

## Peer Review File

Article Information: <https://dx.doi.org/10.21037/atm-23-1641>

### Reviewer A

**Comment 1.** The association between lung cancer and OSA still needs more research. However, I think this manuscript is well-organized and easy to read. It would be nice to write an in-depth review by integrating the results of more clinical papers in the future.

**Reply 1:** Thanks for the comment

**Changes in the text:** No

### Reviewer B

**Comment 1.** In this Editorial the authors analyze the current knowledge about the correlation between obstructive sleep apnea and lung cancer. A through discussion on the possible pathophysiological mechanisms involved is provided. On the other-hand, clinical data are based on a limited number of studies and meta-analyses and further studies are therefore required to confirm the correlation between obstructive sleep apnea (OSA) and lung cancer. The manuscript addresses an original topic and may therefore be of interest. The Authors could discuss in further detail not only the correlation of OSA and lung cancer but also the implications of OSA in the treatment of lung tumors, and strategies to reduce the impact of OSA on lung cancer incidence and treatment.

**Reply 1.** Dear reviewer, thanks for the comment. The problem is that this is not a full review on this topic but only an editorial paper related to pathophysiological mechanisms and clinical data. We would be very grateful if the journal wants us to write a full paper (giving us more space to write it) on the relationship between OSA and cancer addressing not only the point that the reviewer highlights but also other important points.

**Changes in the text:** No

## **Reviewer C**

This is an interesting and timely invited Editorial assessing the relationship between obstructive sleep apnea and lung cancer. The Editorial is very comprehensive, covering everything from mechanisms to actual data assessing this association. This will be of interest to readers, but first minor edits should be made:

**Comment 1:** Intermittent hypoxia should be defined at first use.

In line 138, “studies” should be “studied”

The authors should make it clear that the factors in Table 1 are theorized but not definitively proven, and thus they should change the title from the definitive “factors promoting” to something less definitive like ‘factors hypothesized to promote’

**Reply.** We have done the changes

**Changes in the text:** Page 2. Lines 24-25 “...intermittent hypoxia (IH) defined as the oxygenation-deoxygenation derived from the sleep-disordered breathing.

Page 5, line 138. Changed “studies” by “studied”

Table 1. “Factors hypothesized to promote” has been add in the title of the table

## **Reviewer D**

Critique:

The opportunity of reviewing the authors' work is greatly appreciated. This is an interesting review of the associations between Obstructive sleep apnea (OSA) and lung cancer.

**Comment 1.** Review aim: This was not stated. Although it is implicit, once the background has been provided, a clear objective of the document should be described (see below).

**Reply 1.** This is an editorial paper and not a review or original paper, therefore an objective is not theoretically needed. Anyway according to the reviewer comment we have added (see next point: “change in the text”)

**Change in the text:** Introduction, lines 9-11. “With this editorial we have tried to briefly review the most relevant pathophysiological and clinical finding on the relationship between OSA and cancer”

**Comment 2.** Presentation: The study is not divided into sections, making it more challenging to follow. Only the introduction was highlighted. Suggest adding some sections/subsections.

**Reply 2.** Again, this is not a review but an editorial paper, so probably it is better to delete the word “introduction” from the manuscript

**Changes in the text:** Delete “introduction”

Comments/questions:

**Comment 3.** Line 35: instead of "risk factors", "adverse outcomes" should be used as the consequences of untreated sleep apnea are being highlighted.

Line 38: there's a typo "stablished" should be "established"

Line 38: what other sleep disorders? This is too general as the reader may interpret it as RLS, Narcolepsy, or other sleep disorders may be associated with the studied outcome. The provided citation supports "sleep duration" only; thus, this is what should be described instead.

Line 39: suggest adding "malignant" tumors, for clarity.

Line 40: Citation 10 does not seem to provide support to the statement "this relationship is more pronounced in more severe OSA". On the other hand, Cao Y, Ning P, Li Q, Wu S. Cancer and obstructive sleep apnea: An updated meta-analysis. *Medicine (Baltimore)*. 2022 Mar 11;101(10):e28930. doi: 10.1097/MD.00000000000028930. PMID: 35451384; PMCID: PMC8913079, may support it.

Lines 41-42: "nocturnal desaturations" is implicit in the concepts of apneas/hypopneas and does not constitute a separate event to classify OSA severity. Suggest removing it.

Line 42: What were the histological lines of tumor cells? The provided citation mentions melanoma, bladder, liver, cervix, kidney, pancreas, and lung cancer. This is important to note as this links the exposure (OSA) and the outcome (lung cancer).

