Is obstructive sleep apnea a risk factor for lung cancer?—from pathophysiological mechanisms to clinical data

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Obstructive sleep apnea (OSA) and lung cancer are two major public health problems. On the one hand, more than one billion individuals worldwide suffer from OSA, considered as the presence of at least five respiratory events (apnea or hypopnea) per hour of sleep [apnea-hypopnea index (AHI) ≥5] (1,2). On the other hand, cancer is one of the leading causes of death, with lung cancer being the leading cause of cancer deaths worldwide with an estimated 1.8 million deaths. In 2020, 11.4% of new cancers diagnosed were lung cancers, placing it as the second most common site of incident cancers and the most common cancer in men (3,4).

Although the relationship between OSA and some cardiovascular (5-8) and metabolic (9,10) adverse outcomes is well known, only during the last decade various studies of a pathophysiological nature, as well as murine and clinical models (both in epidemiological and clinical series) have established a relationship between OSA (11,12) and sleep duration (13) and a higher prevalence, incidence or aggressiveness of some malignant tumors. It seems that this relationship is more pronounced in more severe OSA (greater number of sleep-disordered breathing events, such as apneas, hypopneas), as well as in certain histological lines of tumor cells such as melanoma, bladder, liver, cervix, kidney, pancreas and lung cancer (14,15). With this editorial, we have tried to briefly review the most relevant pathophysiological and clinical finding on the relationship between OSA and cancer.

A recent review of the pathophysiological pathways that could explain this phenomenon highlighted some possibilities: (I) cell deficiency or dysfunction (including macrophages, natural killer T-cell, CD8 and CD3 T cells, stem-cell-like and dendritic cells); (II) biological biomarkers [vascular endothelial growth factor (VEGF) and other pro-angiogenic molecules, tumoral growth factor (TGF)-α1, tumoral necrosis factor (TNF)-α, tryptophan, cyclooxygenase (COX)-2, cannabinoid receptors, programmed death-ligand 1 (PD-L1), endostatin, endothelin-1, oxidative stress molecules and paraspeckle protein-1]; (III) genetic factors [glucose genes, hypoxic inducible factor (HIF)-1α genes, common key genes between OSA and cancer, micro-RNA-320β and NF-kB factor genes]; (IV) exosomes; and (V) microbiome (16).

Most alterations in the function, quantity, activation, and deactivation of these cells or molecules seem to be mainly linked to two fundamental features of OSA: sleep fragmentation and, above all, intermittent hypoxia (IH) defined as the oxygenation-deoxygenation derived from the sleep-disordered breathing (whether or not in addition to sustained hypoxia derived from cardiopulmonary

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Table 1 Factors hypothesized to promote lung cancer in OSA patients

Induction of HIF-1α as an expression acting as transcriptional activator of ATAD2
Common genes in OSA and lung cancer (*MOAP1*, *CBX7*, *PDGFB* and *MAP2K3*)
Elevation of PD-L1 monocytes/macrophages induced by exosomes that correlate with HIF-1α expression
Down-regulation of microRNA-320β with increasing of CDT1 via USP37
Promotion of ESM1 via HIF-1α pathway
Promotion of lung CSC-like properties by activation of mtROS mediated by Bach-1
Up-regulation of TGF-β1, VEGF and Foxp3 + Tregs expression
Increased expression of beta-catenin and Nrf2 as tumor growth factors

OSA, obstructive sleep apnea; HIF-1α, hypoxic inducible factor-1α; ATAD2, ATPase family AAA domain-containing protein 2; PD-L1, programmed death-ligand 1; CDT1, chromatin licensing and DNA replication factor 1; USP37, deubiquitinating enzyme family member; ESM1, endothelial cell-specific molecule-1; CSC, cancer stem cells; mtROS, mitochondrial reactive oxygen species; TGF, tumor growth factor; VEGF, vascular endothelial growth factor; Foxp3, forkhead box P3; Nrf2, nuclear factor erythroid-2-related factor-2.

comorbidities or obesity) produced by an excess of sleep-disordered breathing (16).

The first mechanism to be described and that is still considered fundamental today was probably the overexpression of HIF-1α in a hypoxic environment (such as inside tumors), aggravated by superadded IH caused by OSA. HIF-1α overexpression increases the production of proangiogenic molecules (especially VEGF) and, in its turn, the neovascularization of the tumor, with a subsequent increase in the production of distant metastases and tumor growth. In the case of tumorigenesis, it has been speculated that the oxygenation-reoxygenation cycles produced by IH are a potent inducer of the redox system, which is recognized as an important carcinogenic pathway (17). However, it became apparent that things were probably not that simple, and that there were other mechanisms involved, beyond the existence of IH. These are probably genetically mediated or implicate cells and molecules from the immune system (18).

