the basic mechanisms of narrowing of

TABLE 3] Features Associated in Different Studies With Stronger Link Between SDB and Higher Incidence or Poorer Prognosis of Cancer

Young (aged < 65 y)[12,18]
Male sex[12,18]
Lack of excessive daytime sleepiness (except for alcohol- or virus/immune-related cancer)[13,17]
Nonobese patients[17]
Untreated (CPAP or surgical treatment) patients[12,15,17,18]
Patients with other sleep disorders[16]

SDB = sleep-disordered breathing.

the upper airway or neural alterations (whether produced by the tumor itself or by the local treatments applied),[30,31] the few studies of OSA in patients with cancer have been limited to certain types of cancer, such as renal and skin cancer.

OSA in Patients With Specific Cancer Sites

Few studies have analyzed the prevalence or influence of the number and severity of sleep-disordered breathing in the evolution of specific types of tumors. In a multicenter study of 56 consecutive patients diagnosed with malignant cutaneous melanoma, Martínez-García et al[21] observed a high prevalence of sleep-disordered breathing, compared with that expected in a population of the same sex, age, and BMI.[32,33] Thus, although the mean age of the patients was 56.2 years, the mean BMI was 26.8 kg/m^2, and 60% were male, the mean AHI was 13.6 events/hour, > 60% of the subjects had an AHI ≥ 5, and the mean Epworth Sleepiness Scale score was 6. However, the most noteworthy finding was that those patients who presented with a greater estimated growth of their melanoma also presented with a higher incidence and greater severity of sleep-disordered breathing. In the logistic regression analysis, both the AHI (OR, 1.08 [95% CI, 1.02-1.14]) and the oxygen desaturation index (ODI) 3% (OR, 1.08 [95% CI, 1.02-1.11]) and ODI4% (OR, 1.1 [95% CI, 1.02-1.2]) were factors associated with greater tumoral growth, regardless of age, BMI, and sex. Furthermore, AHI, ODI4%, and ODI3% were significantly correlated with other objective aggressiveness factors of melanoma, such as Breslow index, presence of ulceration, and mitotic index.

The encouraging findings of this pilot study led this research group to conduct a larger study that will involve approximately 450 patients with melanoma.[21] They will not only undergo sleep studies but will also give blood and histologicl samples in an attempt to corroborate this association and assess the most relevant pathophysiological pathways that could connect the two diseases. Preliminary results on the first 159 patients included in the study have confirmed the higher-than-expected prevalence of sleep-disordered breathing,[32,34] with a mean AHI of 14.7 events per hour and 76.5% of men and 66.3% of women with an AHI ≥ 5.[33]

A recent study (published as an abstract) on 2,579 patients who underwent radical or partial nephrectomy for clear cell renal cell carcinoma observed a prevalence of self-reported OSA of 6%.[35] More interestingly, a logistic regression model, adjusted for smoking history, age, sex, BMI, American Society of Anesthesiologists' score and tumor size, was used to assess the association with Fuhrman grade and concluded that OSA was associated with intermediate/high Fuhrman grade in both univariate (OR, 1.57 [95% CI, 1.15-2.14]; $P = .004$) and multivariable (OR, 1.47 [95% CI, 1.06-2.03]; $P = .021$) analyses.

Limitations of the Studies

Although seven of the nine studies revealed an association between OSA and cancer incidence or mortality, and two studies showed a probable negative role for OSA in the prognosis in patients with cancer, important limitations prevent us from drawing any strong conclusions from these studies (Table 2).

The major concern is the study design. The Wisconsin[17] and Busselton[16] studies are prospective cohorts, but they were not originally designed to analyze the association between OSA and cancer. The Spanish[18,21] and Canadian[13] cohorts have a retrospective design, and the two studies from Taiwan used health-care records or claims databases, which preclude the assessment of key data such as the AHI or oximetric variables.[14,15] Finally, the study by Christensen et al[19] was based on OSA-related symptoms.

A second flaw is that although intermittent hypoxia seems to be the most likely mechanism involved in the relationship between OSA and cancer, none of the studies, apart from the study by Martínez-García et al,[21] provided any information about the best marker for intermittent hypoxia, namely the ODI. Some studies analyzed the Tsat90% as the sole oximetric variable, even though it is a marker of overnight hypoxia rather than intermittent hypoxia. If OSA did indeed prove to be associated with cancer incidence or progression, we would still not know whether this association is limited to specific cancer sites or types of malignant cells or is

applicable to all types of cancers. It is possible that different types of malignant cells have different adaptive responses to intermittent hypoxia and sleep fragmentation; thus, OSA may be a risk factor for poorer prognosis or higher cancer incidence only in some types of tumors. Four of these studies lacked statistical power to perform any subanalyses based on tumor subtypes, mainly due to the low incidence/mortality rate, and they therefore investigated "all types" of cancer. For example, the most common cancers in the Spanish[12,18] and Canadian[13] cohorts were, respectively, colorectal (43 of 4,910 participants) and prostate (125 of 9,629 participants), whereas in the Wisconsin cohort,[17] the leading cause of cancer death was lung cancer (in 8 of 1,522 subjects). These findings also highlight the fact that all secondary analyses based on stratification according to age, sex, obesity, sleepiness, treatment, and other variables are hampered by a lack of statistical power and should be treated with caution.

