Association Between Obstructive Sleep Apnea and Cancer: A Survival Analysis

by

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Abstract

Epidemiology studies on cancer risk attributable to obstructive sleep apnea (OSA) are inconsistent. There may exist differences in cancer risk when assessing OSA severity by the Apnea-Hypopnea Index (AHI) versus time spent below 90% oxygen saturation (T90%). We examined a clinical population undergoing polysomnography (PSG) to determine the impact of OSA severity on cancer risk by AHI and T90%. We collected records from patients undergoing PSG between 1998-2018 and linked them with electronic medical records to determine time-to-cancer diagnosis following PSG. We constructed a multivariable Cox proportional-hazards model to measure the impact of OSA severity, determined by AHI or T90%, on cancer incidence that adjusted for age, sex, BMI, hypertension, chronic obstructive pulmonary disease, coronary artery disease, diabetes, center, race, and ethnicity. We then used this model to assess the impact of OSA severity on risk for specific cancers. As cancer risk is differential between the sexes, we also stratified our analysis by sex. Among, 37,998 patients undergoing polysomnography, 3,218 cancers were diagnosed during follow-up (median: 5.9 years, interquartile range: 2.4-8.6). AHI was not significantly associated with an increase in cancer risk after adjusting for confounders (Hazard Ratio (HR) 0.93; 95% CI, 0.84 – 1.04; P = 0.22). Sex stratified analyses did not show a strong association between AHI severity and cancer risk. High T90% (T90%>13.3) was found to confer an 18% increase in cancer risk (HR 1.18; 95% CI, 1.05 – 1.33; P = 0.0069) compared to those with low T90%. Among specific malignancies, bladder and lymph/hematological

cancer risks were significantly elevated for those with high T90%. The association between overall cancer risk and high T90% did not vary significantly by sex (P-interaction = 0.20). High T90% was associated with a significant increase in overall cancer among men (HR 1.22; 95% CI 1.02 – 1.46; P = 0.029), particularly bladder and lymph/hematological cancers. Our results have public health significance because they suggest that patients who experience nocturnal hypoxia have elevated cancer risk, and that the increased cancer risk may not be identified AHI alone. Future studies warranted that emphasize both T90% and AHI in determining cancer risk in patients with OSA.

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1.0 Introduction

1.1 Obstructive Sleep Apnea: An Overview

1.1.1 Epidemiology, pathophysiology, and diagnosis of obstructive sleep apnea

Obstructive Sleep Apnea (OSA) is a chronic condition characterized by the recurrent collapse of the pharyngeal airway during sleep, resulting in hypoxia and sleep fragmentation (1). The American Academy of Sleep Medicine (AASM) classifies OSA under sleep-disordered breathing, an umbrella term for a constellation of abnormalities of respiration during sleep. OSA is recognized as a major public health concern that is estimated to be highly prevalent in the population (2). As individuals are often unaware of their condition, approximating the true prevalence of OSA is difficult, however recent models suggest the prevalence ranges from 9% to 38%, and it is typically higher in men than in women (3). Prevalence estimates depend on the cohort examined, time periods of assessment, and how breathing events of OSA are defined. Furthermore, there is strong evidence that the prevalence of OSA is increasing in the United States, most likely as a result of increasing obesity and increased testing for OSA (4).

The pathophysiology of OSA is complex and no single factor is implicated as sufficient for the condition to manifest. OSA is typically present in those with a combination of abnormal structural factors that interact unfavorably with changes in neurological pathways during sleep (5). The loss of muscle tone during sleep causes a decrease in upper airway patency, which leads to full or partial cessation of airflow. Apneas are defined as a pause in respiration for more than 10 seconds, while hypopneas refer to a reduction in ventilation of at least 30% that results in a

decrease in arterial oxyhemoglobin saturation of 3% or more due to partial airway obstruction that also lasts at least 10 seconds (1). The number of apnea and hypopnea events divided by the hours of sleep is commonly referred to as the apnea-hypopnea index (AHI) and is a measurement of OSA severity. Hypoxia and hypercapnia following apneas and hypopneas, result in a burst of sympathetic activity as part of the baroreflex and chemoreflex (6). Sympathetic activity is also related to increased physiological stress (7). Accompanying the burst in sympathetic activity is cortical arousal from increased ventilatory effort to restore upper airway patency. The cycle of airway collapse leading to sympathetic activity can occur many times throughout the night.

There are three well known risk factors for OSA. Obesity is the most impactful risk factor for OSA. This association is biologically plausible in that a crowded upper airway, due to excess adipose tissue, is more easily collapsible. A recent study (N=1042) found that obese individuals had a greater likelihood of having OSA (Odds Ratio (OR)=10.5; 95% Confidence Interval (CI), 7.1-15.7; P<0.001) than individuals of normal weight (8). This study also found that men had a higher prevalence of OSA (OR=4.1; 95% CI, 2.9-5.8; P<0.001) than women. While men typically have a higher risk of having OSA, women are also vulnerable to this condition, especially pregnant women (9). Older age is also associated with OSA, possibly due to the loss of muscle tone in the upper airway (5). In another study, authors noted that the prevalence of AHI ≥5 is greater amongst the elderly, with some age-groups reaching as high as 90% in men and 78% in women (3).

Polysomnography (PSG) is a sleep study that is used to diagnose OSA and determine its severity. PSG is commonly referred to as the "gold-standard" for objective measures of sleep. Unfortunately, PSG is labor-intensive and waiting times to get a sleep study in a hospital can be very long, even up to a few years (10). The recent development of home sleep apnea testing (HSAT) studies have lessened this burden, however HSAT is less sensitive than PSG in the

detection of OSA (11). A typical PSG utilizes electroencephalogram, electro-oculogram, electromyogram, electrocardiogram, pulse oximetry, as well as airflow and respiratory effort, to evaluate the underlying causes of sleep disturbances (12). Split-night PSG refers to sleep studies where the first 2-3 hours includes standard PSG procedures, while the second half is used to establish a suitable level of continuous positive airway pressure (CPAP) to treat OSA. This style of test is useful for patients with severe OSA who immediately present within the first few hours, however it might not be appropriate for all patients, particularly those with mild OSA (13). The severity of OSA is scored based on the PSG results using different sets of criteria. The most popular scoring system is the Apnea-Hypopnea Index (AHI), which refers to the number of apnea and hypopnea events over the total sleep time. The AASM recommends patients who have an AHI $\geq$ 15 events/hr or AHI $\geq$5 events/hr and secondary symptoms receive CPAP therapy or established alternative therapies (14). A recent meta-analysis concluded that CPAP is the most efficacious in complete resolution of OSA, followed by exercise, mandibular advancement devices (MAD), and weight loss (15).

1.1.2 AHI versus T90% as a measure of OSA severity

AHI is the most commonly reported measure for estimating the severity of OSA in patients. The AASM defines the diagnostic criteria for OSA as having five or more predominantly obstructive respiratory events per hour of sleep during PSG (16). Further stratifying OSA burden, AHI is typically categorized into normal (AHI<5 events/hr), mild sleep apnea ($5 \leq$ AHI < 15), moderate sleep apnea ($15 \leq$ AHI < 30) and severe (AHI ≥ 30). This categorization is frequently used when estimating the effect of OSA severity on health outcomes in epidemiological studies. However, AHI could be considered a crude method for describing OSA burden as it assumes that

both apneas and hypopneas have equal physiological impact regardless of the duration or morphology of apnea or hypopnea episodes (17).

Intermittent hypoxia associated with apneas and hypopneas is now being recognized as a potential major factor contributing to the pathogenesis of OSA-related comorbidities (18). Longer breathing cessations and deeper desaturations may have more severe consequences than shorter and shallower ones. Additionally, hypoxemia experienced as a result of reduced lung capacity, such as from smoking or obesity, will influence where oxygen saturation levels start before apneas occur. In a recent study (N=297), markers of inflammation related to OSA severity were found to be significantly different among subgroups based on total sleep time with oxygen saturation <90% (T90%) within AHI severity categories (17). This suggests that it might be prudent to risk stratify based on the severity of oxygen desaturation throughout the night as opposed to AHI categories. It is important to note that T90% was highly correlated with AHI, suggesting that although there are key differences between the two variables, they may both be reasonable approximations of OSA severity. While AHI might offer a clinically relevant measure of OSA severity, T90% may offer a better diagnostic of the impact OSA has on the body.

1.1.3 Long-term morbidity associated with OSA

The physiological changes found in patients with untreated OSA appear to act as intermediate mechanisms responsible for the development of new comorbidities. OSA has only recently been considered as an independent risk factor for comorbidities, such as hypertension and diabetes, since it often co-occurs with important risk factors, particularly obesity (19).

Many studies have examined the role of OSA as a pathogenic factor in cardiovascular and cerebrovascular diseases (20). Systemic hypertension, in particular, is the best studied

cardiovascular comorbidity that is associated with OSA (21). As sleep is often required for the maintenance of normal blood pressure, interruptions to normal sleep patterns could lead to hypertension. Arrhythmias are frequently found in OSA patients, especially atrial fibrillation (AF). A recent meta-analysis demonstrated that recurrent AF risk differed between OSA patients using CPAP and those who do not (Risk Ratio (RR) 0.60; CI 0.51-0.7; $P < 0.0001$) (22).

