Cancer risk in patients with sleep apnoea following adherent 5-year CPAP therapy

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In a multicentre-based cohort of patients with mild-to-severe obstructive sleep apnoea, sustained and adherent CPAP therapy was not associated with a reduction in all-cancer incidence after a median follow-up time of 5.4 years https://bit.ly/3mdiOxI

Cite this article as: Justeau G, Bailly S, Gervès-Pinquié C, *et al*. Cancer risk in patients with sleep apnoea following adherent 5-year CPAP therapy. *Eur Respir J* 2022; 59: 2101935 [DOI: 10.1183/13993003.01935-2021].

This article has an editorial commentary: https://doi.org/10.1183/13993003.02742-2021

Received: 10 July 2021
Accepted: 10 Aug 2021

Abstract

Background Increasing evidence suggests that obstructive sleep apnoea (OSA) contributes to cancer risk; however, limited data are available on the impact of continuous positive airway pressure (CPAP) therapy on cancer incidence. We aimed to determine whether adherence to CPAP therapy is associated with a reduction in all-cancer incidence compared with nonadherent patients with OSA.

Methods The study relied on data collected by the multicentre Pays de la Loire Sleep Cohort study, linked to health administrative data, so as to identify new-onset cancer. We included patients who were prescribed CPAP for OSA, with no history of cancer before the diagnostic sleep study or during the first year of CPAP. Patients with documented CPAP use for ⩾4 h per night were defined as adherent. Those who discontinued or used CPAP <4 h per night constituted the nonadherent group. A propensity score inverse probability of treatment weighting analysis was performed to assess the effect of CPAP adherence on cancer risk.

Results After a median (interquartile range) follow-up of 5.4 (3.1–8.0) years, 437 (9.7%) out of 4499 patients developed cancer: 194 (10.7%) in the nonadherent group (n=1817) and 243 (9.1%) in adherent patients (n=2682). The final weighted model showed no significant impact of CPAP adherence on all-cause cancer risk (subdistribution hazard ratio 0.94, 95% CI 0.78–1.14).

Conclusions Adherence to CPAP therapy in OSA patients was not associated with a reduction in all-cancer incidence. Whether adherent CPAP therapy of OSA might reduce the risk of specific cancer sites should be further evaluated.

Introduction

With nearly 1 billion adults affected worldwide, obstructive sleep apnoea (OSA) is a highly prevalent disease characterised by recurrent episodes of complete or partial upper airway obstruction during sleep [1]. There is increasing evidence from population- and clinic-based cohort studies that the severity of OSA and sleep-related hypoxaemia may adversely affect both overall cancer as well as selective cancer incidence [2–8]. Data from experimental studies using cell cultures or animal models suggest that intermittent hypoxia and sleep fragmentation, the hallmark features of OSA, might promote oncogenesis as

well as enhance tumour growth and metastasis. Several putative intermediate mechanisms invoked by OSA could link intermittent hypoxia and sleep fragmentation to tumour growth, invasion and metastasis, and include sympathetic overactivity, systemic inflammation, oxidative stress, angiogenesis and immunological alterations (see Gozal *et al.* [9] for a comprehensive review). Among the studies that have examined the links between specific cancer sites and OSA, cutaneous malignant melanoma has received the greatest attention, with most studies demonstrating a significant relationship between the prevalence, incidence or aggressiveness of melanoma and OSA severity [10]. Limited by relatively small sample sizes and multiple comparisons, secondary analyses of large retrospective cohort studies have found significant associations of OSA and nocturnal hypoxia with common cancer sites such as lung, breast, colorectal, kidney and smoking-related cancer [7, 8, 11, 12].

A major piece of the puzzle that is yet to be addressed is whether continuous positive airway pressure (CPAP), the first line of therapy for OSA, will reduce cancer risk. The problem when trying to answer this questions lies in the fact that it is now impossible to perform an ethical randomised controlled trial of CPAP *versus* no treatment in patients with symptomatic OSA over a long period of time [13]. To circumvent this issue, propensity score matching of real-world observational data to estimate causal treatment effects represents a promising method for overcoming the sample selection biases described recently in randomised controlled trials of cardiovascular end-points in the context of OSA [13].

We hypothesised that sustained and adherent CPAP therapy of OSA might be associated with a reduction in cancer risk. To address this question and properly account for confounders, we conducted a propensity score inverse probability of treatment weighting (IPTW) analysis using observational data from the multicentre clinic-based Pays de la Loire Sleep Cohort.

