Cancer prevalence is increased in females with sleep apnoea: data from the ESADA study

To the Editor:

There is growing, but debatable evidence for the potential association between obstructive sleep apnoea (OSA) and cancer [1–10]. Available studies have reached contradictory conclusions due to limited sample sizes, and poor characterisation of OSA phenotypes or type of malignancies (all types [1–4] or site specific [6–8]). Several hypotheses have been formulated proposing why carcinogenesis can occur in the context of OSA, including older age, sleep deprivation [11, 12] and concomitant obesity [13]. Intermittent hypoxia and sleep fragmentation may play a significant role *via* alterations in angiogenesis, sympathetic outflow, or modulation of immune function and tumour microenvironment [11, 12]. Gender-specific differences in the association between OSA and cancer prevalence have been poorly studied.

The European Sleep Apnoea Database (ESADA) is a multicentre, multinational study in which sleep laboratories recruit patients with suspected OSA [14]. The purpose of this analysis was to explore the cross-sectional association between the burden of OSA, intermittent hypoxia and cancer prevalence in the ESADA population after controlling for available recognised risk factors for cancer development. Patients older than 18 years enrolled in ESADA between 2007 and 2016 were considered. OSA was assessed by means of a sleep study (either polysomnography (PSG) or polygraphy (PG)) in accordance with the clinical routine of each participating centre [14, 15].

In the statistical analysis, quantitative variables are presented as mean±SD. Anthropometric and sleep variables in patients with or without cancer were compared using either a t-test or the Mann–Whitney U-test. The Chi-squared or Fisher's exact test were used to compare discrete variables. OSA severity was characterised by the apnoea–hypopnoea index (AHI), oxygen desaturation index (ODI), mean and lowest oxygen saturation (S_{pO_2}) recorded *via* pulse oximetry during the study, and time with S_{pO_2} <90% (CT90%) as continuous variables. AHI was stratified as <5 (no OSA); 5 to <15 (mild OSA); 15 to <30 (moderate OSA) and ⩾30 per h (severe OSA). Other OSA severity indices were categorised according to quartiles. Multivariate logistic regression analysis was used to evaluate association between cancer diagnosis and different OSA severity measures, expressed as odds ratios and 95% confidence intervals with continuous variables presented per 10-unit increase. The analysis was adjusted for potential confounders and cancer risk factors: age, gender, body mass index (BMI), smoking and alcohol use. A separate analysis was performed across groups stratified for gender. A p-value of <0.05 was considered statistically significant.

Of 19 556 patients, 388 (2%) had been diagnosed with malignancy (prevalent cancer) (1.7% males and 2.8% females). Patients with malignancy and AHI ⩾5 per h (n=318) were older (60.8±10.4 *versus* 53.5±12.1 years; p<0.001) and were slightly less centrally obese (waist-to-hip ratio 0.96±0.08 *versus* 0.98±0.08; p<0.001) than OSA patients without malignancy. Current and previous smoking history was reported in 14.8% and 45.0% of OSA patients with malignancy, respectively. Cardiovascular and metabolic comorbidity did not differ between OSA patients with cancer *versus* those without cancer, despite a higher prevalence of stroke in cancer patients (5.0% *versus* 2.4%; p=0.003).

A cancer diagnosis was significantly associated with elevated AHI (AHI ⩾5 *versus* AHI <5 per h: OR 1.35, 95% CI 1.02–1.79; p=0.03), CT90% as proportion of recording time (OR 1.08, 95% CI 1–1.17; p=0.03) and CT90% in minutes (OR 1.02, 95% CI 1–1.04; p=0.01) but not ODI (OR 0.98, 95% CI 0.9–1.02; p=0.98) in

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In a cross-sectional analysis of the European Sleep Apnoea Database (ESADA), cancer prevalence was higher in females with OSA and nocturnal hypoxia, but not in males. Further studies are needed to assess causality of gender, OSA and cancer incidence. http://bit.ly/2YuxyZA

