Sleep Disorders and Cancer

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Abstract There is a growing evidence that sleep disorders are associated with an increased incidence and accelerated cancer progression. In the light of the previously established relationship between hypoxemia and cancer, obstructive sleep apnea and its main consequence, intermittent hypoxia, could be associated with a poorer prognosis or higher incidence of cancer. From this pathophysiological starting point, and in the light of animal studies that confirmed this association, two separate research groups observed in large-scale clinical and epidemiological series that the degree of nighttime hypoxia found in patients with obstructive sleep apnea was associated with a higher incidence of cancer, as well as a higher mortality rate although their retrospective nature means that they should be considered with caution. A study currently in progress with a large group of patients with melanoma may soon cast new light on the existence or not of this association and its underlying pathophysiological mechanisms.

Keywords Sleep-disordered breathing · Cancer · Sleep apnea · Intermittent hypoxia · Sleep duration · Melatonin · Shift work

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Introduction

There is a growing evidence of an association between abnormal sleep and the incidence and progression of cancer. Shift work involving the disruption of circadian rhythms has been shown to increase carcinogenesis in animal models. Suppression of melatonin induced by exposure to light at night, coupled with deregulation of clock genes, may potentially contribute to the promotion and induction of cancer, particularly in endocrine tissues. This evidence has led the International Agency for Research on Cancer to classify shift work with circadian disruption as “probably carcinogenic.” As regards sleep duration, its relationship with cancer is less clear and various studies have yielded contradictory findings. Finally, the relationship between obstructive sleep apnea (OSA) and cancer opens up an exciting field of research for the coming years, although at the moment, clinically speaking, it stands on unsteady ground. Nevertheless, both the pathophysiological and animal studies undertaken to date seem to make this association more credible. From a clinical viewpoint, several studies have observed an association between OSA (particularly when evaluated in terms of the resulting hypoxemia) and the incidence of and mortality from cancer, although their retrospective methodology means that further research is needed before any more unequivocal conclusion can be reached. All the indicators seem to suggest that if such an association were to exist, it would be one of the most important discoveries so far in the field of sleep apnea research, as both OSA and cancer share certain common epidemiological characteristics such as high prevalence, a major healthcare impact and a potential treatability. The following review seeks to inform readers of the findings to date on the relationship between sleep disorders, especially OSA and cancer, as well as review the potential pathophysiological mechanisms that would support the plausibility of the hypothesis

that sleep disorders might affect carcinogenesis or cancer progression.

Pathophysiological Aspects

There are several pathophysiological mechanisms that could give biological plausibility to a possible relationship between some sleep disorders including OSA and either the conversion of healthy cells into malignant ones or the spread and growth of a tumor. The main mechanisms or biomolecular pathways that are potentially involved are discussed below.

Melatonin

In addition to its regulatory role of the sleep circadian cycle, melatonin has been shown to inhibit cancer development and growth and improve immune function. This anticancer activity of melatonin involves antimitotic activity, resulting from melatonin's direct effect on hormone-dependent proliferation. Melatonin suppression in shift workers through exposure to light at night can result in an increased release of gonadotropins from the pituitary gland, thereby stimulating hormones such as testosterone or estrogen [1, 2]. Melatonin also neutralizes and removes free radicals and has a protective effect against the DNA-damaging effects of hydrogen peroxide [3]. It inhibits tumor signal transduction and the metabolic activity of cancer cells via the activation of melatonin receptor MT1 and increases the expression of the tumor-suppressor gene p53 [4]. Blunted melatonin secretion may also lead to immune suppression with potential consequences on the development and growth of cancer [1].

Clock Genes

Clock genes play a major role in circadian synchronization and phase shift, but also seem to be important in tumor suppression and promotion [2, 3]. Clock genes regulate cell proliferation and apoptosis by controlling a number of cell cycle-related genes, cell cycle checkpoints, and tumor-suppressor genes that mediate response to DNA damage. Chronic exposure to shift work may disrupt circadian rhythms and stimulate tumor development and progression, partly mediated by epigenetic changes [2, 3, 5–10].