OSA has been shown to play a role in the development of insulin resistance and thus is associated with the metabolic syndrome, a pre-diabetic state. In a study of 13 volunteers, intravenous glucose challenge during hypoxic conditions showed a decrease in insulin sensitivity (23). In a recent review, it was noted that the effects of OSA could contribute independently to the development of glucose intolerance and type 2 diabetes (24). In those with type 2 diabetes, there is evidence to suggest that untreated OSA increases diabetic neuropathy. In a study of 234 patients, OSA was found to be independently associated with diabetic neuropathy (OR, 2.82; 95% CI, 1.44-5.52; $P = 0.003$) after adjusting for relevant confounders, such as obesity and age (25). Conversely, type 2 diabetes might increase predisposition to OSA through increased adiposity, peripheral neuropathy, and abnormalities of ventilatory and upper airway neural control.

OSA is clearly a major contributor to a number of comorbidities. Considering OSA's prevalence in the population, further research is warranted on other conditions where there is biological plausibility. With the availability of electronic healthcare records, there is a wealth of information that can be used to discern OSA's impact as a pathogenic condition.

1.2 Current Evidence of OSA Increasing Cancer Risk

1.2.1 Hypoxia-Inducible Factors as a driving factor in cancer progression

Among the acute physiological changes that occur during apnea/hypopnea events, intermittent hypoxia (IH) is considered to be the most deleterious. IH is known to promote increased oxidative stress, systemic and vascular inflammation with endothelial dysfunction, increased sympathetic activation, and blood pressure elevation (18,26). Hypoxia-Inducible Factors (HIFs) are a key mediator of the cellular response to hypoxia and are likely to be a key driver behind altered tumor behavior in intermittent hypoxia (27). In-vitro studies of IH demonstrate pro-oncogenic properties, in that the recruitment of HIF results in increased expression of vascular endothelial growth factor (VEGF), formation of new capillaries, tumor growth, and metastasis (28,29). Furthermore, tumor hypoxia has long been associated with increased malignancy, poor prognosis, and resistance to radiotherapy and chemotherapy.

1.2.2 Proinflammatory markers in response to intermittent hypoxia

IH also induces systemic physiological stress responses that contribute to the development and metastatic potential of cancer. In-vitro studies have revealed that IH leads to a preferential activation of inflammatory pathways with downstream consequence of expression of pro-inflammatory cytokines, chemokines, and adhesion molecules that may contribute to endothelial dysfunction (30). Murine studies showed that implantation of Lewis lung carcinoma and exposure to cyclic hypoxia promoted the upregulation of proinflammatory cytokines, such as interleukin (IL)-6, CXCL1 and macrophage inflammatory protein 2 (MIP-2) (31). In humans, circulating

microRNAs related to cancer proliferation were detected amongst 48 male subjects with severe OSA (32). Fortunately, markers of inflammation and cancer-associated transcriptional signatures seemed to be attenuated in patients who are adherent with therapy. In a study of eighteen subjects with significant OSA, it was found through whole-genome expression measurement of peripheral blood leukocytes that effective treatment of OSA is associated with suppression of cancer-related pathways (33).

1.2.3 Assessment of global cancer risk in patients with OSA

Over the past seven years, a number of epidemiological studies have been carried out with the goal of assessing OSA as an independent risk factor for all cancer incidence. In 2013, the first multi-center retrospective analysis of cancer incidence in OSA patients was conducted by collecting data from 4910 participants who had undergone polysomnography between 2003 and 2007 among various teaching hospitals in Spain (34). Participants in this study had a mean follow-up time of 4.5 (interquartile range, 3.4-5.2) years. Following adjustments for age, sex, BMI, smoking status, alcohol intake, type of sleep study, and center, elevated AHI was found to not significantly influence cancer incidence (Hazard Ratio (HR) 1.17; 95% CI 0.84-1.65; P=0.33). Interestingly, when stratified into younger and older cohorts (age $\geq$ 65 yr, n=1,203 and age < 65 yr, n =3,707), severe OSA (AHI >43) was found to be independently associated with cancer (HR 1.66; CI 1.04-2.64; P = 0.032) in the younger cohort. In the entire cohort, T90% > 12% was found to be independently associated with all cancer incidence. The study has strengths in that it was carried as part of a multi-center study, however it lacked statistical power to consider individual cancer types (n = 43 for the most common cancer). These findings further highlight the differences in assessing the effect of OSA severity by AHI and T90% on cancer incidence, while also being

one the first population studies to suggest that OSA is independently associated with cancer incidence.

Other researchers have presented similar results that suggest a link between OSA and cancer incidence. In a study on the Busselton Healthy Study Cohort (n = 400), it was determined that moderate-to-severe sleep apnea is independently associated with an increased risk of cancer incidence and mortality after 20 years of follow-up in this community (35). However, this study had a limited sample size with only 99 (25%) participants found to have OSA, of which only 18 had moderate-severe OSA. In another study of veterans in the United States of America, a cohort of 1,377,285 patients were followed for a median of 7.4 years in order to assessment the impact between preexisting OSA and incident cancer. After adjusting for age, sex, year of cohort entry, smoking status, alcohol use, obesity, and comorbidity, the hazard of incident cancer was nearly double in patients with an OSA diagnosis (HR 1.97; CI, 1.94-2.00; P <0.001) (36). This particular study used rigorous methods, but it only assessed the impact of an OSA diagnosis and not severity and was limited to men. While men are at greater risk for OSA, the lack of research on women with OSA is recognized as a problem (9).

In a recent descriptive epidemiology study, Sillah et al. 2018 identified a cohort of individuals with OSA (n = 34,402) using regional administrative databases and population-based cancer registries (37). Using a standardized estimate of cancer incidence from the Cancer Surveillance System of Washington State, cancer incidence was elevated among OSA patients (Standardized Incidence Ratio (SIR)=1.26; 95% CL: 1.20-1.32). Additionally, several primary cancer sites were found to be particularly susceptible to OSA in this population, including kidney (SIR=2.24; 95% CI=1.82–2.72), melanoma (SIR=1.71; 95% CI=1.42–2.03), breast (SIR=1.43; 95% CI=1.76–2.00) and corpus uteri (SIR=2.80; 95% CI=2.24–2.47). Interestingly, lung cancer

and colorectal cancer were lower, suggesting that some malignancies are less prominent among patients with OSA. It is important to note that this is a descriptive study that did not assess OSA's impact as a pathological condition, nor did it adjust for known confounders, most notably BMI and diabetes.

In contrast, three epidemiological studies were unable to find significant increases in cancer risk related to OSA. The first, authored by Kendzerska et al. 2014, assessed patients undergoing PSG derived from the Ontario Cancer Registry (38). Their results showed that the severity of OSA was not independently associated with incident cancer when OSA was assessed by AHI (adjusted HR 1.02; 95% CI 0.8-1.31) or by T90% (adjusted HR 1.00; 95% CI 0.99-1.02). After 7.2 years of median follow up time, the cancer incidence was 6.5% (n = 627). The other study, authored by Gozal et al. (2016), found that in a large nationally representative health insurance database (~5.6 million), OSA was not associated with an increased global cancer risk (39). It is important to note that this study did not assess OSA severity directly, instead Gozal et al. used the presence of an ICD-9 code to distinguish between patients with and without OSA. These results might be biased since there are substantial differences between patients with mild OSA and severe OSA and ICD codes have fairly low specificity for accurately distinguishing patients who actually have OSA. A recent nested case-cohort study (n = 15,332) by Sillah et al. 2019 also indicated that OSA severity was not associated with cancer risk (HR 0.87; 95% CI 0.52-1.45) (40). However, the proportion of patients with severe OSA (AHI $\geq$ 30) was higher among individuals with prostate, melanoma, corpus uteri, lung cancer, thyroid and kidney cancers than among those in the randomly sampled subcohort of individuals with OSA. Given the inconsistency of the results in this area, there is a need for further investigations on the association between cancer and OSA severity.

1.2.4 Targeted assessments of specific cancer types

A number of researchers have targeted particular cancer types, as different cancers might have different adaptive profiles to IH. Previous studies suggest that certain cancer types, such as melanoma, colorectal, and breast cancer, have increased incidence among patients with OSA (40).

The most well-defined association between a cancer subtype and OSA is for melanoma. A number of murine studies have found that mimicking IH conditions found in those with OSA enhances tumor growth and metastatic potential (41,42). This trend was also observed in human studies as presented by research on 443 patients with cutaneous melanoma (41). A recent review by Martinez-Garcia et al. (2019) sums up both biological plausibility evidence and epidemiological evidence to strongly suggest the presence and severity of OSA could be associated with faster tumor growth and greater invasiveness (43).

Colorectal cancer has been shown to have an increased incidence among patients with OSA. In a case-controls study of patients (n = 163) who underwent PSG and subsequent colonoscopy, the odds of detecting advanced colorectal neoplasia among patients with OSA were approximately 3-fold greater than in the controls matched for age, sex, BMI, and smoking (OR 3.03; 95% CI, 1.44-6.34; P =0.002) (44). In a retrospective cohort study by Chen et al. (2019), patients with newly diagnosed OSA (n = 4180) had a significantly higher risk of colorectal cancer (HR 1.80; 95% CI, 1.28-2.52) than those in an age, sex matched cohort (n = 16,720) after adjusting for potential confounders (45).

