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Summary of a systematic literature review of Positive Airway Pressure device use and cancer risk

Introduction

Philips Respironics engaged external scientific experts to perform an independent systematic literature review of epidemiological studies to evaluate whether use of Continuous or Bilevel Positive Airway Pressure (PAP) devices increases the risk of cancer in obstructive sleep apnea (OSA) patients. When investigating this question, it is important to note that OSA itself may increase the risk of cancer,[1,2] as do risk factors for OSA such as aging, tobacco smoking, and obesity.[3] Therefore, cancer risk should ideally be compared between OSA patients with and without use of PAP devices, adjusting for relevant risk factors that differ between these groups.

In accordance with standard guidelines for systematic literature reviews,[4] a search was conducted in PubMed, the U.S. National Library of Medicine's biomedical literature database, to identify studies of humans up to July 14, 2022, that compared risk of overall and site-specific cancers between OSA patients using or not using PAP devices.[5] After excluding non-human studies, studies of OSA patients not treated with PAP therapy, studies lacking a comparison group without PAP device use, and articles without original research data (e.g., reviews, commentaries, and letters), 13 relevant epidemiological studies were identified. The design, methods, and results of each study were evaluated for rigor and risk of bias according to standard epidemiological considerations,[6] as well as for their relevance to the topic of interest.

Two rigorous studies show no statistical association between use of Philips Respironics PAP devices and risk of cancer

Two independent studies provided rigorous evidence to address whether Philips Respironics PAP device use increases the risk of cancer.[7,8] One study, based in Ontario, Canada, linked 6,903 clinically diagnosed OSA patients with the provincial cancer registry to identify all new cancer diagnoses over a median of 7.5 years of follow-up.[7] Manufacturer-specific PAP device use was evaluated based on information from a provincial health database containing approved claims for purchase of PAP devices. After adjusting for multiple risk factors, no statistically significant difference in overall cancer risk was found between users of Philips Respironics PAP devices and users of ResMed, Fisher & Paykel, or all non-Philips-Respironics PAP devices.

The other study, based in France, linked more than 4,400 clinically diagnosed OSA patients with national hospital discharge records to identify all new cancer diagnoses over a median follow-up of up to 7.2 years.[8] Manufacturer-specific PAP device use, including daily adherence (monitored using data downloaded from the devices), was evaluated based on device delivery by a single home respiratory care company. After adjusting for multiple risk factors, no statistically significant difference in risk of overall cancer or lung cancer was found between adherent users of Philips Respironics PAP devices and adherent users of non-Philips-Respironics PAP devices.

Eleven other studies provide minimal additional insights, but show no increased risk of cancer associated with use of PAP devices in general

Another rigorous analysis based in the French sleep study cohort showed no statistically significant difference in overall or site-specific cancer risk (prostate, colon, breast, lung, or other sites) between OSA patients with or without adherence to PAP therapy in general.[9] Otherwise, the remaining ten studies provided little additional insight into the association between PAP device use and cancer risk.

Five studies were considered limited for answering the question at hand mainly because they did not directly report quantitative results on cancer risk in PAP device users vs. non-users. These included a prospective cohort study of 1,522 Wisconsin residents (365 diagnosed with sleep-disordered breathing) followed for mortality[10]; a retrospective cohort study of 5,427 OSA patients in Spain followed for cancer mortality[11]; a retrospective case-cohort study of 1,466 OSA patients (including 328 incident cancer cases) in the University of Washington Medicine system who were followed for cancer incidence[12]; and two alternative analyses of the aforementioned Canadian sleep study cohort that focused on comparisons other than PAP device use vs. non-use.[13,14]

In these studies, instead of directly reporting the relative risk of cancer in PAP device users vs. non-users, the authors stated that no statistically significant association was observed between prescription of a PAP device and cancer risk[12]; that a null association between OSA severity and cancer risk did not change after restriction to patients without PAP treatment[13]; that a positive association between OSA severity and cancer mortality was augmented after excluding PAP-treated patients, suggesting a possible inverse (protective) association with PAP therapy[10,11]; and that cancer risk did not vary between OSA patients with and without use of a PAP device or various surgical interventions, as opposed to PAP therapy alone.[14] Thus, of these five studies, three reported results indicating no statistical association between PAP device use and cancer incidence,[12,13,14] and two indirectly reported an inverse (protective) association between PAP device use and cancer mortality.[10,11] None suggested a positive association between PAP therapy and increased cancer risk.

