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Early View

Research letter

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

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

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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, poor characterization 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 [IH] 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 recognized 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 Student's 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 characterized by the apnoea

hypopnoea index (AHI), oxygen desaturation index (ODI), mean and lowest oxygen saturation (SpO_2) recorded during the study and time with SpO_2<90% (CT90%) as continuous variables. AHI was stratified as <5 (no OSA); 5–<15 (mild OSA); 15–<30 (moderate OSA) and ≥30/h (severe OSA). Other OSA severity indices were categorized according to quartiles. Multivariate logistic regression analysis was used to evaluate association between cancer diagnosis and different OSA severity measures, expressed as odds ratios (OR) and confidence intervals (CI) 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/h (n=318) were older (60.8±10.4 vs.53.5±12.1years, p<0.001) and were slightly less centrally obese (waist-to-hip ratio 0.96±0.08 vs. 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 co-morbidity did not differ between OSA patients with versus those without cancer, despite a higher prevalence of stroke in cancer patients (5.0% vs. 2.4%, p=0.003).

A cancer diagnosis was significantly associated with elevated AHI (AHI≥ 5 vs. AHI<5/h OR: 1.35 (95%CI1.02-1.79), p=0.03), CT90% of recording time (RT)(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 unadjusted models. Only CT90% remained a predictor for cancer diagnosis after adjustment for age, gender, BMI, smoking and alcohol consumption (CT90% of RT OR=1.1, 95%CI 1-1.2, p=0.04, in minutes OR=1.02, 95%CI 1-1.04, p=0.02). In the analysis stratified by gender, increased ORs 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 IH (ODI, 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 vs. <15, OR: 2.23 (95% CI 1.2-.4.14), p=0.01, severe OSA vs. no OSA, OR:2.97(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 IH 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% of RT, 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 IH 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 co-morbidities potentially causing hypoxia, as heart failure, COPD 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%), thyroid (6.9%) cancer, lymphoma (5.4%), lung (4.6%), colon (3.1%) cancer and melanoma (3.1%). The most prevalent cancer in males was prostate cancer (n=56, 33.1%), followed by lymphoma (8.3%), colon (8.3%), ear, nose, and throat cancer (8.3%), lung cancer (5.9%) and melanoma (5.3%). In a subanalysis, 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 [1-3] demonstrating an association between OSA and increased cancer risk. 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]. By contrast, other studies did not find an independent association between OSA and cancer incidence [2, 10] and the reasons remain unclear. IH has been linked to increased tumour proliferation and risk of metastasis. IH 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 between them 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, 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, as physical activity, marital status, education, shift work and genetic propensity. Our study has two major strengths: the multi-centre design and the magnitude of the clinical dataset which increases the generalizability 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 treatment in our population.

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Collaborators in the ESADA project are listed in Appendix.

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Table 1. ORs for cancer prevalence in different OSA categories assessed by AHI and measures of intermittent hypoxia – differences between genders				
	Male (n=13539, c=228)		**Female (n=5629, c=160)**	
OSA categories	**Adjusted* (95% CI)**	**P value**	**Adjusted * (95% CI)**	**P value**
AHI (continuous)	1.00(0.9-1.06)	0.82	**1.09(1.01-1.17)**	**0.03**
AHI≥ 5 vs <5	0.96(0.65-1.54)	0.88	**1.79(1.09-2.95)**	**0.02**
AHI≥ 15 vs. <15	0.85(0.6-1.18)	0.34	**1.58(1.06-2.33)##**	**0.02**
AHI≥ 30 vs.<30	0.88(0.63-1.23)	0.46	1.51(0.99-2.29**)##**	0.054
Mild (5-14.9) vs.0-4.9	1.07(0.63-1.81)	0.8	1.5(0.85-2.63)	0.16
Moderate (15.1-29.9) vs.0-4.9	0.86(0.5-1.46)	0.57	**1.8(1-3.25)**	**0.05**
Severe (≥30) vs.0-4.9	0.87(0.52-1.45)	0.59	**2.15(1.19-3.87)##**	**0.01**
AHI (quartiles) 7-19.4 vs. 0-6.9**	0.95(0.59-1.52)	0.8	1.04(0.6-1.74)	0.88
19.5-41.3 vs. 0-6.9	0.85(0.53-1.36)	0.5	**1.68(1.005-2.8)**	**0.05**
>41.4 vs. 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 vs. <5	1.46(0.99-2.15)	0.05	0.7(0.44-1.08)	0.11
ODI≥10 vs.<10	**0.63(0.44-0.88)**	**0.008**	1.3(0.86-1.95)	0.21
ODI (quartiles) 4.5-14 vs. 0-4.4**	1.02(0.64-1.62)	0.93	1.27(0.78-2.17)	0.37
14.1-36 vs. 0-4.4	0.73(0.45-1.18)	0.19	1.71(0.98-2.97)	0.06
>36.1vs. 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 vs. 0-0.4**	1.01(0.48-2.1)	0.98	0.63(0.26-1.55)	0.3
7.6-48.1vs. 0-0.4	1.09(0.52-2.29)	0.82	2.035(0.97-4.26)#	0.06
>48.2 vs. 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 vs. 0-0.124**	1.04(0.49-2.2)	0.92	0.59(0.23-1.51)	0.3
1.7-10.98 vs. 0-0.124	1.21(0.58-2.52)	0.62	**2.25(1.08-4.67)**	**0.03**
10.99-100 vs. 0-0.124	1.32(0.61-2.86)	0.5	**2.27(1.01-5.12)**	**0.05**

c= cancer patients, OR= Odds Ratio odds ratios (OR)(for continuous variables presented per 10-unit increase), n=number, OSA=Obstructive Sleep Apnoea , AHI= Apnoea Hypopnoea Index, CI= Confidential Intervals, ODI= Oxygen Desaturation Index, CT90%:time with O_2 saturation below 90%

* Adjusted for age, BMI, smoking, alcohol, **Different Quartiles in PSG and PG: AHI quartiles PSG : 0-25:0-11.4, 25-50: 11.41-25.6, 50-75: 25.61-49, 75-100: >49.1, ODI quartiles PSG : 0-25:0-5.4, 25-50: 5.41-17.5, 50-75:17.51-42.1, 75-100: >42.11, CT90 in min quartiles PSG : 0-25:0-0.6, 25-50:0.61-8.2, 50-75:8.21-53.3, 75-100: >53.31,CT90 % of recording time quartiles PSG : 0-25:0-0.137, 25-50:0.138-1.86, 50-75:1.87-12.18, 75-100: 12.19-100, AHI quartiles PG : 0-25:0-4.3, 25-50:4.31-13.1, 50-75:13.2-32.1, 75-100:>32, ODI quartiles PG : 0-25:0-3.7, 25-50: 3.71-11, 50-75: 11.1-29, 75-100: >29.1, CT90 in min quartiles PG : 0-25:0-0.5, 25-50:0.51-6.21, 50-75: 6.22-41, 75-100: >41.1,CT90 % of recording time quartiles PG : 0-25:0-0.1, 25-50:0.11-1.47, 50-75: 1.48-9.33, 75-100: 9.34-100)

Statistically significant in PSG, ## Statistically significant in PG(see in the text for OR)

Appendix:

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