

Sleep Apnoea and Cancer: Is There a Relationship?

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ABSTRACT

In recent decades, obstructive sleep apnoea (OSA) has come to represent a major public health problem due to its prevalence and its health consequences. Although the association between OSA and cardiovascular morbidity and mortality is well recognized, its role as a promoter for the development and extension of neoplasms is less known. In recent years, intensive research on the subject has been developed. Bench and animal studies demonstrate how sleep fragmentation and intermittent hypoxia, characteristic phenomena of OSA, are capable of inducing tumorigenesis in various organs and cell lines. However, clinical and population-based epidemiological studies are showing certain contradictory results. These topics are reviewed and discussed in this paper. (BRN Rev. 2020;6(1):22-35)

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*Sweet is the worker's dream, eat a lot, eat a little;
but the rich man does not let abundance sleep.*

(Ecclesiastes, 5:12)

INTRODUCTION

The usefulness of sleep for the healthy life of humans and mammals in general remains a mystery. Until World War II, sleep was considered an intermediate physical state between wakefulness and death. Here, wakefulness was regarded as the active state including the intellectual functions and death as that of their total suspension¹. However, in the last 70 years, researchers have discovered that sleep is a dynamic behaviour with many physiological changes from wakefulness which can lead to the development of disease if the state of “normal sleep” is disturbed. The Spanish Nobel Prize Ramon y Cajal discovered at the beginning of the last century that the brain was not an amorphous mass of tissues; on the contrary, its main cells communicated with each other. Subsequently, it was demonstrated that this communication was based on biochemical changes that were transformed into electrical impulses. The absence of this activity we now consider as “brain death”. There is no widely accepted definition of what is normal “sleep”. However, it is accepted that sleep must be “restful”, that is, the subjects must wake up “fresh” and throughout the day they must perform their vital functions and work and social routines “without sleepiness”. Also, vital functions (hormonal secretion, cardiopulmonary function, pulmonary gas exchange) must remain intact. If these goals are not achieved, we talk about a sleep disorder.

The prevalence of sleep disorders is increasing in parallel with a progressive increase of studies indicating potential associations between sleep and organ diseases. In particular, in the last decade, numerous studies have been published linking sleep duration and circadian perturbations with increased risk for developing cancer. In this review we will focus on the relationship between obstructive sleep apnoea (OSA), the most common sleep-disordered breathing, and cancer and how the two major components of OSA, namely intermittent hypoxia (IH) and sleep fragmentation (SF) may contribute to the pathogenesis and cancer epidemiology.

GENERAL SLEEP QUALITY AND CANCER

The circadian rhythm is an essential biological function of all living beings and determines their physiological changes and behaviour 24 hours a day. The rhythmicity of its functioning is genetically determined. In shift workers or those highly exposed to light at night, epigenetic modifications have been described in key genes of circadian regulation, which also simultaneously alter the transcription of regulatory genes related to cancer susceptibility². Epidemiological studies carried out in these workers find an association between cancer risk and shift work. The information is especially consistent in the case of breast cancer³. The potential intermediate mechanisms that would explain the relationship between shift work and cancer risk remain undetermined. It is known that melatonin has suppressive oncogenic effects. In vitro, melatonin increases the expression of the PER2 gene (a member

of the Period family of genes expressed in a circadian pattern in the suprachiasmatic nucleus) one of whose effects is to reduce the production of β -catenin. This protein increases the levels of cyclin D, which activates the proliferation of neoplastic cells. On the other hand, several melatonin receptors that affect tumour physiology have been described in the breast cancer cells themselves⁴. In both men and women who work in shifts, the levels of melatonin at night and in urine collected over 24 hours are reduced, and also fluctuate much less than in workers who work fixed shifts in the morning or afternoon⁵. However, to date, a causal relationship between melatonin levels and cancer risk has not been demonstrated. Nor have intervention trials with melatonin been performed on animals or humans. In the general population, few studies have investigated the relationship between sleep quality and cancer incidence. Among Europeans, epidemiological studies did not find association between sleep quality or sleep duration and mortality or incident cancer when adjusting for age, sex, health status and body mass index (BMI)^{6,7}. Recent data from the United Kingdom population-based tri-ethnic Southall And Brent REvisited (SABRE) cohort (4399 participants) showed that mortality association between self-reported sleep quality measures, such as difficulty falling asleep, early morning waking and waking up tired in the morning, and cancer mortality was weak in all studied ethnic groups⁸. The main limitation of these epidemiological studies is that the quality and amount of sleep itself has not been measured by polysomnography. Thus, the relationship between quality of sleep and cancer risk remains a matter of debate⁹.