Methods

The study relied on data collected by the multicentre longitudinal Pays de la Loire Sleep Cohort study, which were further linked with data from the French administrative healthcare database (Système National des Données de Santé (SNDS)). The SNDS contains individualised, anonymous and comprehensive data on healthcare spending reimbursements, and the linkage process between the Pays de la Loire Sleep Cohort and the SNDS database was conducted as previously reported [8, 14]. All patients with newly diagnosed OSA (apnoea–hypopnoea index $\geqslant$5 events·h^{-1} on type 3 home sleep apnoea testing (HSAT) or in-lab polysomnography (PSG)) who were prescribed CPAP for at least 1 year, and who also had available SNDS data and were included in the cohort between 15 May 2007 and 31 December 2018, were eligible for inclusion the present study. Patients were excluded if they had been diagnosed with cancer at any time before the diagnostic sleep study or during the first year of CPAP therapy. Approval was obtained from the University of Angers (Angers, France) Ethics Committee and the Advisory Committee on Information Processing in Health Research (CCTIRS; 07.207bis). All patients had previously given their written informed consent to participate in research.

Baseline evaluation

Each patient enrolled in the Pays de la Loire Sleep Cohort completed surveys including anthropometric data, smoking habits, alcohol consumption, medical history and medication use (see supplementary table S1 for the definition of covariates). Patients were evaluated by either HSAT or PSG, according to pre-test clinical probability of OSA [15]. Respiratory events were scored manually using recommended criteria [16].

CPAP therapy initiation and follow-up

According to the criteria defined by the French National Health Insurance, CPAP therapy was prescribed in patients with severe OSA and in those with mild-to-moderate OSA and cardiovascular comorbidities or those with severe daytime sleepiness. As previously described, a single home respiratory care company (Asten Santé, Beaucouzé, France) was involved in CPAP device delivery and in the follow-up support programme [17]. Follow-up visits with the sleep specialist took place at 5 months, at 12 months and then at least annually. Objective daily positive airway pressure use was monitored at each follow-up visit based on the digital downloads from the CPAP devices and documented in the database.

Patients who had not discontinued CPAP and used it on average $\geqslant$4 h per night during the entire follow-up period were assigned to the CPAP adherent group. Patients who stopped the use of CPAP, whatever the stoppage time was during the follow-up period, or those who used the device on average <4 h per night, including patients with a zero or a near-zero CPAP adherence, constituted the nonadherent group. To take into account immortal time bias [18], a sensitivity analysis was performed by considering only the first year of treatment to define CPAP adherence or nonadherence.

Outcome definition

The primary outcome was defined as the first occurrence of an all-cause malignant neoplasm at any time between the end of the first year of CPAP therapy and the censor date. As described previously [8], the occurrence of cancer was identified based on the French Hospital Discharge database (Programme de Médicalisation des Systèmes d'Information (PMSI)), using an algorithm based on primary, related or associated PMSI diagnostic codes of malignancies (International Classification of Diseases, 10th Revision: C00–C97, D00–D09 and D37–D463). Patients who did not develop cancer were censored at the date of death or at the final follow-up date (31 December 2019). Secondary analyses were conducted by considering the most frequent cancer sites (lung, breast, colon and prostate), while all other tumour sites were considered together.

Statistical analyses

Variables were described by using number (percentage) for qualitative variables and median (interquartile range (IQR)) for quantitative variables. Comparisons between groups (CPAP adherent *versus* nonadherent) were performed by using the Chi-squared test for qualitative variables and the nonparametric Mann–Whitney test for quantitative variables.

Missing values were considered as occurring randomly and therefore multiple imputations were performed in 20 datasets for missing values that were introduced in the multivariable model. Fully conditional regression and Monte-Carlo Markov Chains were performed for variable imputations, and datasets were merged following Rubin's rules to obtain the final results (see supplementary table S2 for the comparisons between imputed and nonimputed datasets).

The cancer incidence values were computed in person-years and a Poisson estimation of the confidence interval was calculated.

To assess the effect of CPAP adherence on cancer risk, we used a causal inference method with IPTW estimator. This method has been extensively described elsewhere [19–21]. Briefly, the principle is to weight each patient by the inverse of his/her probability of being exposed to the treatment (*i.e.* adherent CPAP therapy in our study). This probability is assessed by using a propensity score in which all measured confounders are considered. Weighting each patient in the final model by the inverse of the propensity score (IPTW) allows to constitute a pseudo-population in which each individual is his/her own control on the basis of measured confounders. Two steps were considered. The first step was to assess the probability of being CPAP adherent by using a nonparsimonious logistic regression. Variables introduced into the model were related to CPAP adherence or to the outcome to avoid instrumental variables. The final logistic regression model is presented in supplementary table S3. Weights were computed by using the inverse of the CPAP adherence probability and stabilisation was performed to limit the positivity assumption. Verifying weight distributions assessed the positivity assumption (supplementary figure S1) and standardised differences were computed to control for balance for confounders after weighting (supplementary figure S2). The second step aimed to assess the impact of CPAP adherence on the risk of all-cause cancer. This was performed by using weighted patients in a Fine–Gray time-to-event model to account for death as competing risk [22]. An unadjusted weighted cumulative incidence function (CIF) was computed to illustrate the difference between groups for the primary objective and the log-rank test was used to compare both CIFs. The final result was the subdistribution hazard ratio (sdHR). Subgroup analyses were considered to account for CPAP adherence threshold of 6 h, OSA severity (categories of OSA severity (*i.e.* mild, moderate and severe), tertiles of 3% oxygen desaturation index (ODI) and quartiles of percentage of sleep time with oxygen saturation <90% (T90)), categories of age and body mass index (BMI), and various cancer sites. The same method was applied for all secondary objectives, by computing new weights for each model. A sensitivity analysis was performed by introducing CPAP adherence as a continuous variable in the model. A threshold of 5% was considered as significant. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Population description

