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Original Article

ORIGINAL ARTICLE

# Associations of self-reported obstructive sleep apnea with total and site-specific cancer risk in older women: a prospective study

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## Abstract

**Background and Objectives:** Chronic intermittent hypoxia resulting from obstructive sleep apnea (OSA) may activate multiple carcinogenic pathways and lead to cancer development.

**Methods:** We prospectively examined the association between OSA and cancer risk among 65,330 women in the Nurses' Health Study who were free of cancer in 2008 (mean age: 73.3 years). Incident cancer diagnoses were collected until 2016 and confirmed by pathology reports. Clinically diagnosed OSA was self-reported in 2008 and updated in 2012. We used time-dependent Cox regression to estimate hazard ratios (HR) for the associations of OSA with total and site-specific cancer risk.

**Results:** We documented 5,257 incident cancer diagnoses during follow-up. In the age-adjusted model, OSA was associated with a 15% (95% CI: 1.03, 1.29) increase in total cancer risk. The association became nonsignificant after adjustment for multiple cancer risk factors (HR: 1.08; 95% CI: 0.96, 1.21). When examining cancer risk by site, OSA was associated with significantly increased risk for lung (fully adjusted HR: 1.52; 95% CI: 1.07, 2.17), bladder (fully adjusted HR: 1.94; 95% CI: 1.12, 3.35), and thyroid cancer (fully adjusted HR: 2.06; 95% CI: 1.01, 4.22) and possibly increased risk for kidney cancer (fully adjusted HR: 1.59; 95% CI: 0.84, 3.01). When grouping cancer sites by risk factor profiles, OSA was positively associated with smoking-related cancers (fully adjusted HR: 1.37; 95% CI: 1.11, 1.67), and this association was stronger in never smokers than ever smokers.

**Conclusion:** While OSA was not independently associated with overall cancer risk in older women, significant associations were observed for smoking-related cancers, especially in nonsmokers.

### Statement of Significance

The associations between obstructive sleep apnea and cancer risk are heterogeneous by cancer site, with increased risk observed for overall and several individual smoking-related cancers susceptible to hypoxia-related pathways, including lung, bladder, and kidney cancers. The findings support hypoxia-induced mechanisms of carcinogenesis and may have potential implications for targeted cancer prevention and screening.

**Key words:** obstructive sleep apnea; cancer risk; risk factors; hypoxia; cohort study; women

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## Introduction

The hypoxic microenvironment is an adverse condition that triggers adaptive cellular responses. Consequently, cellular exposure to hypoxia activates hypoxia-inducible factor (HIF) and leads to multiple downstream physiologic changes, including angiogenesis, metabolic reprogramming, genetic instability, tissue invasion, and production of reactive oxygen species (ROS) [1–7], all critical hallmarks of carcinogenesis that provide a favorable environment for tumor initiation, growth, and metastasis. In turn, cancerous cells exacerbate the hypoxic condition due to accelerated proliferation and excess oxygen consumption, which further promotes malignant progression and treatment resistance [8, 9]. As a result, cancer therapeutics targeting tumor hypoxia have been developed to improve prognosis [10], although the role of hypoxia in cancer prevention is less studied.

Obstructive sleep apnea (OSA) is a common disorder characterized by chronic intermittent hypoxia that is associated with incident cardiometabolic disease risk and mortality [11–13]. Emerging evidence from both experimental and epidemiologic studies also suggests a potential link between OSA and cancer [14, 15]. In mouse models of melanoma and lung cancer, experimentally induced intermittent hypoxia markedly enhanced tumor growth, invasiveness, and metastasis [16–20]. By contrast, several epidemiologic studies reported mixed associations between OSA and cancer outcomes. Although initial studies found increased total cancer incidence and mortality associated with more severe sleep-disordered breathing [21–24], several later population-based studies did not replicate these associations [25–29]. Given that cancer is heterogeneous with specific risk factor profiles for different cancer sites, elucidating the associations with specific types of cancer is fundamental for understanding the role of OSA in cancer pathophysiology. However, there is limited and conflicting evidence regarding the associations between OSA and site-specific cancer risk [28–31]. Further, most prior studies did not adequately control for cancer risk factors, such as smoking and alcohol drinking, which could confound or modify the observed associations between OSA and cancer risk.

To address these limitations, we investigated the associations between OSA and incident total and site-specific cancer risk in a large cohort of US women. We further examined the associations with risk of cancers grouped by risk factor profiles (e.g. obesity-related cancers) to provide insight into the underlying etiology.

## Methods

### Study population

Established in 1976, the Nurses' Health Study (NHS) enrolled 121,700 US female registered nurses aged 30–55 years across 11 states. At baseline and every 2 years thereafter, participants reported health-related information, including disease diagnoses, medication use, and lifestyle factors, through mailed questionnaires. The response rate was generally >85% across questionnaire cycles. This analysis included 65,330 women who were free of any diagnosed cancers (except nonmelanoma skin cancer) at the time of reporting OSA diagnosis in 2008, with incident cancers prospectively identified and ascertained through June 2016. The study protocol was approved by the institutional review boards of the Brigham and Women's Hospital (Partners Human Research Committee; 1999P011114).

### Assessment of cancer incidence

On each biennial questionnaire, participants reported whether they had been diagnosed with cancers of the breast, lung, ovary, uterus, colon, rectum, cervix, melanoma, or other sites. If cancers of other sites were reported, participants were asked to specify the site. Self-reported cancer diagnoses were confirmed by a review of medical records or pathology reports with permission from the participants or by linkage to cancer registries or the National Death Index. Information on the date of cancer diagnosis, anatomical site, and additional tumor characteristics for major cancer types were collected and confirmed by collaborating pathologists. International Classification of Diseases, 9th Revision (ICD-9) was used to code confirmed cancer cases.