**Reply 3.** Done, thanks

**Changes in the text:** Modification attending the reviewer comments

**Comment 4.** A description of lung cancer is missing and should be added to the document (i.e. epidemiology, types, etc.), perhaps after the initial description of OSA. Afterward, the authors may present the gap in knowledge and growing evidence to support a relationship between OSA and lung cancer. After the exposure, outcome, and gap have been described, the purpose of the review should be stated.

**Reply.** Please take into account that this is not a review paper but an editorial comment, so the space is limited. Anyway, we have added as the reviewer recommends a short first paragraph on the OSA and lung cancer.

**Changes in the text:** First 10 lines

**Comment 5.** Lines 54-58: a citation should be provided for the proposed mechanisms (sleep fragmentation and intermittent hypoxia).

Lines 61-62: The expression "it produces" is not clear. Does this refer to the HIF-1 $\alpha$  alone or a combination with intermittent hypoxia?

Lines 72-73: what relationship do the authors refer to? Do cancer locations mean histological types?

Lines 78-79: This statement could be a good connector before stating the aim of the present review.

Line 101: suggest changing "it would be very interesting" to something like "Evidence to extrapolate the previously described finding to human populations is desirable"

Line 102: characteristic was used twice; suggest changing one for a different expression.

Line 114: add et al. after Cheong.

Line 123: instead of "less than 120 patients in both groups", suggest describing "lung cancer participants with and without OSA (n=67 and n=45 respectively)." Suggest deleting "Even here"

Lines 127-128: suggest rephrasing the statement to: "Despite inconsistencies in available data on the relationship between OSA and lung cancer, there is an important body of scientific ..."

Line 133: the authors should be careful to use the expression "seem to confirm" as they admitted some inconsistencies in the current evidence. Suggest modifying this to "suggest the presence of a relationship between OSA and lung cancer in humans..."

Line 138: typo "studies", should be "studied"

Lines 139-140: the sentence "It is necessary to carry out studies balanced by gender and age, as these could both be determining factors in the relationship." Given that most lung cancer patients are diagnosed at 65+, is there any evidence to suggest that age would play a role?

**Reply.** We have done all the reviewer suggestions

**Changes in the text:** We have made all the changes (in red).

**Comment 6.** Overall impression:

The document summarized most of the available data about the relationship between OSA and lung cancer. The addition of sections could facilitate the reading. The background of this review needs to be rearranged to improve flow and clarity. The conceptual frame for lung cancer is missing. The writing should be more specific, avoiding expressions such as "this relationship," as it introduces ambiguity and confusion while reading. The flow of the document improves from line 78 and afterward.

**Reply.** Thanks for your comments and corrections that obviously have improved the manuscript. However it is important to take into account that this is an editorial paper and not a full review on the topic, so we have restrictions in the space

**Changes in the text.** We have tried to introduce all the reviewer's comments.

## **Reviewer E**

**Comment 1.** Nice paper, summarizing the most recent evidence on both the clinical and experimental points of view. No other comments.

**Reply 1.** Thanks for the comment

**Changes in the text:** No

## **Reviewer F**

**Comment 1.** Apologize if the evaluation did not meet your expectations. Based on the content of the review article, there are several strengths and limitations that can be identified:

Strengths:

The article provides an overview of the relationship between obstructive sleep apnea (OSA) and the prevalence, incidence, and aggressiveness of tumors, focusing on lung cancer.

It discusses various pathophysiological mechanisms that could explain the association between OSA and tumors, including cell dysfunction, biomarkers, genetic factors, exosomes, and the microbiome.

The review highlights the role of sleep fragmentation and intermittent hypoxia (IH) in the development and growth of tumors.

It references relevant studies, including murine models, clinical series, and meta-analyses, to support the proposed relationship.

The review acknowledges the need for further research and suggests areas for future investigation, such as studying the effects of continuous positive airway pressure (CPAP) treatment on lung cancer.

Limitations:

The review acknowledges that most studies in the field are retrospective with small sample sizes and short follow-up durations, which may limit the strength of the conclusions.

There is a lack of consistent methodology among the studies, making it difficult to compare and generalize the findings.

The review mentions the importance of studying confounding factors, such as smoking, obesity, and other comorbidities, which could influence the relationship between OSA and tumor development.

The limited evidence regarding the relationship between OSA and mortality in lung cancer is acknowledged.

The review does not provide a critical analysis of the quality or biases of the included studies or meta-analyses.

Although there are few strengths, it does have several limitations in terms of the quality and generalizability of the evidence. Therefore, it may be reasonable to approach the findings with caution.

**Reply 1.** We have tried to tone down the some sentences. According to the reviewer comment we have added this sentence “Despite the limitations in the studies carried out so far 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” Pag 4 (two last lines) and page 5 (first three lines)

**Changes in the text:** According to the reviewer comment we have added this sentence “Despite the limitations in the studies carried out so far 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” Pag 4 (two last lines) and page 5 (first three lines)