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CPAP to Reduce the Risk of Cancer in OSA?—A Meta-Analysis of 3 RCTs

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ABSTRACT

Obstructive sleep apnea (OSA) has been hypothesised to promote cancer via intermittent hypoxia, and assessing what happens when OSA is *controlled* by continuous positive airway pressure (CPAP) may provide valuable insight. We conducted a meta-analysis of three randomised controlled trials (SAVE, RICCADSA, ISAACC) assessing cancer incidence from adverse event data on neoplasms among OSA patients randomised to continuous positive airway pressure (CPAP) versus control. Across trials, cancer incidence was similar between groups, and meta-analysis showed no statistically significant difference (CI 0.55–1.68). Treating sleep apnea with CPAP does not appear to markedly reduce the risk of incident cancers.

1 | Introduction

It has been hypothesised that obstructive sleep apnea may cause or accelerate cancer (Gozal et al. 2015; Nieto et al. 2012). Suggested pathways have primarily been through intermittent hypoxia (Hunyor and Cook 2018). Studying this problem in clinically recruited cohorts is not ideal because some cancers are likely to be preferentially detected during sleep apnea diagnosis and treatment (notably prostate and lung cancer) through clinical referral bias. Community-based studies do not suffer from this issue, and two such cohorts have reported sleep apnea cancer connections in 2012 and 2014 (Nieto et al. 2012; Marshall et al. 2014). However, since these publications there has been a puzzling silence from similar cohorts. This could be an effect of too small cohorts or a lack of linkage to cancer registries, which led us to develop the expertise in multi-cohort harmonisation to study the problem (Theorell-Haglöw et al. 2024). In this population-based context, we were not able to show a link between OSA and cancer development (Theorell-Haglöw et al. 2024).

Another way to explore whether OSA causes or accelerates cancer in the context of OSA patients is to look at what happens when OSA is *controlled* by continuous positive airway pressure (CPAP). A recently published meta-analysis of three observational studies (Srivali and De Giacomi 2025), comparing adherent versus non-adherent CPAP patients, did not show a clear effect of CPAP treatment on the risk of cancer. Observational studies, however, are inherently prone to selection bias and, by design, address a different perspective or question than RCTs, which compare treated versus non-treated patients. Combining RCTs and non-randomised controlled trials cannot be validly done as populations in the different types of studies are fundamentally different and thereby also the research question is

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fundamentally different. Therefore, a meta-analysis of RCTs can provide a superior option to meta-analysing data from observational studies. To date, no randomised controlled trials (RCTs) have been specifically designed to address this question; however, exploring and utilising data from RCTs with adverse event data on cancer may provide a useful option if meta-analysing this data. The three large RCTs SAVE (McEvoy et al. 2016) [NCT00738179], RICCADSA (Peker et al. 2016) [NCT00519597], and ISAACC (Sánchez-de-la-Torre et al. 2020) [NCT01335087], all assessing CPAP for OSA, can provide an opportunity to test whether controlling OSA reduces cancer incidence inside a robust randomised design with a control group.

We hypothesised that patients randomised to CPAP would have lower cancer incidence than patients randomised to not using CPAP.

2 | Methods

Using the three RCTs previously identified for meta-analysis by Sánchez-de-la-Torre et al. (2023) and extracting the adverse event data on neoplasms reported in the clinical trial reports (McEvoy et al. 2016; Sánchez-de-la-Torre et al. 2020) and by consulting our own records (author Y.P.), we meta-analysed the data on cancer incidentally detected during these trials (i.e., incidence cancer data). Mean follow-up time for the studies was 37.8 (IQR 25.9–55.2) months for the SAVE trial, 31.3 (13.7–55.0) months for the ISAACC trial, and 52.1 (35.6–70.8) months for the RICCADSA trial (Sánchez-de-la-Torre et al. 2023).

Both random and fixed effect models were tested and results from the random effects model were used. A random effects model is better suited when there is potentially a significant variability between participants, as in the case of meta-analysis of different studies. All statistical analysis was performed using the metan command in Stata 15 (Stata Corp., Texas, USA).

3 | Results

The participants of the three RCTs have been described elsewhere (Sánchez-de-la-Torre et al. 2023) but in short, the participants of these secondary prevention trials were predominantly middle-aged to older, non-sleepy men with overweight/obesity, cardiovascular disease, and moderate to severe OSA. No significant differences in baseline variables were seen for treated versus non-treated patients in the respective studies.