### Assessment of OSA

In the 2008 questionnaire, participants were first asked to report whether they had ever had clinically diagnosed sleep apnea and the year of the first diagnosis. This information was updated in 2012. In a validation study against medical record review, 108 randomly sampled nurses with self-reported sleep apnea were all confirmed to have the diagnosis based on an objective method [32]. Of these, 92% were diagnosed by the gold-standard in-lab polysomnography, 98% were classified as obstructive and 89% were considered to have a moderate-to-severe disease (apnea–hypopnea index [AHI ≥ 15]). While the overall self-reported OSA prevalence in our study population was lower compared with the prevalence of moderate-to-severe OSA measured by polysomnography in community-based samples of US women (primarily due to lower BMI distribution), the BMI-specific prevalence was highly similar [32, 33]. These data suggest that self-reported sleep apnea diagnoses in nurses reliably reflect moderate-to-severe OSA.

### Assessment of cancer risk factors

Birth date and height were reported in 1976 and race/ethnicity in 1992. Participants reported their current weight biennially; self-reported weight was highly correlated with technician-measured weight ($r$ = 0.97) [34]. Family history of cancer was assessed approximately every 4 years by querying diagnoses of common cancers among their biological parents and siblings. Baseline assessment of smoking history and updated biennial assessment of current cigarette smoking were combined to derive lifetime pack-years of smoking. Alcohol intake was assessed using a validated semi-quantitative food frequency questionnaire in 1984, 1986, and every 4 years thereafter [35], and participation in different types of recreational physical activity was assessed using a validated questionnaire in 1986, 1988, and every 4 years thereafter [36]. Cumulative average alcohol consumption and physical activity were calculated from the first available questionnaire for each participant to reflect long-term exposure level. Average hours of sleep per day were self-reported in 2008 and 2012. On every biennial questionnaire, information was collected on duration and type of postmenopausal hormone therapy (HT), regular aspirin use, recent physical exams,

and surgical removal of the uterus or ovaries in the past 2 years, as well as self-reported diabetes diagnosis which was further confirmed by a validated supplemental questionnaire [13].

### Statistical analysis

We used Cox proportional hazards model to examine the associations between OSA and total and site-specific cancer risk. Participants contributed person-time of follow-up from the return date of the 2008 questionnaire to the date of any cancer diagnosis (except nonmelanoma skin cancer), death, or the end of follow-up (June 2016). In site-specific analyses, we focused on cancer types with at least 50 incident cases during the follow-up period (Supplementary Table S1); participants were censored at the time of diagnosis of any other cancers. We excluded participants with hysterectomy in the analysis of uterus cancer and participants with bilateral oophorectomy in the analysis of ovarian cancer, as these women were at no material risk for these cancers but at higher risk for OSA [37]. In the basic model (Model 1), we stratified the analysis by age (in months) and calendar time (in years). In the multivariable model, we further adjusted for race/ethnicity, BMI, height, family history of cancer, pack-years of smoking, alcohol drinking, physical activity, sleep duration, duration of HT use by type, history of type 2 diabetes, aspirin use, and recent physical examination. All covariates, except race/ethnicity, height, and family history, were modeled as time-varying in the analysis. As a sensitivity analysis, we excluded cancer cases diagnosed in the first 2 years of follow-up to evaluate the possibility of reverse causation that early symptoms of cancer may lead to the occurrence and diagnosis of OSA. We further adjusted for several health-seeking behaviors related to cancer prevention and screening, including multivitamin use, mammograms, and colonoscopy/sigmoidoscopy, to test for potential detection bias.

We conducted similar analyses to evaluate the associations with cancer groups sharing a common risk factor. We considered obesity-related cancers, smoking-related cancers, and alcohol-related cancers including additional cancer sites that cannot be assessed individually (e.g. oral cancer was included in both smoking-related and alcohol-related cancers; Supplementary Table S1), according to the summary reports from the National Cancer Institute [38]. To assess whether OSA was associated with cancer risk independent of the known common risk factor, we compared the models with versus without adjustment for that specific risk factor. For example, in the analysis of obesity-related cancers, we estimated their association with OSA with versus without adjusting for BMI. We also conducted a post hoc subgroup analysis by smoking status (ever smokers and never smokers) and BMI (≥25, <25 kg/m$^2$) to evaluate whether smoking or BMI level modified the association between OSA and cancer risk [39]. Statistical significance of the subgroup heterogeneity was evaluated by adding a cross-product interaction term to the model and tested using likelihood ratio tests. As both OSA and smoking are risk factors for cardiovascular disease (CVD), we performed a sensitivity analysis considering major CVD events (including coronary artery bypass graft, coronary heart disease, stroke, and cardiovascular death) as a competing risk for cancer outcomes. Women with prevalent CVD at baseline ($n$ = 7,984) were excluded from this analysis. We used a competing risks Cox model [40] to estimate the associations of OSA with cancer risk and CVD risk separately. The analysis was conducted in the overall population and by smoking status. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

## Results

At baseline in 2008, of 65,330 women (mean age: 73 years; *SD*: 7 years), 3,532 (5.4%) reported having ever received a clinician-diagnosis of OSA. Compared with those without OSA diagnoses, women who reported a prior diagnosis were younger, had higher BMI and lower physical activity and alcohol consumption, and were more likely to have diabetes history, prior hysterectomy/oophorectomy, or estrogen-only HT use (Table 1). Excessive daytime sleepiness and habitual snoring were also more common in women with OSA diagnoses.