OBSTRUCTIVE SLEEP APNOEA, A WORLDWIDE PANDEMIC

Obstructive sleep apnoea is the most frequent sleep disordered breathing in humans and is characterised by recurrent upper airway collapse during sleep, leading to episodic hypoxia and recurrent arousals. At clinical round, OSA severity is classified according to the number of apnoeas-hypopnoeas per hour of sleep, so-called apnoea-hypopnea index (AHI). In the United States of America (USA), the reported prevalence estimates of moderate-to-severe OSA (AHI ≥ 15) in 2013 were 10% among 30-49-year-old men; 17% among 50-70-year-old men; 3% among 30-49-year-old women; and, 9% among 50-70-year-old women¹⁰. These prevalence rates represented a relative increase of between 14% and 55% depending on the subgroup over the previous two decades¹¹. Overweight and obesity are the strongest risk factors for OSA and their prevalence is increasing in parallel with OSA¹² (Fig. 1). Since OSA is linked with traffic accidents¹³, cardiovascular morbidities¹⁴⁻¹⁶, neuro-cognitive disorders¹⁷ and premature death¹⁸, all mortality rates in developed countries are likely increased comparing to levels that would otherwise be expected.

OBSTRUCTIVE SLEEP APNOEA AND RISK OF CANCER

Clinical and epidemiological studies

The association of OSA and cancer has been explored in recent years. We will not cite anecdotal cases of this association here, but we will focus on large well-designed studies. The available information can be grouped in

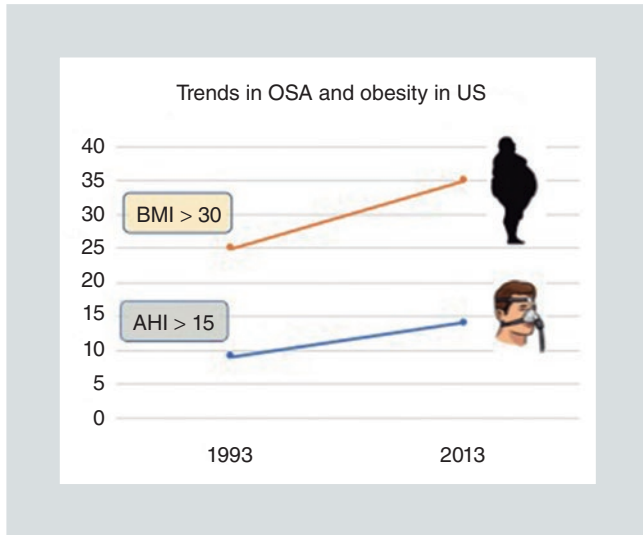


FIGURE 1. Trends in obesity and obstructive sleep apnoea prevalence in United States (US) (in % of the adult population). Obesity is defined by body mass index (BMI) greater than 30 kg/m² and obstructive sleep apnoea (OSA) is defined by an apnoea-hypopnea index (AHI) greater than 15 events per hour of sleep. National Centre for Health Statistics. NHANES, U.S. Available at: http://www.cdc.gov/nchs/nhanes/response_rates_CPS.htm

the following sections according to the type of the studied population: population-based studies, cohort of OSA patients, cohort of specific cancer types (Table 1).

Population-based studies

The first clinical evidence that suggested a relationship between OSA and cancer came from the Wisconsin study¹⁹. The cohort was initiated in 1989 by recruiting more than 1500 employees of the Wisconsin state government. After a median follow-up period of 18 years, there were 50 deaths from cancer. Comparing those with AHI > 30 with those without OSA, the cancer mortality was about 4.8-fold higher. When using the hypoxaemia index (percent sleep time below 90% oxyhaemoglobin saturation [CT90%]), as a marker of OSA

severity, instead of the AHI, the adjusted relative hazards of cancer mortality were 8.6 (95% confidence interval [CI] 2.6-28.7) for subjects with the high hypoxaemia index category (CT90% > 11%) compared to those in the lower category (CT90% < 1%). The association remained evident when patients treated with continuous positive airway pressure (CPAP) were excluded from the analyses. In Australia, 397 people were followed for at least 20 years after being studied with home sleep polygraphy²⁰. In fully adjusted models, moderate-to-severe OSA (respiratory disturbance index [RDI] ≥ 15/h) was significantly associated with all-cause mortality and cancer mortality (HR: 3.4; 95% CI, 1.1-10.2). However, two population-based studies were negative. Of 9629 patients who were free of cancer at baseline and underwent a sleep study in a referred centre from Toronto, 627 (6.5%) had incident cancer over a median follow-up of 7.8 years²¹. The severity of sleep apnoea as assessed by AHI (> 30 versus < 5) was not significantly associated with incident cancer after adjustment for age, sex, BMI and smoking status at baseline (hazard ratio [HR]: 1.02, 95% CI 0.80–1.31). Cancer mortality was not assessed. The Copenhagen City Heart Study (CCHS) is a Danish longitudinal cohort study initiated in 1976 that included an age-stratified sample of men and women age 20 to 93 years²². All subjects had a sleep questionnaire (but not sleep study) at baseline. Among the 8783 participants in whom cancer had not been previously diagnosed, there were no clear associations between snoring, breathing cessations, or the total number of sleep-disordered breathing (SDB) symptoms and total cancer incidence. Interestingly, the high levels of daytime sleepiness as evaluated by the Epworth Sleepiness Scale (e.g. score of 16-24) were associated with a higher cancer

