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Challenging Multi-Morbidities: Obstructive Sleep Apnoea and Cancer

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ABSTRACT

Obstructive sleep apnoea (OSA) is a highly prevalent disorder in adults and has been associated with a large array of end-organ morbidities affecting multiple organ systems. From recent epidemiological studies there is growing evidence linking this sleep breathing disorder with an increased incidence and enhanced mortality in cancer, where the recurrent oxygen desaturations experienced by patients with OSA have been proposed as a major determinant of adverse cancer outcomes. The use of translational models mimicking the intermittent hypoxia and sleep fragmentation that characterize OSA have shown that both challenges can enhance tumour growth and malignancy in several types of cancers including melanoma, kidney cancer, and lung carcinoma. Moreover, translational and basic researches have provided solid emerging evidence implicating the immune system in the adverse cancer outcomes linked to intermittent hypoxia. Here we review all data available to date on the relationship between OSA and cancer from clinical and translational studies. **(BRN Rev. 2016;2:170-84)**

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OBSTRUCTIVE SLEEP APNOEA

Obstructive sleep apnoea (OSA) is a highly prevalent sleep disorder, which, depending on sex and age, can affect between 4 and 10% of the adult population[1] and is characterized by repetitive occlusions of the upper airway during sleep. These repetitive obstructions can lead to recurrent blood oxygen desaturations and sleep fragmentation. As presented in this review, very recent data from epidemiological, clinical, and translational studies have suggested that there is a potential link between OSA and cancer.

EVIDENCES FROM EPIDEMIOLOGICAL AND CLINICAL DATA

Population and Community Based Studies on Obstructive Sleep Apnoea and Cancer

Although there is growing evidence on the possible association between OSA and cancer, the number of studies based on human data is still scarce and present some limitations. For instance, most of the epidemiological and clinical studies are not focused on specific types of cancers. Moreover, other potential cancer risks and/or protective factors are not well controlled because the historical focus of the cohorts was based on respiratory disorders instead of cancer. However, and in spite of these limitations, the majority of these studies show increased cancer incidence, mortality, and aggressiveness in moderate-to-severe OSA patients.

The first population-based study linking both entities was carried out by the Wisconsin cohort, which included 1,522 subjects with a 22-year follow-up. Nieto et al.[2] found an association between the apnoea-hypopnoea index (AHI), the most commonly employed metrics to measure the severity of OSA, with cancer mortality. In particular, after adjusting for well-known confounding factors such as age, sex, body mass index, and smoking habits, OSA presented increased rates of cancer mortality in a dose-response fashion. The adjusted relative hazards of cancer mortality in comparison to non-OSA subjects were 1.1 (95% confidence interval (CI): 0.5-2.7), 2.0 (95% CI: 0.7-5.5), and 4.8 (95% CI: 1.7-13.2) for mild, moderate, and severe OSA patients, respectively. Subsequent analyses from this cohort showed that this association appears stronger when, instead of AHI, oximetry indices were used to characterize OSA severity. From stratified analyses, Nieto et al. found clearer case-control differences among the non-obese OSA patients, evidencing that obesity is an important confounding factor in OSA. Taking into account these findings, it is plausible that, as discussed below, OSA potentiates cancer incidence and mortality through the well-documented metabolic consequences of this sleep breathing disorder.

Similar results on a potential OSA-cancer relationship were found by the Busselton cohort. In that work, Marshall et al.[3] presented a 20-year follow-up of 397 OSA patients. After data adjustment, the authors found that moderate-to-severe OSA was significantly associated with cancer incidence and mortality, presenting a hazard ratio (HR) of 2.5 (95% CI: 1.2-5.0) and 3.4 (96% CI: 1.1-10.2), respectively, in comparison to non-OSA subjects.

Two studies only based on questionnaires did not find a clear interaction between OSA

and cancer incidence. In one of them, all the participants answered questions about snoring and breathing cessations (n = 8,783) and only in a subset of participants was daytime sleepiness also included (n = 5,894)[4]. Although no overall association between symptoms of sleep disordered breathing and incident cancer was observed, in a small group of subjects with high daytime sleepiness, the authors observed a markedly higher cancer incidence (HR: 4.09; 95% CI: 1.58-10.55) in participants under 50 years old[4]. Christensen et al. also found a higher risk of virus/immune-related cancers (HR: 2.73; 95% CI; 1.27-5.91) and alcohol-related cancers (HR: 4.92; 95% CI: 1.45-16.76) among participants with daytime sleepiness. In addition, the sleep disordered breathing symptoms were associated with a higher risk of smoking-related cancers. In the other study based on questionnaires asking about snoring and sleeping time of participants, Cohen et al.[5] did not find any relationship between melanoma incidence and snoring. However, these studies have an important limitation since the participants did not undergo any objective and standard sleep tests to confirm the presence of OSA.