Studies of lung cancer patients show that sleep disordered breathing is highly prevalent. In the Sleep Apnea in Lung Cancer (SAIL) study, consecutive patients with newly diagnosed lung cancer were offered HSAT and a sleep-specific questionnaire was administered prior to initiating treatment (46). Of the sixty-six patients that completed the assessments, 80% had an AHI > 5 and

50% had moderate to severe OSA (AHI > 15) with significant nocturnal hypoxemia (median T90%: 10.9%). In a parallel trial, the Sleep Apnea in Lung Cancer Screening (SAILS) study showed similar results and that nocturnal hypoxemia more than doubles the risk of positive screening findings (47). It is important to note that chronic obstructive pulmonary disease (COPD) and smoking were both highly prevalent in these studies, but it is clear that patients who experience nocturnal hypoxemia are fairly prevalent among patients with lung cancer.

Overall, OSA severity has been shown to have an impact on the cancer incidence in a number of different cancers. As different cancer types have differing responses to IH, it is reasonable to look at both global cancer risk and site-specific cancers in order to understand the impact of OSA severity on cancer risk.

1.3 Gaps in Knowledge

A number of important gaps remain in this area of research. OSA severity has typically been quantified by categories of the AHI, while only a few studies have assessed the effects of intermittent hypoxia directly. As intermittent hypoxia is known to have pro-carcinogenic effects, it is possible that many studies using AHI are subject to misclassification bias. Additionally, a number of studies are disproportionately male and lack an adequate number of female participants (8,9). Furthermore, a number of studies consider either global cancer risk or one particular cancer type and lack statistical power to adequately quantify the impact of OSA severity of cancer risk (37,48). Different cancers have distinct responses to IH exposure and as such there needs to be further investigation on site-specific cancer risk. Finally, the role of confounding must be rigorously addressed in these studies, as OSA and cancer are both impacted by the presence of

older age and obesity (49). Furthermore, a number of other conditions that are frequently found in patients with OSA can also increase the risk of cancer, such as hypertension and diabetes. However, given the evidence that OSA is a cause of elevated blood pressure and glucose tolerance, it is likely that these are intermediate conditions rather than confounding. Thus, disentangling the effects of OSA from comorbidities on cancer risk is a major challenge given this strong confounding.

1.4 Public Health Significance

OSA is an extremely prevalent condition that is expected to grow in the coming years, at least partially due to the surge in obesity in the population (3). While recognized as a legitimate public health problem, OSA has not been fully characterized in regard to cancer risk. Additionally, patients with OSA typically present with other comorbidities, and as such the burden of OSA is multiplicative. Given the tight association between OSA and body size, it is necessary to understand if OSA contributes pro-carcinogenic effects independently of obesity or is simply a marker of this condition. Furthermore, there is a need to establish if AHI is a suitable method for assessing cancer risk in patients with OSA given the heterogeneity of oxygen desaturation profiles found within AHI groups (50).

2.0 Objectives

2.1 Aim 1: Evaluate the Effect of OSA Severity as Determined by AHI Severity and T90% Burden on Incident Cancer Risk

The objective of this research was to examine the association of OSA severity, as determined by AHI or T90%, and incident cancer risk in adults undergoing polysomnography to diagnose OSA. As there may be differential effects of OSA severity by cancer site, we will investigate overall cancer risk and site-specific cancers. Our hypothesis is increased AHI or T90% are independently associated with an increased cancer risk following adjustments for age, sex, BMI, center, hypertension, coronary artery disease, COPD, diabetes, race, and ethnicity.

2.2 Aim 2: Evaluate the Relationship Between OSA Severity and Cancer Risk Stratified by Sex

Sex differences in cancer risk are well known in certain neoplasms, such as hematological malignancies among men. As such, our secondary objective is to assess the association of OSA severity and incident cancer risk among men and women undergoing polysomnography to diagnose OSA. Our hypothesis is that there will be a difference in cancer risk between the sexes using the same models produced from Aim 1.

3.0 Methods

3.1 Study Population

For this paper, data were obtained from electronic medical records of patients undergoing PSG testing at UPMC facilities from 1999 to 2018. Data were collected from UPMC Presbyterian, UPMC St. Margaret, UPMC Mercy, UPMC Northwest, UPMC McKeesport, and UPMC East. PSG tests that were entirely therapeutic, split-night studies of diagnostic and therapeutic testing, and dental studies were excluded, as they tend to produce biased results of AHI or T90% compared to full night PSG. Portable, or at-home sleep studies, were also excluded from the final analysis as they lacked oxygen desaturation measurements. In the case of multiple records, we used the latest PSG that was available. Of the 37,998 PSG records collected, 30,0158 were diagnostic tests and were included in this analysis.

3.2 Outcome Measure

The outcome measure used for this analysis was incident cancer diagnosis following PSG testing as determined by diagnostic codes in the patient's medical record. Following validation studies of determining incident cancer from diagnostic codes, cancer diagnosis was defined as either one in-patient code or two out-patient codes separated by any length of time (51). The type of cancer was identified using ICD-9 or ICD-10 codes and grouped by related neoplasms. The follow up time was defined as the difference between date of PSG and date of first cancer diagnosis

that satisfied the above algorithm. Patients who did not develop cancer were considered censored at their last clinical encounter. Patients who had been diagnosed with cancer prior to PSG were excluded from the analysis.

3.3 Independent Variables

The primary independent variable included in this analysis is Apnea-Hypopnea Index (AHI). AHI was defined as the number of apnea and hypopnea events divided by hours of sleep recorded during PSG. Apneas are defined as pauses in breathing lasting for at least 10 seconds. For adults, AHI is categorized into normal (AHI<5), mild sleep apnea ($5 \leq AHI < 15$), moderate sleep apnea ($15 \leq AHI < 30$) and severe ($AHI \geq 30$).

The second primary independent variable was percent of time spent below 90% oxygen saturation (T90%). As AHI may only represent a small decrease in oxygen saturation depending the patient, T90% has the advantage of directly measure nocturnal hypoxia under laboratory conditions. T90% burden was defined by splitting T90% into tertiles that resulted in the following categories: <1.1%, 1.2% to 13.2%, and >13.2%.

3.4 Other Covariates

A number of patient characteristics were recorded during the diagnostic PSG. Age was recorded to the nearest day. Race, ethnicity, and sex were self-reported and directly collected from the patient's medical record. Body mass index was calculated from self-reported weight and height

measurements at the time of PSG. BMI was categorized as normal ($18.5 \leq BMI < 25$), overweight ($25 \leq BMI < 30$), and Obese ($30 \leq BMI$). Obesity was further divided into three categories ($30 \leq BMI < 35$, $35 \leq BMI < 40$, and $40 \leq BMI$) based on the standard definitions of class 1, 2, and 3 obesity and the potential that these groups have different effects on OSA severity and cancer risk. We also collected information on some comorbidities associated with OSA, including hypertension, coronary artery disease (CAD), COPD, and diabetes mellitus as determined by the presence of ICD-9/ICD-10 codes present in the patient's electronic medical record.

3.5 Statistical Analysis

Two separate analyses were undertaken in order to estimate the effect of each measure of OSA severity on cancer risk. Demographic and clinical characteristics were presented stratified by OSA severity and chi-square tests and Analysis of Variance (Anova) were used to compare values of categorical and continuous variables, respectively by OSA severity category. Kaplan-Meier survival curves were created for each OSA severity category to estimate the freedom from incident cancer, and log rank statistics were used to determine statistical significance. The survival curves were also examined to assess the appropriateness of the proportional hazards assumption. Cox proportional hazards regression was used to estimate the hazard ratio of each exposure category on incident cancer. Regression models were created and reported for both AHI and T90% as continuous and categorical variables as previously defined. Unadjusted models and multivariate adjusted models were created to account for the effects of confounding by age, sex, BMI, COPD, hypertension, coronary artery disease (CAD), diabetes, center, race, and ethnicity. The final multivariate models for the categorical variables were used to assess the

impact of OSA severity on overall cancer risk and site-specific cancers. As power is a concern for site-specific cancer risk due to small numbers, hazard ratios were calculated for only the 11 most common cancers in this cohort, as they contained the most widely reported cancers associated with OSA. As cancers are often differential between the sexes, this analysis was repeated after stratifying the sample by sex. A combined model including sex, OSA and the cross-product term between sex and OSA was created, and the significance of the interaction term was used to assess whether sex modified the effect of OSA on cancer risk. Two-sided $\alpha=0.05$ was used as the significance threshold for analyses considered. SAS version 9.4 was used for all analyses and the generation of the survival curves. Graphpad version 8.0 was used to create the forest plots of hazard ratios.

4.0 Results

4.1 Survival Analysis of Incident Cancer Risk by AHI

4.1.1 Patient Characteristics

Figure 1 depicts the derivation of the final analytic sample for both AHI analyses and T90% analyses. Of the N=37,998 PSG results collected, N=33,146 (87.2%) were diagnostic tests. Of these, 3,004 (9%) were found to have a cancer diagnosis prior to the sleep study as indicated by their electronic medical records. Of the remaining 30,158 patients, 10,344 were found to have missing oxygen saturation values and were not included in the T90% analyses. Missing T90% data were found to be associated with records from a particular center. Thus, the total analytic sample for the AHI analyses was N=30,158 and N=19,814 for T90% analyses (Figure 1).

