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## Do I Have to be Worried About Cancer if I Have Obstructive Sleep Apnea?

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### Abstract

Obstructive sleep apnea (OSA) is a common sleep breathing disorder, characterized by recurrent upper airway obstruction triggered by complete or partial upper airway collapse during sleep. It is a major public health issue, and it has been strongly associated with cardiovascular and metabolic morbidity and mortality, as well as behavioral and cognitive dysfunction. Recently, OSA has been associated with an increased solid tumor prevalence and poorer outcome, suggesting these patients are at higher risk to develop solid tumor malignancies or to die from oncological complications. The underlying mechanisms are not completely understood, but intermittent hypoxia is considered to be a major factor of OSA for promoting tumor invasion and metastasis. We discuss in the present review the current evidence of obstructive sleep apnea and cancer relationship.

**Keywords:** Obstructive sleep apnea; Cancer; Intermittent hypoxia; Cognitive dysfunction; Breathing disorder

### Introduction

Obstructive sleep apnea (OSA) is a common sleep breathing disorder, characterized by recurrent upper airway obstruction triggered by complete or partial upper airway collapse during sleep. It is a major public health issue, and it has been strongly associated with cardiovascular and metabolic morbidity and mortality, as well as behavioral and cognitive dysfunction [1,2]. Recently, OSA has been associated with an increased solid tumor prevalence and poorer outcome, suggesting these patients are at higher risk to develop solid tumor malignancies or to die from oncological complications [3]. The underlying mechanisms for this OSA-like intermittent hypoxia (IH) induced tumor metastasis are not completely understood, but IH is considered to be a major factor of OSA for promoting tumor invasion and metastasis [4,5]. The hypothesis that oxidative stress and inflammation response may play an important role in the association between cancer and sleep-disordered breathing has been analyzed in recently published studies. We discuss in the

present review the current evidence of obstructive sleep apnea and cancer relationship, the physiopathology aspects and what we do know about the association between OSA and cancer incidence and cancer mortality.

### Physiopathology

Animal studies have shown that intermittent hypoxia, as occurs in patients with OSA, was associated with tumor growth and progression. Hypoxia is an important feature of the intra-tumoral microenvironment, and it can induce growth and dissemination of tumors through the regulation of hypoxia-inducible factor-1 $\alpha$  (HIF-1 $\alpha$ ). OSA-like IH includes a phase of post-hypoxic re-oxygenation (ROX), which results in the production of reactive oxygen species (ROS) and increases oxidative stress and inflammation responses. These represent important pathological links between OSA and injuries of multiple organs including the myocardium, carotid body, adrenal gland and brain [6]. Up-regulation of inflammatory molecules or cytokines is associated with tumor proliferation, invasiveness and metastasis. OSA-like IH significantly increases the levels of NF- $\kappa$ B, as well as those of inflammatory markers, including TNF- $\alpha$  and IL-6 [7].

The cyclic hypoxia phenomenon in cancer, particularly in rapidly growing tumors, has been attributed to changes in solid tumor perfusion. The overexpression of the hypoxia inducible factor-1 $\alpha$  leads to an up-regulation of proangiogenic mediators, such as vascular endothelial growth factor, that can increase tumor vasculature and accelerate tumor growth development of new vascular networks and intermittent and aberrant blood circulation [8]. Almendros et al. [9,10] have recently shown in a mouse model of melanoma that intermittent hypoxia mimicking OSA enhances tumor growth and increases lung metastasis [9,10]. IH also can elicit changes in the host immune response, and pro-inflammatory and angiogenic molecules may be released from different tissues and organs contributing to the oncogenic processes [8].

The relationship between OSA and cancer is not only attributable to intermittent hypoxia, but it can also be modulated by sleep fragmentation (SF) as recently illustrated by Hakim et al. [11]. They found that SF enhanced tumor size and weight by changes in tumor associated macrophages (TAM)

polarity, TLR4 signaling and the presence of M2 macrophage markers.