Within the SAVE trial, a total of 42 (3.1%) cancers were reported in the CPAP arm and 34 (2.5%) in the control arm ($p = 0.36$) (McEvoy et al. 2016). The RICCADSA trial reported 2 (1.6%) events in the CPAP group versus 1 (0.8%) in the control group ($p = 0.56$) (Peker et al. 2016). Finally, the ISAACC trial reported 15 (2.4%) events in the CPAP arm and 24 (3.8%) in the control arm ($p = 0.05$) (Sánchez-de-la-Torre et al. 2020).

The results from the meta-analysis are shown in Figure 1. Using a fixed effects model did not change the results.

4 | Discussion

We did not observe a statistically decreased or increased risk for incident cancers in patients with OSA when treated with CPAP. However, the confidence intervals around this estimate are quite wide (0.55–1.68) meaning that we cannot rule out the possibility that untreated OSA either increases or decreases the risk of cancer.

The strength of meta-analysing RCT data is the robust reduction of confounding effect that can never be ruled out in observational studies (Patel et al. 2024; Phillips et al. 2025). The disadvantage is that these studies are too small, too short, and not primarily designed to look at cancer, and also too small to look at any specific cancer. In addition, the patients in the current meta-analysis were selected to be at high risk for cardiovascular disease rather than cancer, and that makes the trials less efficient for detecting this effect if it is real. Combining randomised controlled trials (RCTs) and non-randomised controlled trials is not methodologically valid, as the populations in these study designs differ fundamentally, leading to inherently different research questions.

RCTs are often criticised for having low CPAP adherence. Null results have however, also been reported from prominent non-randomised clinical cohorts showing no differences in incident cancers between sleep apnea patients using or not using CPAP

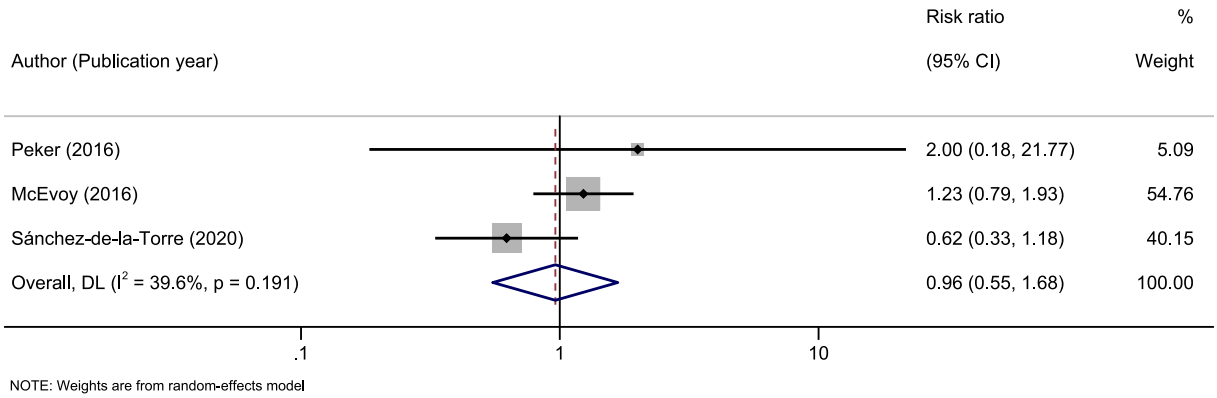


FIGURE 1 | Overall risk ratio forest plot for cancer. Effect estimates to the left of 1 risk ratio favour CPAP in reducing cancer and effect estimates to the right of the 1 risk ratio favour Control in reducing cancer incidence. Results from meta-analysis using a random effects model.

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(Justeau et al. 2022). For the current meta-analysis, no data was available in such detail that we could have meta-analysed the results according to CPAP use or OSA severity. In addition, there was no access to individual level data from the three RCTs which could have provided further insight into the research question.

5 | Conclusion

Treating sleep apnea with CPAP in high-quality randomised controlled trials does not appear to markedly affect the risk of incident cancers. The result of this meta-analysis is clearly an unsatisfying answer as the confidence limits are quite wide because these trials are too short/underpowered to provide a definitive answer. However, in the absence of any large suitable RCT currently recruiting, this uncertainty is likely the answer we will have to live with for the foreseeable future.

Author Contributions

Jenny Theorell-Haglöw: visualization, formal analysis, writing – original draft, writing – review and editing, methodology, project administration, data curation. **Yüksel Peker:** methodology, writing – review and editing, investigation, data curation. **Nathaniel S Marshall:** writing – review and editing, data curation, conceptualization, writing – original draft, methodology.

Disclosure

Dr. Peker declares institutional grants from ResMed Foundation. Dr. Theorell-Haglöw and Dr. Marshall have nothing to declare.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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