There are two more Taiwanese series studies analysing data provided from their National Health Institute. In the first series, the cohort consisted of women diagnosed with OSA (n = 846) with a follow up of five years[6]. The authors observed that OSA patients had a greater risk of developing a breast cancer (HR: 2.09; 95% CI: 1.06-4.12) compared to control subjects[6]. In contrast to the previous studies including all types of cancer, the risk of breast cancer seems to be higher in older women. In particular, the HR was 2.06 (95% CI: 0.90-4.70) in women aged 30-59 years and 3.05 (95% CI: 0.9010.32) in those over 60 years old as compared with those aged between 0-29 years. This is a relevant finding considering the potential metabolic disorders associated to menopause in women. The other Taiwanese study included 23,055 OSA patients matched by age and sex to subjects without OSA[7]. The authors evaluated the incidence of primary malignant central nervous system (CNS) cancers over a 10-year period and found that the incidence density (10,000 individual/year) was 2.14 and 1.28 in OSA patients and non-OSA subjects, respectively. The risk of incidence in CNS cancers presented an HR of 1.54 (95% CI: 1.01-2.37) after adjusting for some common confounding variables such as age, sex, and obesity.

Very recently, Fang et al.[8] published a case-control study by searching the outpatient and inpatient claims databases with any cancer from the Taiwan National Health Insurance program. The study included 68,422 patients; each one was matched with two controls. After adjustment for several confounders, OSA significantly increased the risks of breast cancer (HR: 2.10; 95% CI: 1.16-3.80), nasal cancer (HR: 5.96; 95% CI: 2.96-11.99), prostate cancer (HR: 3.69; 95% CI: 1.98-6.89), and bladder cancer (HR: 2.91; 95% CI: 1.30-6.50).

Clinical Studies on Obstructive Sleep Apnoea and Cancer

The first clinical study appeared in 2013 from the Spanish Sleep Group. This work was a retrospective and multicenter study with a follow-up of 4.5 years and composed of 4,910 OSA patients not previously diagnosed with cancer[9]. Campos-Rodríguez et al.

showed a clear association between the severity of OSA and the incidence of all types of cancer. The AHI and the percentage of sleep time presenting values of oxygen saturation < 90%, or TSat(90), were categorized by tertiles and used as surrogates of OSA severity. Compared with the lowest TSat(90) category (< 1.2%), the adjusted hazards of cancer incidence for increasing categories were 1.58 for TSat(90) between 1.2 and 12%, and 2.33 for TSat(90) > 12%. The AHI was not associated with cancer incidence in the adjusted analyses, except for patients younger than 65 years. In a subsequent study on the same group of OSA patients, Martínez-García et al.[10] investigated cancer mortality and found a pattern similar to that observed in cancer incidence[9]. Specifically, log-transformed TSat(90) was independently associated with increased cancer mortality. Also, according to previous findings, the strongest association was found in those patients less than 65 years old. Interestingly, a posterior sub-analysis including only patients previously diagnosed with cancer found that TSat(90) was an independent predictor of cancer prognosis.

The increased cancer incidence observed in OSA patients from the Australian, Taiwanese, and Spanish works was not reproduced in a study from the Ontario health administrative databases. In that work, Kendzerska et al.[11] included 10,149 patients who underwent a sleep study and 5% of them had a cancer diagnosis at baseline. After a follow-up of 7.8 years, 6.5% of those OSA patients free of cancer suffered incident cancer. After adjustment for age, sex, body mass index, and smoking status at baseline, the authors did not find an association with either prevalence or incidence of cancer. However, in a subgroup of patients they found that oxygen desaturation, but not AHI, was significantly associated with smoking-related cancers.

More recently, the first study based on a specific type of cancer and OSA has been published. Martínez-García et al.[12] analysed the potential relationship between OSA with cutaneous malignant melanoma (CMM) aggressiveness. This was a multicenter observational study that included 56 patients diagnosed with CMM. All patients underwent a complete sleep study, and tumour mitotic rate, Breslow index, presence of ulceration, stage of disease, and growth rate of melanoma were assessed as markers of CMM aggressiveness. The prevalence of OSA was higher in patients diagnosed with CMM. In particular, 60.7% of them presented an AHI ≥ 5 events/hour and 14.3% had severe OSA (AHI ≥ 30). In fully adjusted multivariate analyses, AHI and oxygen desaturation indices were independently associated with an increased skin depth and growth rate of melanoma.

The last reported preliminary data aimed at assessing the association between OSA and clinical markers is focused on kidney tumour progression measured by Fuhrman grade and tumour size in patients with renal carcinoma[13]. The retrospective study included 2,579 patients who underwent radical or partial nephrectomy for renal carcinoma. OSA was not found to be associated with tumour size. However, more patients with OSA had high Fuhrman grade compared to those without OSA (51 vs. 38%; 13% risk difference; 95% CI: 5-20%). On multivariable analysis, the association remained significant (odd ratio: (OR): 1.41; 95% CI: 1.00-1.99).

Taking into account the entire patient studies already available to date, it seems that the association between OSA and cancer mortality is more consistent and clearer than in cancer incidence. This fact could be explained by other potential risk factors such as genetic background, obesity, and the presence of carcinogenic environmental factors, which can play a crucial role in tumourigenesis (Table 1).