Oxidative Stress

The pattern of desaturation and reoxygenation that defines intermittent hypoxia is a characteristic of OSA and represents a major stimulus to the activation of the oxidative stress system through the production of reactive oxygen species (ROS) [11, 12]. This leads to an imbalance between the production and degradation of certain oxidants and antioxidants. This

phenomenon has been related to an increase in both acute and chronic mutagenesis, various alterations in cellular function and structure, damage to DNA, and instability in the genome, which can result in greater cellular proliferation and neoplastic transformation. Lastly, oxidative stress has been related to transcription factors such as activating protein 1 (AP-1) and nuclear factor κ B (NF- κ B), which are involved in a greater propensity to develop cancer [13].

Hypoxia-Induced Factor (HIF-1)

All the cell types have various compensatory mechanisms in response to hypoxia, whether continuous or intermittent (as in OSA). One of the most powerful mechanisms is the increased production of a key molecule known as hypoxia-induced factor (HIF-1) (Fig. 1). HIF-1 orchestrates the regulation of genes that codify mediators allowing cells to adapt to situations of tissue hypoxia. HIF-1 is made up of two subunits: HIF-1 α and HIF-1 β , the former being the most important molecule in the regulation of tissue hypoxia [14]. Hypoxic compensation occurs when HIF-1 α sets in motion a series of mechanisms that activate the production of angiogenic cytokines, most notably the vascular endothelial growth factor (VEGF), which regulates the formation of new collateral blood vessels that supply the hypoxic area with more oxygen and avoid areas with vascular obstruction [15–21]. Although this process is an important compensatory mechanism in cardiovascular diseases with associated tissue ischemia, it seems to have a damaging effect in cancer patients. Large hypoxic areas (with pO₂ below 10 mmHg) can be found inside tumors, and these are powerful activators of the compensation systems mediated by HIF-1. When this chronic hypoxia that frequently characterizes solid tumors is aggravated by the intermittent hypoxia that occurs in cancer patients with OSA, the resulting tumor neovascularization may therefore provide a greater opportunity for cancer cells to reach the circulatory system and metastasize to other organs. Furthermore, this neovascularization occurs at the expense of fragile, anomalous vessels and so the reoxygenation is far from optimal.

Systemic Inflammation

There is an increase in both local and systemic inflammation in OSA [22, 23]. The role of OSA as a cause of systemic inflammation is the most important aspect of the possible association between cancer and OSA. As noted above, an oxidant/antioxidant imbalance and an increase in ROS have been associated with a systemic increase in the concentration of pro-inflammatory substances, including the tumoral necrosis factor (TNF- α), interleukin (IL)-6, and IL-8, via the above-mentioned activation of transcription factors NF- κ B and AP-1. The NF- κ B factor is considered to play a key role in the transcription of many genes related to inflammation,

Fig. 1 Pathophysiological relationship between obstructive sleep apnea and cancer. Obesity as a confounding factor. *HIF-1* hypoxia inducible factor-1, *VEFG* vascular endothelial growing factor, *ROS* reactive oxygen species

atherosclerosis, and cancer. Intermittent hypoxemia seems to be the most important element in the activation of this inflammatory element in patients with OSA [22, 23].

The inflammation associated with obesity, which could be described as chronic low-degree inflammation created by adipocytes in response to an excess of calories and nutrients, seems to be an important element in this relationship and could be independent of the existence of OSA since the prevalence of obesity in patients with OSA is abnormally high [24] and obesity has been associated with increased risk of some types of tumors [25–28].

Immune System

Macrophages are the most abundant component of tumor stroma and play an important role in most of malignant processes. These cells can modify their phenotype from pro-inflammatory or classically activated macrophages (M1) to an alternative activated form (M2), characterized by expression of angiogenic and tissue remodeling molecules [29]. Application of intermittent hypoxia (IH) can increase the number of macrophages in some tissues such as adipose and aortic walls. Those macrophages IH-induced macrophages present a shift toward classical activation phenotype which has been linked to the metabolic and cardiovascular consequences observed in OSA patients [30, 31]. The increased number of macrophages can result from an accelerated proliferation of the preexisting resident macrophages as well as an increased release of bone marrow-derived monocytes [32]. In terms of cancer, inflamed macrophages within the adipose tissue surrounding the tumor have been proposed as a depot of macrophages to the tumor [33]. Although the M1 phenotype induced by IH is associated to tumor surveillance, later has been shown that IH not only promoted increased number

of resident and bone marrow macrophages in the adipose tissue but also accelerated reeducation toward M2 in the tumor boundaries and increase their recruitment [34].