In any case, one prominent characteristic of this relationship is that the impact of OSA does not seem to be related equally to all cancer sites. Furthermore, it can vary even with respect to the same cancer site, depending on the line of tumor cell involved—probably due to the different sensitivity of cancer cells to the action of IH and its consequences (for example, the different densities of active VEGF receptors in tumor cells) (19).

Table 1 shows the different pathophysiological mechanisms described to establish a relationship between OSA and lung cancer. As can be seen, and as occurs with most other tumors, many of the intimate molecular mechanisms that associate OSA with a greater progression or incidence of lung cancer are linked to the overexpression of HIF-1α and the various mechanisms that this sets in motion (20-25). A genetic component cannot be entirely ruled out, however, since OSA and lung cancer share some common genes (26).

It is worth noting that most of the studies were conducted in non-small cell lung cancer (NSCLC), and the evidence in small cell tumors is therefore very limited. Moreover, it is also striking that not all NSCLC cell lines responded in the same way to IH. In an interesting study of a mouse model, Marhuenda *et al.* (27) observed how cell proliferation "*in vitro*" responded differently to varying intensities of IH or sustained hypoxia, according to the cell lines exposed. The cell lines used were: H522, H1437 [human adenocarcinoma; p53 mutant and epidermal growth factor receptor (EGFR) wild-type], H1975 (human adenocarcinoma; p53 mutant, EGFR mutant) and H520 (human squamous cell lung cancer; p53 mutant, EGFR wild-type). It was observed that the H520 line (squamous cell lung cancer) proliferated faster in the presence of IH than in that of sustained hypoxia, and also faster than the adenocarcinoma lines. Within the three different lines of adenocarcinoma, IH did not seem to have any effect, although sustained hypoxia did produce a significant increase in cell proliferation. Evidence to extrapolate the previously described finding to human populations is desirable, as IH is a hallmark of OSA and sustained hypoxia is characteristic of other cardiopulmonary diseases or obesity that can coexist with OSA, and therefore, depending on these circumstances, the type of hypoxia created (intermittent, sustained or mixed) could produce different responses in the proliferation of the various lung cancer cell lines.

From a clinical point of view, two recent meta-analyses agree that the presence of OSA is a risk factor, independent of other confounding factors, for a higher incidence of lung cancer although there is much less scientific evidence for any relationship with higher mortality. Cheong *et al.* (28) found that patients with OSA were approximately 30% more likely to develop lung cancer than patients with no OSA. Ma *et al.* (29), for their part, included seven studies to reanalyze the relationship between OSA and cancer incidence, observing results similar to those of Cheong *et al.* (28). Furthermore, this higher incidence seemed to be independent of smoking, as it was replicated in a sensitivity analysis that used three studies without smokers [risk ratio (RR) 1.34; 95% CI: 1.22 to 1.48]. Moreover, subgroup analysis suggested that the association between OSA and a higher risk of lung cancer was not significantly affected by study characteristics such as design, source of population, sample size, evaluation methods for OSA, follow-up duration, methods for validation of lung cancer or study quality scores (28). Finally, Chen *et al.* (30) concluded in a third meta-analysis that OSA was not a risk factor for higher lung cancer mortality, although their analysis only included three small studies including 67 patients with lung cancer and comorbid OSA and 45 patients with lung cancer and no OSA. However, the odds ratio (OR) showed double the mortality for the group of lung cancer and OSA, although this was not statistically significant (probably due to the small sample size and the lack of analysis of the main confounders).

Despite inconsistencies in available data on the relationship between OSA and lung cancer in terms of the quality and generalizability of the evidence and therefore it is reasonable to approach some findings with caution, there is an interesting body of scientific evidence on the biological plausibility of this relationship. It seems that the overexpression of HIF-1α as a consequence of IH is the most important pathophysiological factor, although not all lung cancer cell lines respond in the same way. The existing data from clinical series, as gathered in meta-analyses, suggest the presence of a relationship between OSA and lung cancer in humans, although the following limitations of these studies need to be addressed in future research: (I) most of the studies were retrospective, included few patients and had short follow-ups; (II) small cell lung cancer was very little studied; (III) some confounders (especially smoking, obesity and other comorbidities) could be determining factors and should be studied in-depth; (IV) the methodology of the studies was quite heterogeneous; (V) it is necessary to carry out studies balanced by gender, as these could both be determining factors in the relationship; (VI) mortality studies in lung cancer are needed to shed more light on the effect of OSA on the aggressiveness of cancer; (VII) finally, and probably most importantly, it is necessary to carry out clinical studies on the effect of continuous positive airway pressure (CPAP)—which eliminates IH—on the incidence and aggressiveness of lung cancer, as well as its interaction with other anti-cancer treatments.

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Footnote

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