Role of Immune System Changes Linking Obstructive Sleep Apnoea and Cancer

There are two very recent clinical studies suggesting potential mechanisms that could partially explain the increased incidence of cancer in OSA patients. Both works, although with different aims, suggest that the immune changes induced by OSA could facilitate malignant cells to leave the tumour and thus metastasize. In a first work, Gharib et al.[14] investigated the transcriptome of peripheral blood leukocytes (PBL) in response to continuous positive airway pressure (CPAP), which constitutes the first line of treatment for OSA. In order to explore the molecular pathways affected by CPAP, authors quantified the whole genome expression of PBLs by microarray analysis from severe OSA patients before and after treatment. As expected, CPAP treatment improved most of the sleep variables measured in OSA patients. Interestingly, and unexpected by the authors, the gene set enrichment analysis from PBLs revealed a number of enriched gene sets and many neoplasm-related pathways that were downregulated after CPAP treatment. Further network analyses identified several densely connected genes, which are already known as key modulators of cancer progression.

In a second work, Gaoatswe et al.[15] investigated whether invariant natural killer T (iNKT) cells could be reduced in OSA patients. The iNKT cells are prominently activated when foreign lipids are present and play an important role in cancer immunity. In fact, a reduction in iNKT cell numbers in the peripheral blood has been correlated with several autoimmune or inflammatory conditions and cancers[16]. The authors showed that patients with severe OSA presented considerably fewer iNKT cells (0.18%) compared to patients with moderate (0.24%) or no OSA (0.35%). In fact, the authors found that the amount of iNKT cells correlated negatively with AHI ($r = -0.58$; $p = 0.001$), oxygen desaturation index ($r = -0.58$; $p = 0.0003$), and TSat(90) ($r = -0.5407$; $p = 0.005$). Interestingly, changes in these immune system cells were reverted after 12 months of nasal CPAP therapy. Moreover, application of hypoxia to these cells in culture resulted in increased apoptosis and impaired cytotoxicity, supporting the notion that OSA-induced iNKT cell alterations could facilitate tumourigenesis and tumour progression.

Circadian Rhythm Alterations and Poor Sleep Quality as Risk Factors of Cancer

Although not directly focused on OSA, several epidemiological studies related to sleep duration and cancer outcomes have started to emerge recently[17-30]. The disruption of the circadian rhythm could augment the risk of several types of cancer[31-33]. Nightshift work and

Table 1. Summary of the available epidemiological and clinical studies on the association between obstructive sleep apnoea and cancer incidence (green) and mortality/aggressiveness (red)

References	Subjects	Study design	Diagnosis	Outcome	Association OSA-cancer	Main findings
Nieto et al.[2] 2012	1,522	Population-based study (22-year follow-up)	PSG or RP	Cancer mortality	Yes	SDB was associated with cancer mortality, especially with TSat(90). The relationship was stronger in non-obese population and non-treated patients with CPAP
Christensen et al.[4] 2013	8,783	Prospective cohort study (13-year follow-up)	Questions about OSA symptoms	Cancer incidence	Limited to cancer type	No relationship between OSA symptoms with cancer incidence except for patients younger than 50 years with smoking-related cancers
Campos-Rodriguez et al.[9] 2013	4,910	Multicenter retrospective clinical cohort study (4.5-year follow-up)	Full PSG	Cancer incidence	Yes	Severe OSA presented increased incidence of cancer in patients under 65 year old
Marshall et al.[3] 2014	397	Population-based study (20-year follow-up)	Respiratory disturbance index	Cancer incidence and mortality	Yes	OSA was associated with cancer mortality and cancer incidence
Chen et al.[7] 2014	23,055 OSA and 69,165 controls	Population--based-study (10-year follow-up)	Full PSG	Central nervous system cancer incidence	Limited to cancer type	Higher central nervous system cancer incidence (especially brain cancer) in OSA patients in comparison with control group without OSA
Chang et al.[6] 2014	846 women with OSA and 4,230 controls	Population--based-study (5-year follow-up)	Full PSG	Breast cancer incidence	Limited to cancer type	Higher breast cancer incidence in OSA with respect to healthy women
Martínez-García et al.[10] 2014	5,427	Multicenter retrospective clinical cohort study (4.5-year follow-up)	Full PSG or RP	Cancer mortality	Yes	OSA variables TSat(90) and AHI were associated with higher cancer mortality, stronger in male patients under 65 years
Martínez-García et al.[12] 2014	56 with melanoma	Multicenter	RP	Melanoma aggressiveness	Yes	High prevalence of OSA in patients diagnosed with melanoma; OSA associated with melanoma malignancy
Kendzerska et al.[11] 2014	10,149	Multicenter retrospective clinical cohort study (7.8 year-follow-up)	Full PSG	Cancer incidence	Limited to cancer type	Non-significant relationship between OSA and incident of cancer after adjusting variables. Smoking-related cancer was associated with TSat(90)
Cohen et al.[5] 2015	2,301,445	Prospective cohort study (from 2008)	Self-reported snoring and sleeping time	Cancer incidence	No	No relationship between SDB (evaluated as snoring) and cancer incidence was observed
Fang et al.[8] 2015	68,422 OSA and 136,844 controls	Prospective cohort study (10-year follow-up)	Full PSG	Cancer incidence	Yes	OSA was associated to increased incidence of nasal, breast, prostate and bladder cancer

AHI: apnoea-hypopnoea index; CPAP: continuous positive airway pressure; OSA: obstructive sleep apnoea; PSG: polysomnography; RP: respiratory polygraphy; SDB: sleep-disordered breathing; TSat(90): oxygen saturation < 90%.

the use of social technologies during the night are the most representative forms of circadian rhythm alteration in modern society. Shift work has been widely associated with an increased prevalence of breast, prostate, and colorectal cancers[31-34].