Out of 6803 eligible patients, 1617 were not linked to the SNDS dataset and 651 were diagnosed with cancer before the diagnostic sleep study was performed or during the first year of CPAP therapy. In addition, 36 subjects died during the first treatment year (figure 1). Thus, the final study sample comprised 4499 patients with a median (IQR) age of 63 (54–72) years. As shown in table 1, the study population consisted of typical patients with OSA (median (IQR) AHI 37 (27–52) events·h^{-1}), predominantly male (69%), obese or overweight (median (IQR) BMI 31 (27–36) kg·m^{-2}), and frequently presenting cardiovascular and metabolic comorbidities. During follow-up, the median (IQR) CPAP adherence was 5.9

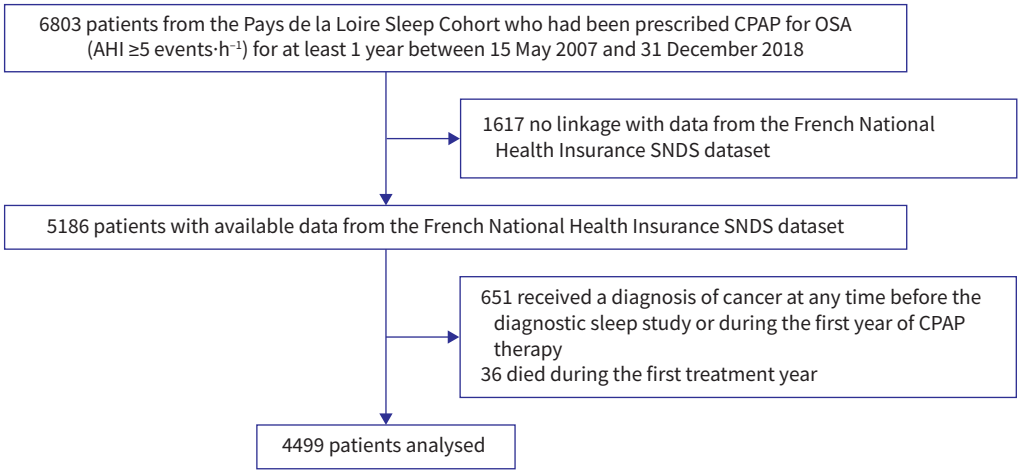


FIGURE 1 Flow diagram of study subjects. CPAP: continuous positive airway pressure; OSA: obstructive sleep apnoea AHI: apnoea–hypopnoea index; SNDS: Système National des Données de Santé.

(4.1–7.2) h per night (see supplementary figure S3 for the distribution of CPAP adherence). In accordance with previous data from the Pays de la Loire Sleep Cohort [17], 2682 patients (60%) were CPAP adherent and 1817 constituted the nonadherent group (median (IQR) daily CPAP use 6.7 (5.7–7.6) and 3.0 (2.1–3.6) h, respectively). Compared with the adherent group, nonadherent patients were younger, had lower BMI and had less severe OSA. Significant intergroup differences were also observed for tobacco and alcohol consumption, socioeconomic status, and cardiovascular comorbidities (table 1).

Cancer incidence during follow-up

After a median (IQR) follow-up duration of 5.4 (3.1–8.0) years, 437 patients (9.7%) received a diagnosis of cancer: 194 (10.7%) in the nonadherent group and 243 (9.1%) among CPAP adherent patients (p=0.03). Overall, the all-cancer incidence rate was 16.4 (95% CI 14.8–18.0) cases per 1000 person-years, with an incidence of 17.5 (95% CI 15.0–20.1) per 1000 person-years in the nonadherent group and 15.6 (95% CI 13.7–17.7) per 1000 person-years in the adherent group. Figure 2 shows the incidence of different cancer sites according to CPAP adherence.

