Early View

Research letter

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


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

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"Take home" message: 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.
To the Editor

On June 14, 2021 Philips 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. reported no increased all-cancer risk in 1,220 patients treated for OSA with a PR device over a median follow-up time of 7.5 years [2]. 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. 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 [3].

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-hypopnea index [AHI] of at least 5 events/h on Type 3 home sleep apnoea testing [HSAT] or on in-lab polysomnography [PSG]) included in the cohort between May 15, 2007 and December 31, 2018, who were prescribed CPAP therapy for at least one year, and had
available data from the French administrative health care 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 (ASTE Santé, Beaucouzé, France) was involved in CPAP device delivery and in the follow-up support program [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 ref [4, 5] for details). Patients who did not develop cancer were censored at the date of death or at the final follow-up date (December 31, 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 vs non-PR CPAP devices and all-cancer incidence. Sub-group 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).

The study population consisted of 4,447 patients (median [interquartile range, IQR] age: 63 [54-72] years), with moderate-to-severe OSA (median AHI: 37 [27-52] events/h), predominantly male (63%), obese or overweight (median body-mass index: 31 [27-36] kg/m2), frequently presenting comorbidities (hypertension, 39.6%; diabetes, 17.8%; cardiac diseases, 18.4%; chronic obstructive pulmonary disease, 9.8%), among whom 1,648 had been treated with PR devices and 2,799 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/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-year (95% Confidence Interval,
CI [15.6-18.8)], 16.4 [14.0-19.2] and 17.5 [15.6-19.7] per 1000 person-year in the PR and the non-PR group 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, chronic obstructive pulmonary disease, indices of nocturnal hypoxia, and CPAP daily usage. Using PR vs non-PR devices was not associated with all-cancer incidence. On multivariate analysis, only age and the Epworth score were associated with all-cancer incidence. Sub-group analyses showed no increased all-cancer incidence in patients treated with PR compared to non-PR devices in patients using CPAP≥ 6h/night (n= 2,150, 235 incident cancers, HR: 0.97 [0.75-1.26]) and in patients with follow-up duration≥ 7.2 years (n=2,222, 304 incident cancers, HR: 0.91 [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[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 Philips Respironics 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 (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≥ 6h/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 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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References


status on long-term adherence with continuous positive airway pressure in sleep apnea patients.


<table>
<thead>
<tr>
<th></th>
<th>Unadjusted HR [95% CI]</th>
<th>p value</th>
<th>Adjusted* HR [95% CI]</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, year (1SD)</td>
<td>1.75 [1.58-1.94]</td>
<td>&lt;0.0001</td>
<td>1.66 [1.48-1.87]</td>
<td>&lt;0.0001</td>
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<tr>
<td>Body mass index, kg/m² (1SD)</td>
<td>1.01 [0.92-1.11]</td>
<td>0.8391</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Epworth Sleepiness Score (1SD)</td>
<td>0.75 [0.68-0.83]</td>
<td>&lt;0.0001</td>
<td>0.85 [0.76-0.94]</td>
<td>0.0019</td>
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<tr>
<td>Male vs female gender</td>
<td>1.07 [0.87-1.32]</td>
<td>0.5007</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Daily alcohol intake (yes vs no)</td>
<td>1.26 [1.04-1.53]</td>
<td>0.0181</td>
<td>1.05 [0.85-1.30]</td>
<td>0.6459</td>
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<tr>
<td>Smoking habits</td>
<td>ref.</td>
<td>-</td>
<td>ref.</td>
<td>-</td>
</tr>
<tr>
<td>Never</td>
<td>0.90 [0.68-1.18]</td>
<td>0.0375</td>
<td>1.30 [0.95-1.77]</td>
<td>0.0974</td>
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<td>Current</td>
<td>1.35 [1.09-1.66]</td>
<td>0.0213</td>
<td>1.22 [0.97-1.54]</td>
<td>0.0943</td>
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<tr>
<td>Prevalent diseases</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Diabetes (yes vs no)</td>
<td>1.59 [1.28-1.97]</td>
<td>&lt;0.0001</td>
<td>1.26 [0.98-1.63]</td>
<td>0.0698</td>
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<td>Hypertension (yes vs no)</td>
<td>1.29 [1.07-1.56]</td>
<td>0.0079</td>
<td>0.88 [0.70-1.10]</td>
<td>0.2479</td>
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<td>CVD (yes vs no)</td>
<td>1.37 [1.09-1.72]</td>
<td>0.0072</td>
<td>0.85 [0.65-1.11]</td>
<td>0.2347</td>
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<td>COPD (yes vs no)</td>
<td>1.52 [1.14-2.01]</td>
<td>0.0037</td>
<td>1.11 [0.81-1.51]</td>
<td>0.5252</td>
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<td>PSG (vs HSAT)</td>
<td>0.83 [0.68-1.01]</td>
<td>0.0667</td>
<td>1.04 [0.82-1.32]</td>
<td>0.7374</td>
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<tr>
<td>ln oxygen desaturation index</td>
<td>1.13 [0.99-1.28]</td>
<td>0.0520</td>
<td>-</td>
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<tr>
<td>ln apnoea-hypopnea index</td>
<td>1.09 [0.99-1.19]</td>
<td>0.0888</td>
<td>-</td>
<td>-</td>
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<tr>
<td>ln T90</td>
<td>1.20 [1.08-1.34]</td>
<td>0.0010</td>
<td>0.97 [0.86-1.09]</td>
<td>0.6101</td>
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<tr>
<td>CPAP daily usage, h (1SD)</td>
<td>1.16 [1.04-1.29]</td>
<td>0.0097</td>
<td>1.07 [0.96-1.20]</td>
<td>0.2194</td>
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<td>PR devices (vs non-PR devices)</td>
<td>0.94 [0.77-1.14]</td>
<td>0.5437</td>
<td>0.91 [0.74-1.12]</td>
<td>0.3835</td>
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<tr>
<td>Years of follow-up (1SD)</td>
<td>1.01 [0.88-1.15]</td>
<td>0.9405</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviations: HR, hazard ratio; CI, confidence interval; CVD, cardiovascular diseases; COPD, chronic obstructive pulmonary disease; HSAT, Type 3 home sleep apnoea testing; PSG, polysomnography; T90, % of sleep (recording) time with oxygen saturation <90%; CPAP, continuous positive airway pressure; 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.