TABLE 1. Relevant clinical studies on association between obstructive sleep apnoea and cancer

1st author, year (#ref.)	Design	Outcomes	Findings	Comments
General Population				
Nieto et al. (2012) ¹⁹	Prospective, 1306 active workers, median follow-up: 18 yr	Death from cancer	AHI > 30 versus AHI < 5 <i>HR: 4.8</i>	Confounders: age, gender, BMI, smoking, diabetes.
Marshall et al. (2014) ²⁰	Prospective, 397 people, 20 yr follow-up	Death from cancer	RDI > 15 versus RDI < 5 <i>HR: 3.4</i>	Confounders: age, gender, smoking, and obesity
Kendzerska et al. (2014) ²¹	Retrospective, 9629 subjects, median follow-up: 7.8 yr	Cancer incidence	AHI > 30 versus AHI < 5 <i>HR: 1.02 (0.80 -1.31)</i>	Confounders: age, gender, BMI, smoking
Christensen et al. (2013) ²²	Prospective, 8783 people, median follow-up: 13 yr	Cancer incidence	EES >15 versus EES: < 10 <i>HR: 4.09</i>	Confounders: age, gender, BMI, smoking, alcohol
Gozal et al. (2016) ²³	Retrospective, 5.6 million mean follow-up: 3.2 yr	12 types of cancer incidence	OSA versus general population <i>HR: 0.98 (0.90-1.00)</i>	Confounders: age, gender, and comorbidities No OSA severity available
Cohorts of OSA patients				
Campos-Rodriguez et al. (2013) ²⁴	Retrospective, multicentre 4910 OSA patients, median follow-up: 4.5 yr	Cancer incidence	CT90% > 12% versus < 1.2% <i>HR: 2.33</i>	Confounders: age, sex, BMI, smoking status and alcohol intake
Martinez-Garcia et al. (2014) ²⁵	Retrospective, multicentre 5427 OSA patients, median follow-up: 4.5 yr	Cancer mortality	Upper versus lower CT90% tertiles <i>HR: 14.4</i>	Confounders: age, sex, BMI, smoking status and alcohol intake
Sillah et al. (2018) ²⁶	Database cohort of 34.402 OSA patients, mean follow-up: 5.3 yr	Cancer incidence	OSA versus general population <i>SIR: 1.26</i>	No confounders No OSA severity available
Sillah et al. (2019) ²⁷	Case-cohort study of 1162 OSA patients, follow-up: 5.1 yr	Cancer incidence	AHI > 30 versus AHI < 15 <i>HR: 0.87 (0.52-1.45)</i>	Confounders: age, sex, BMI, and smoking status

AHI: apnoea-hypopnea index; BMI: body mass index; CT90%: percent of night-time spent with oxygen saturation < 90%; EES: Epworth sleepiness scale; OSA: obstructive sleep apnoea; RDI: respiratory disturbance index; SIR: age-sex standardised cancer incidence ratio.

risk among the younger (< 50 years) (HR: 4.09, 95% CI 1.58-10.55), but not the older participants. In addition, in a separate analysis with total cancer mortality as outcome, the authors found a slightly stronger effect of the number of SDB symptoms on cancer mortality compared with cancer incidence. Finally, in a longitudinal nationwide-based health insurance database for working adults and retirees with employer-sponsored health insurance coverage (5.6 million individuals), Gozal et al.²³ matched 1:1 OSA diagnosed with non-OSA diagnosed subjects and looked for incidence of 12 types of cancer. After at least two years of enrolment, with a mean follow-up of 3.2 years,

the incidence of global cancer was not different among patients with OSA. However, the study indicates that some cancers (i.e., pancreas, kidney and melanoma) exhibited increased incidence, whereas others (i.e., colon, rectal, lung) showed reduced incidence. The presence of OSA was not associated with an increased risk for metastasis or death. However, BMI and race, both important risk factors for cancer, could not be controlled for in this cohort, AHI was not available, and, lastly, the cause of death was unknown. Altogether, these population-based studies revealed markedly discrepant risks for incident cancer and did not provide compelling evidence that OSA could

be considered a general risk factor for incident cancer and for adverse cancer outcomes, except in a very restricted set of malignancies such as pancreatic and renal cancer and melanoma.