During 8 years of follow-up (444,771 person-years), 5,257 incident cancers were diagnosed (Table 2). In the age-adjusted model, a prior diagnosis of OSA was associated with a 15% (95% CI: 1.03, 1.29) increased total cancer risk. Additional adjustment for multiple cancer risk factors, particularly BMI, attenuated the association (HR: 1.08; 95% CI: 0.96, 1.21).

The site-specific analysis considered 13 cancer sites with at least 50 incident cases, including breast cancer, lung cancer, melanoma, colorectal cancer, uterine cancer, non-Hodgkin lymphoma, ovarian cancer, bladder cancer, pancreatic cancer, leukemia, kidney cancer, thyroid cancer, and multiple myeloma (Figure 1). OSA was significantly positively associated with four cancer sites in age-adjusted analyses. The HR (95% CI) comparing women with versus without OSA diagnoses was 1.45 (1.04, 2.04) for lung cancer, 1.77 (1.05, 2.97) for bladder cancer, 2.19 (1.20, 4.02) for kidney cancer, and 2.50 (1.28, 4.90) for thyroid cancer. Further adjustment for cancer risk factors yielded somewhat stronger associations for lung (HR: 1.52; 95% CI: 1.07, 2.17) and bladder cancer (HR: 1.94; 95% CI: 1.12, 3.35), but weaker associations for kidney (HR: 1.59; 95% CI: 0.84, 3.01) and thyroid cancer (HR: 2.06; 95% CI: 1.01, 4.22). No significant associations were noted for the other nine cancer sites examined. The results for total and site-specific cancer risks were similar when excluding cancer cases diagnosed in the first 2 years of follow-up (Supplementary Table S2), except that the association for bladder cancer was no longer statistically significant and a suggestion of positive association emerged for melanoma (HR: 1.45; 95% CI: 0.95, 2.22). Adjustment for additional variables related to health-seeking behaviors did not change the results (data not shown).

OSA was associated with a 37% increased risk (95% CI: 1.12, 1.67) of smoking-related cancers, and this association remained unchanged regardless of adjustment for pack-years of smoking (Table 3). In contrast, OSA was not strongly associated with alcohol-related cancers, with or without controlling for the amount of alcohol intake. There was a suggestion of a positive association between OSA and obesity-related cancer risk before adjustment for BMI (HR: 1.13; 95% CI: 0.98, 1.30), although this was attenuated after accounting for BMI (HR: 1.05; 95% CI: 0.91, 1.21).

The multivariable-adjusted association for total cancer risk did not differ significantly between never smokers (HR: 1.13; 95% CI: 0.95, 1.35) and ever smokers (HR: 1.05; 95% CI: 0.89, 1.22; $p$ for interaction = 0.38; Table 4). When further dividing ever smokers into current and past smokers, the increased cancer risk associated with OSA was suggested only in past smokers (HR: 1.08;

**Table 1.** Age-standardized characteristics of the study population at baseline

| | OSA status | |
|---|---|---|
| | No OSA | OSA |
| N | 61,798 | 3,532 |
| Age, years | 73.6 (6.9) | 72.1 (6.4) |
| Non-white, % | 6 | 6 |
| Family history of cancer, % | 49 | 52 |
| Height, cm | 163.7 (6.2) | 164.2 (6.3) |
| Body mass index, kg/m$^2$ | 26.3 (5.2) | 30.8 (6.8) |
| History of diabetes, % | 13 | 26 |
| Current aspirin use, % | 58 | 61 |
| Smoking status, % | | |
| Never | 48 | 47 |
| Past | 47 | 50 |
| Current | 4 | 3 |
| Pack-years of smoking* | 23.3 (21.2) | 24.2 (21.2) |
| Alcohol use, g/day | 5.5 (8.4) | 4.1 (7.2) |
| Sleep duration, h | 7.2 (1.2) | 7.2 (1.4) |
| Excessive daytime sleepiness, % | 4 | 13 |
| Habitual snoring, % | 16 | 44 |
| Physical activity, MET-hours/week | 18.7 (17.4) | 14.3 (13.0) |
| Ever estrogen-only HT, % | 44 | 52 |
| Duration of estrogen-only HT, months* | 123.3 (102.9) | 124.1 (102.8) |
| Ever estrogen-progestin HT, % | 39 | 41 |
| Duration of estrogen-progestin HT, months* | 76.9 (56.7) | 75.4 (56.6) |
| Recent physical exams, %† | 95 | 96 |
| Prior hysterectomy, % | 43 | 51 |
| Prior oophorectomy, % | 27 | 32 |

*Among ever users.
†Included any physical exams in the past 2 years for either screening or symptoms reported by the participants.