Primary objective

The weighted CIF is shown in figure 3. The final weighted model (supplementary table S4) showed the absence of any significant impact of CPAP adherence on all-cause cancer risk (sdHR 0.94, 95% CI 0.78–1.14; p=0.52). The unweighted model showed a similar result. Sensitivity analysis considering CPAP adherence in the first year of follow-up showed a nonsignificant impact of CPAP adherence on the risk of cancer (sdHR 1.13, 95% CI 0.92–1.38). Subgroup analyses according to age, BMI and OSA severity revealed no significant effects of CPAP adherence on all-cause cancer (figure 4). By comparing adherence ⩾6 *versus* <4 h, there was no significant difference (sdHR 1.04, 95% CI 0.84–1.30; p=0.71). However, there was a trend toward a significantly lower all-cancer incidence in CPAP adherent patients with more severe nocturnal hypoxaemia during the diagnostic test (sdHR 0.78, 95% CI 0.58–1.05, and 0.79, 95% CI 0.60–1.05, for the highest tertile of ODI and quartile of T90, respectively). By considering CPAP adherence as a continuous variable, there was no significant effect of CPAP adherence on all-cause cancer risk (sdHR 1.01, 95% CI 0.97–1.07; p=0.55).

Secondary objective

The analyses for specific cancers showed no significant association between CPAP adherence and specific cancer sites (figure 5). However, there was a trend toward a significantly lower incidence of lung cancers in CPAP adherent patients (sdHR 0.49, 95% CI 0.22–1.09).

Discussion

Using IPTW estimations to control for confounding factors within a large multicentre clinic-based cohort of patients with OSA, we found that CPAP adherence did not reduce all-cancer incidence when compared with nonadherent patients. A borderline statistically significant reduction in lung cancer risk was observed in CPAP adherent patients.

TABLE 1 Baseline characteristics of the entire population, continuous positive airway pressure (CPAP) nonadherent patients and adherent patients

	All patients (n=4499)	Nonadherent (n=1817)	Adherent (n=2682)	p-value	Missing data
Age, years	63 (54–72)	62 (52–72)	64 (55–72)	<0.01	0
Male	3112 (69.2)	1235 (68.0)	1877 (70.0)	0.15	0
BMI, kg·m^{-2}	31 (27–35.5)	30.5 (26.7–35.4)	31.4 (27.7–35.6)	<0.01	20
Alcohol intake	2014 (46.3)	772 (44)	1242 (47.8)	0.02	145
Smoking habits					
Former and current smokers	2628 (59.2)	1104 (61.6)	1524 (57.6)	<0.01	63
Nonsmokers	1808 (40.8)	688 (38.4)	1120 (42.4)		
Socioprofessional category					
Farmer	190 (5.0)	75 (5.0)	115 (5.1)	0.21	727
Craftsman	411 (10.9)	181 (11.9)	230 (10.2)		
Executive	616 (16.3)	261 (17.2)	355 (15.7)		
Intermediate	754 (20)	304 (20.1)	450 (19.9)		
Employee	682 (18.1)	274 (18.1)	408 (18.1)		
Worker	1119 (29.7)	420 (27.7)	699 (31.0)		
ESS score	10 (7–14)	11 (7–14)	10 (7–14)	0.90	126
Prevalent diseases					
Depression	1246 (28.0)	560 (31.2)	686 (25.8)	<0.01	48
Diabetes	717 (17.7)	299 (18.3)	418 (17.2)	0.36	443
Hypertension	1600 (39.7)	608 (37.6)	992 (41.1)	0.02	470
Cardiac disease	787 (18.1)	327 (18.7)	460 (17.7)	0.41	161
Heart failure	214 (4.8)	101 (5.6)	113 (4.2)	0.04	0
CHD	252 (5.6)	108 (5.9)	144 (5.4)	0.41	0
Atrial fibrillation	374 (8.3)	171 (9.4)	203 (7.6)	0.03	0
Stroke	249 (5.5)	90 (5.0)	159 (5.9)	0.16	0
Indices of OSA severity					
AHI, events·h^{-1}	37 (27–52)	34 (24–48)	38 (30–55)	<0.01	10
5– <15	243 (5.4)	109 (6.0)	134 (5.0)	<0.01	10
15– <30	1012 (22.5)	486 (26.9)	526 (19.6)		
⩾30	3234 (72.0)	1215 (67.1)	2019 (75.4)		
ODI, events·h^{-1}	30 (17–47)	27 (15–43)	32 (19–50)	<0.01	164
T90, %	6 (1–22)	5 (1–19)	7 (1.3–24)	<0.01	37
CPAP adherence, h per night	5.9 (4.1–7.2)	3.0 (2.1–3.6)	6.7 (5.7–7.6)	<0.01	0
Follow-up, years	5.4 (3.2–8.1)	5.8 (3.2–8.3)	5.2 (3.1–7.8)	<0.01	0
Cancer incidence	437 (9.7)	194 (10.7)	243 (9.1)	0.03	0

Data are expressed as n (%), median (interquartile range) or n, unless otherwise stated. BMI: body mass index; ESS: Epworth Sleepiness Scale; CHD: coronary heart disease; OSA: obstructive sleep apnoea; AHI: apnoea–hypopnoea index; ODI: 3% oxygen desaturation index; T90: percentage of sleep time with oxygen saturation <90%. Comparisons between nonadherent and adherent patients were performed using the Mann–Whitney test for quantitative variables or the Chi-squared test for qualitative variables.