Recent research has shown that alterations in the immune response induced by IH and SF can mediate in part the accelerated tumor progression observed during both conditions. Almendros et al. revealed that IH increased the recruitment of tumor-associated macrophages, lymphocyte T regulatory cells (Tregs) and myeloid-derived stem cells to the tumor [35].

Evidence from Animal Models

Animal Models on Circadian Disruption and Cancer

In support of the hypothesis of a causal relation between shift work and cancer, there is a strong evidence from animal models that repeated disruption of the circadian rhythms, dysregulation of some of the clock genes, and experimental melatonin-suppressing manipulations promote the development and growth of malignancies.

Shah et al. [36] exposed female rats to constant light immediately after birth, provoking melatonin deprivation. The loss of inhibitory regulatory control over the hypothalamic-hypophysis axis led to constant availability of estrogen and increased the risk of mammary cancer. Administration of melatonin reduced cancer incidence. Blask et al. [37] showed that exposure of rats bearing human breast cancer xenografts to increasing intensities of white fluorescent light during each 12-h dark phase resulted in a dose-dependent suppression of nocturnal melatonin blood levels and a stimulation of tumor growth. When these tumors were perfused with physiologically melatonin-rich blood collected from healthy, premenopausal female volunteers during the night, the proliferative activity

was largely suppressed, suggesting that tumor growth response to exposure to light during darkness is intensity dependent.

Filipsky et al. [38] tested the effect of functional disruption of the circadian system on tumor progression in an experimental model of chronic jet lag. B6D2F₁ mice were synchronized with 12 h of light and 12 h of darkness or underwent repeated 8-h advances of the light/dark cycle every 2 days before inoculation with Glasgow osteosarcoma. The authors observed that the tumor grew faster in the jet-lagged animals as compared to controls, whereas exposure to constant light or darkness had no effect. Whereas the expression of mPer2 mRNAs showed significant circadian rhythms in controls, these were suppressed in jet-lagged mice. The same authors conducted another study in which the suprachiasmatic nuclei of mice were destroyed by bilateral electrolytic lesions and Glasgow osteosarcoma or pancreatic adenocarcinoma was inoculated [39]. Disruption of circadian rhythms was confirmed by measuring body activity, temperature, and plasma corticosterone levels. Both types of tumors grew two to three times faster in mice with destroyed suprachiasmatic nuclei compared to sham-operated mice.

Animal Models on OSA and Cancer

Intermittent hypoxia and sleep fragmentation mimicking OSA accelerate tumor growth and invasiveness

The potential effects of intermittent hypoxia (IH) and sleep fragmentation (SF) on tumor progression have been investigated recently in some types of cancer. Almendros et al. showed that melanoma increased tumor growth, metastasis, and mortality in mice subjected to IH [40, 41•, 42]. Mice were subjected to IH consisting in cycles of 20 s of hypoxia (5 % FiO₂) followed by 40 s of normoxia (21 % FiO₂) 6 h/day during 14 days to study tumor growth or 28 days for mortality and incidence of metastasis. The results from those studies showed that IH double increased tumor size as well as promotes a marked increase in number and metastatic area in the lungs [40, 41•]. Later, a similar model that used lung carcinoma was employed to test tumor growth and malignancy in response to either IH (90 s hypoxia (6 % FiO₂) followed by 90 s normoxia (21 % FiO₂)) 12 h/day during 28 days [34, 35]. As occurred in melanoma tumors, lung carcinoma experienced increased growth and invasiveness toward adjacent tissues in response to both paradigms.

Models using SF showed similar results than those using IH. Application of SF during 6 weeks in male mice was able to increase lung carcinoma growth with increased number of TAMs in those peripheral areas where invasion process occurs [43]. In this work, Hakim et al. proposed that the cancer malignancy induced by SF could be mediated in part through TLR4 receptors and their downstream pathways mediated

by MyD88 and TRIF molecules. In addition, an increased expression of metalloproteinase 9, a well-known molecule participating in extracellular matrix degradation, was observed overexpressed by intravital microscopy in SF condition *in vivo*. Although another type of tumors still needs to be evaluated, the data from animal models support the notion that both the IH and SF can enhance tumor aggressiveness.