**Table 2.** OSA and total cancer risk

| | Cases | Person-years | Model 1* | Model 2† |
|---|---|---|---|---|
| | | | HR (95% CI) | |
| OSA status | | | | |
| No | 4,931 | 420,644 | 1.00 (ref) | 1.00 (ref) |
| Yes | 326 | 24,127 | 1.15 (1.03, 1.29) | 1.08 (0.96, 1.21) |

*Stratified by age in months and calendar time.
†Model 1 + adjusted for race/ethnicity (white and non-white), BMI (continuous), height (continuous), family history of cancer (yes and no), pack-years of smoking (none, 0.1–4.9, 5.0–19.9, 20.0–39.9, and ≥40.0 pack-years), physical activity (<3.0, 3.0–8.9, 9.0–17.9, 18.0–26.9, and ≥27.0 metabolic equivalents of task hours [MET-hours] per week), alcohol consumption (none, 0.1–4.9, 5.0–14.9, 15.0–29.9, and ≥30.0 g/day), sleep duration (≤5, 6, 7, 8, and ≥9 h/day), duration of estrogen-only HT (none, 0.1–4.9, 5.0–9.9, and ≥10.0 years), duration of estrogen + progestin HT (none, 0.1–4.9, 5.0–9.9, and ≥10.0 years), history of diabetes (yes and no), aspirin use (yes and no), and recent physical examination (yes and no).

95% CI: 0.94, 1.22) but not in current smokers (HR: 0.83; 95% CI: 0.42, 1.64). For smoking-related cancers as well as lung, bladder, and kidney cancers individually, the risk estimates were consistently stronger in never smokers than in ever smokers. The fully adjusted HR (95% CI) for smoking-related cancers was 1.75 (1.27, 2.43) in never smokers and 1.22 (0.94, 1.59) in ever smokers ($p$ for interaction = 0.06). The corresponding estimates were 2.96 (1.42, 6.18) and 1.37 (0.91, 2.06) for lung cancer ($p$ for interaction = 0.09), 3.97 (1.81, 8.67) and 1.12 (0.50, 2.50) for bladder cancer ($p$ for interaction = 0.02), and 2.54 (1.20, 5.37) and 0.52 (0.12, 2.25) for kidney cancer ($p$ for interaction = 0.02). However, this difference by smoking status was not observed for thyroid cancer ($p$ for interaction = 0.44). Of note, we were not able to evaluate these individual cancer types separately in past and current smokers as the model did not converge in current smokers who comprised only 4% of our sample. Further, the associations of OSA with total, obesity-related, and smoking-related cancers were similar between women with BMI ≥25 kg/m$^2$ versus <25 kg/m$^2$ ($p$ for interaction > 0.22; Supplementary Table S3).

In the sensitivity analysis considering CVD events as a competing risk, the associations between OSA and cancer risk were similar to those observed in the primary analyses (Supplementary Table S4). For example, the HR (95% CI) for total cancer comparing women with versus without OSA was 1.12 (0.99, 1.28) in the age-adjusted model and 1.05 (0.92, 1.20) in the multivariable model. By contrast, the HR (95% CI) for CVD was 1.49 (1.16, 1.93) and 1.24 (0.96, 1.61), respectively. We also observed that the association between OSA and cancer risk was somewhat stronger in never smokers compared with ever smokers when CVD was modeled as a competing event.

## Discussion

In this prospective study among older US women, a history of OSA diagnosis was not significantly associated with total cancer risk after controlling for established cancer risk factors. However, the association with OSA was heterogeneous across different cancer sites, with increased risk observed for lung, bladder, kidney, and thyroid cancers. Further, adjustment of pack-years of smoking did not alter the positive association between OSA and smoking-related cancers, and the associations with smoking-related cancers as well as lung, bladder,