Increasing evidence suggests that OSA and its nocturnal hypoxia-related consequences may contribute to the risk of cancer development and tumour progression [9]. However, limited data are available regarding the potential impact of CPAP therapy on cancer risk. Gharib *et al*. [23] comprehensively profiled the circulating leukocyte bulk transcriptome of patients with severe OSA. Despite modest changes in global gene expression, the authors found that many of the perturbed pathways mapped to neoplasia-related gene pathways. Furthermore, effective CPAP therapy appeared to downregulate the coordinated expression patterns of these cancer-related pathways. More recently, Hernández-Jiménez *et al*. [24] demonstrated that patients with untreated OSA have altered immune cell phenotypes, particularly involving monocytes and natural killer cells. The impaired immune phenotypes did not persist in patients with OSA who had received at least 6 months of CPAP, implying the presence of a moderating role associated with effective OSA therapy. To date, there is no clinical evidence that treatment with CPAP reduces the incidence or progression of cancer in patients with OSA. Most of the previous studies that have analysed the association between OSA and cancer incidence or mortality were not able to evaluate the impact of effective OSA therapy due to the lack or scarcity of data on CPAP prescription and usage [2, 3, 7, 11, 25–28]. Our recent study involving the Pays de la Loire Sleep Cohort showed an association between the severity of nocturnal hypoxaemia and all-cancer incidence [8]. It is worth noting that the association appeared stronger when CPAP adherent patients were excluded from the analysis. Conversely, there was no association between nocturnal hypoxaemia and cancer risk in patients receiving adequate CPAP therapy, raising the possibility of a protective effect afforded by adherent CPAP treatment. A similar finding was reported previously in

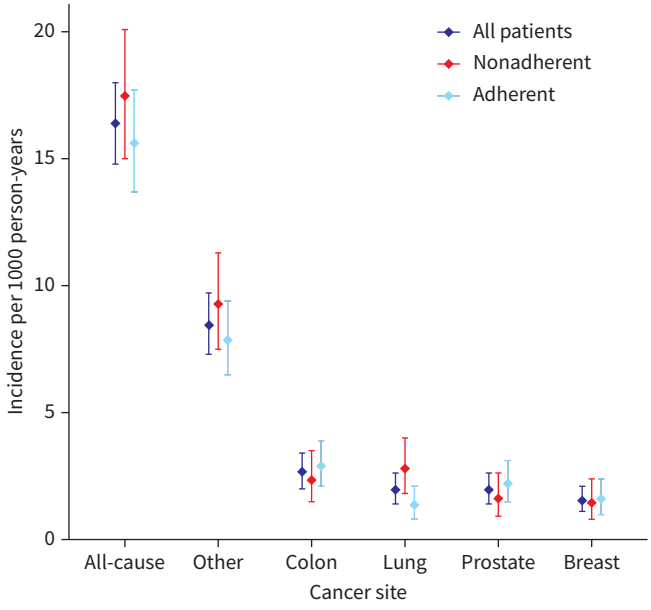
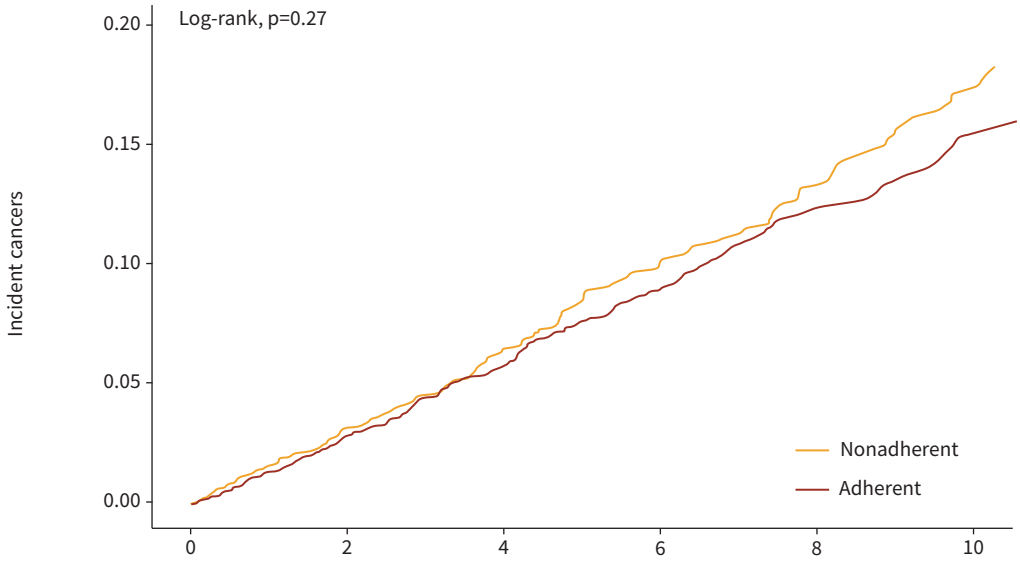