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unadjusted models. Only CT90% remained a predictor for cancer diagnosis after adjustment for age, gender, BMI, smoking and alcohol consumption (CT90% as proportion of recording time: OR 1.1, 95% CI 1–1.2; p=0.04; CT90% in minutes: OR 1.02, 95% CI 1–1.04; p=0.02). In the analysis stratified by gender, increased odds ratios for cancer in different categories of OSA severity and degree of nocturnal hypoxia were identified in females but not in males (table 1). In males, ODI was close to significance, confirming previous studies indicating a stronger relationship between a cancer diagnosis and measures of intermittent hypoxia (ODI and CT90%) rather than AHI [1, 3, 10]. When patients were stratified according to sleep study methodology, the association between OSA and cancer prevalence remained significant in females assessed by PG (AHI ⩾15 *versus* <15 per h: OR 2.23, 95% CI 1.2–0.4.14; p=0.01; severe OSA *versus* no OSA: OR 2.97, 95% CI 1.19–7.43; p=0.02; 75th to 25th percentile of AHI: OR 3.63, 95% CI 1.42–9.21; p=0.007; ODI: OR 1.17, 95% CI 1.02–1.33; p=0.02; 75th to 25th percentile of ODI: OR 3.53, 95% CI 1.46–8.51; p=0.005). In female patients assessed by PSG, nocturnal intermittent hypoxia was associated with cancer prevalence (75th to 25th percentile of CT90% in minutes: OR 3.01, 95% CI 1.09–8.32; p=0.03; CT90% as proportion of recording time: OR 1.17, 95% CI 1.01–1.36; p=0.04). The different results between PG and PSG might be attributed to the fact that AHI is highly linked to intermittent hypoxia in PG, whereas AHI is partly linked to arousal in PSG [16]. Sleep quality measures like "sleep efficiency" and "total sleep time", excessive daytime sleepiness measured by Epworth Sleepiness Scale, as well as comorbidities potentially causing hypoxia, such as heart failure, chronic obstructive pulmonary disease or respiratory failure, did not modify the adjusted models after stratifying for gender and sleep study. The most prevalent cancer in women was breast cancer (n=70, 43.8%), followed by gynaecological (12.3%) and thyroid (6.9%) cancer, lymphoma (5.4%), lung (4.6%) and colon (3.1%) cancer, and melanoma (3.1%).

TABLE 1 Odds ratios for cancer prevalence in different obstructive sleep apnoea (OSA) categories assessed by apnoea–hypopnoea index (AHI) and measures of intermittent hypoxia: differences between genders

OSA categories	Male (n=13 539, c=228)		Female (n=5629, c=160)	
	Adjusted OR[#] (95% CI)	p-value	Adjusted OR[#] (95% CI)	p-value
AHI (continuous)	1.00 (0.9–1.06)	0.82	**1.09 (1.01–1.17)**	**0.03**
AHI ⩾5 *versus* <5	0.96 (0.65–1.54)	0.88	**1.79 (1.09–2.95)**	**0.02**
AHI ⩾15 *versus* <15	0.85 (0.6–1.18)	0.34	**1.58 (1.06–2.33)****	**0.02**
AHI ⩾30 *versus* <30	0.88 (0.63–1.23)	0.46	1.51 (0.99–2.29)**	0.054
Mild (AHI 5–14.9) *versus* 0–4.9	1.07 (0.63–1.81)	0.8	1.5 (0.85–2.63)	0.16
Moderate (AHI 15.0–29.9) *versus* 0–4.9	0.86 (0.5–1.46)	0.57	**1.8 (1–3.25)**	**0.05**
Severe (AHI ⩾30) *versus* 0–4.9	0.87 (0.52–1.45)	0.59	**2.15 (1.19–3.87)****	**0.01**
AHI (quartiles)[¶] 7–19.4 *versus* 0–6.9	0.95 (0.59–1.52)	0.8	1.04 (0.6–1.74)	0.88
AHI 19.5–41.3 *versus* 0–6.9	0.85 (0.53–1.36)	0.5	**1.68 (1.005–2.8)**	**0.05**
AHI >41.4 *versus* 0–6.9	0.99 (0.6–1.6)	0.96	1.5 (0.83–2.75)**	0.17
ODI (continuous)	0.92 (0.82–1.00)	0.06	**1.09 (2.45–5.41)****	**0.01**
ODI ⩾5 *versus* <5	1.46 (0.99–2.15)	0.05	0.7 (0.44–1.08)	0.11
ODI ⩾10 *versus* <10	**0.63 (0.44–0.88)**	**0.008**	1.3 (0.86–1.95)	0.21
ODI (quartiles)[¶] 4.5–14 *versus* 0–4.4	1.02 (0.64–1.62)	0.93	1.27 (0.78–2.17)	0.37
ODI 14.1–36 *versus* 0–4.4	0.73 (0.45–1.18)	0.19	1.71 (0.98–2.97)	0.06
ODI >36.1 *versus* 0–4.4	0.7 (0.4–1.2)	0.2	**1.93 (1.04–3.58)****	**0.04**
CT90% (minutes, continuous)	1.01 (0.98–1.04)	0.44	**1.03 (1.01–1.062)**	**0.01**
CT90% (minutes) (quartiles)[¶] 0.5–7.5 *versus* 0–0.4	1.01 (0.48–2.1)	0.98	0.63 (0.26–1.55)	0.3
CT90% (minutes) 7.6–48.1 *versus* 0–0.4	1.09 (0.52–2.29)	0.82	2.035 (0.97–4.26)*	0.06
CT90% (minutes) >48.2 *versus* 0–0.4	1.02 (0.46–2.28)	0.95	2.16 (0.95–4.92)*	0.07
CT90% (% of recording time)	1.04 (0.9–1.21)	0.55	**1.17 (1.04–1.32)***	**0.01**
CT90% (% of recording time) (quartiles)[¶] 0.125–1.69 *versus* 0–0.124	1.04 (0.49–2.2)	0.92	0.59 (0.23–1.51)	0.3
CT90% (% of recording time) 1.7–10.98 *versus* 0–0.124	1.21 (0.58–2.52)	0.62	**2.25 (1.08–4.67)**	**0.03**
CT90% (% of recording time) 10.99–100 *versus* 0–0.124	1.32 (0.61–2.86)	0.5	**2.27 (1.01–5.12)**	**0.05**