Campos Rodriguez et al. [12] found that patients who spent more than 12% of nighttime with  $SO_2$  below 90% had more than twofold greater adjusted risk cancer incidence, and even those who spent more than 1.2% of nighttime in this situation were at increased risk of cancer. Increasing continuous TSat90 was associated with increasing cancer incidence with an adjusted HR of 1.07 (95% CI, 1.02-1.13, per 10-unit increase in TSat90).

To sum up, patients diagnosed with obstructive sleep apnea suffer sleep-related respiratory events, which leads to SF and IH. This has been proved to increase the risk of carcinogenesis, mainly through the production of carcinogenic molecules. Other mechanisms, such as the involvement of the immune system or the sympathetic system are being studied currently [13].

IH stimulates hypoxia-inducible factor 1 (HIF-1) which leads into an increased activity of NADPH oxidase, altering the mitochondrial function and reducing antioxidant levels *via* hypoxia-inducible factor 2 (HIF-2), resulting in an increased oxidative stress. An overstimulation of HIF-1 may as well contribute to angiogenesis *via* increased expression of VEGF [14].

Both SF and IH increase sympathetic outflow. Cole et al. [15] suggest that this situation not only results in an activation of adrenergic receptors, but also can potentiate angiogenesis and stromal cell support of tumors. Similarly, SF and IH can affect the immune system by altering the function and phenotype of M1 macrophages (antitumoral), turning them into M2 macrophages (tumor-supportive), hence increasing tumor growth, invasion and metastasis [16].

When it comes to OSA diagnosis, static and dynamic magnetic resonance imaging (MRI) has been proved to be relevant, since it can detect the level, degree, and cause of obstruction in the upper airway that guide the clinical diagnosis and treatment, as well as the monitoring and follow-up of patients [17]. Because of the well-known importance of MRI in diagnose and staging of cancer [18,19], advance imaging with MRI could be useful in the overall management of these patients. Further studies would need to be conducted to analyze the role of MRI in such cases.

### Association between OSA and cancer incidence and cancer mortality

The association between OSA and an increased incidence of cancer was first established by the Spanish Sleep Network. Campos-Rodriguez et al. [12] conducted a multicenter, retrospective study with 4190 participants. They demonstrated that severe OSA (percent nighttime with oxygen saturation less of 90%-Tsats 90%) was associated with a higher incidence of cancer, particularly in younger men (<65-years-old) who were not treated with CPAP. Nieto et al. [3] assessed for the first time the association between severe sleep disorder breathing and cancer mortality.

On the other hand, Gozal et al. [20] analyzed a cohort of approximately 5.6 million individuals. In the first group (patients diagnosed with obstructive sleep apnea), the incidence of 12

cancer types was assessed and compared with a control group. In the second group (patients diagnosed with primary cancer), the risk of metastatic disease or cancer mortality was determined according to the presence or absence of obstructive sleep apnea. The results showed that the incidence of all cancer diagnoses combined was similar in patients with obstructive sleep apnea and in the retrospectively matched cases.

Furthermore, when cancer mortality and metastatic risk were studied, the presence of obstructive sleep apnea, not only was not associated with a higher mortality or a poorer prognosis, but in some types of cancer, it seemed to reduce these risks. However, after analyzing the cancer type's subgroups, some malignancies were proved to have an increased incidence in patients with obstructive sleep apnea, such as melanoma (HR=1.13), pancreatic (HR=1.14) and kidney (HR=1.30) cancers.

### Conclusion

In summary, although the implications of intermittent hypoxia and sleep fragmentation in the physiopathology of carcinogenesis have been established, human trial findings have been inconsistent when it comes to assessing the association between obstructive sleep apnea and overall cancer incidence, cancer mortality and risk of metastasis. Nonetheless, there is evidence suggesting that some subtypes of cancer (e.g. melanoma, pancreatic cancer and kidney cancer) may have an increased incidence in patients who suffer from obstructive sleep apnea. Further studies need to be conducted in order to accumulate stronger evidence in this matter. The answer to the question: Do I have worried about cancer if I have sleep apnea? Would be NO. In light of the available evidence, our best concern should be to correctly perform CPAP treatment. A good adherence to CPAP is the best way to improve our health status.

### Conflict of Interest

Authors declare do not have any conflict of interest related to the content of this manuscript.

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