The mean age of the patients included in the AHI analysis was 50.1 ± 14.4 years old (Table 1). A majority of the patients were women (51.6%) and white (84.1%). Amongst patients undergoing PSG testing at UPMC facilities between the years 1999-2018, 66% were diagnosed with at least mild OSA (AHI ≥ 5) and 19.8% were diagnosed with severe OSA (AHI ≥ 30) (Table 1). Patients with a higher AHI were significantly older than those with mild or no OSA. BMI was highest among those with severe OSA (AHI ≥ 30), and 78.5% of participants in this category were obese (BMI ≥ 30). Hypertension was relatively common in this sample and was highest among patients with severe AHI (55.3%, n = 5965). The median follow-up time for

the entire cohort was 5.35 (IQR 2.4-8.6) years, providing a total of 177,138 person-years of follow-up.

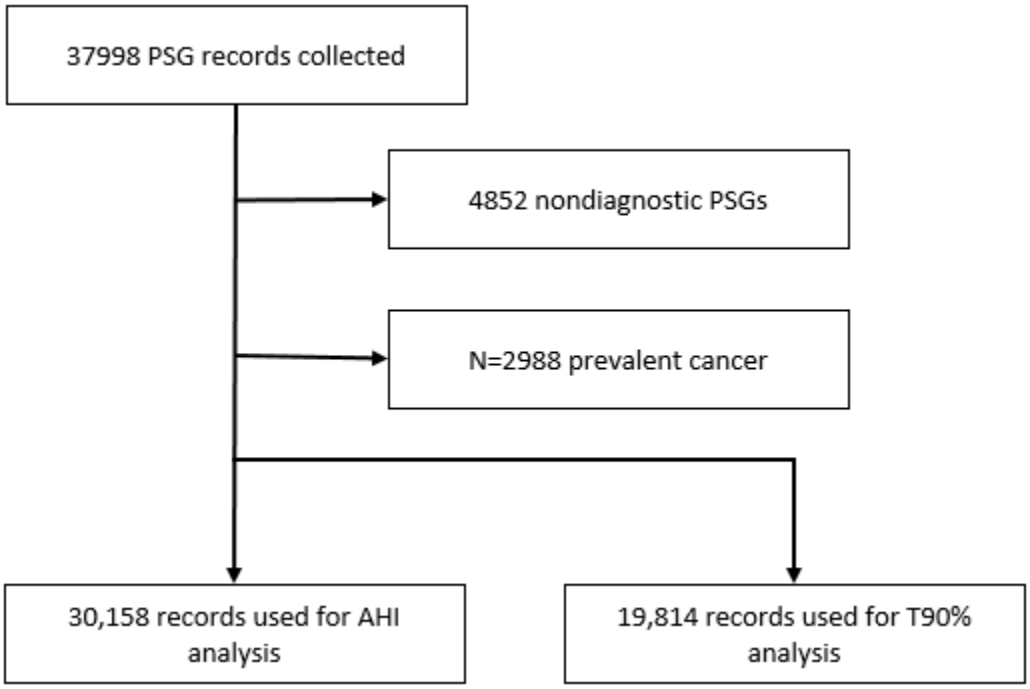

Figure 1. The Analytical Sample

Table 1. Demographic Characteristics of Patients undergoing PSG by AHI

	Mean ± Standard Deviation or N (%)				
	Total (n = 30158)	AHI < 5 (n = 10187)	5 ≤ AHI < 15 (n = 8710)	15 ≤ AHI < 30 (n = 5296)	AHI ≥ 30 (n = 5965)
Age, years	50.1 ± 14.4	44.9 ± 14.7	50.9 ± 13.7	53.8 ± 13.0	54.3 ± 13.5
Sex, Male	14584 (48.4)	3572 (35.1)	3929 (45.1)	2971 (56.1)	4112 (68.9)
Race, White	25048 (84.1)	8379 (83.5)	7169 (83.2)	4496 (85.69)	5004 (84.8)
Ethnicity, Hispanic	127 (0.4)	42 (0.42)	41 (0.48)	21 (0.4)	23 (0.4)
Body Mass Index, kg/m^2	34.1 ± 8.6	31.6 ± 8.2	34.5 ± 8.5	35.1 ± 8.4	36.8 ± 8.7
BMI < 25	3536 (11.7)	2112 (20.7)	827 (9.5)	352 (6.7)	245 (4.1)
25 ≤ BMI < 30	7179 (23.8)	2864 (28.1)	2073 (23.8)	1210 (22.9)	1032 (17.3)
30 ≤ BMI< 35	7528 (25.0)	2253 (22.1)	2265 (26)	1427 (26.9)	1583 (26.5)
35 ≤ BMI < 40	5306 (17.6)	1385 (13.6)	1554 (17.84)	1072 (20.2)	1295 (21.7)
BMI > 40	6609 (21.9)	1573 (15.4)	1991 (22.86)	1235 (23.3)	1810 (30.3)
COPD	3245 (10.8)	1012 (31.2)	977 (30.1)	570 (17.6)	686 (11.5)
CAD	4053 (13.4)	901 (22.2)	1191 (29.4)	818 (15.5)	1143 (28.2)
Hypertension	13549 (44.9)	3374 (33.1)	4106 (30.3)	2771 (52.3)	3298 (55.3)
Diabetes Mellitus	5668 (18.79)	1368 (24.1)	1641 (28.9)	1149 (20.3)	1510 (26.6)
Median Follow up Time (years)	5.35	4.86	5.57	5.76	5.42
Center – Presbyterian	14813 (49.2)	5968 (58.6)	4122 (47.4)	2463 (41.3)	2260 (42.7)
Center – St. Margaret	10297 (34.2)	2383 (23.4)	3241 (37.2)	2143 (40.5)	2530 (42.4)
Center – Mercy	2642 (8.8)	1071 (10.5)	692 (7.9)	458 (8.6)	421 (7.1)
Center – Northwest	1501 (5.0)	494 (4.9)	381 (4.3)	282 (5.3)	344 (5.8)
Center – McKeesport	886 (2.9)	263 (2.6)	266 (3.1)	152 (2.9)	205 (3.5)

- All demographic variables were significantly different ($p<0.05$) by AHI category except for ethnicity

Of the site-specific cancers that were identified in this analysis, the top 11 cancer sites were consistent with those most commonly discussed in the context of OSA (Table 2). The total

number of patients with incident cancer was 3,210. The most common cancer sites were lymphatic/hematological, breast, and colorectal. Patients who did not have sleep apnea (21%) had the highest rate of lymphatic/hematological cancers. In contrast, moderate OSA ($15 \leq AHI < 30$) patients had the highest proportion of breast cancer and colorectal cancer cases. Those in the severe OSA category had the highest rate of cancer cases for prostate cancer and bladder cancer.

Table 2. Site-Specific Cander Rates by AHI Severity Site-Specific Cancer Rates by AHI Severity

	N (%)				
	Total (n = 3276)	AHI < 5 (n = 906)	5 ≤ AHI < 15 (n = 943)	15 ≤ AHI < 30 (n = 660)	AHI ≥ 30 (n = 767)
Lymph/Heme	605 (18.5)	190 (21.0)	183 (19.4)	107 (16.2)	125 (16.3)
Breast*	348 (10.6)	109 (12.0)	102 (10.8)	75 (11.4)	62 (8.1)
Colorectal	312 (9.5)	78 (8.6)	87 (9.0)	75 (10.6)	62 (10.3)
Non-Melanoma Skin	284 (8.7)	52 (5.7)	87 (9.2)	68 (10.3)	77 (10.1)
Lung	255 (7.8)	88 (9.7)	68 (7.2)	42 (6.4)	57 (7.4)
Head/Neck	244 (7.5)	71 (7.8)	69 (7.3)	48 (7.3)	56 (7.3)
Prostate**	225 (6.8)	46 (5.1)	43 (4.6)	60 (9.1)	75 (9.8)
Uterine*	197 (6.0)	52 (5.7)	67 (7.1)	43 (6.5)	35 (4.6)
Bladder	107 (3.3)	22 (2.5)	31 (3.3)	20 (3.0)	34 (4.4)
Thyroid	102 (3.1)	41 (4.5)	28 (3.0)	15 (2.3)	18 (2.4)
Melanoma	86 (2.6)	21 (2.3)	28 (3.0)	16 (2.4)	21 (2.7)

- * analysis of cancer site was restricted to women.
- ** analysis of cancer site was restricted to men.