Schernhammer et al.[35] prospectively studied the relationship between rotating nightshift work and breast cancer. Among 115,022 women without cancer at baseline, 1,352 finally developed breast cancer during the following 12 years. In this study, only those women who reported more than 20 years of exposure to rotating nightshift work increased their relative risk of breast cancer (RR: 1.79; 95% CI: 1.06-3.01). Very similar results were found recently by Åkerstedt et al.[36] from a Swedish prospective cohort study where twins born were included. Data on cancer were obtained from the Swedish Cancer Registry and from the Cause of Death Register, and linked to the twins by using the unique person identification number available for all Swedish citizens. The results obtained in this study showed an association between long exposure to night work (> 20 years) with breast cancer in women. Similarly, Viswanathan et al.[37] prospectively studied a cohort of 121,701 women; 53,487 of them reported rotating nightshift work in 1988 and were followed during the following 16 years. Invasive endometrial cancer was diagnosed in 515 women. The authors reported that women exposed to nightshift work during at least 20 years had a significantly increased risk of endometrial cancer (RR: 1.47; 95% CI: 1.03-1.14). In further stratified analyses, the authors found that the coexistence of obesity with shift work markedly enhanced their baseline risk of endometrial cancer (multivariate RR: 2.09; 95% CI: 1.24-3.52) compared with obese women not working at night. Hansen et al.[38] compared 7,035 women aged 30-54 years with primary breast cancer retrieved from the Danish Cancer Registry. Female controls, free of cancer at the time of diagnosis, were matched individually considering age. After accounting for reproductive history and socioeconomic status, they found a 1.5-fold increase in the risk (95% CI: 1.2-1.7) of primary breast cancer in women who had been employed for at least six months with predominantly night work (> 60%). Schernhammer et al.[34], in a prospective study, explored the potential association between working rotating nightshifts and the risk of colorectal cancers among female participants. From 78,586 women followed up for 10 years, the authors reported that long-term shift work (> 15 years) promoted an increased risk of colorectal cancer of 1.35 (95% CI: 1.03-1.77) compared with women without experience of rotating night shifts of 1.00 (95% CI: 0.84-1.19).

EVIDENCES FROM TRANSLATIONAL MODELS AND POTENTIAL MECHANISMS

Hypoxia and Tumour Malignancy

Hypoxia is one of the most common conditions encountered within the tumour microenvironment, and has been related to an enhanced metastatic potential, resistance to chemo- and radiotherapy, and poor prognosis[39-42]. In fact, the strong association between the development of metastasis and the proportion of hypoxic cells in primary tumours suggests that hypoxia can drive tumour cells to a more aggressive and metastatic phenotype. It has

been postulated that hypoxia can itself upregulate a wide array of genes associated with tumour progression and metastasis through the transcriptional activity of hypoxia-inducible factors (HIF-1, HIF-2)[43,44]. Currently, clinically tested systemic therapeutic strategies are employed to directly target hypoxic tumour cells to control the growth and progression of primary tumours.

Another characteristic of solid tumours is their heterogeneous distribution of blood flow, with significant hypoxia in low-flow regions. When malignant cells are distant to blood vessels, there is an imbalance between oxygen delivery and consumption, leading to a hypoxic and acidic cell microenvironment. However, in the periphery, *i.e.* in areas where the tumour is advancing, the newly formed vessels are poorly developed and disorganized, resulting in some regions that are over-perfused and other areas poorly irrigated[45,46]. In addition, it is well known that the blood flow is aberrant and intermittent in a substantial percentage of vessels[47]. Therefore, tumour cells are likely subjected to an erratic pattern of cyclical hypoxia, as recently revealed by means of oxygen partial pressure (PtO_2) electrodes in human tumours[48].

The oscillatory pattern of oxygen availability observed within the tumour awoke the interest in investigating the effects of cyclic hypoxic oscillations on tumour behaviour. These studies have uncovered clear evidence that intermittent hypoxia (IH) can promote tumour malignancy and resistance to conventional therapy[49]. In particular, there are studies showing that a short hypoxic stimulus is sufficient to promote the emergence of spontaneous microscopic metastases[50-52]. Interestingly, cells pre-exposed to cyclic hypoxia, with a frequency pattern similar to that experienced in OSA, increased the metastatic potential in a rodent model[52,53].