For continuous variables, odds ratios are presented per 10-unit increase. c: cancer patients; ODI: oxygen desaturation index; CT90%: time with oxygen saturation below 90%. [#]: adjusted for age, body mass index, smoking and alcohol. [¶]: different quartiles in polysomnography (PSG) or polygraphy (PG) are as follows. AHI quartiles PSG: first quartile: 0–11.4 per h; second: 11.41–25.6; third: 25.61–49; fourth: >49.1. ODI quartiles PSG: first quartile: 0–5.4 per h; second: 5.41–17.5; third: 17.51–42.1; fourth: >42.11. CT90% (in minutes) quartiles PSG: first quartile: 0–0.6 min; second: 0.61–8.2; third: 8.21–53.3; fourth: >53.31. CT90% (proportion of recording time) quartiles PSG: first quartile: 0–0.137%; second: 0.138–1.86%; third: 1.87–12.18%; fourth: 12.19–100%. AHI quartiles PG: first quartile: 0–4.3 per h; second: 4.31–13.1; third: 13.2–32.1; fourth: >32.12. ODI quartiles PG: first quartile: 0–3.7 per h; second: 3.71–11; third: 11.1–29; fourth: >29.1. CT90% (in minutes) quartiles PG: first quartile: 0–0.5 min; second: 0.51–6.21; third: 6.22–41; fourth: >41.1. CT90% (proportion of recording time) quartiles PG: first quartile: 0–0.1%; second: 0.11–1.47%; third: 1.48–9.33%; fourth: 9.34–100%. *: statistically significant in PSG. **: statistically significant in PG (refer to the text for odds ratios).

The most prevalent cancer in males was prostate cancer (n=56, 33.1%), followed by lymphoma (8.3%), colon cancer (8.3%), ear, nose, and throat cancer (8.3%), lung cancer (5.9%) and melanoma (5.3%). In a sub-analysis, there was no independent influence of OSA on the prevalence of breast and prostate cancer.

The main finding of our study was that OSA was associated with a cancer diagnosis, especially in females. Nocturnal hypoxia (expressed by CT90%) associated with cancer after adjusting for potential confounders and risk factors in both genders. Our findings were in agreement with previous studies demonstrating an association between OSA and increased cancer risk [1–3]. In one study, cancer prevalence was associated with CT90% and, in a subgroup analysis of smoking-related cancers, with ODI but not with AHI [10]. In contrast, other studies did not find an independent association between OSA and cancer incidence [2, 10], and the reasons for these differences remain unclear. Intermittent hypoxia has been linked to increased tumour proliferation and risk of metastasis. Intermittent hypoxia in OSA may elicit both preconditioning or cell death [5, 12]. Interestingly, data on sex differences in the association between cancer and OSA remain sparse [3, 8, 9]. The prevalence of cancer subtypes in our cohort broadly mirrors that reported in Western populations. The design of our study does not allow speculations about a causal relationship between cancer prevalence and OSA. However, the observed interaction suggests a possible OSA-related mechanism in carcinogenesis, with higher susceptibility in females. Potential factors include cancer subtype, hormonal influences on both tumour cell growth and immune responses, and duration of OSA exposure, as well as gender-specific exposure patterns to cigarette smoking not fully captured in our analysis [5, 9, 12].

The prevalence of cancer in our dataset was low (2%) compared to previous studies [10], suggesting under-referral of cancer patients, especially those with severe or lethal cancer. This referral bias may rather underestimate the true association between OSA and cancer. Cancer patients may have a different clinical presentation with insomnia affecting the results of sleep studies. It is important to further examine the influence of OSA on cancer types. However, the small number of cases limited our analysis to breast and prostate cancer. Furthermore, adjustment was not made for important confounders of cancer risk, such as physical activity, marital status, education, shift work and genetic propensity. Our study has two major strengths: the multicentre design and the magnitude of the clinical dataset; these increase the generalisability of our results and the substantial statistical power in the gender-specific subgroup analyses.

In conclusion, our findings suggest that cancer prevalence is higher in European females with OSA. In an ongoing follow-up study, we evaluate cancer incidence, mortality, aggressiveness and effect of OSA treatment in our population.

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