Evidence in Humans

Shift Work and Cancer

Evidence of an association between chronic circadian disruption and cancer in humans is more limited than that derived from animal models. Several epidemiological studies have revealed, however, that human night shift workers might be at an increased risk of cancer. Against this background of laboratory animal and human findings, the World Health Organization International Agency for Research on Cancer (IARC) concluded in 2007 that shift work involving circadian disruption is probably carcinogenic in humans [44].

Given that melatonin is one of the most likely mechanisms involved in this association, most human research has focused on endocrine cancers such as breast, prostate, and endometrial tumors. Schernhammer et al. [45] prospectively studied the relationship between rotating night shift work and breast cancer risk in 115,022 premenopausal nurses. After 12 years of follow-up, the risk of breast cancer was found to be slightly higher in women who worked for 20 or more years on rotating night shifts, compared with those who never did so (multivariate RR 1.79; 95 % CI 1.06–3.01). In a similar study, Viswanathan et al. [46] reported that women who worked for 20 or more years on rotating night shifts had a significantly increased risk of endometrial cancer (RR, 1.47; 95 % CI 1.03 to 1.14) and that total years working on rotating night shifts was associated with an increased endometrial cancer risk (*P* trend = 0.04).

Hansen et al. [47] compared 7035 women aged 30–54 years with a diagnosis of breast cancer with a similar number of matched controls and obtained similar results. After accounting for confounders, they found a 1.5-fold increase in the risk (95 % CI, 1.2 to 1.7) of primary breast cancer in women who had worked for least half a year in any trade with predominantly night work. A trend was observed of risk increasing in accordance with increased duration of nighttime employment.

A study in Finland of 10,935 women with visual impairment showed an inverse association between breast cancer incidence and the degree of visual impairment, suggesting a dose-response relationship between visible light (and thus a very probable involvement of melatonin) and the risk of breast cancer [48].

This association has also been shown in males. Kubo et al. [49] prospectively examined the association between shift work and the risk of prostate cancer incidence in 14,052 working men in Japan. Compared with day workers, rotating shift workers were significantly more at risk of prostate cancer (RR 3.0, 95 % CI 1.2 to 7.7).

Sleep Duration and Cancer

Although some studies have found that short sleep duration is related to an increased risk of some types of cancer, particularly breast cancer, the data are controversial and other studies have neither reported any association nor even shown any association between long sleep duration and cancer [50–57]. Two main reasons may explain these disparate findings. Most studies were based on self-reported sleep duration instead of objective measures such as actigraphy or polysomnography. Additionally, sleep duration is usually measured only once, at baseline, but in long-term follow-up studies sleep, duration is likely to change throughout the follow-up, which may also influence the outcomes. Table 1 depicts the results of the most important studies to address this association.

Sleep Apnea and Cancer

Unfortunately, very few studies to date have analyzed the possible association between OSA and cancer in humans (Table 2).

Population-Based Studies

The first population-based study to analyze the association between OSA and cancer was the Wisconsin cohort, comprising 1522 subjects followed up for 22 years [58•]. This study found a dose-response association between the severity of OSA, as measured by the apneas-hypopnea index (AHI), and total cancer mortality. This association remained after adjusting for various confounders, and severe OSA ($\text{AHI} \geq 30$) even proved to be an independent predictor of mortality from cancer. This association was even stronger when an oxymetric index, the percentage of nighttime sleep with oxygen saturation $<90\%$ (Tsat90 %), was used instead of the AHI as a marker of the severity of OSA. This association was stronger in non-obese patients.

Furthermore, the Busselton cohort, comprising 400 subjects followed up for 20 years, also found an association between moderate-severe OSA ($\text{AHI} \geq 15$) and greater mortality (HR 3.4, 95 % CI 1.1–10.2) and cancer incidence (HR 2.5, 95 % CI 1.2–5.0) [59].

Finally, two large Taiwanese series [60, 61], using data from their National Health Institute, observed that OSA patients had a greater risk of developing breast cancer (HR 2.09; 95 % CI 1.06–4.12) [60] or a primitive cancer of the central

nervous system (HR 1.54; 95 % CI 1.01–2.37) [61], compared to control groups with no OSA. Both these studies presented significant limitations, however, such as a lack of data on the severity of OSA and of any adjustment for several basic confounding variables.

One study that used symptoms as markers of OSA did not find any association between the presence of snoring, witnessed pauses or excessive daytime sleepiness, and a greater incidence of cancer [65]. This association, however, may have been underestimated since the participants did not undergo any objective sleep tests to confirm or rule out the presence of OSA.