Large cohorts of patients

The Spanish Sleep Network was the first group to report an increase incidence of cancer among patients attending Sleep Clinics. In a multi-centre, clinical cohort study including consecutive patients investigated for suspected OSA between 2003 and 2007 in seven Spanish teaching hospitals, a total of 4910 patients were analysed for a median follow-up of 4.5 yr²⁴. Compared with the lower cumulative sleep time percentage with pulsioxymetry oxyhaemoglobin saturation (SpO₂) < 90% (CT90%) category (< 1.2%), those with a CT90% greater than 12% had an HR of cancer incidence of 2.33 (95% CI: 1.57-3.46). The AHI was associated with cancer incidence in the adjusted analyses, only for patients younger than 65 years (adjusted HR for AHI > 43 versus < 18.7, 1.66; 95% CI, 1.04–2.64). In a subsequent study, the same group evaluated the mortality associated with incident cancers²⁵. A close association was shown in patients < 65 years in both the AHI (upper versus lower AHI tertile: HR, 3.98; 95% CI, 1.14–3.64) and the CT90% (upper versus lower CT90% tertile: HR, 14.4; 95% CI, 1.85–111). For now, a larger and last published clinical-based study comes from the USA. Sillah et al.²⁶ identified 34,402 adults diagnosed with OSA using an administrative database in Western Washington State. Linking this cohort with a population-based cancer registry, they recorded 1575 first incident cancers during a mean follow-up period of 5.3 years. Compared with non-OSA subjects, they found an increase

in standardised cancer incidence ratios (SIRs) of 1.26 (95% CI 1.20-1.32). The observed significantly elevated cancer incidence occurred for breast, uterus, kidney and melanoma but confounders (e.g., BMI, smoking, diabetes) were not measured. In an additional case-cohort study, the authors found that overall cancer risk in individuals with moderate or severe OSA was not significantly different from individuals with mild OSA. However, they consistently found a higher proportion of severe OSA among patients with kidney, prostate, melanoma, corpus uteri, and lung cancers²⁷. Again, as in most studies described above, no information regarding OSA treatment was recorded.

Specific cancer types

The majority of available studies agree that patients with OSA have a higher risk of suffering from some types of malignant tumours such as kidney cancer²³, breast cancer^{28,29} and melanoma²³. More controversial is the relationship of OSA with other tumours such as prostate^{23,28} or colon cancer²³. To date, in the most recent and large study of Sillah et al.²⁶, mentioned above, among 1575 first incident cancer in 34,402 subjects with OSA, a significantly increased incidence for kidney, melanoma, breast, and uterus carcinomas was observed, while risk for lung and colorectal cancer was lower²⁶. The design of these clinical studies does not allow to hypothesise about the potential relationship between specific anatomical origins and OSA. We can only speculate with the possibility that IH, SF, and epigenetic dysfunction that characterise OSA, can affect the constitutive cells and tissues from different organs in a different way.

The tumour that has received the most attention in its relationship with OSA has been melanoma. On the one hand, the American retrospective cohorts using large administrative databases reported that OSA was independently associated with a higher risk of incident melanoma but not with higher mortality^{23,26}. On the other hand, a study that evaluated three prospective U.S. cohorts (Nurses' Health Study -NHS-, NHS-II and Health Professionals Follow-Up Study [HPFS]), during 2,301,445 person-years of follow-up did not observe any relationship between sleep duration or physician-diagnosed OSA and the risk of melanoma³¹. This study is limited by the lack of information about the baseline BMI, the severity of OSA and the unavailable information about OSA treatment. So far, there is only one study specifically designed to address the issue of the relationship between OSA and the aggressiveness and prognosis of melanoma. The Spanish Sleep Network conducted one large multicentre study enrolling 443 newly diagnosed patients with melanoma who underwent home sleep study. Considering a Breslow depth > 1 mm as a marker of aggressiveness, patients with an AHI in the upper tertile had a 1.94 (95% CI, 1.14–3.32) times to have this Breslow marker positive at baseline compared to those patients in the lower tertile of AHI, supporting the concept that the severity of OSA was independently associated with the aggressiveness of the melanoma³¹. Martinez-Garcia et al.³¹ have recently provided a critical review of the pathophysiological mechanisms and epidemiological links between these two disorders. After reviewing all clinical and basic studies carried out in this field, they concluded that the presence and severity of OSA could be associated with faster tumour growth and greater invasiveness.

However, they realised that the current data were insufficient to conclusively establish the validity and causal relationship between OSA and melanoma. The relationship between tumour aggressiveness and the presence of OSA has also been identified in renal carcinoma. In patients with clear cell renal cell carcinoma, those with self-reported OSA at diagnosis had higher Fuhrman grades and multivariate analysis, OSA correlate with tumour aggressiveness and poorer prognosis³².

Despite the growing information, there are too many caveats in clinical studies linking OSA and cancer. The main limitations are due to the fact that the majority of available studies are not prospective and therefore potential risk factors for cancer have not been taken into account.