4.1.2 Survival Analysis by AHI severity

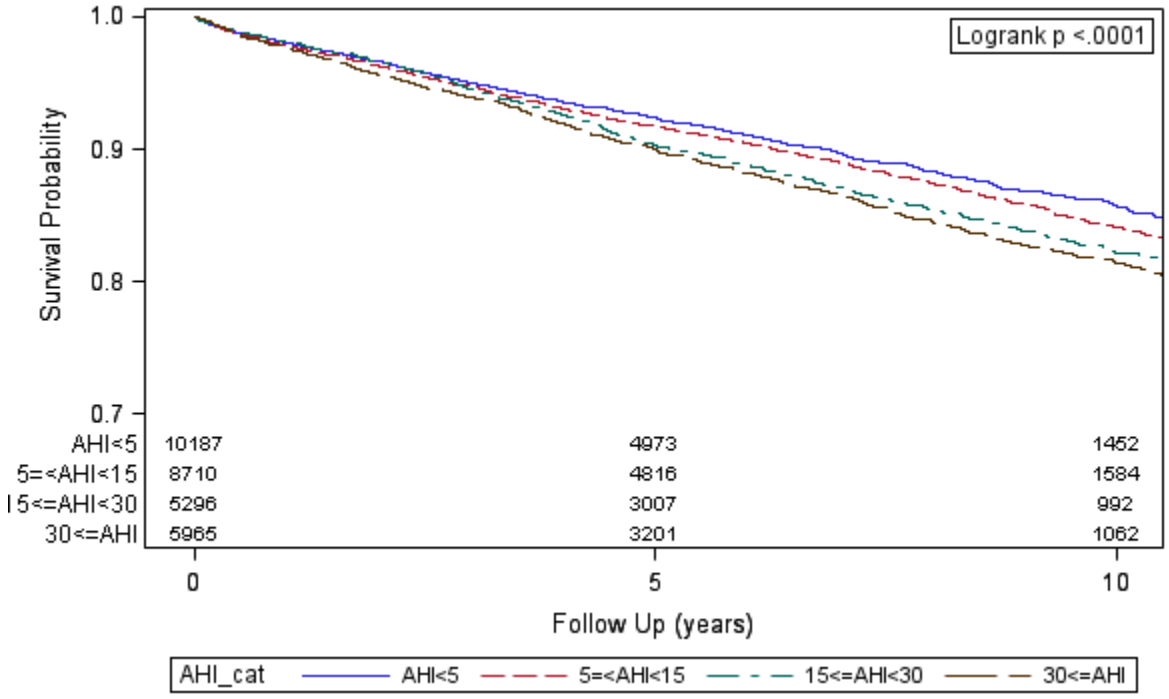

Figure 2. Kaplan Meier Survival Curves by AHI Category

There were significant differences in time-to-incident cancer by AHI severity, where moderate and severe OSA were associated with a lower rate of cancer-free survival (Figure 2). The estimated proportion free from cancer at 5 years from figure 2 was calculated to be 88.7% AHI<5, 85.0% 5≤AHI<15, 82.1% 15≤AHI<30, and 82.6% AHI≥30, (log rank p-value<0.0001). Unadjusted Cox proportional hazards regression showed that AHI as a continuous variable is associated with cancer incidence (HR 1.003 per 1 event/hr in AHI; 95% CI, 1.002-1004; P<0.0001) (Table 3). This association was also evident when AHI was analyzed as a categorical variable. The risk of incident cancer in patients with mild OSA was 9.6% greater than those with no OSA (HR 1.096; 95% CI, 1.000-1.201; P = 0.0512) and was 31% higher for those with severe OSA

(AHI ≥ 30) compared to those without OSA (HR 1.31; 95% CI, 1.188- 1.443; P < 0.0001). Adjusting for age, sex, BMI, center, race, cardiovascular comorbidities, and ethnicity, increased AHI was not associated with greater cancer risk. Overall, the risk of cancer diagnosis was not statistically different for patients with severe OSA compared to those without OSA (HR 0.935; 95% CI, 0.841 – 1.041; P = 0.2199).

Table 3. Cox Regression Analysis by AHI Severity

OSA Category	Hazard Ratio	95% Confidence Interval	P Value
Unadjusted HR			
AHI (Continuous, per 1 event/hr)	1.003	1.002 - 1.004	<0.0001
Categories			
<5 (ref)	1	-	-
5-14.9	1.096	1.000 - 1.201	0.0512
15-29.9	1.228	1.110 – 1.359	<0.0001
≥30	1.310	1.188 – 1.443	<0.0001
Adjusted HR*			
AHI (Continuous, per 1 event/hr)	0.999	0.997 – 1.001	0.2871
Categories			
<5 (ref)	1	-	-
5-14.9	0.911	0.828 – 1.001	0.0516
15-29.9	0.927	0.834 – 1.031	0.1651
≥30	0.930	0.836 – 1.035	0.1859

* adjusted for age, sex, BMI categories, hypertension, COPD, CAD, diabetes, race, ethnicity, and center

4.1.3 Site-Specific cancer hazards by AHI severity

The results from the adjusted Cox regression model for site-specific cancers were heterogeneous (Figure 3). In patients with severe AHI compared to those without OSA, the risk of non-melanoma skin cancers was elevated amongst those with severe OSA as measures by AHI

(Figure 3). No significant increases in the hazard of head/neck, melanoma, thyroid, bladder, colorectal, or lymph/heme neoplasms were detected. Severe OSA was associated with a decrease in risk for lung cancers relative to patients without OSA.

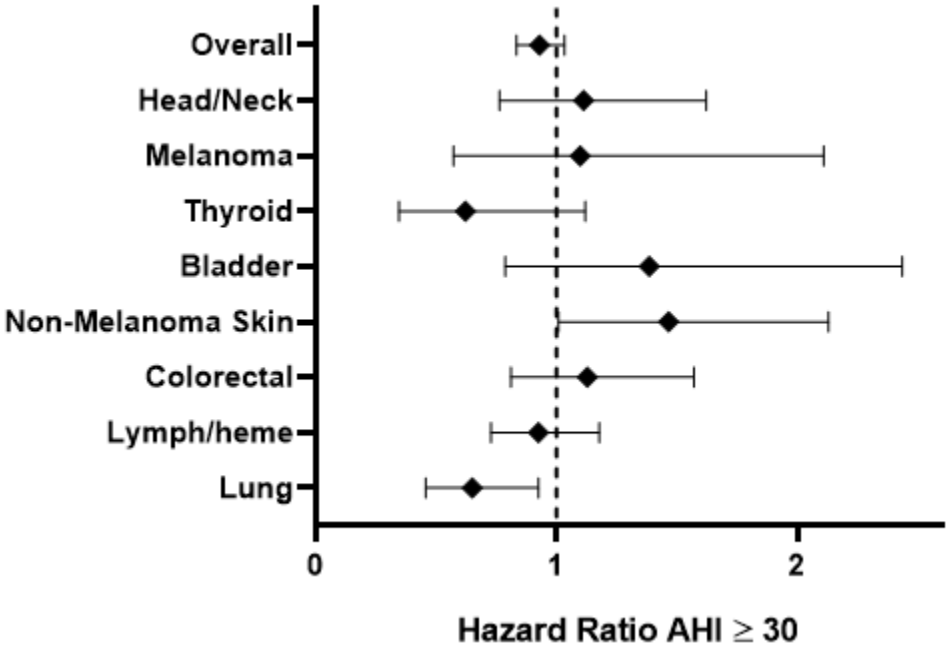

Figure 3. Cox Regression Analysis of site-specific cancers (n = 29329)

As there are appreciable differences in cancer incidence and OSA by sex, this cohort was stratified by sex for further analysis. Among men (n = 14322), there was no elevated risk of cancer diagnosis overall with severe AHI (HR 0.961; 95% CI 0.823 – 1.034; P = 0.6195) (Figure 4). When considering site specific cancers, there was no significant associations between AHI severity and cancer diagnosis. In women (n = 15398), the overall risk of cancer diagnosis for those with severe OSA relative to those without OSA was not significantly different (HR 0.899; 95% CI 0.768 – 1.052; P = 0.2350) (Figure 5). All of the hazard ratios for site specific cancers were nonsignificant, with the exception of lung cancer. Female patients with severe AHI had a 60%

reduction in lung cancer diagnosis compared to those with no OSA (HR 0.459; 95% CI 0.259 – 0.816; P = 0.0355).

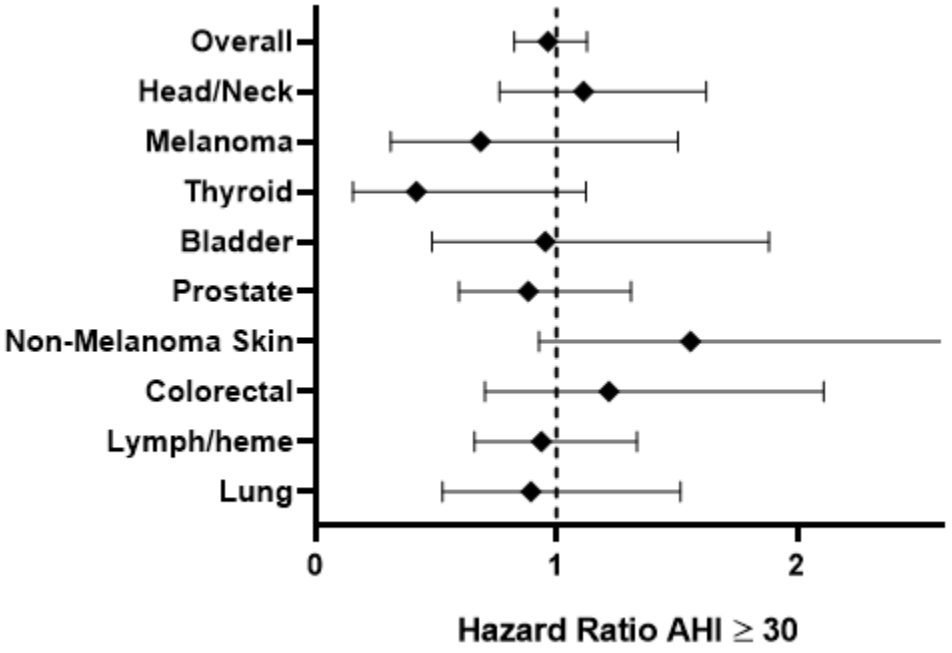

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Figure 4. Cox Regression Analysis of site-specific cancers in males (n=14322)