Clinical Studies

In 2013, the Spanish Sleep Group published the first clinical study to analyze the association between OSA and cancer. This was a retrospective, multicenter study with a mean follow-up of 4.5 years. An initial analysis studied the association between the severity of OSA and the incidence of any type of cancer in 4910 patients without previous cancer [62•]. After adjusting for various possible confounders, a significant association was found between the incidence of cancer and the severity of OSA as measured by the Tsat90 %, but not as measured by the AHI. The strongest association was found in the group of patients <65 years, where the incidence of cancer was related to both the AHI and the Tsat90 %. When the mortality in this series was analyzed, the results were very similar to those obtained for incidence, with a significant association between mortality from cancer and Tsat90 % as a marker of the severity of OSA, particularly in subjects aged under 65 years [63]. A sub-analysis including only patients with cancer ($n = 527$) found that Tsat90 % was an independent predictor of cancer lethality.

These results were not reproduced, however, in another very recent study in Toronto that analyzed 10,149 patients with suspicion of OSA between 1994 and 2010, with a follow-up of 7.8 years [64]. After adjusting for several variables, the authors did not find any greater incidence of cancer in patients with severe OSA measured by either AHI or Tsat90 %, compared to patients with no OSA ($\text{AHI} > 30$ vs. < 5 : adjusted HR 1.02, 95 % CI 0.80–1.31; Tsat90 %: adjusted HR 1.00, 95 % CI 0.99–1.02). These results did not vary when the authors used the same cutoff points for AHI and Tsat90 % as the *Spanish Sleep Group Study*.

Although five of the seven studies carried out to date have found an association between the severity of OSA, especially when measured by oxymetric markers, and cancer incidence and mortality [58•, 59–61, 62•, 63–65], all these studies present several limitations that oblige us to approach their conclusions with caution and continue researching this association. None of the series were specifically designed to analyze the association between OSA and cancer; most of them

Table 1 Studies that have addressed the association between sleep duration and cancer incidence in humans

Author (year)	Design	Number of participants	Follow-up	Type of cancer	Main findings
Verkasalo (2005) [50]	Cross-sectional, population-based study. Sleep duration and breast cancer risk factors were assessed by self-administered questionnaires given in 1975 and in 1981. Breast cancer incidence data for 1976 to 1996 was obtained from cancer registries.	12,222 women born before 1958 with sleep duration data in 1975	–	Breast cancer incidence	<ul style="list-style-type: none"> - Hazard ratios for breast cancer in the short (≤ 6 h), average (7–8 h), and long sleep (≥ 9 h) duration groups were 0.85 (95 % CI, 0.54–1.34), 1.0 (referent), and 0.69 (95 % CI, 0.45–1.06), respectively. - Analysis restricted to the 7396 women whose sleep duration in 1975 and 1981 were in the same duration group (stable sleepers) yielded Hazard ratios of 1.10 (95 % CI, 0.59–2.05), 1.0, and 0.28 (95 % CI, 0.09–0.88), with a decreasing trend ($P = 0.03$). - The study suggests a decreased risk of breast cancer in long sleepers. No statistically significant effects were observed for sleep insufficiency.
Kakizaki (2008) [51]	Population-based, prospective study. Sleep duration and breast cancer risk factors were assessed by self-administered questionnaires. Breast cancer incidence data were obtained from cancer registries.	23,995 women	–	Breast cancer incidence	<ul style="list-style-type: none"> - Short sleep duration was associated with higher risk of breast cancer. - Compared with women who slept 7 h per day, the multivariate hazard ratio of those who slept ≤ 6 h per day was 1.62 (95 % CI 1.05 to 2.50; P for trend = 0.03).
Wu (2008) [52]	Prospective, population-based cohort. Sleep duration and lifestyle factors were obtained through in-person interviews. Breast cancer incidence data were obtained from cancer registries.	33,528 women	11 years	Breast cancer incidence	<ul style="list-style-type: none"> - A significant decline in postmenopausal breast cancer risk was found with increasing self-reported hours of sleep (P trend = 0.047). - This inverse association was observed primarily in lean women [body mass index below the median value (23.2 kg/m²)] ($P = 0.024$).
Pinheiro (2006) [53]	Prospective cohort. Sleep duration and breast cancer risk factors were assessed by self-administered questionnaires. Breast cancer was confirmed by blinded medical chart review.	77,418 women aged 30 to 55 years at entry	16 years	Breast cancer incidence	<ul style="list-style-type: none"> - Compared with women sleeping 7 h, adjusted hazard ratios and 95 % confidence intervals for those sleeping ≤ 5, 6, 8, and ≥ 9 h were 0.93 (0.79–1.09), 0.98 (0.91–1.06), 1.05 (0.97–1.13), and 0.95 (0.82–1.11), respectively.
Vogtman (2013) [54]	Prospective cohort study. Sleep duration and lifestyle factors were obtained through in-person interviews. Medical records, pathology report review, and death certificates were used to confirm breast cancer.	110,011 Postmenopausal women aged 50 to 79 years	1,190,565 cumulative person-years of follow-up	Breast cancer incidence	<ul style="list-style-type: none"> - No statistically significant associations were found between sleep duration, sleep quality, and insomnia with the risk of breast cancer after multivariable adjustment.

