Linking obstructive sleep apnoea and lung cancer: a further step down the road

Miguel Angel Martinez-Garcia [1,2,3]

[1]Respiratory Department, Hospital Universitario y Politécnico La Fe, Valencia, Spain. [2]Instituto de Investigación Sanitaria la Fe, Valencia, Spain. [3]Centro de Investigación Biomédica en Red (CIBERES), Instituto de Salud Carlos III, Madrid, Spain.

Corresponding author: Miguel Angel Martinez-Garcia (mianmartinezgarcia@gmail.com)

Shareable abstract (@ERSpublications)
There are various pathophysiological pathways linking obstructive sleep apnoea and lung cancer https://bit.ly/48qtqOO

Cite this article as: Martinez-Garcia MA. Linking obstructive sleep apnoea and lung cancer: a further step down the road. *ERJ Open Res* 2024; 10: 01050-2023 [DOI: 10.1183/23120541.01050-2023].

Received: 29 Dec 2023
Accepted: 5 Jan 2024

Although the relationship between obstructive sleep apnoea (OSA) and its main pathophysiological consequence, intermittent hypoxaemia (IH), with cardiovascular, neurocognitive and metabolic diseases has been studied since the 1980s, the first studies on OSA's relationship with an increase in the prevalence, incidence and aggressiveness of cancer date back less than 15 years ago. In 2007, Abrams [1] was the first to introduce the hypothesis of a potential relationship between cancer and OSA through the resulting hypoxaemia that the author christened "the hypoxia connection". It was only a decade ago, however, that studies first began to be carried out in murine and human models on large populations or clinical series [2–6]. These confirmed an increased incidence and mortality of all-type cancer in patients with OSA, especially in severe forms of the disease and cases with greater associated hypoxaemia. One of the first pathophysiological pathways to give biological plausibility to these clinical findings was IH's activation of the expression of a key molecule, hypoxia inducible factor (HIF)-1α, which in turn induced an increase in the concentration of molecules associated with greater tumour neovascularisation, especially vascular endothelial growth factor (VEGF), and thus a greater probability of tumour growth and aggressiveness [7].

Based on these findings, several avenues of study were opened in an attempt to answer some key questions. Were all types of tumours related in the same way to OSA or IH? Were there any other pathophysiological pathways, in addition to those related to HIF-1–VEGF, capable of explaining an association between OSA and different types of cancer? Recent studies seem to demonstrate that not all tumours are related to IH-related OSA, although melanoma is the most studied and apparently the most consistent in presenting this association in the various studies [8]. Furthermore, a focus on the relationship between OSA and lung cancer led to the discovery of other alternative pathophysiological pathways not necessarily associated with the hyperexpression of HIF-1α, but sometimes related to other immune cell deficiencies or dysfunction, biomarkers and genetic factors, and even changes in the microbiome [9].

In the current issue of *ERJ Open Research*, Cubillos-Zapata *et al.* [10] add new evidence of other possible pathophysiological pathways to explain the association of OSA with lung cancer, in this case represented by various biomarkers of immune evasion (programmed cell death-1 (PD-1) and programmed cell death ligand-1 (PD-L1)), lymphangiogenesis (midkine (MDK)) and intrinsic tumour cell aggressiveness (paraspeckle component-1 (PSPC1) and transforming growth factor (TGF)-β1), whose expression is shown to increase in the present study in both patients with moderate–severe OSA with established lung cancer and individuals with a high risk of suffering from lung cancer participating in a screening programme.

This study presents some new and interesting findings. First, although some molecules, such as TGF-β1 [11] or PD-1/PD-L1 [12], had already been studied in the relationship between OSA and lung cancer,

others such as MDK [13] and PSPC1 [14] had not been specifically studied in this context (although they have been studied in other tumours such as melanoma). These markers of lymphangiogenesis or tumour cell aggressiveness open up new pathophysiological possibilities that strengthen the relationship between OSA and lung cancer. Secondly, it is very interesting to highlight how the authors analysed a series of individuals with a high risk of suffering from lung cancer (basically heavy smokers aged >55 years) who were subjected to a screening programme and presented an increased expression of biomarkers related to the induction of tumour aggressiveness pathways (PSPC1, TGF-β1), lymphangiogenesis (MDK) and immune evasion (PD-1/PD-L1). Given the current discussion on the cost-effectiveness of these massive screening programmes based on age and smoking habit in the population [15], the finding of an increase in some biomarkers of aggressiveness or tumorigenesis and a higher prevalence of some comorbidities such as OSA (also related to an increase in these biomarkers) could serve as a starting point for future studies more specifically designed to identify the types of patients who could benefit most from such programmes and thereby optimise their cost-effectiveness.