Animal studies

At the beginning of the investigation on the intermediate mechanisms that justified the high morbidity and mortality of patients with OSA, the dog was a good animal model of experimentation. In this model, the phenomena of IH and SF characteristic of OSA in humans were reproduced³³. Using the dog as an animal model of OSA for the study of carcinogenesis is unfeasible. However, there are a few murine models that used a tracheostomy, inflatable balloon in the trachea or nasal mask to obstruct the airway to mimic the effects of OSA. Unfortunately, most cancer related OSA studies employ the airtight box model to generate IH or SF independent of the other physiological effects associated with OSA (Fig. 2). Using these models of IH mimicking OSA showed an enhanced cancer growth, invasion,

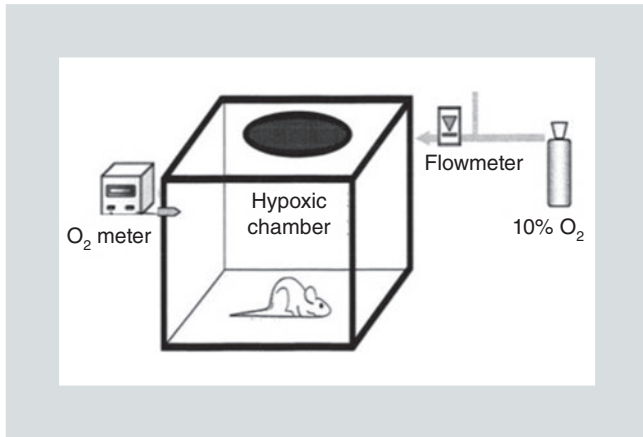


FIGURE 2. Graphical sketch of a typical intermittent hypoxic chamber.

O₂: oxygen.

and metastasis independent of the other effects of OSA (e.g., SF, hypercapnia, and sympathetic activation)^{34–36}. Simultaneously, in murine models of SF, without inducing associated IH, SF leads to increased tumour proliferation and invasion as well³⁷. The biological level of these changes is unknown. The space of this review does not allow extending in methodological details of these studies and we refer the reader to the excellent review from Hunyor and Cook on the topic³⁸.

In vitro models

For decades, in vitro models, including cell cultures, have been essential research tools to understand the molecular pathways that explain the onset and development of diseases. At present, there are some models to study the molecular pathways affected by OSA-driven IH. Most of these models involve alternating gas exposure over cells bathed in culture media that reproduce the fast and pronounced oxygen desaturations characteristic of OSA. In these models it has been shown that IH generates reactive oxygen species (ROS), which

likely increases oxidative stress and deoxyribonucleic acid (DNA) damage and could lead to increased angiogenesis and tumour growth (Fig. 3). These experiments have demonstrated how IH activates transcription factors such as hypoxia-inducible factor-1 (HIF-1), to express specific genes involved in angiogenesis and metastasis³⁹. It also increases nuclear factor (NF)-κB activation in breast cancer cells⁴⁰. NF-κB exists in most cells as an inactive form in the cytoplasm. However, upon IH stimulation, NF-κB is activated, moving into the nucleus and begin transcription of NF-κB target genes involved in apoptosis inhibition, proliferation, immunity, metastasis, and angiogenesis⁴¹. Tumour necrosis factor (TNF)α and interleukin (IL)-8 are elevated in patients with OSA and these cytokines are both NF-κB and HIF target genes⁴². Treatment with CPAP reduces TNFα^{42,43} and NF-κB^{44,45} levels. It seems therefore that the basic studies are partly reproducing the experimental animal trials. However, more accurate in vitro models of intermittent hypoxia reflective of OSA are needed to better elucidate underlying molecular pathways linking sleep apnoea with cancer.

Epigenetics, obstructive sleep apnoea and cancer

There is a growing interest in the role of hypoxia-mediated epigenetic regulation in cancer. Epigenetics refers to inheritable mechanisms responsible for regulating gene expression and the rates of gene transcription. Epigenetic mechanisms that modify genes activity include histone modifications, non-coding RNAs, and DNA methylation. Epigenetic alterations have been associated with hypoxia in cancer and the complex relationship between hypoxia

