1.a. Full Title: Sleep apnea severity and risk of cancer incidence and mortality: Results from the Atherosclerosis Risk in Communities and Cardiovascular Health Study

   b. Abbreviated Title (Length 26 characters): Sleep apnea severity and risk of cancer incidence and mortality

2. Writing Group:
ARIC co-authors: Pamela Lutsey, Anna Prizment, Elizabeth Platz,

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __AS___ [please confirm with your initials electronically or in writing]

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3. Timeline: About a year from approval date

4. Rationale:
Obstructive sleep apnea (OSA) afflicts an estimated 25 million US adults, particularly in older adults\(^1\). It is characterized by recurrent cessations of breathing during sleep resulting in significant
disturbances in sleep duration and timing. Animal and in-vitro cancer cell culture models of OSA demonstrate enhanced oncogenic pathways in the presence of intermittent hypoxia — the central physiological consequence of OSA. Suggested mechanisms include the generation of excessive reactive oxygen species, overexpression of the transcriptional regulator hypoxia-inducible factor-1alpha (HIF-1α) and suppressed immune function.

The plausibility of OSA carcinogenic consequences has led to a few observational studies, including several that have noted between 1.3-2.0 fold higher incidence of cancer among those with OSA versus no OSA while others have noted no association. With respect to mortality, three community-based longitudinal studies have noted 3.4 to 4.8-fold elevated rates of cancer mortality among individuals with OSA. However, another study found that among individuals with a diagnosis of cancer, the presence of OSA was not associated with increased risk for death.

Despite the inconsistency across studies, a recent study showed that among people with OSA, the prevalence of severe OSA was higher than expected for patients with several different cancer types including melanoma, breast, lung and kidney cancers. In another recent study, the severity of OSA was shown to be independently associated with greater aggressiveness of melanoma in a cohort of patients evaluated for OSA at the time of cancer diagnosis, suggesting a dose-response relationship between OSA severity and cancer progression and outcomes.

Since OSA and cancer mortality and cancer incidence has scarcely been studied, and with inconsistent results for cancer overall, further investigations are warranted, as well as with respect to specific types of cancer. Furthermore, given the high prevalence of OSA in older populations, the ARIC-Sleep Heart Health Study (ARIC-SHHS, N= 1,920) will provide a unique opportunity to examine this question. Additionally, we will do a pooled analysis with the Cardiovascular Health Study (CHS-SHHS, N=1240) data to improve precision of our estimates.

5. Main Hypothesis/Study Questions:
The overarching goal of this proposal is to investigate the association of baseline OSA with cancer mortality and incidence. To accomplish this goal, we propose the following aims:

**Aim-1**: Determine the relationship of baseline OSA with cancer incidence.

*Hypothesis*: We hypothesize that baseline severe OSA will be adversely associated with cancer incidence compared to those with normal sleep breathing patterns

**Aim-2**: Determine the relationship of baseline OSA with cancer mortality.

*Hypothesis*: We hypothesize that baseline severe OSA will have higher cancer mortality as compared to those with normal sleep breathing patterns.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

**Exposure:**
We will utilize the subset of ARIC participants who were enrolled in the SHHS. We will use Apnea-hypopnea index (AHI) and time in oxygen saturation <90% (Tsat90%) to establish severity of sleep apnea based on standardized cutoffs and previously published work (normal, mild, moderate and severe) and as a continuous measure (Table 1).

### Table 1. OSA severity measures defined based on clinical guidelines and prior studies

<table>
<thead>
<tr>
<th>Measure</th>
<th>Definition</th>
<th>Categories</th>
</tr>
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<tbody>
<tr>
<td>AHI</td>
<td># apnea or hypopnea events per hour of sleep</td>
<td>Normal &lt; 5&lt;br&gt;Mild = 5-14.9&lt;br&gt;Moderate = 15-29.9&lt;br&gt;Severe ≥ 30</td>
</tr>
<tr>
<td>Hypoxemic burden, Tsat90%</td>
<td>% of sleep time spent with oxygen saturation levels &lt;90%</td>
<td>Normal = &lt;1.2%&lt;br&gt;Mild-Moderate = 1.2-12%&lt;br&gt;Severe = &gt;12%</td>
</tr>
<tr>
<td>RDI</td>
<td>Respiratory Disturbance Index</td>
<td>None =&lt; 5&lt;br&gt;Mild = 5 - 15&lt;br&gt;Moderate= 15-29.9&lt;br&gt;Severe ≥ 30</td>
</tr>
</tbody>
</table>

**Outcomes:**
The analysis of cancer incidence will use data from state cancer registries and hospital abstracted data which goes through 2015. We will assess the incidence of cancer overall (all sites) [total in Aric = 483, total in CHS = 179] and common cancer sites in the combined ARIC, CHS data including breast, lung, kidney, colorectal and prostate (we anticipate that power will be inadequate to comprehensively analyze all sites). Additional secondary analysis will include combining all smoking-related, obesity-related and all cancers minus cancers previously found to be negatively associated with OSA (prostate and colorectal cancers) consistent across the two most recent study reporting associations across multiple cancer sites. Cancer-specific mortality will be ascertained using adjudicated cause of death (censoring lost to follow-up or death from other causes; total cancer deaths 398 in ARIC and 179 in CHS).

**Inclusion and Analysis:**
For the cancer incidence analysis, a final analytic sample will include participants free of cancer at baseline. For the cancer mortality study, we will assess subsequent cancer mortality regardless of baseline cancer status.

We will use Cox proportional hazard models to examine the associations of obstructive sleep apnea severity with the subsequent cancer incidence and mortality, reporting hazard ratios (HRs) and their 95%CIs and controlling for potential confounders such as age, sex, race*center (5-level variable), BMI, and smoking for both outcomes. These results will be pooled with the CHS study results examining the same questions. Specifically, to obtain a single pooled estimate, we will use a random effect model to combine the HRs from the two studies. The study-specific relative risks will be weighted by the inverse of the sum of their variance and the estimated between-studies variance component. We will provide overall, sex and racial group specific estimates.
7.a. Will the data be used for non-CVD analysis in this manuscript? Yes
   b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = “CVD Research” for non-DNA analysis, and for DNA analysis RES_DNA = “CVD Research” would be used? Yes
   (This file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = “No use/storage DNA”? Yes

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/aric/mantrack/maintain/search/dtSearch.html
   Yes

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? Yes

11.b. If yes, is the proposal
   __X__ A. primarily the result of an ancillary study (list number* __1995.12  Sleep Heart Health Study (SHHS) (PI: Punjabi NM) and the ARIC cancer group ________)
   ___  B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* __________ __________ __________)

*ancillary studies are listed by number at https://www2.cscc.unc.edu/aric/approved-ancillary-studies

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is your responsibility to upload manuscripts to PubMed Central whenever the journal does not and be in compliance with this

References:


