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Sleep Medicine

Editorial

Sleep-disordered breathing and cancer incidence: an association for the next decade?

Despite sharing some intermediate mechanisms, the possible association between sleep-disordered breathing (SDB) and cancer has largely been overlooked. Only very recently has any interest in this topic emerged, and studies in animal models of sleep apnea and data from human cohorts have developed in parallel. Whereas various studies in rodent models of SDB have concurred to show that intermittent hypoxia (IH) and sleep fragmentation mimicking the one experienced by SDB patients enhance both the growth and progression of tumors, we lack any evidence on the pathophysiological mechanisms that could explain a carcinogenic role in SDB [1–4]. Disruption of the normal circadian rhythms, particularly night shift work, may increase the risk of breast or prostate cancer [5,6]. Similarly, short sleep duration has also been associated with breast cancer [7]. However, the potential role of IH and sleep disruption as they occur in SDB has not been explored. It is known that IH stimulates the production of reactive oxygen species (ROS), leading to oxidative stress and systemic inflammation, which can damage proteins, lipids and DNA. An increased transcription of the hypoxia inducible factor (HIF)-1 promoted by IH may also participate in some of the processes linking IH to ROS production [8,9]. It could therefore be speculated that these consequences of IH result in mutations leading to tumorigenesis, particularly in the setting of systemic inflammation found in patients with SDB.

As regards human studies, the evidence, as in the case of basic research, is very limited. To date, only five studies have analyzed the association between SDB and cancer incidence [10–14]. In the present issue of Sleep Medicine, Shantha conducted a meta-analysis of these studies, and found that patients with SDB had an increased risk of cancer incidence (relative risk, RR: 1.53; 95% confidence interval, CI: 1.31–1.79; p < 0.0015) [15]. This association was attenuated after adjustment for traditional cancer risk factors but remained significant (RR: 1.40, 95% CI: 1.01–1.95, p = 0.04). However, the authors recognize that despite the large number of patients included in the meta-analysis (34,848 patients with SDB and 77,380 patients without SDB), it is not possible to infer any independent association, largely due to two major limitations: the original design of the studies and the great differences between them.

The design of the studies is probably the main limitation that prevents us from drawing any strong conclusions from this meta-analysis. The Busselton Health Study is a prospective cohort but it was not originally designed to analyze cancer incidence as an outcome [11]. The Spanish and Canadian cohorts have a retrospective design [10,14], and the two studies from Taiwan use healthcare records or claims databases, which preclude the assessment of important confounding risk factors for cancer, as well as significant data related to SDB, such as the apnea–hypopnea index [12,13]. Another flaw derived from the retrospective and non-specific design of these studies is the scarcity of data on oxymetric variables. Although IH seems to be the most likely mechanism involved in both SDB and cancer, none of the five studies provided any information about the best surrogate for IH, namely the oxygen desaturation index. Only two of the studies defined SDB severity on the basis of the percentage of nighttime spent with oxyhemoglobin saturation below 90%, but this is a marker of overnight hypoxia, rather than of IH [10,14].

The heterogeneity of the studies is the other great concern. Some of them are population-based whereas others are clinical cohort studies. There are multicenter as well as single-center studies. The apnea–hypopnea index is not provided in all of them, the diagnosis is based on either conventional polysomnography or simplified respiratory polygraphy, and the follow-up period varies greatly, from 4.5 to 20 years. Finally, the types of cancer analyzed in the studies are also different. Only two of them addressed organ-specific cancers, namely breast and primary central nervous system cancers [12,13]. The other three studies analyzed all types of cancers, since the small number of incident cases precluded any specific analysis of cancer location.

In the light of this evidence, the association between SDB and the development of a new cancer is still weak in humans. Nevertheless, the findings of this meta-analysis, even with its limitations, should prompt new research specifically designed to investigate this association. Given the role of cancer as one of the leading causes of mortality and disability, and the high prevalence of SDB, determining the relationship between these two disorders is of utmost interest for public health policies, especially considering that SDB has an effective treatment, which could make it a controllable risk factor for cancer.

The first question that needs to be answered in future studies is whether SDB is a relevant risk factor for cancer incidence, and more specifically whether it is a risk factor for all types of cancer, or only for some organ-specific tumors. Different types of malignant cells may have different adaptive responses to IH and sleep fragmentation, so it cannot be ruled out that SDB is associated with certain types of cancers but not with others. Additional concerns that need to be addressed include the pathophysiological mechanisms that would be involved in this association, mainly how IH and sleep fragmentation could start tumorigenesis, identification of specific groups at risk of developing cancer in the setting of SDB and the polysomnographic indices that best predict this association.

In conclusion, we are still a long way from confirming that SDB is a risk factor for cancer incidence. Considering the scarcity of the

evidence, the challenge for research posed by this possible association, and its profound implications in terms of public health, it is hoped that investigation into the relationship between SDB and cancer incidence will attract greater interest in the near future. To shed some light on this association, experimental research in animal models, which can more accurately control for most of the confounding variables, should be combined with large, prospective human cohorts with a prolonged follow-up adopting multicenter and multinational strategies.

Conflict of interest

The author has no conflicts of interest.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2015.05.010.

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