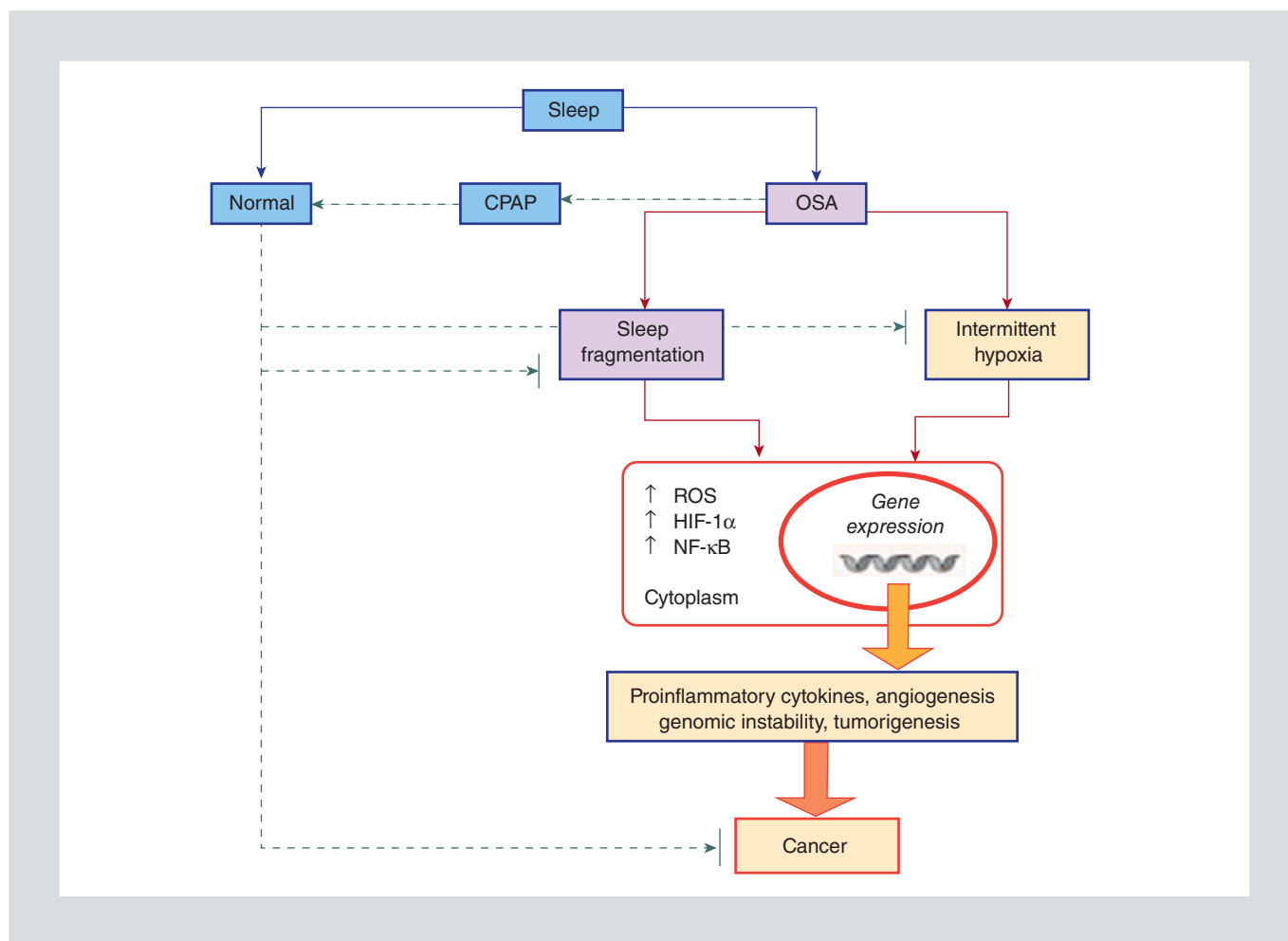


FIGURE 3. Mechanisms linking obstructive sleep apnoea (OSA) and cancer. Among many others apnoeic effects, sleep fragmentation and intermittent hypoxia are two main consequences of obstructive sleep apnoea that generates oxidative stress and reactive oxygen species (ROS). ROS activate Ca²-dependent calpain proteases increasing hypoxia-inducible factor (HIF)-1 α protein levels and releases nuclear factor (NF)- κ B in the cytoplasm. Both HIF-1 α and NF- κ B translocate to the nucleus, enabling transcription of HIF-1 α /NF- κ B target genes. Many of these genes are promoters of carcinogenesis.

and epigenetic mechanisms have been reviewed elsewhere⁴⁶. Mice engrafted with epithelial lung cancer cells exposed to IH, increased tumour size and invasiveness and hypermethylation of the tumour-promoting Rab3a gene⁴⁷. There are more than 2000 of non-coding ribonucleic acids (RNAs), such as micro(mi)RNAs and long non-coding (lnc)RNAs that either transcriptionally silence or degrade targeted messenger RNAs. Today there have been identified 180 oncogenic miRNA genes proven to be regulated by DNA methylation in many cancer

types⁴⁸, and some of them are hypoxia-related. For example, hypoxia-induced miR-210 promoter demethylation enhances proliferation and angiogenesis of schwannoma cells⁴⁹. According to this basis research, we have recently described an upregulation in miRNA-210 in patients with severe OSA without comorbid conditions⁵⁰. Interestingly, after one year of treatment with CPAP, there was a decrease in miRNA-210 whereas those levels stayed high in untreated patients (Fig. 4). It seems therefore that it is vital to understand the epigenetic mechanisms that