Table 1 (continued)

Author (year)	Design	Number of participants	Follow-up	Type of cancer	Main findings
Von Ruesten (2012) [55]	Sleep duration, lifestyle habits, and medical history were assessed through in-person interviews. Cancer incidence was self-reported, but verified with cancer registries.	23,620 middle-aged men and women	7.8 years	Incidence of overall cancer	- Compared to persons sleeping 7 to 8 h/day, participants with sleep duration of <6 h had a significantly increased risk of overall cancer (HR = 1.43, 95 % CI 1.09–1.87) - Relative to women who slept 7.0 to 7.9 h/night, the multivariate odds ratio for developing breast cancer among women who slept an average of 9 h or more per night was 1.13 (95 % CI 0.93–1.37). - No evidence was found, however, that sleeping <7 h per night was associated with breast cancer risk.
McElroy (2006) [56]	Population-based case-control study. Sleep duration, lifestyle habits, and medical history were assessed through in-person interviews. Cancer was confirmed with cancer registries.	4033 women with invasive breast cancer and 5314 community women without breast cancer	–	Breast cancer incidence	- Compared to sleep at an average of 7 h, ≥9 h of sleep was significantly associated with a higher risk of colorectal cancer only in men (HR = 1.35, 95 % CI 1.00–1.82), but not in women (HR = 1.11, 95 % CI 0.85–1.44) - The risk associated with longer sleep was restricted to individuals who regularly snored (men: HR = 1.80, 95 % CI 1.14–2.84; women: HR = 2.32, 95 % CI 1.24–4.36) and to overweight individuals with body mass index ≥25 kg/m ² (men: HR = 1.52, 95 % CI 1.04–2.21; women: HR = 1.37, 95 % CI 0.97–1.94). - Short sleep duration (≤5 h) was not associated with an increased risk of colorectal cancer in the entire sample or in subgroups stratified by snoring or body mass index.
Zhang (2013) [57]	Prospective cohort study. Sleep duration and breast cancer risk factors were assessed by self-administered questionnaires. Cancer incidence was self-reported, but verified with medical and pathological reports.	30,121 men aged 41 to 79 years and 76,368 women aged 40 to 73 years	22 years	Colorectal cancer incidence	

Table 2 Summary of the most important studies on the association between obstructive sleep apnea and cancer in humans

