



Editorial

Sleep Apnea and Tumor Aggressivity[☆]



Apnea del sueño y agresividad tumoral

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Both cancer and obstructive sleep apnea (OSA) constitute 2 serious public health problems, due to their high prevalence among the general population and their negative impact on health.^{1,2} OSA has been associated with various cardiovascular, neuropsychiatric and metabolic diseases, and most studies have focused on intermittent hypoxemia and sleep fragmentation as the mechanisms potentially underlying this association.² With respect to cancer, many research groups continue to look for clinical or genetic causes, particularly those that are potentially preventable or treatable.

For some time, intermittent hypoxia (IH), rapid cycles of hypoxia/tissue reoxygenation, an almost pathognomonic feature of OSA, has been known to be capable of activating pathogenic mechanisms associated with carcinogenesis and promoting increased aggressivity in an existing tumor.³ The primary mechanism by which IH achieves this effect is paradoxically related with a compensatory system to avoid tissue death in situations of hypoxia, namely, increased vascularization to ensure sufficient supply of oxygen to the cells.⁴ This mechanism, which may have saved many lives from a cardiovascular point of view, does not seem to be of benefit in tumor tissue (very hypoxic), since it can promote the development of metastasis and growth of the primary tumor, and thus increase its aggressivity. Two molecules appear to be particularly involved in this pathogenic mechanism: hypoxia-induced factor (HIF-1 α), which is overexpressed in hypoxic tissues, and vascular endothelial growth factor (VEGF), the concentration of which increases as a direct consequence of HIF-1 α overexpression.^{3,4} The mechanism is not, however, as simple as it seems, since both molecules can alter their expression as a result of the action of different pathogenic pathways, and produce effects that may occasionally even be paradoxical, depending on the cell environment under consideration.^{3,4} In recent years, attention has also been focused on alternative pathogenic mechanisms possibly associated with another of the characteristics of OSA, sleep

fragmentation, via the activation of the Sympathetic overactivity or activation system changes.³ Experimental animal studies have shown that in IH conditions, tumor-associated macrophages (TAM) differentiate to a more protumoral phenotype (M2) instead of acting as tumor cell phagocytes (macrophages with anti-tumor phenotype or M1).⁵ Finally, a promising line of research involves exosomes, microvesicles generated by multiple cells that promote intracellular communication, by way of increased tumor adhesion, formation, invasion and metastastization (aggressivity); these molecules increase in concentration in situations of hypoxia, mediated by HIF-1 α concentrations, and even by sleep fragmentation.⁶

But looking beyond biological plausibility, what conclusions have been drawn from studies in humans? Although some studies, both clinical and populational,^{7–9} have shown increases in the incidence of cancer or cancer mortality in individuals with OSA, very few studies have been performed in patients with a specific type of cancer.¹⁰ Gozal et al. recently published a retrospective study of 1.7 million OSA patients and 1.7 million controls adjusted for different variables, and concluded that while OSA was associated with an increase in the incidence of some tumors, such as melanoma, or renal or pancreatic cancer, it was also paradoxically associated with a reduced incidence of other gastrointestinal, prostate and breast tumors, and in no case was it associated with an increase of any type of cancer death.¹¹ Perhaps the research that throws more light on the possibility of a relationship between OSA and increased tumor aggressivity is the recently completed study of the SEPAR Spanish Sleep Group (GES). This study of 443 melanoma patients appears to support the physiopathological hypothesis of an association between OSA and increased tumor aggressivity. The authors found that several polygraphic variables, such as the apnea-hypopnea index, and, moreover, different desaturation indices were associated with well-validated markers of aggressivity in melanoma, such as the Breslow index or the Clark index, among others.

A collateral finding of this study was also of enormous interest: the association appeared to occur in younger patients only.¹² This observation had already been made in previous studies that analyzed the association of OSA with both cancer⁷ and cardiovascular disease.¹³ This finding has still not been clearly explained. The cardiovascular community speculates that it may be due to what is called “hypoxic preconditioning”, that is to say, the very protection

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generated by IH by inducing the genesis of neovascularization in ischemic regions.¹⁴ However, this explanation is unconvincing in the case of cancer. It might be speculated, perhaps, that in cancer patients these hypoxia compensation mechanisms somehow deteriorate over time, and this is why tumor aggressivity is greater in younger patients with OSA. An alternative explanation may be that, as tumors are more common in elderly patients, the appearance of a new predisposing factor, in this case OSA, might have a relatively lower impact than in younger individuals.

There is still much to explore in this exciting field of research in terms of confirming the nature of this association, assessing the role of confounding variables (particularly obesity), analyzing which subgroups of individuals are most affected and what types of cancer are more likely to be affected, or determining the potential role of treatment with CPAP, among other issues. Although studies published by GES and other research groups point to an association between both diseases, we should still take a prudent approach. As Confucius said, “The cautious seldom err”, and this is particularly important in a disease with the repercussions of cancer. However, prudence does not have to be an adversary of aspiration and hard work, and our task as investigators must be to persevere with this line of research. We must endeavor to substantiate this hitherto underexplored association, in the belief that such a confirmation might constitute one of the great findings in current respiratory medicine.

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