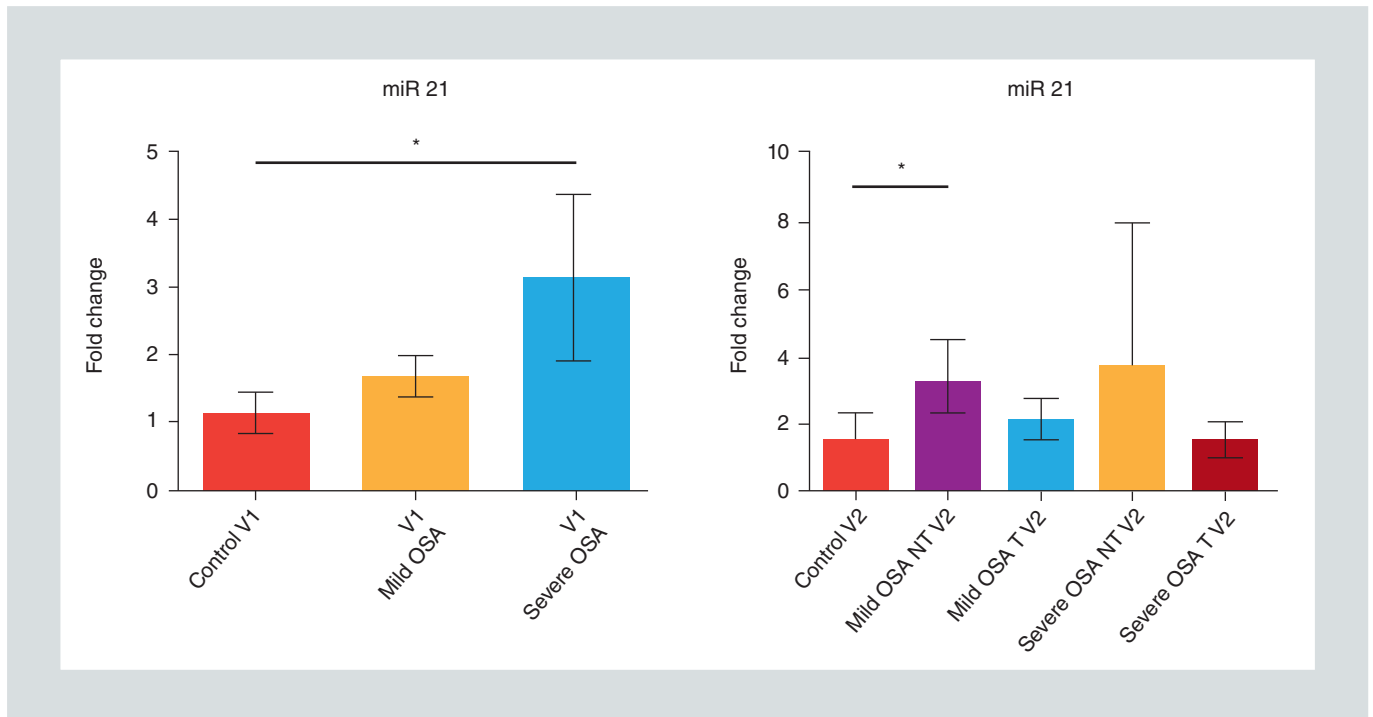


FIGURE 4. Exosomes miR-21 levels in obstructive sleep apnoea. At baseline (visit 1 –V1) and at one year of follow-up (V2), among controls healthy subjects without obstructive sleep apnoea (OSA), mild OSA and severe OSA, non-treated (NT) or treated with continuous positive airway pressure (CPAP).

regulate the development of many consequences of OSA, including cancer and specifically, the role of IH.

OBSTRUCTIVE SLEEP APNOEA IN CANCER PATIENTS

As described above, there is great interest in the study of OSA as a potential cancer risk factor. The opposite aspect has been much less studied, that is if cancer patients have a higher risk of developing OSA and whether or not OSA co-existence implies a worse prognosis for tumours. The sleep disorders most likely to affect patients with cancer are insomnia and an abnormal sleep-wake. Obvious reasons for cancer patients to have a bad sleep quality include stress about having cancer or side effects of anti-tumour

treatments including surgery or radiation. The tumour itself may cause many problems that impair sleep such as pain, cough, itching, fever, nausea, diarrhoea, urine incontinence, etc... It has been reported that one-third to one-half of cancer patients experience sleep disturbance⁵¹. There are few clinical studies conducted in patients with cancer in whom sleep studies have been conducted to identify the prevalence of sleep disorders in general and OSA in particular. However, there is relevant information on two types of tumours: head and neck and breast cancer.

Obstructive sleep apnoea in patients with head and neck cancer

In some studies that included patients with cancer of the oral cavity and oropharynx scheduled

for primary surgical resection, OSA was present in 13 of 17 patients, yielding a striking prevalence of 76% in this patient group. Interestingly, this relationship was independent of the size of the primary malignancy in this patient population with tumours^{52,52}. Structural alterations, as a flaccid epiglottis and neurosensory dysfunction can occur after surgery and/or radiation, thus affecting the balance between airway dilating and collapsing forces and leading to sleep apnoea⁵⁴. In fact, laryngeal function preservation surgery for laryngeal cancer results in the occurrence of OSA by altering the anatomical structure of the larynx and pharynx. In one study, patients who underwent partial laryngectomy for carcinoma of the larynx showed during laryngoscopy narrowed retro-palatal and retro-lingual space post-operatively. OSA was more severe in parallel with the residual narrow airway⁵⁵. It is therefore concluded that after surgery/radiotherapy of this type of tumours, a sleep study should be performed routinely.