Author (year)	Design	Number of subjects	Follow-up	Outcomes	Main findings
Nieto et al. (2012) [58••]	Prospective population-based study. Diagnosis by full PSG.	1522	22 years	Cancer mortality	Dose-response association between OSA severity (AHI and Tsat90 %) and cancer mortality especially when OSA severity was measured by Tsat90 % (Tsat90 % >11.2 %; adjusted HR 8.6, 95 % CI 2.6 to 28.7).
Marshall (2014) [59]	Prospective population-based study. Diagnosis by full PSG	397	20 years	Cancer incidence and mortality	Moderate-to-severe OSA (IAH $\geq$ 15) was independently associated with cancer mortality (HR 3.4, 95 % CI 1.1 to 10.2), and cancer incidence (HR 2.5, 95 % CI 1.2 to 5.0).
Chang (2014) [60]	Prospective poblational study. in Taiwan	846 women with OSA codes and 4230 controls paired by age	5 years	Breast cancer incidence	Higher breast cancer incidence in OSA patients in comparison with controls without OSA (adjusted HR 2.09; 95 % CI 1.06 to 4.12).
Chen (2014) [61]	Prospective poblational study in Taiwan	23,055 OSA y 69,165 controls paired by age and gender	10 year	CNS cancer incidence	Higher CNS cancer incidence in OSA patients in comparison with control group without OSA (adjusted HR 1.54, 95 % CI 1.01 to 2.37) especially brain tumor.
Campos-Rodriguez (2013) [62••]	Multicentric retrospective clinical cohort study. Diagnosis by PSG y RP	4910 subjects with clinical suspicion of OSA	4.5 years	Cancer incidence	Severe OSA (Tsat90 %) was an independent predictor of incident cancer especially in patients less than 65 years (Tsat90 % >12 % vs Tsat90 % <1.2 %, adjusted HR 2.33, 95 % CI 1.57 to 3.46).
Martínez-García (2014) [63]	Multicentric retrospective clinical cohort study. Diagnosis by PSG y RP	5427 subjects with clinical suspicion of OSA	4.5 years	Cancer mortality	There was an association between Tsat90 % and cancer mortality especially in patients less than 65 years (Tsat90 % >13 % vs Tsat90 % <1.2 %; adjusted HR 2.06, 95 % CI 1.72 to 4.58).
Martínez-García (2014) [63]	Multicentric prospective pilot study. Diagnosis by RP	56 subjects with cutaneous melanoma	–	Association between OSA and markers of aggressiveness of melanoma	The prevalence of moderate-to-severe OSA (IAH $\geq$ 15) in patients with melanoma was 30.3 %. AHI and Tsat90 % were independent predictors of fast-growing melanoma (adjusted OR 1.08, 95 % CI 1.02 to 1.14 and adjusted OR 1.08; 95 % CI 1.02 to 1.11, respectively).
Kendzierska (2014) [64]	Retrospective clinical cohort study. Diagnosis by PSG	10,149 subjects with clinical OSA suspicion	7.8 years	Cancer incidence and prevalence	No relationship between AHI and cancer prevalence No relationship between severe OSA (AHI/Tsat90 %) and cancer incidence

Table 3 Future research challenges on the relationship between sleep apnea and cancer

To identify which cancer types have more robust association with intermittent hypoxia and sleep fragmentation
To further analyze the role of the possible confounders especially obesity
To identify high-risk groups related to age, gender, diurnal hypersomnia or the presence of obesity
To identify the main pathophysiological pathways
To establish which polysomnographic variables better predict cancer risk
To analyze the role of CPAP treatment on modifying the association between OSA and cancer risk
To establish the effect of sleep duration on the relationship between sleep apnea and cancer

did not study a specific type of tumor, histology or site (different cells can have a different sensitivity to the action of hypoxia); no valid marker of intermittent hypoxemia was used [56, 57, 61, 62•, 65], and the relatively limited power for subgroup analyses (e.g., non-obese, <65 years, etc.) due to the relatively small number of events.

Studies in Progress

At present, only one prospective study seeking to analyze the association between OSA and a specific type of tumor (skin melanoma) has been conducted by the *Spanish Sleep Group*. The study aims to verify whether the severity of OSA is associated with more aggressive behavior from this tumor. There was an initial pilot study in which 56 patients diagnosed with melanoma were subjected to respiratory polygraphy [66•]. The prevalence of OSA was high in this series; 60.7 % of the patients presented an AHI ≥ 5 and 14.3 % had an AHI ≥ 30 . Moreover, the severity of OSA, whether measured by the AHI or the desaturation index (DI), was found to correlate with greater skin depth of the tumor and a higher rate of tumor growth. After adjusting for confounders, both the AHI and the DI proved to be independent predictors of faster melanoma growth. These findings have led to conduct a larger, multicenter study that will try to confirm these preliminary results.

Conclusions

Despite the growing interest in the possible association between sleep disorders and cancer, the scarcity of data and the limitations in the design of the studies undertaken so far make the latter little more than generators of hypotheses that produce more questions than answers, although they do encourage us to carry out further better designed studies to clarify this possible association (Table 3).

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Compliance with Ethical Standards

Conflict of Interest Miguel Ángel Martínez-García, Francisco Campos-Rodríguez, and Isaac Almendros declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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