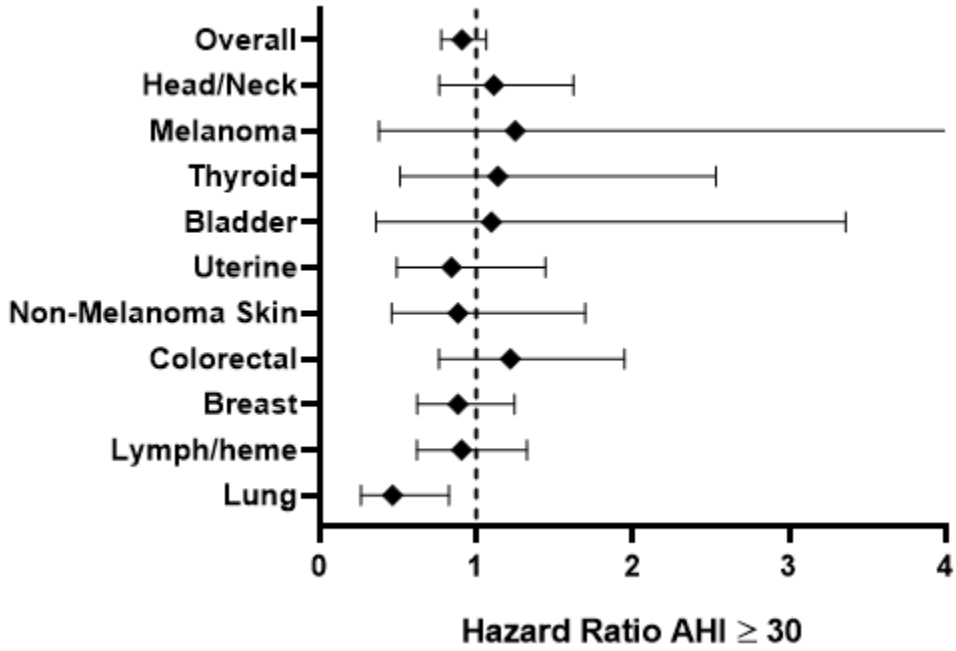

Figure 5. Cox Regression Analysis of site-specific cancers in females (n = 15398)

4.2 Survival Analysis of Incident Cancer Risk by T90%

4.2.1 Patient Characteristics

The selection of patient records for the T90% was described earlier. The mean age of the patients included in this cohort was 50.1 ± 14.4 years old. The majority of patients included in this analysis were women (52.4%) and white (81.0%). Of the 19,814 patients undergoing PSG testing at UPMC facilities with full data on oxygen desaturation, categories of T90%, the percent of sleep time below 90% SpO2 were defined as: T90%<1.1% (37.8%), 1.2%-13.2% (34.3%) and ≥13.2% (severe, 27.9%) (Table 4). Patients who experienced significant oxygen desaturation during sleep tended to be older, male, and white. BMI was highest among those with severe sleep apnea (T90% ≥ 13.2%) and 78.3% of participants included in this category were obese (BMI ≥ 30). All of the comorbid conditions were elevated in those with significant T90%. The median follow-up time for the entire cohort was 5.35 years, accounting for 114,016 person-years. All missing data for T90% was associated with records collected from one facility.

Table 4. Demographic Characteristics of Patients Undergoing PSG by T90%

	Mean ± Standard Deviation or N (%)			
	Total (n = 19814)	T90% < 1.1% (n = 7491)	1.2% ≤ T90% < 13.2% (n = 6787)	T90% ≥ 13.2% (n = 5536)
Age, years	50.1 ± 14.4	43.8 ± 16.2	50.9 ± 13.8	55.5 ± 13.0
Sex, Male	9421 (47.6)	3102 (41.4)	3318 (48.9)	3001 (54.2)
Race, White	15793 (81.0)	5995 (81.6)	5355 (79.9)	4443 (81.2)
Ethnicity, Hispanic	98 (0.5)	37 (0.5)	36 (0.5)	25 (0.5)
Body Mass Index, kg/m^2	33.7 ± 8.6	30.8 ± 7.9	34.4 ± 8.3	36.7 ± 8.7
BMI < 25	2620 (13.2)	1767 (23.6)	593 (8.8)	257 (4.6)
25 ≤ BMI < 30	4862 (24.5)	2282 (30.5)	1631 (24.0)	949 (17.2)
30 ≤ BMI< 35	4860 (24.5)	1590 (21.2)	1812 (26.7)	1458 (26.4)
35 ≤ BMI < 40	3379 (17.1)	858 (11.4)	1289 (19.0)	1232 (22.3)
BMI ≥ 40	4093 (20.7)	994 (13.3)	1459 (21.5)	1640 (29.6)
COPD	2057 (10.4)	449 (6.0)	598 (8.8)	1010 (18.2)
CAD	2502 (12.6)	515 (6.9)	884 (13.0)	1103 (19.9)
Hypertension	8402 (42.4)	2050 (27.4)	3127 (46.1)	3225 (58.3)
Diabetes Mellitus	3581 (18.1)	789 (22.0)	1267 (35.4)	1525 (42.6)
Median Follow up Time (years)	5.35	5.6	5.2	4.5
Center – Presbyterian	14781 (74.7)	5745 (76.7)	5055 (74.5)	3981 (71.9)
Center – St. Margaret	.	.	.	.
Center – Mercy	2637 (13.3)	874 (11.7)	959 (14.1)	804 (14.5)
Center – Northwest	1496 (7.6)	573 (7.7)	477 (7.0)	446 (8.1)
Center – Mckeesport	884 (4.5)	292 (3.9)	292 (4.3)	300 (5.4)
Center - Monroeville	442 (2.2)	193 (2.6)	155 (2.3)	94 (1.7)

- All variables were significantly different by T90% category ($p<0.05$) except for ethnicity

The trends in site-specific cancers when distinguishing patients by T90% was similar to that of AHI (Table 5). The total number of patients with incident cancer was 2,188. The most common cancer sites were lymphatic/hematological, breast, and colorectal neoplasms. Patients who did not have significant decreases in oxygen saturation during sleep had the highest rate of lymphatic/hematological cancers (20.6%). Patients with severe oxygen desaturations (T90% ≥ 13.2%) had the highest rate of cases breast cancer and colorectal cancer cases. Patients in the highest T90% category had the highest proportion of cancer cases for lung, prostate, and bladder neoplasms.

Table 5. Site-Specific Cancer Rates by T90%

	N (%)			
	Total (n = 2188)	T90% < 1.1% (n = 680)	1.2% ≤ T90% < 13.2% (n = 780)	T90% ≥ 13.2% (n = 728)
Lymph/Heme	416 (19.0)	140 (20.6)	150 (19.2)	126 (17.3)
Breast*	226 (10.3)	70 (10.3)	78 (10.0)	78 (10.7)
Colorectal	212 (9.7)	65 (9.6)	76 (9.7)	71 (9.7)
Non-Melanoma Skin	151 (6.9)	61 (9.0)	54 (6.9)	36 (4.9)
Lung	168 (7.7)	44 (6.5)	61 (7.8)	63 (8.6)
Head/Neck	189 (8.6)	54 (7.9)	75 (9.6)	60 (8.2)
Prostate**	153 (7.0)	35 (5.2)	57 (7.3)	61 (8.4)
Uterine*	131 (6.0)	41 (6.0)	47 (6.0)	43 (5.9)
Bladder	68 (3.1)	12 (1.7)	24 (3.1)	32 (4.4)
Thyroid	75 (3.4)	32 (4.7)	29 (3.7)	14 (1.9)
Melanoma	44 (2.0)	18 (2.6)	13 (1.7)	13 (1.8)

- * analysis of cancer site was restricted to women.
- ** analysis of cancer site was restricted to men.