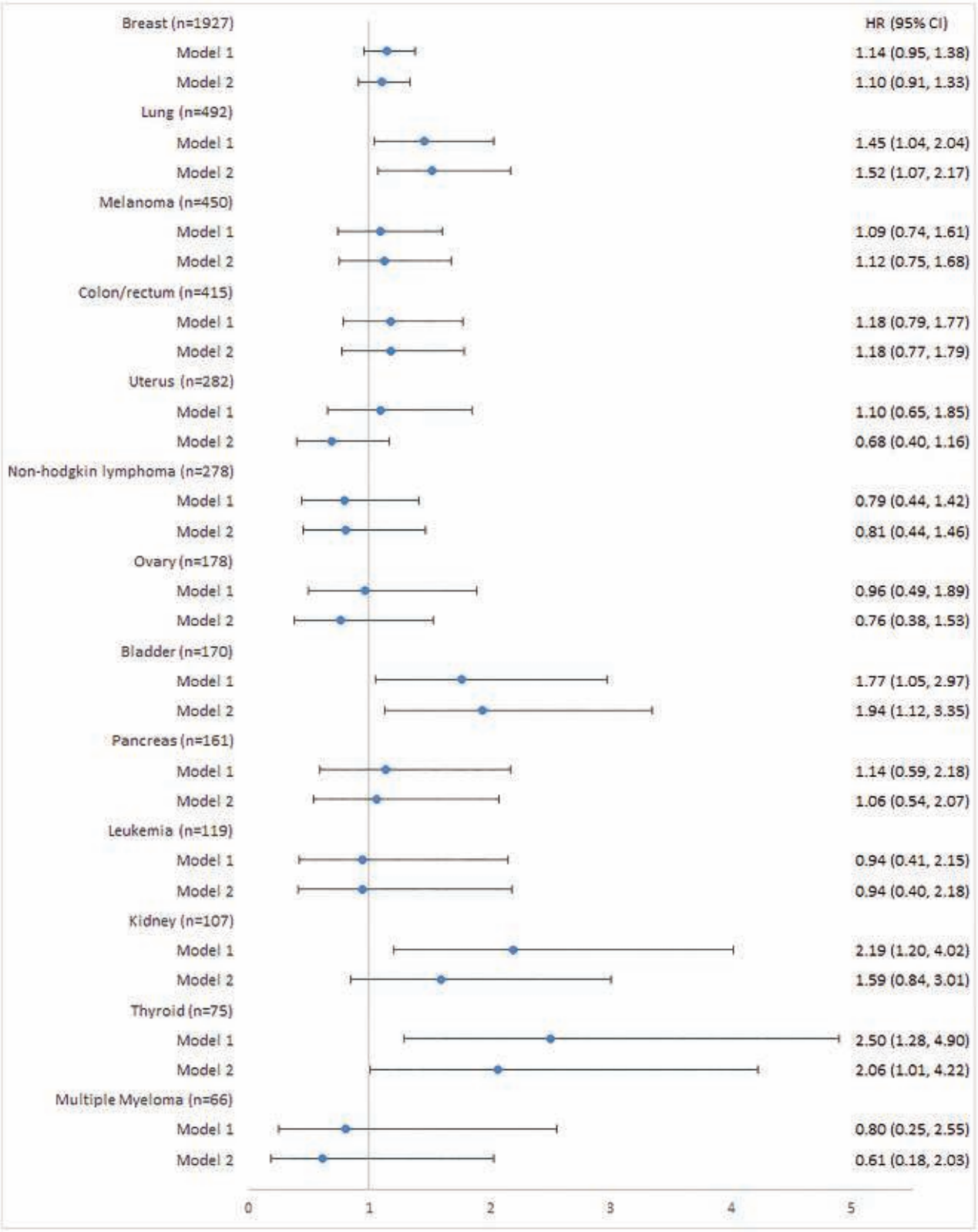


**Figure 1.** OSA and cancer risk by site. Model 1: Stratified by age and calendar time. Model 2: Model 1 + race/ethnicity, family history of cancer, BMI, height, pack-years of smoking, alcohol drinking, physical activity, sleep duration, duration of HT use by type, history of type 2 diabetes, aspirin use, and recent physical examination.

and kidney cancers individually were stronger among never smokers compared with ever smokers.

Four prior population-based studies reported dose–response relationships of OSA severity, measured by percent sleep time with oxygen saturation <90% [21–23] or by frequency of apneas and hypopnea [22–24], with total cancer incidence or mortality. While these studies did not examine site-specific associations, cancers of the lung or respiratory tract were the

primary contributors in the analyses examining total cancer mortality [22, 23]. Two other studies, which evaluated OSA by polysomnographic measures [25] or self-reported symptoms [26], did not find an association with overall cancer risk, although both studies noted significantly increased risk for smoking-related cancers. Similar to our results, Kendzerska et al. found significant positive associations between AHI or sleep time with oxygen saturation <90% and total cancer risk in univariate analyses, which was attenuated toward the null after adjustment for age, sex, BMI, and smoking status [25]. No association between OSA and total cancer risk or mortality was observed in several larger studies using a health insurance database or national patient register [27–29]. The results were even more conflicting for studies of site-specific cancer risk [28–31], of which two reported positive associations with melanoma [28, 29], kidney cancer [28, 29], and breast cancer [29, 30] and the others individually reported associations with pancreatic cancer [28], uterus cancer [29], and central nervous system cancers [31]. In conjunction with our results, these findings suggest that associations of OSA with cancer risk appear to vary by cancer site, and more studies are needed to understand the mechanisms underlying these site-specific associations, such as variations in the sensitivity of different cancer sites to OSA-activated pathways.

The HIF pathway, which regulates the transcription of numerous downstream genes in a hypoxia-dependent manner, is considered as the major mechanism that drives carcinogenesis. Increased expression of HIF-α subunits has been shown to activate oncogenes (e.g. Ras and Myc) but silence tumor suppressor genes (e.g. p53 and PTEN) [1–3], stimulate angiogenesis by upregulating vascular endothelial growth factor (VEGF) [41], produce ROS and amplify oxidative stress [42], and promote cell mobility, migration, and invasion by enhancing degradation of the extracellular matrix [43]. In addition, hypoxia is associated with alterations in other cancer-related pathways, such as PI3K/AKT/mTOR, MAPK, and NFκB, which regulate the cell cycle and immune responses [2]. Most relevant to OSA, prior studies have linked intermittent hypoxia to greater tumor weight, elevated circulating VEGF, and increased lung metastasis in a mouse model of melanoma [18, 19]; intermittent hypoxia also leads to altered tumor-associated macrophages and increased exosome release that enhances malignant potential in a mouse model of lung cancer [16, 20]. Experimental evidence also supports a role of hypoxia signaling pathways in the pathogenesis of kidney cancer, with HIF1α and HIF2α exhibiting potentially distinct functions in tumorigenesis [44, 45]. HIF1α-mediated pathways have been shown to promote cell migration and invasion in bladder cancer [46]. In patients with OSA, CPAP treatment was shown to downregulate leukocyte transcriptional profiles involved in the neoplastic process [47]. Further, fragmented and disrupted sleep, which is another hallmark of OSA, may contribute to cancer development and progression independent of intermittent hypoxia [48, 49]. Other mechanisms, such as

**Table 3.** OSA and risk of smoking-related cancers, alcohol-related cancers, and adiposity-related cancers

| | Cases | Model 1* | Model 2† |
|---|---|---|---|
| | | HR (95% CI) | |
| Smoking-related cancers | | | |
| No OSA | 1,409 | 1.00 (ref) | 1.00 (ref) |
| OSA | 109 | 1.37 (1.12, 1.67) | 1.37 (1.11, 1.67) |
| Alcohol-related cancers | | | |
| No OSA | 2,321 | 1.00 (ref) | 1.00 (ref) |
| OSA | 151 | 1.08 (0.91, 1.29) | 1.09 (0.92, 1.30) |
| Obesity-related cancers | | | |
| No OSA | 3,148 | 1.00 (ref) | 1.00 (ref) |
| OSA | 212 | 1.13 (0.98, 1.30) | 1.05 (0.91, 1.21) |

*Adjusted for covariates in Model 2 except pack-years for smoking-related cancers, alcohol consumption for alcohol-related cancers, and BMI for adiposity-related cancers.
†Stratified by age and calendar time, and adjusted for race/ethnicity, BMI, height, family history of cancer, pack-years, physical activity, alcohol consumption, sleep duration, duration of HT by type, diabetes, aspirin use, and recent physical examination.