FIGURE 2 Incidence (95% confidence interval) of different cancer sites according to continuous positive airway pressure adherence.

cohort studies that evaluated the association of OSA and cancer mortality [2, 4]. However, CPAP adherence in the present study was not associated with a significant reduction in all-cancer incidence, even though the association became stronger in subgroups with more severe nocturnal oxygen desaturations as



At risk, n:

All patients	4499	4022	2963	1942	1130	367
Adherent	2682	2413	1742	1092	619	193
Nonadherent	1817	1609	1221	850	511	174

FIGURE 3 Weighted cumulative incidence function for all-cause cancers according to continuous positive airway pressure adherence.

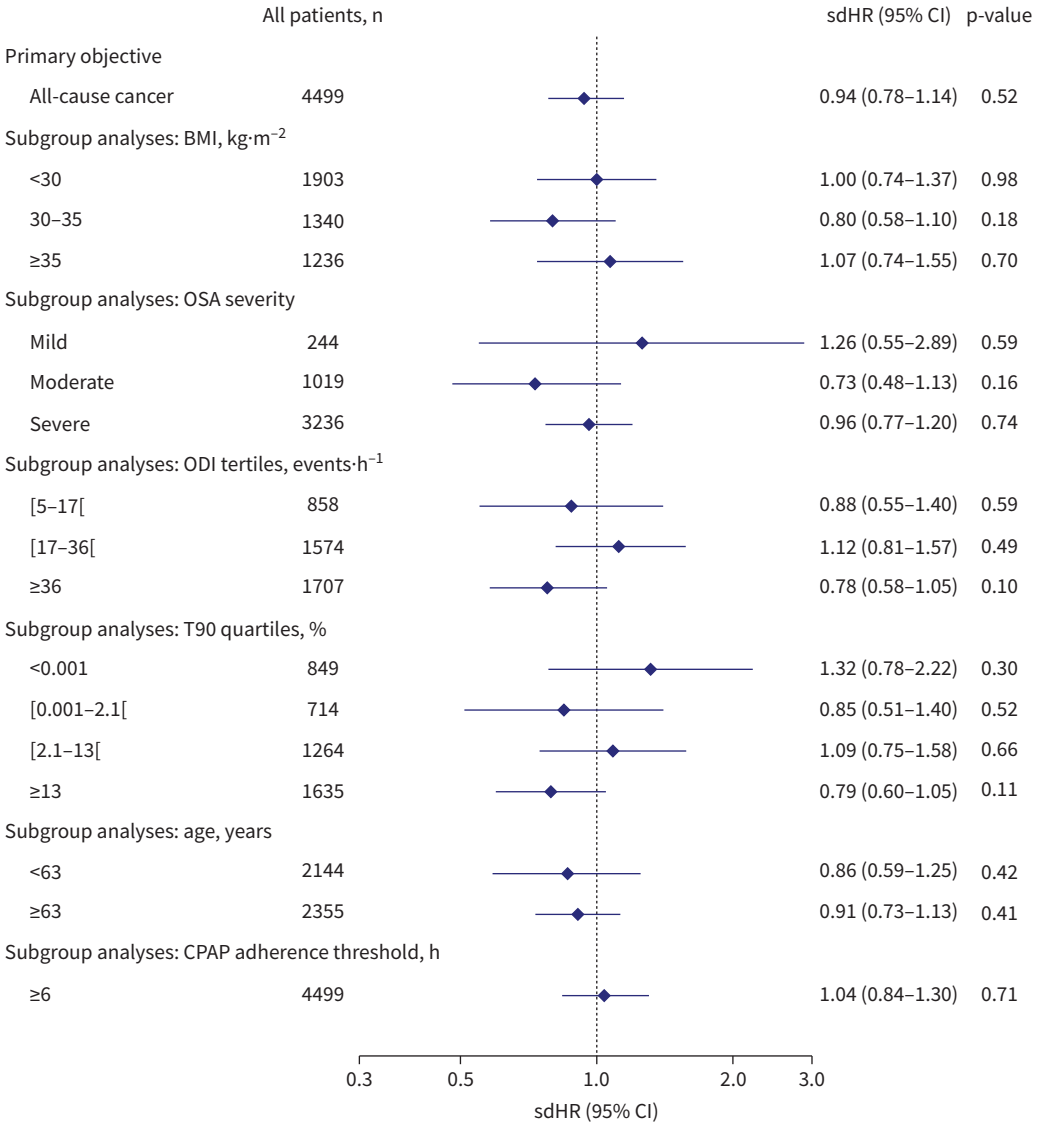


FIGURE 4 Summary of subdistribution hazard ratios (sdHRs) for the primary objective. The following commonly used cut-offs for the apnoea–hypopnoea index were used to define categories of obstructive sleep apnoea (OSA) severity: <5 events·h^{-1} (no OSA), 5–<15 events·h^{-1} (mild OSA), 15–<30 events·h^{-1} (moderate OSA) and ⩾30 events·h^{-1} (severe OSA). BMI: body mass index; ODI: 3% oxygen desaturation index; T90: percentage of sleep time with oxygen saturation <90%; CPAP: continuous positive airway pressure.