4.2.2 Survival Analysis by T90% tertiles

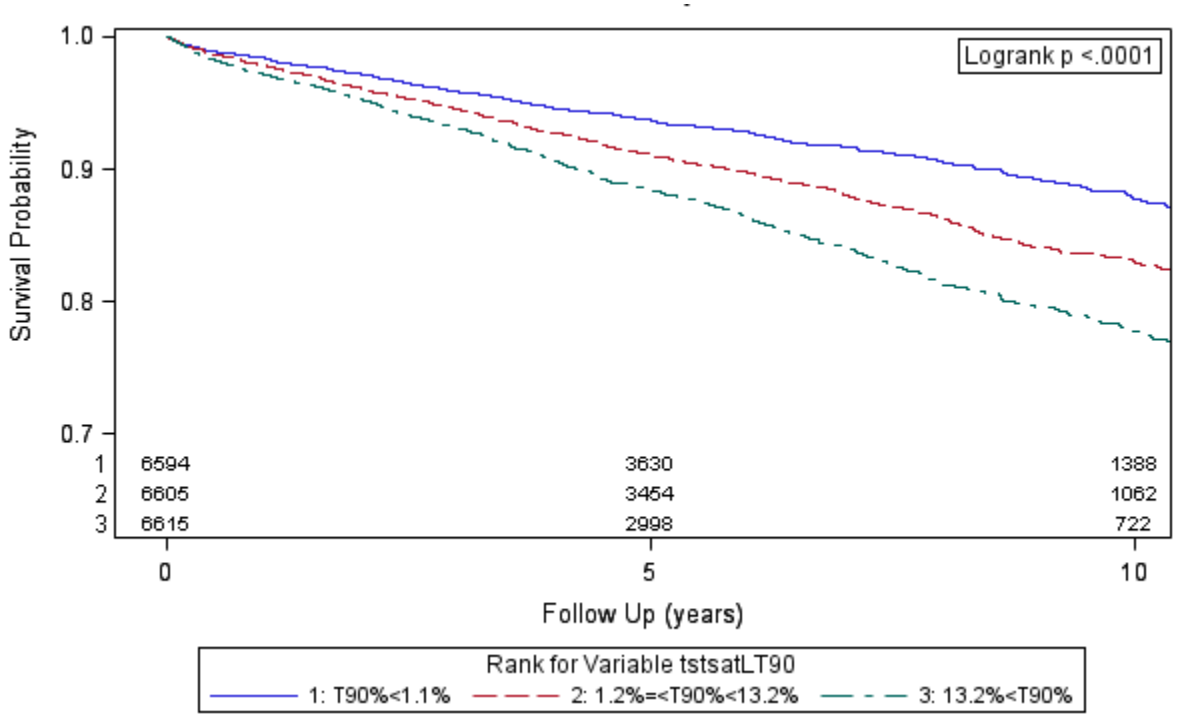

Figure 3. Kaplan Meier Survival Curves by T90 Tertile Category

There were significant differences in time-to-incident cancer by T90% tertiles, where moderate and significant time spent below 90% SpO2 was associated with a lower cancer-free survival. (Figure 6). The estimated proportion free from cancer at 5 years from figure 2 was calculated to be 88.3% T90%<1.1%, 85.0% 1.2%<T90%<13.2%, and 84.4% T90%≥13.2%, (log rank p-value = 0.0005). Unadjusted Cox proportional hazards regression showed that T90% as a continuous variable is associated with cancer incidence (HR 1.007; 95% CI, 1.006-1009; P<0.0001) (Table 6). This association was also significant for T90% tertiles. Adjusting for age, sex, BMI, cardiovascular morbidities, diabetes, center, race, and ethnicity, continuous T90% was associated with a 0.2% increase cancer risk for each percentage increase in T90% (HR 1.002; 95% CI, 1.000 – 1.004; P = 0.0128). The highest tertile, representing patients with T90% ≥

13.3%, had a 17.8% increased risk of cancer diagnosis compared to those in the lowest tertile (HR 1.178; 95% CI, 1.046 – 1.327; P = 0.0069).

Table 6. Cox Regression Analysis by T90% Tertiles

OSA Category	Hazard Ratio	95% Confidence Interval	P Value
Unadjusted HR			
T90% (Continuous, per 1%)	1.007	1.006 - 1.009	<0.0001
Categories			
<1.1%	1	-	-
1.2% - 13.2%	1.388	1.251 – 1.540	<0.0001
≥ 13.2%	1.823	1.639 – 2.027	<0.0001
Adjusted HR*			
T90% (Continuous, per 1%)	1.002	1.000 – 1.004	0.0128
Categories			
<1.1%	1	-	-
1.2% - 13.2%	1.086	0.973 – 1.211	0.1398
≥ 13.2%	1.178	1.046 – 1.327	0.0069

* adjusted for age, sex, BMI categories, hypertension, COPD, CAD, diabetes, race, ethnicity, and center

4.2.3 Site-Specific cancers hazards by T90% severity

The adjusted Cox regression model results for severe T90% and site-specific cancers were heterogeneous (Figure 7). Risk of bladder and lymph/heme neoplasms was significantly higher in the severe T90% category compared to those without significant T90%. No significant increase in risk head/neck, melanoma, thyroid, or colorectal cancers was detected for the highest T90% tertile. Conversely, the highest T90% tertile was associated with a 24% reduction in risk of non-melanoma skin cancers.

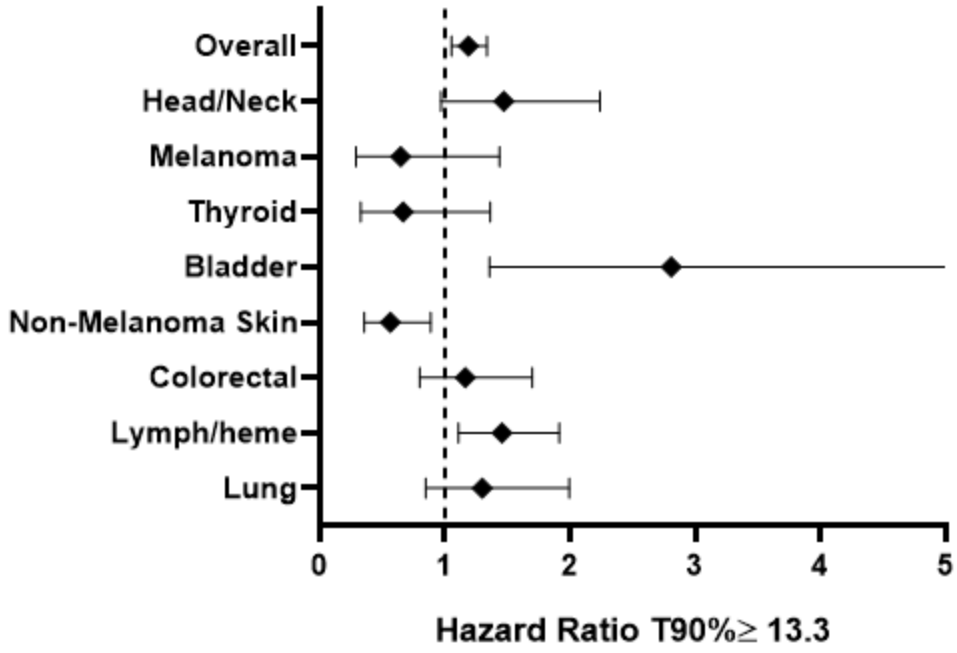

Figure 4. Cox Regression Analysis of Site-specific Cancers (n=19501)

The cancer analysis was further stratified by men and women to examine potential sex effects. Among men (n = 8996), there was a 22% increase in risk of cancer diagnosis for those in the highest T90% tertile compared to the lowest tertile (HR 1.221; 95% CI 1.021 – 1.462; P = 0.0291) (Figure 8). When considering specific neoplasms, a significant increase in the risk of lymph/heme and bladder related neoplasms in those with high T90% were noted. The risk of non-melanoma skin cancers was lower in those with the highest T90%. No significant differences in cancer risk were detected amongst any of the other sites considered. Among women (n = 10,293), the overall risk of cancer diagnosis for those in the highest T90% tertile relative to those in the lowest T90% tertile was elevated but statistically non-significant (HR 1.158; 95% CI 0.986 – 1.361; P = 0.0743) (Figure 9). In the combined model, the interaction between sex and T90% was not statistically significant (p=0.21) indicating that the effect of

T90% on cancer risk was not significantly different between the sexes. When analyzing site-specific cancers, none of the considered categories were significantly elevated.

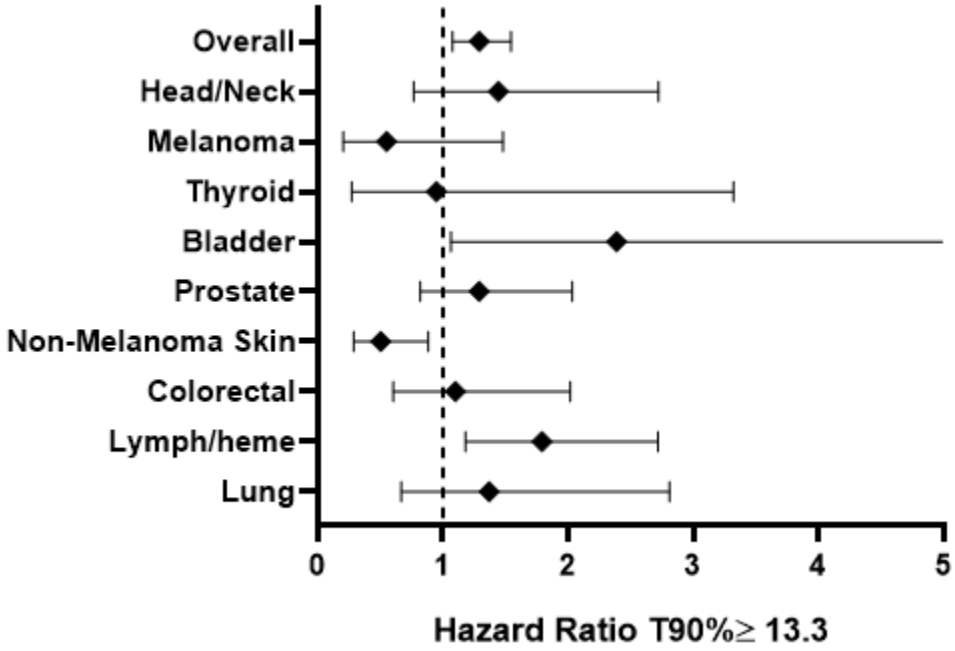

Figure 5. Cox Regression Analysis of Site-specific Cancers in Males (n=8996)

