Can CPAP protect from cancer incidence in obstructive sleep apnoea patients? No evidence yet

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Shareable abstract (@ERSpublications)
Basic research has shown the biological plausibility of a relationship between OSA and cancer. However, clinical evidence of a positive effect of OSA treatment on incidence of cancer is still lacking. https://bit.ly/3mqXrbI

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The relationship between obstructive sleep apnoea (OSA) and cancer has been increasingly studied in recent years, with special regard to the effects of intermittent hypoxia (IH). OSA is only one of the different models of IH in cancer, and the effect of IH on cancer biology appears to vary with cycle length [1]. On the other hand, the role of sleep disorders other than OSA, including circadian rhythm alterations or insomnia, on cancer incidence at different sites has been recently summarised, highlighting a possible protective role of regular sleep against tumour development [2].

Retrospective epidemiological studies and meta-analyses on the incidence of cancer in OSA patients have reported discordant results, since several confounding factors make it difficult to clearly establish the relationship between OSA and cancer [3–6]. Current available data have been mostly derived from large databases without details on OSA severity or treatment for OSA, and cancer types or comorbidities were often assessed based on International Classification of Diseases codes. To date, the cornerstone of the fascinating relationship between OSA and cancer is the biological plausibility that emerged from numerous studies on mouse models or on human cell cultures *in vitro* [7]. Recent reviews on this topic have clarified how IH, the main feature of OSA, is responsible for the activation of the hypoxia inducible factor 1, and the release of reactive oxygen species, pro-inflammatory (nuclear factor κB) or angiogenetic (vascular endothelial growth factor) mediators, and DNA mutations [6–11]. Interestingly, IH can also cause deregulation of the immune system, resulting in up-regulation of programmed death ligand 1 and potentially decreased immunological surveillance towards cancer cells [12]. Besides IH, sleep fragmentation, another main characteristic of OSA, has been shown to cause oxidative stress and deregulation of the immune system in experimental models [13]. In some studies on mice exposed to IH and sleep fragmentation, there was not only an increase in the size of the tumour, but also in its aggressiveness, as evidenced by the presence of tumour-activated macrophages [14]. Sleep fragmentation would also induce a downregulation of toll-like receptor 4 and mutations in exosomal miRNAs, with consequent alteration in the biological properties of tumour cells, which led to an increase in proliferation and tendency to migrate [15]. OSA, therefore, could contribute to the activation of biological mechanisms which are also typical of tumourigenesis.

If, on the biological side, a potential link between OSA and cancer appears clear and strong, on the clinical side the overall picture is much less clear. The natural history of both OSA and cancer development in humans is multifactorial and requires many years, and the timing of their possible interaction cannot be reliably assessed clinically. Many studies reported a higher incidence of cancer in patients with OSA than in those without, but diagnostic data on OSA, *i.e.* apnoea–hypopnoea index (AHI), oxygen desaturation index (ODI) or daytime sleepiness, were often not included. Obesity may also play a role [16]. The

response to OSA oncogenic triggers varies according to individual cancer cell lines, further complicating data analysis [17, 18]. Furthermore, the evidence on the effects of IH on tumour aggressiveness derived from experimental studies has been insufficiently verified in prospective clinical studies, with the notable exception of patients with malignant melanoma [18–21].

If OSA may increase the risk of cancer, one may expect such risk to be reduced in patients on treatment for OSA with continuous airway positive pressure (CPAP), but so far there has been no real-life assessment of cancer incidence in CPAP-treated OSA patients. The paper by Justeau *et al.* [22] published in this issue of the *European Respiratory Journal* represents a major step forward in this direction. The study used data from the multicentre Pays de la Loire Sleep Cohort study, linked to health administrative data, to assess the effects of CPAP on incidence of cancer in OSA patients.

The study evaluated 4499 OSA patients without cancer at 1 year after start of CPAP treatment. Median age was 63 years and median AHI was 37 events·h^{-1}. Most patients (69%) were overweight males with a median BMI of 31 kg·m^{-2}. The median follow-up was 5.4 years. 60% of the patients adhered to CPAP treatment (median daily CPAP use of 6.7 h), with the rest of the sample showing a median daily use ⩽3 h. Non-adherent patients were younger, had lower BMI and less severe OSA. During follow-up, 437 patients (9.7%) were diagnosed with cancer, 10.7% and 9.1% in non-adherent and adherent patients, respectively. The final weighted model found that there was no significant impact of CPAP adherence on all-cause cancer risk, with a subdistribution hazard ratio (sdHR) of 0.94 (95% CI 0.78–1.14; p=0.52). Sensitivity analysis considering CPAP adherence in the first year of follow-up showed no significant impact of CPAP adherence on cancer risk (sdHR 1.13, 95% CI 0.92–1.38). Subgroup analyses based on age, BMI severity and OSA did not reveal any significant effect of CPAP adherence on all-cause cancer. No significant difference was found when comparing adherence ⩾6 h *versus* <4 h (sdHR 1.04, 95% CI 0.84–1.30; p=0.71). However, there was a trend for a lower tumour incidence in CPAP-adherent patients with more severe nocturnal hypoxaemia on diagnostic test (sdHR 0.78, 95% CI 0.58–1.05, for the highest tertile of ODI, and 0.79, 95% CI 0.60–1.05, in the highest quartile for percentage of sleep time with oxygen saturation <90%). Considering CPAP adherence as a continuous variable, there was no significant effect of CPAP adherence on the risk of cancer for all causes (sdHR 1.01, 95% CI 0.97–1.07; p=0.55). Regarding secondary outcomes, analyses for specific tumours showed no significant association between CPAP adherence and specific cancer sites. However, the incidence of lung cancer in CPAP-adherent patients tended to be lower (sdHR 0.49, 95% CI 0.22–1.09).

This study is the first to evaluate whether the risk of developing cancer in patients with OSA is modified by adherence to CPAP therapy, with the aim of translating the current biological and epidemiological evidence to clinical practice. The study used sophisticated statistical methods (causal interference method with inverse probability treatment weighting) that strengthen the reliability of results obtained in a longitudinal observational cohort.

Although cancer incidence was not significantly different between CPAP adherent and non-adherent patients, there was a trend towards an increased incidence of cancer in the latter group. The limited duration of follow-up does not allow us to exclude that such a difference might become significant after longer follow-up. Furthermore, it would have been interesting to compare cancer incidence in OSA patients to that in the general population in the same geographical area. Finally, the number of patients diagnosed with cancer was small, limiting the reliability of the analysis for individual site cancers.

Before dismissing the hypothesis that CPAP might protect from cancer incidence, longer follow-up in large samples is needed to verify the effects of OSA treatment with CPAP on the incidence and natural history of cancer. The study by Justeau *et al.* [22] of the Pays De La Loire Sleep Cohort represents an important first step in this direction. Future studies should focus on younger OSA patients, since ageing seems to diminish the effects of IH on cancer development [23]. The field is still in an early stage, and definitely deserves attention, with special regard to the most common cancer localisations, *i.e.* lung, breast, prostate and colorectal cancer, and to their different biological profiles. Among other aspects to be explored, the interaction between genetic risk of cancer and sleep features [24] or the relative role of sleep fragmentation *versus* predominant IH during sleep, alone or combined, are highly interesting areas of future research.

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