assessed by ODI and T90. This finding is consistent with previous studies showing that indices of nocturnal hypoxaemia are stronger predictors of cancer incidence or mortality than AHI [5, 8, 11]. However, indices of nocturnal hypoxaemia, particularly T90, might be not only related to OSA but also to the effects of smoking and comorbid lung diseases. Several factors might explain the lack of effects of adherent CPAP therapy of OSA on all-cancer incidence. Being a chronic disease, it is likely that patients were exposed to intermittent hypoxia and other related consequences of OSA for many years before starting CPAP therapy. Furthermore, cancer causation is multifactorial and modelling studies have suggested that >60% of tissue cancer burden may be due to factors that are intrinsic to human cell biology and thus not modifiable [29].

Previous clinic-based cohort studies have demonstrated a significant association between sleep-related breathing disorders and the prevalence or incidence of smoking-related cancers [8, 11, 30]. Nocturnal hypoxaemia may be a key variable linking OSA and lung cancer, although the patterns of hypoxia may elicit divergent responses among different lung tumour cell types [31], and therefore the predictability of

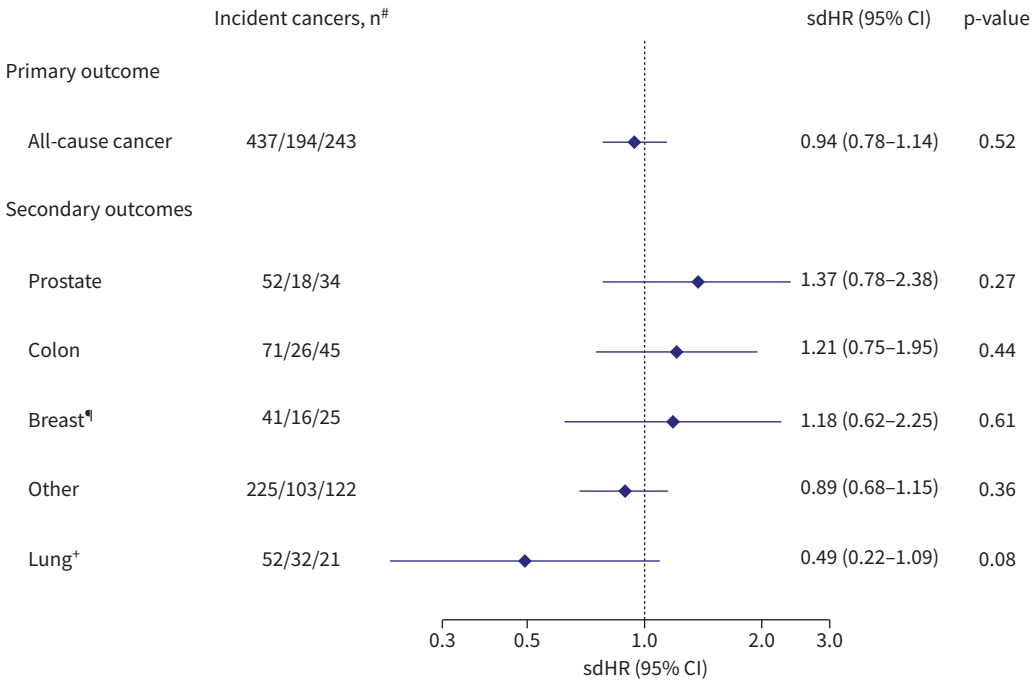


FIGURE 5 Summary of subdistribution hazard ratios (sdHRs) for primary and secondary outcomes. #: all patients/nonadherent/adherent; ¶: breast cancer model was not adjusted on gender; +: lung cancer model was adjusted for tobacco consumption.

