# Cancer risk in adherent users of polyurethane foam-containing CPAP devices for sleep apnoea



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*To the Editor*:

On 14 June, 2021 Philipps Respironics (PR) emitted a voluntary recall notification for several sleep and respiratory care products, including continuous positive airway pressure (CPAP) devices used for obstructive sleep apnoea (OSA) therapy and ventilators. The polyester-based polyurethane (PE-PUR) sound abatement foam may break down into particles, which may enter the device's air tube and be inhaled or swallowed by the user. The volatile gas products (diethylene glycol, toluene di-isocyanate isomers, toluene diamine isomers) released during the degradation process have been suspected to present potential toxic and carcinogenic effects [1]. Whether prolonged exposure to these volatile compounds is associated with an increased risk of cancer in patients using PR devices for OSA is a crucial issue. Using clinical data from a retrospective longitudinal multicentre cohort linked with health administrative data, Kendzerska *et al.* [2] reported no increased all-cancer risk in 1220 patients treated for OSA with a PR device over a median follow-up time of 7.5 years. However, the lack of therapy adherence data did not make it possible to evaluate cancer risk in CPAP-adherent patients. Using propensity score matching within a nationwide study of patients with OSA, Palm *et al.* [3] reported an increased all-cancer and lung cancer incidence in counties prescribing ⩾80% of CPAP devices containing polyurethane foam (PUF-CPAP) compared to patients from counties prescribing <10% of PUF-CPAP. However, the association disappeared in the sensitivity analysis excluding a Swedish county with known higher smoking rates.

Our group has extensively studied the association of OSA and its treatment on cancer risk using data collected by the clinic-based multicentre Pays de la Loire Sleep Cohort, linked to health administrative data, such as to identify new-onset cancer [4, 5]. Using the same cohort, the present study aimed to determine whether patients receiving long-term CPAP therapy of OSA using PR-devices had an increased cancer incidence compared to those treated with non-PR devices.

All patients with OSA (apnoea–hypopnoea index (AHI) of at least 5 events·h$^{-1}$ on type 3 home sleep apnoea testing or on in-laboratory polysomnography) included in the cohort between 15 May, 2007 and 31 December, 2018, who were prescribed CPAP therapy for at least 1 year, and had available data from the French administrative healthcare database (SNDS), were eligible for 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. 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 [6].

The primary outcome was defined as the first occurrence of cancer at any time between the end of the first year of CPAP therapy and the censor date, identified based on the French Hospital Discharge database (see reference [4, 5] for details). Patients who did not develop cancer were censored at the date of death or at the final follow-up date (31 December, 2019). As a low rate of missing values was observed, a simple imputation was performed by considering median value for quantitative variables and most observed frequency for qualitative variables. Cox proportional analyses were conducted to evaluate the association between the use of PR *versus* non-PR CPAP devices and all-cancer incidence. Subgroup analyses were considered to account for CPAP adherence and follow-up duration. Associations were considered statistically significant for a p-value <0.05. All statistical analyses were performed with SAS 9.4 software (SAS Institute, Cary, NC).

Shareable abstract (@ERSpublications)
**Sustained and adherent CPAP therapy of obstructive sleep apnoea using Philips Respironics devices containing polyester-based polyurethane foam, was not associated with an increased risk of cancer after a median follow-up time of 7.2 years** https://bit.ly/3vBpUQE

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The study population consisted of 4447 patients (median (interquartile range) age 63 (54–72) years), with moderate-to-severe OSA (median AHI 37 (27–52) events·h$^{-1}$), predominantly male (63%), obese or overweight (median body mass index 31 (27–36) kg·m$^{-2}$), frequently presenting comorbidities (hypertension, 39.6%; diabetes, 17.8%; cardiac diseases, 18.4%; COPD, 9.8%), among whom 1648 had been treated with PR devices and 2799 with non-PR devices (median adherence during the follow-up period 6.6 (5.2–7.6) and 6.4 (4.7–7.5) h per night respectively; p=0.0118). Being mainly made up of ResMed devices (80.2%), the non-PR devices were gathered into a single group. After a median follow-up of 7.2 (4.9–9.7) years (6.7 (4.8–9.5) and 7.5 (4.9–9.9) for PR and non-PR devices; p<0.0001), 437 patients (9.7%) had received a diagnosis of cancer, 149 (9.0%) in the PR group and 243 (9.1%) in the non-PR group (p=0.2768). Overall, the all-cancer incidence rate was 17.1 cases per 1000 person-years (95% CI 15.6–18.8); 16.4 (95% CI 14.0–19.2) and 17.5 (95% CI 15.6–19.7) per 1000 person-years in the PR and the non-PR groups, respectively.

Variables associated with all-cancer incidence are detailed in table 1. On univariate Cox proportional analysis, all-cancer incidence was associated with age, Epworth Sleepiness Score, alcohol and smoking habits, cardio-metabolic comorbidities, COPD, indices of nocturnal hypoxia, and CPAP daily usage. Using PR *versus* non-PR devices was not associated with all-cancer incidence. On multivariate analysis, only age and the Epworth Sleepiness Score were associated with all-cancer incidence. Subgroup analyses showed no increased all-cancer incidence in patients treated with PR compared to non-PR devices in patients using CPAP ⩾6 h per night (n=2150, 235 incident cancers; HR 0.97, 95% CI 0.75–1.26) and in patients with follow-up duration ⩾7.2 years (n=2222, 304 incident cancers; HR 0.91, 95% CI 0.74–1.12). When the analysis was restricted to incident lung cancer (n=52), we found no association with the use of PR-devices (HR 0.68, 95% CI 0.36–1.29).

