CHEST

# Putative Links Between Sleep Apnea and Cancer
## From Hypotheses to Evolving Evidence

*David Gozal, MD, FCCP; Ramon Farré, PhD; and F. Javier Nieto, PhD*

In recent years, the potentially adverse role of sleep-disordered breathing in cancer incidence and outcomes has emerged. In parallel, animal models of intermittent hypoxia (IH) and sleep fragmentation (SF) emulating the two major components of OSA have lent support to the notion that OSA may enhance the proliferative and invasive properties of solid tumors. Based on several lines of evidence, we propose that OSA-induced increases in sympathetic outflow and alterations in immune function are critically involved in modifying oncologic processes including angiogenesis. In this context, we suggest that OSA, via IH (and potentially SF), promotes changes in several signaling pathways and transcription factors that coordinate malignant transformation and expansion, disrupts host immunologic surveillance, and consequently leads to increased probability of oncogenesis, accelerated tumor proliferation, and invasion, ultimately resulting in adverse outcomes. CHEST 2015; 148(5):1140-1147

**ABBREVIATIONS:** AHI = apnea-hypopnea index; HI = hypoxemia index; HIF = hypoxia-inducible factor; HR = hazard ratio; IH = intermittent hypoxia; SF = sleep fragmentation; SH = sustained hypoxia; TAM = tumor-associated macrophage

The last two decades have witnessed parallel research efforts in the exploration of the mechanistic roles of hypoxia in cancer biology and also how sleep duration and biologic clock perturbations may be epidemiologically associated with increased risk for either developing cancer or adversely affecting cancer outcomes. Consequently, it was not surprising that such parallel fields of investigation would ultimately spark the hypothesis that a highly prevalent sleep disorder, namely OSA, may be a major modulator of tumor biology. Here, we perform an up-to-date critical review of the evidence supporting possible associations between OSA and cancer and further explore any putative biologically relevant mechanisms.

Hypoxia can elicit divergent responses that are either adaptive or maladaptive and are contingent on different levels of stimulus severity and presentation.[1-3] Most of the existing work has thus far revolved around the characterization of how sustained or monophasic hypoxia modulates the transcriptional

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**AFFILIATIONS:** From the Department of Pediatrics (Dr Gozal), Pritzker School of Medicine, Biological Sciences Division, The University of Chicago, Chicago, IL; the Unitat de Biofísica i Bioenginyeria (Dr Farré), Facultat de Medicina, Universitat de Barcelona-IDIBAPS, Barcelona, Spain; CIBER de Enfermedades Respiratorias (Dr Farré), Bunyola, Spain; and the Department of Population Health Sciences (Dr Nieto), School of Medicine and Public Health, University of Wisconsin, Madison, WI.

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**CORRESPONDENCE TO:** David Gozal, MD, FCCP, Department of Pediatrics, Pritzker School of Medicine, The University of Chicago, 5721 S Maryland Ave, MC8000, K160, Chicago, IL 60637-1470; e-mail: dgozal@uchicago.edu



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activity of a large group of redox-sensitive transcription factors (eg, hypoxia-inducible factors [HIFs], nuclear factor-κB/Rel family). However, it is becoming increasingly clear that intermittent hypoxia (IH) and sustained hypoxia (SH) may elicit quite different cellular responses and that the duration and cycling frequency of IH, as occurs in sleep apnea, may also elicit contradictory cellular phenomena, namely preconditioning or cell death.[1-3] In addition, SH, and more prominently IH, will promote the formation of excessive reactive oxygen species and inflammatory products that damage or alter function of proteins, lipids, and DNA.[4]

The occurrence of cellular hypoxia in tumors emanates from the high proliferative rates of malignant cells that are not accompanied by parallel and commensurate angiogenesis to match the bioenergetics needs of the tissue. It is, therefore, likely that different regions of solid tumors will undergo both SH and IH, which can then elicit discrepant activation of transcription factors such as HIF-1 and HIF-2.[5,6] In the absence of diseases associated with IH, such as OSA, the time constants of intratumoral oxygen tension are markedly lengthy. However, patients with OSA are characteristically sustaining IH episodes that are concurrent with the repetitive obstructions of the upper airway during sleep. The oscillatory nature of tissue $Po_2$ in these patients imposes similar repercussions on tissue $Po_2$ with a much shorter time constant[7] and could be a predisposing factor for increased incidence of malignancies. This is particularly relevant when considering that oxidative stress is a major risk factor in oncogenesis and that increased oxidative stress enhances the probabilistic mutational rate of rapidly replicating cells.[8,9] Second, mechanisms enhancing tumor growth, invasion, and regional and distant metastatic potential are enhanced by IH.[6,10-12] However, studies examining how IH may affect cancer progression have revolved around the replication of the putative changes in tissue oxygenation that develop during the fast tumor growth and the concomitant and uneven process of vascularization (ie, processes with oscillatory frequencies in the range of hours to even days).[10] These hypoxia/reoxygenation cycles are at least one order of magnitude longer and certainly vastly different from those experienced by patients with moderate to severe OSA. Since some of the molecular pathways triggered by IH are stringently dependent on the frequency and cumulative number of IH events,[2,13] it was important to explore the effects of IH in the frequency and severity range occurring in OSA in cancer.

In comparison with the possible role of IH, much less is currently known on the potential impact of sleep fragmentation (SF) on tumorigenesis. There is growing evidence, however, suggesting that poor sleep quality or sleep discontinuity (collectively termed SF here) may in fact have a carcinogenic role. In a review by Haus and Smolensky,[14] the summary evidence presented conclusively indicated that lifestyle patterns that disrupt the stability and homeostasis of sleep and circadian rhythms (eg, shift work) are associated with epigenetic modifications of several key circadian genes, which in turn modify transcriptional regulation and affect the expression of cancer-related susceptibility genes, while also disrupting gene networks that coordinate cell division and DNA repair.

In the following paragraphs, we summarize initially some of the bench-based evidence linking IH and SF to solid tumor biology and follow these with the currently available epidemiologic literature suggesting a link between OSA and cancer in human populations. Finally, we attempt to present a holistic mechanistic view of potential pathways that may account for the observations reported herein that merit future research in both human- and animal-based models.

## Animal Models of IH, SF, and Cancer

### *Does Fast Hypoxia/Reoxygenation Cycling Mimicking OSA Facilitate Malignant Transformation in Otherwise Normal Cells?*

Karoor et al[15] injected chemical carcinogenic agents in mice and observed the appearance of lung tumors when the animals were under normoxia, continuous hypoxia (SH), and IH and found that although SH increased tumor formation, no changes occurred in IH (Fig 1). More recently, Zhang et al[16] reported that alteration in brain-derived neurotrophic factor (which prevents neuronal damage by oxidative stress and is linked to changes in leptin production and β-adrenergic receptors) and miR (a target of P53 promoting cell cycle arrest and tumor suppression) occurs with IH exposures. These findings may reflect indirect evidence of increased propensity for tumorigenesis.[15-17]

### *Does IH Affect Tumor Growth?*

Rofstad et al[18] induced intradermal A-07 human melanoma xenografts in mice and subjected the animals to 4 h of IH, after which tumors had increased blood perfusion, microvascular density, and vascular endothelial growth factor expression. Almendros et al[19] subjected mice to a realistic IH paradigm mimicking oxygenation