However, any study of the relationship between OSA and lung cancer is most probably much more complicated than it might first appear, due fundamentally to the heterogeneity of OSA itself and the difficulty of reliably measuring the real impact of IH. Furthermore, the relative weight of the multiple pathophysiological pathways already discovered in this relationship is still unknown, while the cell lines that form part of what is collectively known as "lung cancer" are characterised by their enormous variety. Different cell lines can sometimes even be found in the same tumour, but will not respond identically to the same stimulus, such as IH. A recent study by Marhuenda *et al.* [16] casts greater light on this aspect. These authors observed in an *in vitro* study on different lung cancer cell lines (specifically 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)) that cell proliferation varied according to the cell type, even with the same exposure to IH or sustained hypoxia. Thus, the H520 line of the squamous cell lung cancer proliferated faster than the adenocarcinoma lines, and faster in the presence of IH compared to sustained hypoxia. IH did not seem to have any effect, however, on the three different lines of lung adenocarcinoma, although sustained hypoxia did produce a significant increase in cell proliferation.

The relationship between OSA and lung cancer is as fascinating to investigate as it is difficult to analyse, given its complexity and the heterogeneity of its different components. Future studies should specifically focus on the most frequent cell subtypes found in the clinical setting, on a more real measurement of the impact of IH (some studies are already producing promising results with alternative metrics to the now classic apnoea–hypopnoea index and indices of desaturations such as hypoxic burden [17]), and above all, on an aspect not yet specifically studied for lung cancer despite its great importance: the impact of continuous positive airway pressure treatment on the relationship of lung cancer with OSA.

Provenance: Commissioned article, peer reviewed.

Conflict of interest: None declared.

References

1 Abrams B. Cancer and sleep apnea – the hypoxia connection. *Med Hypotheses* 2007; 68: 232.
2 Campos-Rodriguez F, Martinez-Garcia MA, Martinez M, *et al.* Association between obstructive sleep apnea and cancer incidence in a large multicenter Spanish cohort. *Am J Respir Crit Care Med* 2013; 187: 99–105.
3 Nieto FJ, Peppard PE, Young T, *et al.* Sleep-disordered breathing and cancer mortality: results from the Wisconsin Sleep Cohort Study. *Am J Respir Crit Care Med* 2012; 186: 190–194.
4 Almendros I, Montserrat JM, Ramírez J, *et al.* Intermittent hypoxia enhances cancer progression in a mouse model of sleep apnoea. *Eur Respir J* 2012; 39: 215–217.
5 Almendros I, Montserrat JM, Torres M, *et al.* Obesity and intermittent hypoxia increase tumor growth in a mouse model of sleep apnea. *Sleep Med* 2012; 13: 1254–1260.
6 Martínez-García MA, Campos-Rodriguez F, Durán-Cantolla J, *et al.* Obstructive sleep apnea is associated with cancer mortality in younger patients. *Sleep Med* 2014; 15: 742–748.
7 Gozal D, Farré R, Nieto FJ. Obstructive sleep apnea and cancer: epidemiologic links and theoretical biological constructs. *Sleep Med Rev* 2016; 27: 43–55.
8 Martinez-Garcia MA, Campos-Rodriguez F, Almendros I, *et al.* Cancer and sleep apnea: cutaneous melanoma as a case study. *Am J Respir Crit Care Med* 2019; 200: 1345–1353.
9 Martínez-García MÁ, Oscullo G, Gómez-Olivas JD, *et al.* Is obstructive sleep apnea a risk factor for lung cancer? From pathophysiological mechanisms to clinical data. *Ann Transl Med* 2023; 11: 422.

10 Cubillos-Zapata C, Troncoso-Acevedo F, Díaz-García E, *et al.* Sleep apnoea increases biomarkers of immune evasion, lymphangiogenesis and tumour cell aggressiveness in high-risk patients and those with established lung cancer. *ERJ Open Res* 2024; 10: 00777-2023.
11 Li J, Shen C, Wang X, *et al.* Prognostic value of TGF-β in lung cancer: systematic review and meta-analysis. *BMC Cancer* 2019; 19: 691.
12 Han Y, Liu D, Li L. PD-1/PD-L1 pathway: current researches in cancer. *Am J Cancer Res* 2020; 10: 727–742.
13 Cubillos-Zapata C, Martínez-García MÁ, Díaz-García E, *et al.* Proangiogenic factor midkine is increased in melanoma patients with sleep apnea and induces tumor cell proliferation. *FASEB J* 2020; 34: 16179–16190.
14 Cubillos-Zapata C, Martínez-García MÁ, Díaz-García E, *et al.* Obstructive sleep apnoea is related to melanoma aggressiveness through paraspeckle protein-1 upregulation. *Eur Respir J* 2023; 61: 2200707.
15 Adams SJ, Stone E, Baldwin DR, *et al.* Lung cancer screening. *Lancet* 2023; 401: 390–408.
16 Marhuenda E, Campillo N, Gabasa M, *et al.* Effects of sustained and intermittent hypoxia on human lung cancer cells. *Am J Respir Cell Mol Biol* 2019; 61: 540–544.
17 Martinez-Garcia MA, Sánchez-de-la-Torre M, White DP, *et al.* Hypoxic burden in obstructive sleep apnea: present and future. *Arch Bronconeumol* 2023; 59: 36–43.