**Table 4.** OSA and cancer risk by smoking status

| | Cases in OSA/no OSA | HR (95% CI)* | *P* for interaction |
|---|---|---|---|
| All cancers | | | 0.38 |
| Ever smokers | 183/2,816 | 1.05 (0.89, 1.22) | |
| Never smokers | 143/2,115 | 1.13 (0.95, 1.35) | |
| Smoking-related cancers | | | 0.06 |
| Ever smokers | 65/940 | 1.22 (0.94, 1.59) | |
| Never smokers | 44/469 | 1.75 (1.27, 2.43) | |
| Lung cancer† | | | 0.09 |
| Ever smokers | 28/384 | 1.37 (0.91, 2.06) | |
| Never smokers | 9/65 | 2.96 (1.42, 6.18) | |
| Bladder cancer† | | | 0.02 |
| Ever smokers | 7/113 | 1.12 (0.50, 2.50) | |
| Never smokers | 9/41 | 3.97 (1.81, 8.67) | |
| Kidney cancer† | | | 0.02 |
| Ever smokers | 2/47 | 0.52 (0.12, 2.25) | |
| Never smokers | 10/48 | 2.54 (1.20, 5.37) | |
| Thyroid cancer | | | 0.44 |
| Ever smokers | 6/30 | 3.21 (1.21, 8.53) | |
| Never smokers | 4/35 | 1.43 (0.46, 4.42) | |

*Stratified by age and calendar time, and adjusted for race/ethnicity, BMI, height, family history of cancer, physical activity, alcohol consumption, pack-years of smoking (in ever smokers), sleep duration, duration of HT by type, diabetes, and regular physical examination.
†Lung cancer, bladder cancer, and kidney cancer were classified as smoking-related cancers.

elevated inflammation, altered immunity, insulin resistance, and hormonal dysregulation induced by OSA and associated sleep disturbances, may also act as important mediators leading to carcinogenesis [50–52].

Interestingly, the observed positive associations between OSA and smoking-related cancers remained essentially unchanged after accounting for smoking exposure and were largely observed in never smokers. It is well known that smoking leads to substantial tissue hypoxia both acutely and chronically [53–55]. Although the contributions of hypoxia-related pathways in smoking-induced carcinogenesis are unclear, OSA may promote the development of smoking-related cancers through hypoxia-activated pathways, particularly considering that individual types of smoking-related cancers associated with OSA in this study, including lung, bladder, and kidney cancers, are known to be highly sensitive to hypoxia and HIF signaling [1–7, 44–46]. However, the potent and long-lasting effects of known tobacco carcinogens on DNA damage likely override those from intermittent hypoxia among ever smokers, thus masking the associations with OSA among smokers. Smoking-related cancers also tended to occur at a younger age in ever smokers prior to the study baseline, resulting in exclusion of these participants from the current analysis and undermining our ability to assess OSA-cancer associations in ever smokers. Further, the associations of OSA with lung and bladder cancers were somewhat strengthened after adjustment for smoking. Such "negative confounding" may be explained by the inverse association between current smoking and OSA previously reported in this cohort and by others [32, 56]. Other cancer risk factors that attenuated the associations for other cancer sites, such as obesity, were in general not strong risk factors for these cancers [38].

Study strengths included the prospective study design, large sample size, ascertainment of cancer endpoints, and updated assessment of cancer risk factors. However, several limitations should be borne in mind when interpreting the results. First, although our prior work supports the reliability of self-reported OSA in nurses [32], misclassification due to undiagnosed mild-to-moderate OSA may result in underestimation of the associations if milder forms of sleep-disordered breathing also increase the risk of certain cancers. Also, we did not have quantitative measures of intermittent hypoxia or OSA treatment (i.e. CPAP use), and future studies are needed to evaluate these to provide further insights into the underlying mechanisms. Second, reverse causation and detection bias may play roles in some of the associations we observed. For example, enlarged neck mass, a key sign of thyroid cancer, may precipitate the occurrence of OSA by narrowing the upper airway; women who reported OSA diagnoses may be more likely to have an earlier cancer diagnosis due to more frequent/regular clinic visits. However, lagged analysis excluding incident cases diagnosed in the first 2-years of follow-up and additional adjustment for health-seeking behaviors suggested that the observed associations were unlikely to be explained by reverse causation or detection bias. Third, it should be noted that our study included predominantly white, older female registered nurses, which had limited generalizability to other populations. Notably, some prior studies suggest that associations between OSA and cancer may be stronger in men and younger individuals [21, 57], although a recent study reported higher cancer prevalence in women with OSA [58]. Thus, replication of our findings in other populations encompassing both men and women with a wider age range and more diverse racial/ethnic composition is warranted. Finally, we had limited statistical power for the analyses of certain cancer sites and by smoking status (particularly for current smokers). For example, melanoma has been associated with intermittent hypoxia in animal models and with OSA in several epidemiologic studies [18, 19, 28, 29]. While our results were consistent with a potential positive association between OSA and melanoma risk, the association did not reach statistical significance.