In the present multicentre clinic-based cohort, long-term use of PR devices containing PE-PUR sound abatement foam for OSA therapy was not associated with an increased all-cancer incidence compared to patients using non-PR devices. These findings are consistent with the first real-world published data [2] on incident cancer risk following the PR recall announcement. Moreover, access to CPAP adherence data enabled us to demonstrate the lack of increased cancer incidence in a cohort of CPAP adherent users

**TABLE 1** Cox proportional hazard models including relevant factors and their association with incident cancer (n=437) in 4447 patients treated with continuous positive airway pressure (CPAP) for obstructive sleep apnoea over a median follow-up of 7.2 years

| | Unadjusted HR (95% CI) | p-value | Adjusted[#] HR (95% CI) | p-value |
|---|---|---|---|---|
| **Age, years (1SD)** | 1.75 (1.58–1.94) | <0.0001 | 1.66 (1.48–1.87) | <0.0001 |
| **Body mass index, kg·m$^{-2}$ (1SD)** | 1.01 (0.92–1.11) | 0.8391 | – | – |
| **Epworth Sleepiness Score (1SD)** | 0.75 (0.68–0.83) | <0.0001 | 0.85 (0.76–0.94) | 0.0019 |
| **Male *versus* female gender** | 1.07 (0.87–1.32) | 0.5007 | – | – |
| **Daily alcohol intake (yes *versus* no)** | 1.26 (1.04–1.53) | 0.0181 | 1.05 (0.85–1.30) | 0.6459 |
| **Smoking habits** | | | | |
| Never | Ref. | – | Ref. | – |
| Current | 0.90 (0.68–1.18) | 0.0375 | 1.30 (0.95–1.77) | 0.0974 |
| Former | 1.35 (1.09–1.66) | 0.0213 | 1.22 (0.97–1.54) | 0.0943 |
| **Prevalent diseases** | | | | |
| Diabetes (yes *versus* no) | 1.59 (1.28–1.97) | <0.0001 | 1.26 (0.98–1.63) | 0.0698 |
| Hypertension (yes *versus* no) | 1.29 (1.07–1.56) | 0.0079 | 0.88 (0.70–1.10) | 0.2479 |
| CVD (yes *versus* no) | 1.37 (1.09–1.72) | 0.0072 | 0.85 (0.65–1.11) | 0.2347 |
| COPD (yes *versus* no) | 1.52 (1.14–2.01) | 0.0037 | 1.11 (0.81–1.51) | 0.5252 |
| **PSG (*versus* HSAT)** | 0.83 (0.68–1.01) | 0.0667 | 1.04 (0.82–1.32) | 0.7374 |
| **ln oxygen desaturation index** | 1.13 (0.99–1.28) | 0.0520 | – | – |
| **ln apnoea-hypopnoea index** | 1.09 (0.99–1.19) | 0.0888 | – | – |
| **ln T90** | 1.20 (1.08–1.34) | 0.0010 | 0.97 (0.86–1.09) | 0.6101 |
| **CPAP daily usage, h (1SD)** | 1.16 (1.04–1.29) | 0.0097 | 1.07 (0.96–1.20) | 0.2194 |
| **PR devices (*versus* non-PR devices)** | 0.94 (0.77–1.14) | 0.5437 | 0.91 (0.74–1.12) | 0.3835 |
| **Years of follow-up (1SD)** | 1.01 (0.88–1.15) | 0.9405 | – | – |

HR: hazard ratio; CVD: cardiovascular diseases; HSAT: type 3 home sleep apnoea testing; PSG: polysomnography; T90: % of sleep (recording) time with oxygen saturation <90%; PR: Philips Respironics. [#]: adjusted for variables with a p-value below 0.15 in the univariate Cox model and for a competing risk of death.

(median daily CPAP use 6.6 (5.2–7.6) in the PR device group). There was also no excess risk of cancer in highly adherent patients (CPAP use ⩾6 h per night) and in those with long follow-up duration (⩾7.2 years).

The recent report from Palm *et al*. [3] suggested that long-term use of PUF-CPAP might be responsible for adverse respiratory health outcomes in OSA patients, including mild deterioration of obstructive lung disease control as assessed by an increased use of short-acting beta-agonists and oral corticosteroids, and an increased lung cancer incidence which was no longer significant in sensitivity analyses. However, that study had no data on smoking status and might be biased by regional disparities in respiratory diseases [7, 8]. In our study, patients using PR devices were not at higher risk of lung cancer but this finding should be interpreted with caution due to the low number of events.

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 PR devices on cancer risk. The presence of potential unmeasured confounding factors cannot be excluded. The size of our cohort and the median follow-up of 7.2 years may have been insufficient to identify a link between the use of PR devices and the development of certain cancer types.

Despite these limitations, our findings, in addition to previous clinical studies, provide reassuring data for patients who have been treated with PR devices containing PE-PUR foam and for the clinicians who have prescribed these devices. However, further studies are needed to confirm these results.

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