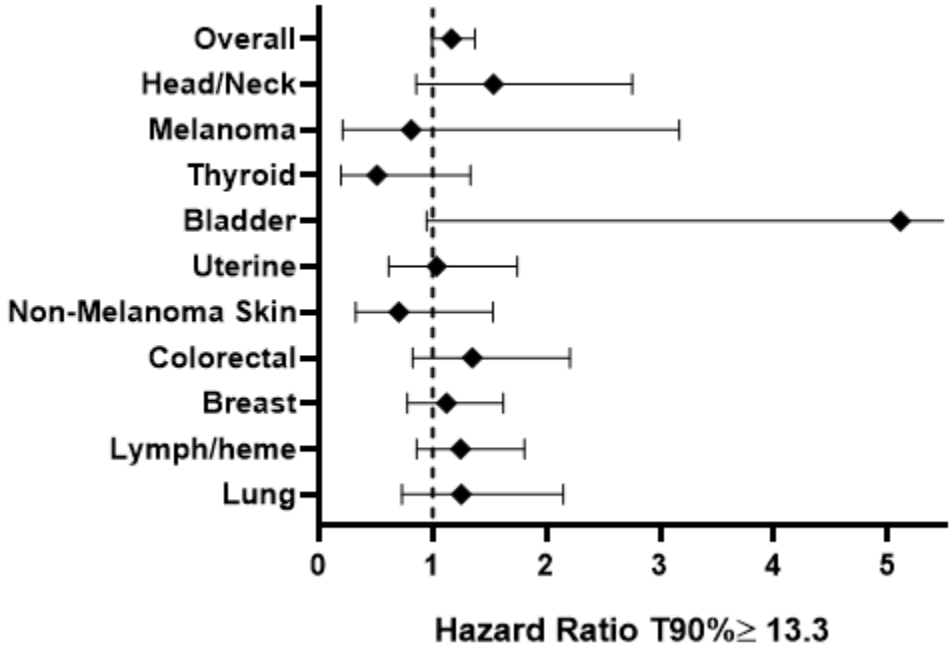

Figure 6. Cox Regression Analysis of Site-specific Cancers in Females (n=10293)

5.0 Discussion

Our hypothesis was that increased OSA severity, as determined by AHI or T90%, would be positively associated with increased incident cancer risk. This hypothesis was not well supported for AHI following adjustments for common confounders, such as age and BMI. Furthermore, we did not observe significant associations between OSA severity, as measured by high AHI, and site-specific cancers using multivariable adjusted models. High AHI was not associated with any of the site-specific cancers considered and only slight differences were detected after stratification by sex. In contrast, the highest category of T90% was associated with an increased risk for incident cancer after adjusting for potential confounders. Overall, a 17.8% higher risk of cancer was detected (HR 1.178; 95% CI, 1.046 – 1.327; P = 0.0069) for those with severe drops in SpO2 saturation during sleep compared to those with minimal drops. While overall cancer risk was elevated, this effect was not consistently observed for all types of cancers.

In order to examine the complex relationship between OSA and cancer, we first explored the most commonly reported measure of OSA severity, AHI. Unadjusted hazards models revealed that increased AHI was associated with incident cancer diagnosis in a dose-response manner. Furthermore, we noted that patients with increased AHI also had shorter time-to-cancer diagnosis compared to those with no OSA or mild OSA. These associations were not significant after adjusting for age, BMI, hypertension, COPD, CAD, diabetes, center, race, and ethnicity. This result is not consistent with a number of other studies that also explored the association between OSA and cancer. For example, OSA was found to significantly increase the risk of cancer diagnosis amongst a cohort of veterans after adjusting for age, sex, smoking status, alcohol use, obesity, and comorbidity (36). When considering site-specific cancers, there were appreciable

differences between the present study and previous literature. For instance, we found no difference in risk for those with high AHI in colorectal and melanoma cancers, but a number of studies suggest otherwise (43,44). The results of our analysis, in comparison to similar investigations, suggest that cancer risk attributable to OSA severity is heterogenous when AHI is used as a diagnostic of severity.

As AHI is not sensitive to the characteristics of an apnea/hypopnea, such as the depth or duration of oxygen desaturation, we repeated the analysis using the percentage of sleep time under 90% SpO2 for OSA severity (17,50). There was remarkable heterogeneity in the characteristics of patients in the three T90% tertile groups, with older, obese males typically presenting with the highest T90%. We also noted that patients in the highest T90% tertile had increased rates of comorbid conditions, such as hypertension and diabetes. After adjusting for confounding factors, those in the highest tertile had significantly higher incident cancer risk compared to those in the lowest tertile. We observed a significant increase in overall cancer risk among men, but not women in covariate adjusted models. However, the association between T90% and cancer risk did not vary significantly by sex (interaction $P = 0.21$), and the magnitude of the two hazard ratios were similar in the two sexes. Power to detect significant differences by OSA within the sex subgroups was limited in this study. We noted differential effects of T90% and site-specific cancers, such that those in the highest tertile had an elevated risk of bladder and lympth/heme neoplasms, but decreased risk in non-melanoma skin cancer. A recent review highlighted the importance of intermittent hypoxia on cancer biology, however there are few studies that directly compare T90% on subsequent cancer risk in patients with OSA (31). Our results are in agreement with the original multi-center Spanish Sleep study that found an overall increase in cancer incidence among patients with an increased T90% (34). Interestingly, there was no increased risk of melanoma amongst

those in the highest T90% tertile, which directly counters a number of studies on the effects of intermittent hypoxia and melanoma risk.

The estimated cancer risk for severe OSA when using AHI or T90% were somewhat disparate. One explanation for this difference may be that AHI does not directly quantify the degree of intermittent hypoxemia found in patients with OSA. As such, some patients may be more at risk than others within the same AHI category (50). As hypoxia is a primary driver of tumor development, it is important to directly quantify the extent of T90% as it may be a more accurate assessment of cancer risk in this patient population. The results are significant for public health, as it provides further evidence that OSA may confer an increased risk of cancer in patients with significant oxygen desaturations.

Previous epidemiological studies on the association between OSA severity and cancer risk have shown remarkable heterogeneity and our study is no exception (3). In both analyses, there were significant differences between severity categories (AHI or T90%) by age and BMI. In the T90% analysis, the prevalence of hypertension, COPD, CAD, and diabetes were significantly increased amongst those in the most severe category. Among the confounding factors included in the hazards model, age was by far the most significant confounder to the adjusted hazards models. This is not surprising given that increased age is associated with both increased OSA severity and cancer. Unfortunately, exploratory analysis by age group did not reveal substantial difference in the hazard of OSA severity on incident cancer. Another factor that is important to the results of this analysis is the distribution of incident cancers. For AHI, there was only marginal increases in the number of cancer diagnoses in those with AHI $\geq$ 30 relative to those with AHI < 5 or AHI between 5 and 15. Furthermore, the number of each site-specific cancer was fairly low, and hence

this analysis had modest power to estimate the risk of cancer incidence by OSA category for each site.

The heterogeneity of our results compared to previous research highlights the issue of using insurance databases to conduct population studies versus clinical populations actively undergoing treatment. It is well known that ICD codes have low specificity for OSA and are unable to determine the severity of OSA, let alone T90%. As our data comes directly from PSG, we have a high degree of certainty in the ascertainment of exposures used for this study. A major limitation of this study is our lack of ability to determine lifestyle factors that impact cancer risk, particularly smoking. However, by adjusting for relevant comorbidities, such as diabetes and hypertension, we theorize that our model is able to capture some of the residual confounding. Furthermore, the inclusion of comorbidities is warranted given that they confer increased cancer risks (52,53). The inclusion of comorbidities, such as hypertension or diabetes, may lead to overfitting the model and bias estimates. Sensitivity analyses of the hazards models with and without comorbidities were significantly different, but the overall conclusions were consistent between models. Variability is expected when assessing cancer risk in a population, and as further research is warranted to examine the role of nocturnal hypoxia on cancer risk.

Our study has a number of strengths in that we were able to capture a large cohort of patients undergoing PSG. As PSG is the gold standard for sleep apnea testing, we can be sure that the exposures were accurately measured within this cohort (12). Furthermore, linking PSG reports to the EMR of patients allowed us to ascertain a number of comorbid conditions that may confound our results. Our assessment of the outcome, cancer incidence, was determined using a validated algorithm designed to be implemented for health claims databases. All statistical analyses were performed using validated methods and software capable of doing so.

In conclusion, the present study highlights the impact of OSA severity on subsequent cancer incidence. We found a substantial difference between AHI and T90% as measures of OSA severity, suggesting that direct quantification of oxygen desaturation is necessary for adequately describing cancer risk. This work has public health significance in that there has been a substantial increase in the number of patients presenting with OSA and as such a fuller understanding of the burden of OSA will allow clinicians to make better recommendations for patients seeking treatment. As OSA seems to impart some measurable increase for cancer incidence, there is a greater need for treatment of this condition in order to adequately suppress cancer risk in patients with an OSA diagnosis.

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