Specifically concerning OSA, there is increasing evidence that IH plays a mechanistic role in the development of well-established cardiovascular, metabolic, and cognitive consequences of OSA through activation of oxidative stress and inflammatory pathways. In fact, IH is one of the most widely studied hallmark features of this sleep breathing disorder. The IH pattern in most animal-based studies aiming to replicate OSA reproduce high frequency hypoxic cycles, low fraction of inspired oxygen (FIO_2) and the application of the IH challenge during the sleep period[54]. Therefore, the selected IH parameters aim to recapitulate the AHI and oxygen desaturation indices that characterize the moderate and severe OSA patients[55]. These specific conditions manifest pathological outcomes, disabling adaptive processes reported by cyclic hypoxia with a lower frequency oscillation of oxygen tension and with less severe hypoxic levels[56]. Furthermore, in tumours presenting higher metabolic rates, IH may worsen the availability of oxygen in those areas where blood flow is already compromised. Of note, tumour regions that are well perfused will experience oxygen oscillations in blood as a result of the recurrent hypoxemic events applied. Furthermore, tumour cells will also receive the systemic IH-induced molecules released from distant tissues, including reactive oxidative species, proinflammatory cytokines, and angiogenic soluble factors, which can ultimately modulate the

immune response[57-61]. Hypoxia inducible factor-1 (HIF-1) has been widely studied in OSA and cancer as a pivotal molecule in both diseases[62-65]. This transcriptional factor is composed of two subunits, one constitutively expressed and an O_2-regulated subunit[66]. Thus, HIF-1 can be induced by hypoxia as a consequence of HIF prolyl-hydroxylase inhibition since it uses oxygen as a co-substrate[63,67]. The HIF induces the expression of a diverse set of genes that assist cells to adapt to hypoxic environments. All these aforementioned considerations make it biologically plausible that IH mimicking OSA could impose an important challenge in those well-irrigated tumour areas where processes such as cancer invasion and metastasis primarily occur.

Animal Models Linking Obstructive Sleep Apnoea and Cancer

The complexity of OSA provided the motivation to use animal models of cancer. Such studies facilitate our understanding of how OSA may facilitate cancers to appear, why primary tumours may more likely metastasize, and whether specific preventive interventions and treatments can be used to slow the progression of cancer. Also, the employment of animal models avoids the interaction of most common confounders such as obesity or other metabolic disorders associated to OSA, which are well known to promote cancer progression.

Concerning the IH challenge, very recent exploratory studies mimicking the repetitive oxygen oscillations observed in moderate-to-severe OSA patients have been employed in an increasing number of tumour models. In most of these studies, tumour growth in mice subjected to IH was faster compared to control conditions and the studies have shown increased malignant properties including invasion, metastasis, vascularization, and infiltration of pro-tumoural cells (Fig. 1). In particular, IH promotes more adverse outcomes in all three types of cancer investigated to date, namely melanoma[68-71], lung adenocarcinoma[72,73], and kidney cancer[74] (Table 2). Also, a very recent study has shown that IH not only increases tumour malignancy, but also promotes spontaneous cancer incidence in aged wild-type mice[75]. Indeed, outbreed mice (Swiss CD1) were subjected to IH (8 hours/day; 3 months) applied from age 15 to 18 months, equivalent to a human age of 50-60 years. The authors employed two severity paradigms of IH: 80 s air/40 s 12% oxygen (n = 49), or 7.5% oxigen (n = 53). Tumoural masses were found in 36.4% of control mice (8 liver, 7 lung, 5 skin), in 38.8% in those mice exposed to mild IH (12% oxygen) (11 liver, 7 lung, 1 skin) and in 63.5% in mice exposed to severe IH (7.5% oxygen; p = 0.005 vs. control) (11 liver, 15 lung, 7 skin). On the other hand, a previously well-established mouse model of sleep fragmentation reproducing OSA was used to assess the potential role of sleep fragmentation on tumour behaviour[76]. Hakim et al. imposed sleep fragmentation on two syngeneic murine models involving lung epithelial tumour models (TC1 and LLC) and found a twofold tumour growth when compared with normal sleep control conditions. Also, sleep fragmentation-induced tumours showed increased invasion and infiltration toward the surrounding tissues[77]. Zheng et al.[78] showed similar results and they found the transgenic ablation of nitric oxidase 2 (Nox2) resulted in enhanced oncogenic properties. These

Table 2. Summary of the available experimental studies on the effects of intermittent hypoxia and sleep fragmentation mimicking obstructive sleep apnoea in cancer incidence and aggressiveness. This table indicates whether intermittent hypoxia or sleep fragmentation increased tumour proliferation, invasion, metastasis and/or vascularization. All studies were carried out in mice

