



Editorial

Sleep and Cancer[☆]

Sueño y cáncer

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The sleep of a laborer is sweet, whether they eat little or much, but as for the rich, their abundance permits them no sleep.

Ecclesiastes 5:12

The quantity and quality of sleep has always been a concern for mankind, and it is known to be essential for sustaining life in general and human life in particular. All patients with acute and chronic disease suffer altered sleep patterns. Cancer patients, in particular, suffer fatigue and difficulties falling or staying asleep. This editorial does not address this topic, but instead discusses the influence of primary sleep-disordered breathing on the development of cancer, and the role of the respiratory medicine specialist now and in the future.

The circadian rhythm is an essential biological function in all living beings, and determines physiological changes and behavior over a 24-h period. In mammals, the circadian “pacemaker” is located in the suprachiasmatic nucleus (SCN) in the hypothalamus. Circadian rhythms are genetically determined, and preliminary studies have reported the presence of certain genetic polymorphisms that might determine disorders in the sleep–wake pattern. Epigenetic modifications in key genes for circadian regulation have been reported in shift workers and individuals exposed to high levels of light at night, modifications that simultaneously alter the transcription of regulatory genes related with susceptibility to cancer.¹ Epidemiological studies performed in these workers have found an association between the risk of cancer, particularly breast cancer,² and shift work. The intermediary mechanisms that might explain the relationship between shift work and the risk of cancer are unknown. Melatonin is known to have anti-oncogenic effects, and *in vitro* studies have shown it to increase expression of the PER2 gene which, among other things, reduces the production of β -catenine. This protein increases cyclin-D levels, activating the proliferation of neoplastic cells. Various melatonin receptors affecting tumor physiology have been described in breast cancer tumor cells. In both male and female shift workers, melatonin levels at night and in 24-h urine are reduced and fluctuate much less than in day-time workers.³ This finding would support the laboratory

studies mentioned above, but to date no causal relationship has been identified between melatonin and the risk of cancer, and no interventional trials been performed with melatonin in animals or in humans.

Sleep duration, whether too short or too long, and its relationship with the risk of cancer, has been evaluated in some population studies, with inconsistent results. Instead of studying real “sleep time”, which is difficult to establish since it is based on reported questionnaires, it is easier to study sleep fragmentation (SF) and its relationship with the risk of cancer. In animal models in which SF was induced while preserving sleep time and eliminating the potential effect of intermittent hypoxia (IH), the degree of SF was determined to be associated with greater proliferation rates and tumor development.⁴ In another animal study, Almendros et al. evaluated the effect of IH, but this time the effect of SF was eliminated. They showed clearly that IH was associated with a faster melanoma growth rate and an early and more intense development of distant metastasis.⁵ To date, no experimental studies have been conducted to evaluate the relative importance of these 2 intermediate mechanisms (SF and IH) in the same animal model. What intermediate mechanisms might favor oncogenesis induced by SF and IH? Recent experiments in rat models have shown that IH did not induce direct dysplastic changes, but instead changed the polarity of the macrophages, transforming them into a less immunocompetent phenotype (M2) that would allow greater tumor proliferation.⁶ M2 macrophages also were elevated in animal models of SF, in this case increasing toll-like receptor 4 expression.⁴ It seems, then, that the 2 main components of obstructive sleep apnea (OSA), SF and IH, cause changes in innate immunity.

Confirmation of these phenomena in humans would suggest that anticancer surveillance and neoplastic growth control phenomena are less effective in patients with OSA. The Spanish Sleep Group demonstrated almost simultaneously with the Wisconsin group that untreated OSA patients had a greater incidence of cancer,^{7,8} providing epidemiological data to support the results of the *in vitro* research. However, a Canadian population study was unable to confirm this association.⁹ Interested readers can consult the excellent review by Martínez-García on this subject that appeared recently in Archivos de Bronconeumología.¹⁰

What are the clinical implications of these studies on the relationship between sleep and cancer? In my opinion, no robust

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studies establishing the relationship between the amount and the quality of sleep and cancer have yet been published. For now, we must insist on the need for good sleep hygiene and avoid treatments that alter natural sleep. As respiratory medicine specialists, we are in the front line of treating patients with OSA. There is still no evidence to establish a causal relationship between OSA and cancer, so there is no need to actively investigate for cancer the first time we see a patient with OSA, nor do we need to change our current therapeutic practice. However, the available information obliges us to be more alert to the potential risk of cancer as a comorbidity in OSA patients and to monitor them regularly, but without causing alarm.

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