Sleep duration, which is reportedly associated with cancer incidence,[36-39] was not taken into account in these studies; neither were sleep circadian rhythm disturbances, some of which are related to sleep apnea. Similarly, only two of the studies observed that insomnia and lack of excessive daytime sleepiness were associated with poorer cancer-related outcomes.[15,17] Given that recent animal models have shown that sleep fragmentation may accelerate tumor growth,[2] it would have been interesting for those studies that used polysomnography to have provided some clues about the effect of arousals or other measures of sleep fragmentation on cancer outcomes, but unfortunately none of them did so. However, the Spanish cohort, which used both conventional polysomnography and respiratory polygraphy, found no differences in cancer incidence when patients who underwent one or another type of sleep study were assessed separately.

Conclusions

Bearing all these limitations in mind, this group of studies produces many more questions than answers. Although the evidence they provide is not strong enough to allow us to affirm that OSA may cause cancer or worsen its natural evolution, the largely convergent findings suggesting an association between these two disorders merit further research and should encourage new studies that would confirm or rule out the effect of OSA on cancer development or progression. While we await more extensive scientific evidence from the studies that are now underway, it is important to encourage health professionals who assess patients with cancer (or with a high probability of cancer) to incorporate information about the most prevalent sleep-related disorders into the clinical history of these patients, with a particular emphasis on insomnia, sleep fragmentation/duration, and sleep apnea. These data would provide further evidence of any possible association between cancer and these disorders, as well as a higher risk of cancer or a poorer prognosis for a preexisting cancer. This scenario will enable us to establish the appropriate diagnostic and therapeutic mechanisms.

Because any possible relationship between the incidence or severity of sleep-disordered breathing and the inception or prognosis of cancer is extremely important, and due to the fact that OSA is a treatable disease, it is vital to undertake better designed clinical studies that would corroborate this relationship and shed new light

TABLE 4] Main Characteristics and Objectives of Future Clinical Studies to Investigate the Relationship Between Cancer and Sleep Apnea

Large population or clinical-based samples to examine common cancer subtypes from different locations ("big data" studies and meta-analysis of individual data)
Long-term follow-up to encompass extended cancer preclinical periods and make it possible to distinguish carcinogenic from cancer-prognosis effects of SDB
Objective measurements of SDB
Robust assessment of important potential confounders, especially age, obesity and metabolic disorders, alcohol, and tobacco smoke
Establishment of better sleep test measurements and better cutoff of risk
Subgroups of special interest (age, sex, obese, and symptomatic patients)
Avoidance of publication bias
Meta-analysis of individual patient data
Prospective studies of patients with cancer to assess prognosis and progression in terms of metastasis, relapse, mortality, new tumors, and treatment response
Polysomnographic studies to evaluate the role of sleep fragmentation and sleep duration
Role of CPAP treatment in clinical trials
Analysis of biomarkers
Role of important confounders (obesity, age, sex, smoking habit, alcohol intake, comorbidities, and occupational and cancer therapy)
Role of other sleep disorders such as insomnia, short/long sleep duration, sleep circadian rhythm disturbances and parasomnias, and their relationship with sleep apnea

SDB = sleep-disordered breathing.

on it. The recent trend for "big data" studies could provide an opportunity to explore more deeply and produce working hypotheses for prospective studies. Other interesting areas of research would be the effect of OSA treatment on the incidence or aggressiveness of cancer and the role played by various confounders, particularly obesity, as well as the analysis of particular subgroups. In this respect, some investigators have concluded that treatment of sleep apnea could alter cancer-associated transcriptional signatures in circulating leukocytes.[40] Table 4 details the methodologic characteristics and principal objectives that should be adopted by any clinical studies seeking to analyze this relationship.

One basic decision for the design of a new study focusing on the impact of OSA or the effect of CPAP treatment on different outcomes of cancer with a poor prognosis would be the choice of neoplasia for investigation. The ideal choice would be one that occurs frequently in the general population (possibility of a sufficient number of patients), with a significant degree of aggressiveness (possibility of a sufficient number of outcomes with a poor prognosis in a short period), previously validated markers of aggressiveness, a high clinical impact (conclusions directly applicable to clinical practice), and a cellular line with proven sensitivity to the effect of intermittent hypoxemia, sleep fragmentation, or other pathophysiologic characteristics related to sleep apnea and cancer. Certain types of cancer could comply with some of these criteria (eg, melanoma; colon, lung, breast, or prostate cancer). Once the type of neoplasia has been chosen, the study should have a prospective, multicenter design to ensure both a sufficient number of patients and outcomes, as well as sufficient statistical power. The fundamental outcomes for evaluation could be the development of various markers of aggressiveness, tumoral relapse, response to treatment, lymph node or distant metastasis, and death, or a composite of these variables.

Going one step further, having demonstrated an association between cancer and sleep apnea, the best design for a study of the effect of CPAP would be a clinical study on tumors with an expected outcome of a poor prognosis within a period no longer than 2 to 3 years. Whatever methodology is used, the study should incorporate measurements in biopsy samples, peripheral blood, or other tissues and markers of aggressiveness; neovascularization (eg, vascular endothelial growth factor); or the expression of molecules related to inflammation, sleep fragmentation, the immune system, and tissue hypoxia (hypoxia-inducible factor-1), as well as genetic and epigenetic markers. Studies of patients with sleep apnea should be undertaken on the basis of prospective data with a sufficient number of cancer-related outcomes to evaluate incidence, mortality, and the effect of CPAP on cancer. This design would demand access to large multinational databases with thousands of patients and an extensive follow-up, which is currently difficult to achieve (even more so when the aim is to investigate different subtypes of cancer).

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