References	Cancer type	Tumour size/ proliferation	Invasion	Metastasis	Vascularity	Main findings
Almendros et al. 2012[68]	Melanoma (B16F10)	Yes	–	–	–	IH accelerates tumour growth
Almendros et al. 2012[70]	Melanoma (B16F10)	Yes	–	–	Yes	IH and obesity have no synergistic effect on tumour growth
Almendros et al. 2013[69]	Melanoma (B16F10)	Yes	–	Yes	–	Cancer mortality and metastasis are increased under IH conditions
Eubank et al. 2013[82]	Melanoma (B16F10)	No	–	Yes	–	Application of IH increases tumour spread
Perini et al. 2016[71]	Melanoma (B16F10)	Yes	–	–	–	Melanoma malignant molecules increased under IH
Almendros et al. 2014[72]	Lung carcinoma (TC1)	Yes	Yes	–	–	IH promoted a shift toward a pro-tumoural phenotype in tumour-associated macrophages
Hakim et al. 2014[77]	Lung carcinoma (TC1)	Yes	Yes	–	–	Sleep fragmentation increased tumour growth through changes in the host immune response
Cortese et al. 2015[73]	Lung carcinoma (TC1)	Yes	Yes	–	–	The exposure to IH increases the shedding of cirDNA into circulation carrying specific epigenetic modifications
Zheng et al. 2015[78]	Lung carcinoma (TC1)	Yes	Yes	–	–	Perturbed sleep could adversely affect innate immunity within the tumour by altering NOX2 expression and activity
Almendros et al. 2015[83]	Lung carcinoma (TC1)	Yes	Yes	–	–	IH-inflamed adipose tissue is a potential source of immune cells to the tumour
Gallego-Martín et al. 2015[75]	–	–	–	–	–	Incidence of cancer is augmented in aged mice exposed to IH
Vilaseca et al. 2016[74]	Kidney cancer (RENCA)	No	–	–	Yes	IH promotes angiogenesis in renal tumours

B16F10: mouse melanoma cancer cell line (american type culture collection, ATCC); IH: intermittent hypoxia; NOX: nitric oxidase; RENCA: renal adenocarcinoma (ATCC); TC1: lung carcinoma cell cancer line (ATCC).

findings demonstrated for the first time that the type of sleep disruption experienced by OSA patients enhances tumour aggressiveness in absence of hypoxia. The potential mechanisms involved in IH- and sleep fragmentation (SF)-induced tumour malignancy have been also studied in further translational studies as outlined below.

Immune Changes Induced by Intermittent Hypoxia and Sleep Fragmentation

The tumour microenvironment is composed by multiple cell types such as cancer cells, endothelial cells, fibroblasts, and immune cells. These cells are heterogeneous, and