Obstructive sleep apnoea in patients with breast cancer

Basic research has reported that intra-tumoral hypoxia promotes tumour cell proliferation, invasion and angiogenesis⁵⁶. Using an immunocompetent and syngeneic murine model of breast cancer, Chen et al.⁵⁷ exposing mammary tumour cells to intermittent hypoxia promoted clonal diversity, upregulated metastasis-associated gene expression, induced a pro-tumorigenic secretory profile, increased stem-like cell marker expression, and gave rise to tumour-initiating cells at a relatively higher frequency. This

work demonstrates that IH, but not chronic hypoxia, induces a number of genetic, molecular, biochemical, and cellular changes that facilitate tumour cell survival, colonisation, and the creation of a permissive microenvironment and thus enhances metastatic growth. Further, considering that IH is one of the hallmarks of OSA, it is reasonable to hypothesise an association between the coexistence of OSA and poor prognosis in patients with breast cancer. In a recent study from Spain, Campos-Rodriguez et al.⁵⁸ studied 83 consecutive women diagnosed of breast cancer home respiratory polygraphy. They found no differences in the association between the presence or severity of OSA and breast cancer aggressiveness as evaluated by the Ki67 proliferation index, a surrogate of cell proliferation⁵⁸. However, in this series, the median AHI was 5.1 and there were few patients with AHI greater than 15 events/hour. We believe that OSA did not have enough severity to influence breast cancer aggressiveness in this study and further studies are needed to definitively clarify the role of OSA coexistence in the prognosis of breast cancer. In addition, prospective studies are warranted to investigate to what extent OSA is caused or exacerbated by the cancer itself or by cancer treatment.

UNCERTAINTIES AND FUTURE CHALLENGES

In the era of evidence-based medicine, randomised control trials (RCTs) are the star studies. Randomised, placebo-controlled trials have indicated that treating OSA with CPAP improves quality of life, driving simulator

performance, blood pressure, and sleepiness. These RCTs are developed over a short period of time (for example weeks or months). To demonstrate that a therapeutic intervention impacts robust health outcomes (e.g. incidence of stroke, myocardial infarction, cancer or mortality), the RCT must be developed for many years. This is not feasible when there is an effective treatment to improve the symptoms of any medical process. The alternative are large prospective cohort studies. We have reviewed here some positive and negative studies that have looked at the OSA-cancer relationship. All recruited participants were selected based on AHI. Although this index is the recommended biomarker to define OSA severity, it does not reflect the complexity of OSA. During an apnoeic event, other consequences such as cortical arousals, autonomic response and the magnitude of the oxygen desaturation, can stimulate different responses on the immune, cardiovascular or metabolic system. No specific biomarkers reflecting these abnormalities have been studied to date. Therefore, in the epidemiological studies mentioned above or in the new observational studies, we believe that other biomarkers predictors of negative outcomes should be evaluated (in this case cancer). Some of these candidates may include density of nocturnal hypoxaemia, duration of apnoea, response of heart rate or degree of daytime sleepiness. This multidimensional evaluation will dilute the heterogeneity of OSA and establish more precisely the OSA-cancer relationships in particular and OSA health burden relationship in general.

Regarding recently diagnosed cancer patients, in the current state of knowledge, systematic studies of sleep cannot be recommended.

However, we believe that all patients with head and neck cancer who are going to undergo non-radical surgery or radiotherapy of the upper airway should have a sleep study after treatment given the high probability of occurrence of OSA. In women with breast cancer, one should be alert of the possibility of OSA coexistence, since it seems that this cancer-OSA association is related to increased tumour aggressiveness. For these cases, current guidelines for OSA treatment with CPAP should not be so rigid and should consider patients with moderate OSA as candidates.

CONCLUSIONS

To summarise the available scientific information discussed above, currently, from the clinical point of view, we cannot recommend changes in clinical practice or changes in the public health strategies concerning OSA. There are still no robust studies to establish a relationship between the quantity and quality of sleep and cancer. Importantly, there is no evidence as yet to establish a causal relationship between OSA and cancer. Accordingly, it is not necessary to actively search for neoplasms in the first consultation of a patient with OSA, nor should our current practice be modified. However, the information available forces us to increase our alert about the potential risk of cancer as comorbidity in patients with OSA, and to follow our patients with some regularity but without alarm.

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DISCLOSURES

Dr. Marin, Dr. Vicente and Dr. Marin-Oto have nothing to disclose.

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