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GUEST EDITORIAL

Does obstructive sleep apnea confer risk to induce or enhance tumor malignancy?



In the last three years, several studies have emerged indicating a possible relationship between obstructive sleep apnea (OSA) and cancer. In this issue of *Sleep Medicine Reviews*, Gozal and colleagues [1] summarize the results collected from all the clinical and animal studies carried out to date. Due to the different nature of the perturbation, OSA and sleep quality/duration epidemiological studies were divided into two separate sections to explore their possible links with cancer. First, and in less detail, Gozal et al. [1] describe the potential cancer risk induced by poor sleep quality such as changes in sleep duration and circadian clock that are typically seen among shift workers. Those decade-spanning studies show a clear relationship between poor sleep quality and cancer incidence for several types of cancer. However, potential cancer links in OSA patients emerged from the epidemiological data in 2012, and are discussed with greater detail in this review.

Sleep fragmentation (SF) and intermittent hypoxia (IH), two of main hallmarks of OSA, have been proposed as the main causes of most of the cardiovascular, cognitive and metabolic consequences associated with OSA. Both perturbation paradigms, which are usually present in moderate/severe OSA and are associated to the poor-sleep quality reported among these patients, could contribute to an increased cancer risk. On the other hand, there is growing evidence that the presence of an hypoxic microenvironment, or the development of IH in tumors as a consequence of aberrant vasculature within the tumors can facilitate cancer malignancy [2]. These findings, indicating a possible relationship between cancer and OSA, awakened the interest of researchers at both the basic and clinical levels, promoting the emergence of the initial papers on this topic [3–6]. As discussed by Gozal and colleagues [1] most of the cohorts employed until now are based on previous clinical data with a retrospective nature presenting some methodological limitations. Also, the complexity of OSA, considering the numerous phenotypes and severity degrees of the disease and the coexistence of other confounding factors including age, gender, smoking habits and obesity make it difficult to extrapolate consistent conclusions from the different cohorts studied. It is important to mention that most of the clinical studies published are not focused on a specific type of cancer, and it is possible that the potential adverse effect of OSA may affect different tumors differently. This review comprehensively summarizes and discusses all the available data, indicating each limitation from each study and explaining the possible controversies found. In terms of cancer incidence, the

majority of studies show an increased risk of cancer in OSA patients, but some authors did not find any relationship or only limited to certain types of cancer. However, in terms of cancer mortality and aggressiveness the data are most robust showing increased rates in moderate/severe OSA when paired against a population without OSA. Some sub-analyses further show that the relationship between OSA and cancer appears to be stronger in the context of nocturnal hypoxemia indices, and the associations are more evident in younger, non-obese and male populations. However, due to its emerging nature, the available literature still opens new questions and further research that should aim at exploring the potential effects of OSA in well-designed cancer-specific studies [7].

In a second part of the review, Gozal et al. examine [1] all the potential mechanisms explored to date in response to SF and IH in mice. Also, the authors discuss other potential mechanisms that remain unexplored but clearly present biological plausibility and could participate in the adverse cancer outcomes observed in animals and OSA patients. The use of animals has the major advantage that it allows the study of specific contributions of SF and IH separately from other common confounding factors such as obesity. In fact, the first basic study carried out in a melanoma model [3] was employed as proof-of-concept to corroborate the first epidemiological studies and later, other tumor models were employed to confirm the previous findings observed with melanoma, and to explore potential mechanisms. Accordingly, the review describes in detail recent findings carried out in two lung carcinoma models (LLC1 and TC1 cancer cells) which support the notion that the immune changes induced by IH and SF can participate in the increased malignancy observed in response to both stimuli [4,8]. Concretely, Gozal and colleagues explicitly describe these recent papers on how SF and IH can accelerate the re-education of macrophages from a pro-inflammatory to a pro-tumoral phenotype within the tumor microenvironment, and also modify other populations such as lymphocytes (regulatory T cells) and myeloid derived suppressor cells (MDSCs) [4,8]. Also, the review summarizes some recent studies focused on the inflammatory and angiogenic pathways triggered by continuous hypoxia and IH that have been investigated in the context of cancer malignancy and prognosis, but unrelated to OSA [2]. Finally, the authors propose other potential mechanisms such those IH/SF-induced changes in the sympathetic outflow that will need further investigation. Although these animal models support the

clinical findings, it is important to mention that the types of tumors evaluated are still scarce (melanoma and lung carcinoma), and that the experimental stress generated by each treatment (SF and IH) could generate some artifacts, and also be cautious since the response could differ between mice and humans.

In conclusion, the current available data suggest a potential association between OSA and cancer that seems to be more robust in tumor malignancy rather than affect cancer incidence. The published basic research carried out in animal models shows increased tumor malignancy in response to SF and IH and studies regarding cancer incidence are still unavailable. Considering that IH and/or SF could protect or facilitate certain types of tumors, the evaluation of OSA patients as a single unified cohort could introduce confusing results. Therefore, new clinical studies specifically designed to examine the potential association between OSA phenotypes and specific tumors are still needed before the fog on this issue dissipates.

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