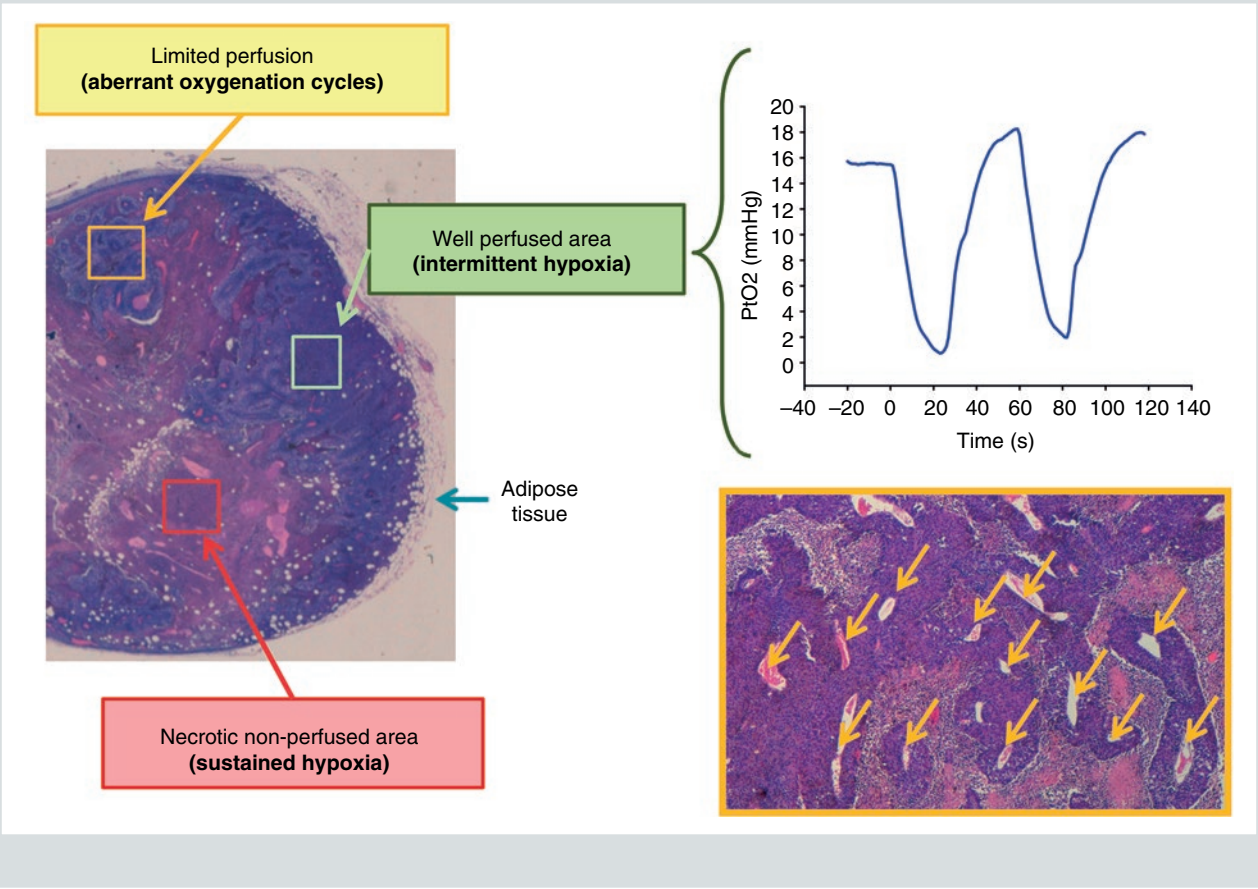

Figure 1. Tumors are characterized by the heterogeneous distribution of blood flow inside them. The image illustrates the potential effect of systemic intermittent hypoxia inside the tumour. Regions more distant to vessels and usually in the core of the tumour are subjected to sustained hypoxia and are mainly necrotic. In other areas the viability of tumour cells depends on the presence of a large vessel (yellow arrows) providing irregular blood flow, thereby leading to aberrant oxygenation cycles. By contrast, there are well-irrigated regions where the tumour grows and expands to the periphery. These regions are the most exposed to the obstructive sleep apnoea-induced recurrent oxygen desaturations as can be observed by the experimental oxygen partial pressure swings experienced in response to intermittent hypoxia. The figure includes an example of real-time oxygen partial pressure measurement by means of an oxygen microelectrode placed in a well-irrigated region of the tumour: subjecting the mouse to intermittent hypoxia mimicking obstructive sleep apnoea produced repeated marked decreases in tumour oxygenation. PtO_2: oxygen partial pressure.

based on patterns of gene expression and function, they have been commonly classified as classically (M1) or alternatively (M2) activated[79]. In terms of cancer, macrophages designated as tumour-associated macrophages (TAM) also present these two phenotypes and constitute the most abundant fraction of leukocytes in the tumour stroma. The presence of certain molecules in the tumour microenvironment facilitates TAM re-education from M1 phenotype (anti-tumour properties) towards M2 (pro-tumoral phenotype), which is known to release factors promoting tumour growth and aggressiveness. The hypoxic microenvironment characteristic of solid tumours has been proposed as a determinant factor in the recruitment of TAMs and their re-education towards the alternative activated M2 form[80]. Indeed, the changes induced by hypoxia on the phenotypic characteristics

