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COMMENTARY

Emerging from the Shadows: A Possible Link between Sleep Apnea and Cancer

Commentary on Marshall 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;10:355-362.

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Obstructive sleep apnea (OSA) is an important public health concern, due to its prevalence and important long-term adverse health effects. There is significant data linking OSA to cardiovascular disease, stroke, metabolic dysfunction, motor vehicle crashes, and death[1]; much of this is gained from longitudinal cohort studies. New evidence is emerging that links OSA to cancer as well.

Inspired by recent *in vitro* and animal studies that found that intermittent hypoxemia facilitates tumor progression,[2] two established cohort studies looked for an independent association between objectively measured OSA and cancer outcomes. The first of these was in the Wisconsin Sleep Cohort, which followed a random sample of 1,522 state employees aged 30-60 for a mean of 22 years.[3] This study found an adjusted relative hazard of cancer mortality of 4.8 in subjects with an apnea-hypopnea index (AHI) ≥ 30. The second study was performed in a larger multi-center Spanish cohort of 4,910 subjects who were followed for a median of 4.5 years.[4] In contrast to the Wisconsin study, this was a sleep clinic based sample. This study found an adjusted relative hazard for incident cancer of 1.66 in patients under age 65 with AHI > 43. Furthermore, hypoxemia (time spent with oxygen saturation < 90%) was more strongly associated with incident cancer than AHI, a finding that was also noted for cancer mortality in the Wisconsin study. Both studies adjusted for many (but not all) known confounders and demonstrated dose response relationships with OSA measures, findings that are looked for when assessing causality.

In this issue, Marshall et al. provide the results of 20 years of follow-up in the Busselton Sleep Cohort.[5] The Busselton Sleep Cohort is a subset of the larger population-based Busselton Health Study Cohort in Western Australia, which was begun in 1966 as a long-term observational study. In the Busselton Sleep Cohort, 293 men and 104 women underwent a four-channel out-of-center sleep study in 1990 and had follow-up through 2010. The authors found that after adjusting for important confounders (including obesity), moderate to severe OSA (defined as a respiratory disturbance index > 15) was associated with a relative hazard of 2.5 for cancer incidence and 3.4 for cancer mortality, without evidence for a dose response relationship.

There are several limitations to the study by Marshall et al. The exposure (OSA) was assessed using a non-standard out-of-center sleep-testing device (MESAM IV). There was also no assessment of the duration of hypoxemia, and the sample size was relatively small. Nevertheless, we have yet another cohort where OSA has been found to be independently associated with an increased risk of cancer outcomes. In the Bradford Hill criteria for assessing causality, an important factor is whether the association has "been repeatedly observed by different persons, in different places, circumstances and times."[6] Additional long-term longitudinal studies which include objective assessment of OSA, more extensive ascertainment of important confounders, and detailed cancer outcomes are needed. Indeed, a variety of study types, including mechanistic and interventional studies, would help more fully ascertain whether a causal relationship between OSA and cancer exists.

If OSA is an independent risk factor for cancer and cancer mortality, this finding has enormous public health significance, given the high prevalence of OSA. Already, OSA has been linked in some manner to four of the ten leading causes of death in the U.S. (heart disease, stroke, accidental death and diabetes). Cancer was the second leading cause of death in 2010 with over 575,000 victims, a close second to heart disease which was responsible for over 597,000 deaths. Medical costs and lost productivity due to cancer in that same year was estimated at $263.8 billion.[7] Diagnosis and treatment of OSA with CPAP is already highly cost-effective, with a cost effectiveness ratio of $15,915 per QALY in a high-risk population, using an economic model that considered improvements in quality of life and life expectancy due to a decreased risk of myocardial infarction, stroke, and motor vehicle crashes.[8] Perhaps a reduced risk of cancer morbidity and mortality will one day need to be considered as well.

The cumulative effects of chronic health conditions often require decades to appreciate. Long-term data from studies such as the Busselton Sleep Cohort, with near-complete follow up of all recorded subjects after 20 years, prove to be invaluable in this regard. Such studies require sustained resources and great personal commitment on the part of the researchers and study participants. But thanks to these efforts, another potential

risk factor for cancer is emerging from the shadows, providing yet another powerful reminder that as sleep clinicians, reducing the burden of OSA in our patient population is of the utmost importance.

CITATION

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