In summary, while OSA was not independently associated with total cancer risk, OSA was associated with increased risk of thyroid cancer as well as overall and several smoking-related cancers, including those regulated by HIF-1 pathways. Further, the positive associations of OSA with overall and several smoking-related cancers were more apparent in never smokers than in ever smokers. Whether OSA and smoking share certain common pathways of carcinogenesis requires further investigation. More studies are needed to confirm the observed heterogeneity in the association by cancer sites and identify additional heterogeneity by immunohistochemical, molecular, and genetic features for individual cancer sites.

## Supplementary material

Supplementary material is available at *SLEEP* online.

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## References

1. Harris AL. Hypoxia–a key regulatory factor in tumour growth. *Nat Rev Cancer.* 2002;**2**(1):38–47.
2. Muz B, *et al.* The role of hypoxia in cancer progression, angiogenesis, metastasis, and resistance to therapy. *Hypoxia (Auckl).* 2015;**3**:83–92.
3. Jun JC, *et al.* Hypoxia-inducible factors and cancer. *Curr Sleep Med Rep.* 2017;**3**(1):1–10.

4. Pouysségur J, *et al*. Hypoxia signalling in cancer and approaches to enforce tumour regression. *Nature*. 2006;**441**(7092):437–443.
5. Eales KL, *et al*. Hypoxia and metabolic adaptation of cancer cells. *Oncogenesis*. 2016;**5**:e190.
6. Ullmann P, *et al*. Hypoxia- and MicroRNA-induced metabolic reprogramming of tumor-initiating cells. *Cells*. 2019;**8**(6):528.
7. Bristow RG, *et al*. Hypoxia and metabolism. Hypoxia, DNA repair and genetic instability. *Nat Rev Cancer*. 2008;**8**(3):180–192.
8. Trédan O, *et al*. Drug resistance and the solid tumor microenvironment. *J Natl Cancer Inst*. 2007;**99**(19):1441–1454.
9. Ackerman D, *et al*. Hypoxia, lipids, and cancer: surviving the harsh tumor microenvironment. *Trends Cell Biol*. 2014;**24**(8):472–478.
10. Wilson WR, *et al*. Targeting hypoxia in cancer therapy. *Nat Rev Cancer*. 2011;**11**(6):393–410.
11. Yaggi HK, *et al*. Obstructive sleep apnea as a risk factor for stroke and death. *N Engl J Med*. 2005;**353**(19):2034–2041.
12. Gottlieb DJ, *et al*. Prospective study of obstructive sleep apnea and incident coronary heart disease and heart failure: the sleep heart health study. *Circulation*. 2010;**122**(4):352–360.
13. Huang T, *et al*. A population-based study of the bidirectional association between obstructive sleep apnea and type 2 diabetes in three prospective U.S. cohorts. *Diabetes Care*. 2018;**41**(10):2111–2119.
14. Gozal D, *et al*. Putative links between sleep apnea and cancer: from hypotheses to evolving evidence. *Chest*. 2015;**148**(5):1140–1147.
15. Martínez-García MÁ, *et al*. Cancer and OSA: current evidence from human studies. *Chest*. 2016;**150**(2):451–463.
16. Almendros I, *et al*. Intermittent hypoxia-induced changes in tumor-associated macrophages and tumor malignancy in a mouse model of sleep apnea. *Am J Respir Crit Care Med*. 2014;**189**(5):593–601.
17. Almendros I, *et al*. Intermittent hypoxia enhances cancer progression in a mouse model of sleep apnoea. *Eur Respir J*. 2012;**39**(1):215–217.
18. Almendros I, *et al*. Obesity and intermittent hypoxia increase tumor growth in a mouse model of sleep apnea. *Sleep Med*. 2012;**13**(10):1254–1260.
19. Almendros I, *et al*. Intermittent hypoxia increases melanoma metastasis to the lung in a mouse model of sleep apnea. *Respir Physiol Neurobiol*. 2013;**186**(3):303–307.
20. Almendros I, *et al*. Tumor cell malignant properties are enhanced by circulating exosomes in sleep apnea. *Chest*. 2016;**150**(5):1030–1041.
21. Campos-Rodriguez F, *et al*. Association between obstructive sleep apnea and cancer incidence in a large multicenter Spanish cohort. *Am J Respir Crit Care Med*. 2013;**187**(1):99–105.
22. Nieto FJ, *et al*. Sleep-disordered breathing and cancer mortality: results from the Wisconsin Sleep Cohort Study. *Am J Respir Crit Care Med*. 2012;**186**(2):190–194.
23. Martínez-García MA, *et al*. Obstructive sleep apnea is associated with cancer mortality in younger patients. *Sleep Med*. 2014;**15**(7):742–748.
24. Marshall NS, *et al*. Sleep apnea and 20-year follow-up for all-cause mortality, stroke, and cancer incidence and mortality in the Busselton Health Study cohort. *J Clin Sleep Med*. 2014;**10**(4):355–362.
25. Kendzerska T, *et al*. Obstructive sleep apnea and the prevalence and incidence of cancer. *CMAJ*. 2014;**186**(13):985–992.
26. Christensen AS, *et al*. Symptoms of sleep disordered breathing and risk of cancer: a prospective cohort study. *Sleep*. 2013;**36**(10):1429–1435.
27. Rod NH, *et al*. Sleep apnea, disability pensions, and cause-specific mortality: a Swedish nationwide register linkage study. *Am J Epidemiol*. 2017;**186**(6):709–718.
28. Gozal D, *et al*. Sleep apnea and cancer: analysis of a nationwide population sample. *Sleep*. 2016;**39**(8):1493–1500.
29. Sillah A, *et al*. Sleep apnea and subsequent cancer incidence. *Cancer Causes Control*. 2018;**29**(10):987–994.
30. Chang WP, *et al*. Sleep apnea and the subsequent risk of breast cancer in women: a nationwide population-based cohort study. *Sleep Med*. 2014;**15**(9):1016–1020.
31. Chen JC, *et al*. Sleep apnea increased incidence of primary central nervous system cancers: a nationwide cohort study. *Sleep Med*. 2014;**15**(7):749–754.
32. Huang T, *et al*. Sex differences in the associations of obstructive sleep apnoea with epidemiological factors. *Eur Respir J*. 2018;**51**(3):1702421.
33. Peppard PE, *et al*. Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol*. 2013;**177**(9):1006–1014.
34. Rimm EB, *et al*. Validity of self-reported waist and hip circumferences in men and women. *Epidemiology*. 1990;**1**(6):466–473.
35. Willett WC, *et al*. The use of a self-administered questionnaire to assess diet four years in the past. *Am J Epidemiol*. 1988;**127**(1):188–199.
36. Wolf AM, *et al*. Reproducibility and validity of a self-administered physical activity questionnaire. *Int J Epidemiol*. 1994;**23**(5):991–999.
37. Huang T, *et al*. Type of menopause, age at menopause, and risk of developing obstructive sleep apnea in postmenopausal women. *Am J Epidemiol*. 2018;**187**(7):1370–1379.
38. National Cancer Institute. Risk factors for cancer. https://www.cancer.gov/about-cancer/causes-prevention/risk. Accessed August 13, 2019.
39. Almendros I, *et al*. Obesity, sleep apnea, and cancer. *Int J Obes (Lond)*. 2020;**44**(8):1653–1667.
40. Lunn M, *et al*. Applying Cox regression to competing risks. *Biometrics*. 1995;**51**(2):524–532.
41. Pugh CW, *et al*. Regulation of angiogenesis by hypoxia: role of the HIF system. *Nat Med*. 2003;**9**(6):677–684.
42. Lavie L. Oxidative stress in obstructive sleep apnea and intermittent hypoxia–revisited–the bad ugly and good: implications to the heart and brain. *Sleep Med Rev*. 2015;**20**:27–45.
43. Gilkes DM, *et al*. Hypoxia and the extracellular matrix: drivers of tumour metastasis. *Nat Rev Cancer*. 2014;**14**(6):430–439.
44. Gudas LJ, *et al*. The role of HIF1α in renal cell carcinoma tumorigenesis. *J Mol Med (Berl)*. 2014;**92**(8):825–836.
45. Shen C, *et al*. Genetic and functional studies implicate HIF1α as a 14q kidney cancer suppressor gene. *Cancer Discov*. 2011;**1**(3):222–235.
46. Peixoto A, *et al*. Hypoxia enhances the malignant nature of bladder cancer cells and concomitantly antagonizes protein O-glycosylation extension. *Oncotarget*. 2016;**7**(39):63138–63157.
47. Gharib SA, *et al*. Treatment of obstructive sleep apnea alters cancer-associated transcriptional signatures in circulating leukocytes. *Sleep*. 2014;**37**(4):709–14, 714A.
48. Hakim F, *et al*. Fragmented sleep accelerates tumor growth and progression through recruitment of tumor-associated macrophages and TLR4 signaling. *Cancer Res*. 2014;**74**(5):1329–1337.

49. Khalyfa A, *et al*. Circulating exosomes potentiate tumor malignant properties in a mouse model of chronic sleep fragmentation. *Oncotarget*. 2016;**7**(34):54676–54690.
50. Unnikrishnan D, *et al*. Inflammation in sleep apnea: an update. *Rev Endocr Metab Disord*. 2015;**16**(1):25–34.
51. Sephton S, *et al*. Circadian disruption in cancer: a neuroendocrine-immune pathway from stress to disease? *Brain Behav Immun*. 2003;**17**(5):321–328.
52. Gómez-González B, *et al*. Role of sleep in the regulation of the immune system and the pituitary hormones. *Ann N Y Acad Sci*. 2012;**1261**:97–106.
53. Sørensen LT, *et al*. Acute effects of nicotine and smoking on blood flow, tissue oxygen, and aerobe metabolism of the skin and subcutis. *J Surg Res*. 2009;**152**(2):224–230.
54. Jensen JA, *et al*. Cigarette smoking decreases tissue oxygen. *Arch Surg*. 1991;**126**(9):1131–1134.
55. Fricker M, *et al*. Chronic cigarette smoke exposure induces systemic hypoxia that drives intestinal dysfunction. *JCI Insight*. 2018;**3**(3):e94040.
56. Nieto FJ, *et al*. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. *JAMA*. 2000;**283**(14):1829–1836.
57. Torres M, *et al*. Aging reduces intermittent hypoxia-induced lung carcinoma growth in a mouse model of sleep apnea. *Am J Respir Crit Care Med*. 2018;**198**(9):1234–1236.
58. Pataka A, *et al*. Cancer prevalence is increased in females with sleep apnoea: data from the ESADA study. *Eur Respir J*. 2019;**53**(6):1900091.