The five remaining studies had important methodological limitations for assessing the relationship between PAP device use and cancer risk.[15,16,17,18,19] These were a proportional mortality study of cancer deaths among 4,502 OSA patients in a sleep study cohort in Scotland[15]; a Spanish prospective cohort study of cancer mortality among 9,317 OSA patients on PAP therapy, compared with non-OSA patients without PAP therapy[17]; a German

prospective cohort study of cancer incidence among type 2 diabetes mellitus patients with OSA, comparing those who did and did not report use of PAP therapy[18]; a Swedish group-level geographic (ecological) comparison of cancer incidence among OSA patients living in counties that mostly prescribed PAP devices containing polyurethane foam versus counties that mostly prescribed non-polyurethane-foam PAP devices[19]; and an alternative analysis of the French sleep study cohort that focused on comparisons other than PAP device use vs. non-use.[16]

For addressing the topic of this literature review, methodological shortcomings of these five studies included use of a reference group of patients without OSA (and without PAP use)[17]; analysis of cancer mortality instead of incidence[15,17]; reliance on self-reported, unvalidated information on PAP use[18]; reliance on grouped county-level data on PAP device prescription patterns, without any individual patient-level data on PAP use[19]; estimating proportional mortality ratios (based only on deaths) rather than relative risks[15]; loss to follow-up of the majority of the study cohort[15]; and minimal or no control for major cancer risk factors.[15,16,18,19]

Among these five studies, two found a statistically significantly lower risk of overall cancer mortality (as well as lower risk of all-cause mortality, no difference in risk of cardiovascular mortality, and inconsistent findings on respiratory mortality) among PAP-treated OSA patients than the reference group[15,17]; one found a statistically significantly higher risk of overall cancer incidence in PAP-treated than PAP-untreated OSA patients, with no adjustment for confounding[16]; one found no statistical difference in overall cancer risk between PAP-treated and PAP-untreated OSA patients with type 2 diabetes[18]; and one found no statistical difference in overall cancer or lung cancer risk between counties by PAP device prescription pattern (≥ 80% vs. < 10% with polyurethane foam) after excluding one county with known higher smoking rates.[19] The latter study also reported more frequent prescription of respiratory relief medications among patients with both OSA and obstructive lung disease in counties prescribing mostly polyurethane foam PAP devices, but no statistical difference in hospitalization for obstructive lung disease between counties.

Taken together, the identified epidemiological studies show no statistical increase in cancer risk due to use of PAP devices, including Philips Respironics PAP devices

In summary, based on 13 epidemiological studies identified from a systematic literature review, no association has been established between use of PAP devices, including Philips Respironics PAP devices, and risk of cancer in patients with OSA. Two rigorous independent studies showed no statistical difference in cancer risk between OSA patients who used Philips Respironics PAP devices versus other brands of PAP devices.[7,8] Eleven other epidemiological studies provided little additional insight into this question, but their results generally suggested no excess risk of cancer associated with PAP use for OSA.[9–19] Philips Respironics and external experts will continue to monitor newly published studies on this topic.

Limitations

Only published sources identified via PubMed were included in this systematic literature review. Abstracts, other reports, and unpublished data could not be systematically searched, and therefore were excluded. Despite Philips Respironics' and external experts' efforts review to identify all relevant sources available through the described search strategy, some sources with relevant information may have been overlooked. In addition, relevant sources may have been missed by the described search strategy. Understanding of each study's methods and results was based on information made available by authors in published, peer-reviewed journal articles. Philips Respironics and external experts did not have access to study data other than what was provided in the published articles. Conclusions are based on the currently available published epidemiological literature, and may change as additional studies are published in the future.

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[5] The following search string was used: *(apnea [title/abstract] OR apnoea [title/abstract] OR "positive airway pressure" [title/abstract]) AND (cancer* [title/abstract] OR carcinoma* [title/abstract] OR adenocarcinoma* [title/abstract] OR sarcoma* [title/abstract] OR malignan* [title/abstract] OR lymphoma* [title/abstract] OR leukemia* [title/abstract] OR melanoma* [title/abstract]) AND (association OR risk OR rate OR ratio OR incidence)*.

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