such relationships may differ depending on the unique intrinsic characteristics of the tumours being evaluated. Lung tumour cell malignant properties were found to be enhanced *in vivo* by circulating exosomes released under intermittent hypoxia conditions mimicking OSA [32]. Li *et al.* [33] recently reported that OSA severity was a risk factor that contributed to short overall survival in patients with lung cancer. The authors identified molecular convergence between hypoxia and lung cancer that reflected their clinical profiles and revealed molecular pathways involved in hypoxic-induced lung cancer progression. In the present study, secondary analyses for specific cancers found that the incidence of lung cancer was reduced by ∼50% (sdHR 0.49, 95% CI 0.22–1.09) under adequate CPAP therapy compared with nonadherent patients. Further studies are required to determine whether CPAP therapy of OSA with good adherence exerts a protective effect against lung cancer development and which types of lung cancer appear to be susceptible to such effect.

The strength of the current study includes a multicentre design, a relatively large sample size, long and complete follow-up with access to comprehensive SNDS data, and objective measurement of CPAP adherence. This study also has limitations, the most important being its observational design, which does not allow for definitive conclusions to be drawn regarding the impact of CPAP on cancer risk. Furthermore, partitioning of CPAP adherence to more subgroups to assess for a dose-response to treatment was not possible, since the resultant cohort sizes would be insufficiently sized to derive meaningful deductions. The presence of potential unmeasured confounding factors cannot be excluded. Given the established benefits of CPAP, and the danger sleepy individuals can present to themselves and others, it is no longer conceivable to ethically randomise excessively sleepy patients with OSA to no therapy for extended periods of time, as would be required for assessment of cancer incidence events [13]. However, the use of an exhaustive medical administrative database combined with a clinical database can reasonably mitigate the risk of bias related to unmeasured confounders. Although observational data can lead to biases, the use of adequate approaches such as IPTW estimators are acknowledged to address confounding in real-world studies when randomised clinical trials are not possible, as is the case here.

Conclusions

CPAP therapy of OSA with good adherence (defined as ⩾4 h per night) was not associated with a reduction in all-cause cancer incidence compared with nonadherent patients. Whether adequate CPAP

therapy of OSA might reduce the risk of specific cancer sites, particularly among those OSA patients with more severe nocturnal hypoxaemia, should be further evaluated.

Acknowledgements: The authors thank the French National Health Insurance for providing access to the French administrative healthcare database (SNDS); the ERMES study group (Centre Hospitalier Universitaire, Angers: Christine Person, Pascaline Priou; Centre Hospitalier, Le Mans: Olivier Molinier, Audrey Paris); the Institut de Recherche en Santé Respiratoire des Pays de la Loire (Christelle Gosselin and Jean-Louis Racineux), sponsor of ERMES, from which the data for this study were derived; Frédéric Balusson and Emmanuel Oger (EA 7449, Pharmacoepidemiology and Health Services Research, REPERES, Rennes University, Rennes University Hospital, Rennes, France); and Julien Godey, Laetitia Moreno and Marion Vincent (sleep technicians in the Dept of Respiratory and Sleep Medicine of Angers University Hospital, Angers, France).

Conflict of interest: G. Justeau has nothing to disclose. S. Bailly reports consulting fees for methodology and statistical analyses from Institut Recherche en Santé Respiratoire des Pays de la Loire, outside the submitted work. C. Gervès-Pinquié has nothing to disclose. W. Trzepizur has nothing to disclose. N. Meslier has nothing to disclose. F. Goupil has nothing to disclose. T. Pigeanne has nothing to disclose. S. Launois has nothing to disclose. L. Leclair-Visonneau has nothing to disclose. P. Masson has nothing to disclose. A. Bizieux-Thaminy has nothing to disclose. J-L. Racineux has nothing to disclose. D. Gozal reports NIH grants, outside the submitted work. F. Gagnadoux reports support for the present manuscript from Institut Recherche en Santé Respiratoire des Pays de la Loire to the University Hospital of Angers; consulting fees from Nyxoah, Sefam and ResMed; payment or honoraria for lectures from Cidelec, Asten Santé and Boehringer Ingelheim; payment for expert testimony from Boehringer Ingelheim; support for attending meetings and/or travel from Asten Santé and Actelion; participation on a data safety monitoring board or advisory board for Jazz Pharmaceutical; receipt of equipment, materials, drugs, medical writing, gifts or other services from Inspire to the University Hospital of Angers, outside the present work.

Support statement: This study was supported by a grant from the Institut de Recherche en Santé Respiratoire des Pays de la Loire (IRSR), Beaucouzé, France. Funding information for this article has been deposited with the Crossref Funder Registry.

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