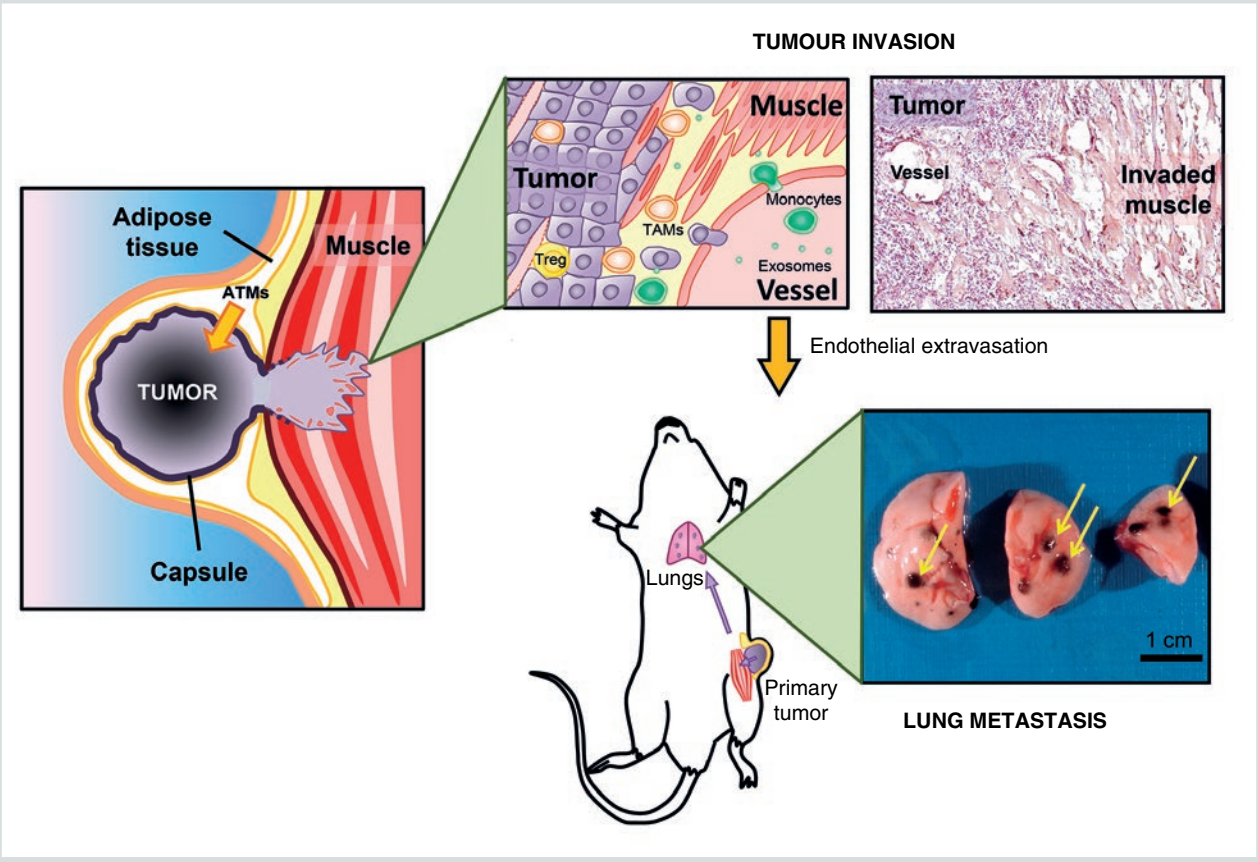

Figure 2. Scheme of main mechanisms described in response to intermittent hypoxia and sleep fragmentation. At short term, both entities promote tumour growth and invasiveness toward surrounding tissues. It has been described that inflamed ipsilateral adipose tissue is a depot of pro-tumoural resident macrophages and other immune suppressor cells such as regulatory T-cells. Monocytes from bone marrow are also recruited within the tumour and exosomes promote endothelial disruption. Exosomes and tumour-associated macrophages have been proposed as mediators of the increased lung melanoma metastasis (yellow arrows) reported at long term.
ATM: adipose tissue macrophage; TAM: tumour-associated macrophage; Treg: regulatory T-cell.

of TAMs include the secretion of mitogenic factors, pro-angiogenic cytokines, and immunosuppressive agents[40,81].

Recent studies have shown that IH and SF can accelerate the re-education of TAMs toward M2 phenotype[77]. Concretely, SF increased the infiltration of TAMs in the periphery of the tumour and accelerated their polarization toward M2[77]. Hakim et al. also assessed metalloproteinase-9 (MMP-9) protein levels, a typical marker of extracellular matrix degradation, in the tumour periphery, revealing an increased activity under sleep fragmentation condition. Of note, TAMs from SF-exposed mice showed higher expression of toll-like receptor-4, which seems to mediate the enhanced tumour progression.

Furthermore, experiments carried out applying IH in mice showed that, similarly to sleep fragmentation, TAMs experience an accelerated

shift toward M2 phenotype. Assessment of their phenotype correlated with the higher proliferation, migration, invasiveness, and capacity to disrupt the endothelial monolayer of naive tumour cells exposed to TAMs isolated from those mice[72]. In a similar approach, Eubank et al.[82] observed an increase in expression of MMP7 and a decrease in MMP9 and MMP12 in murine melanoma. These authors suggested that the observed metastatic capacity induced by IH depends on the specific regulation of MMPs.

In a subsequent study, Almendros et al.[83] studied the potential source of macrophages to the tumour. In absence of tumour, resident macrophages in the adipose tissue (AT) of mice exposed to IH manifest increased M1 polarization[84]. These findings, in contrast with the increased M2 polarity of TAMs in tumours exposed to IH, suggest that the tumour microenvironment is needed to reverse the classical M1 activation of AT macrophages (ATM) induced by IH. However, when AT is subjected to the tumour microenvironment, IH operates to recruit such cells and also seems to modulate tumour-AT interactions, enhancing the re-education toward M2 phenotype, resulting in enhanced migration of resident ATMs and bone marrow-derived monocytes to the tumour, thereby enhancing tumour malignancy (Fig. 2).

In addition to TAMs, the presence of other potent immune suppressor cells, such as regulatory T-cells (T_{reg}) and adipose stem cells appear to be mobilized by hypoxic areas which can generate a complex constellation of interactions[85-88]. Also, preliminary data carried out from mice exposed to IH during six weeks showed that circulating exosomes released under IH conditions are able to increase the migratory capacity (~ 46%) and invasion (~ 2.1-fold) of tumour cells when compared to exosomes obtained from normoxic mice[89]. Similarly, exosomes derived from mice exposed to SF increased tumour cell proliferation (~ 13%), migration (~ 2.3-fold), and extravasation (~ 10%) when compared to exosomes from normal sleep exposed mice[90].

CONCLUSIONS

There are increasing epidemiological and clinical studies that strongly suggest a potential relationship between OSA and cancer. However, most of the current human studies to date, with some exceptions, have important limitations since the available databases were not initially designed to study cancer. In parallel to human studies, a considerable number of mechanistic studies carried out in mice have appeared in the last years. However, there are deficits in the knowledge on the vast array of pathways involved in oncogenic processes, which in most cases are similar to responses triggered by IH and SF. Current translational research using OSA models from different laboratories and carried out *in vivo* and *in vitro* suggest that IH and SF may independently increase tumour progression. At a clinical level, it is expected that new studies will focus on specific types of cancer, prospectively and with well-controlled potential carcinogenic confounders. At both a basic and translational level it is necessary to better understand the role played by the mechanisms involved as well as the potential synergistic effect of SF, IH, and hypercapnia in specific types of cancer.

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