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LETTERS TO THE EDITOR

Does obstructive sleep apnea increase the risk of breast cancer in women during and after menopause?

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During and after menopause, women begin to experience signs and symptoms that negatively interfere in their health and social life. Vasomotor symptoms, detriments to sexual life, obesity, cardiovascular diseases, and sleep disturbances are the most frequent complaints of women in this time of life. Obstructive sleep apnea (OSA) is one of the most common sleep disturbances in men, and becomes prevalent in women after menopause, when sexual hormone levels decrease, triggering physiological alterations in a woman's body. OSA can affect more than 40% of women in menopause[1] and its effects are increasingly recognized by medical professionals, especially in cardiovascular and immunological fields. The consequences are beyond the sleep disruption by itself and involve intermittent hypoxia, which has been strongly attributed to pathological states in different tissues.

OSA has significant repercussions in body physiology and has been demonstrated to increase cancer mortality by 4.8-fold,[2] although the mechanisms involved in this outcome are not well understood. The literature describes extensive deleterious effects of intermittent hypoxia—predominant in OSA—including angiogenesis and tumor development; however, the potential association between OSA and breast cancer in women during menopause has not been fully investigated.[3,4] There is a need to evaluate this association since menopause is the period of life when the incidence of both of these diseases is increased.

Worldwide, female breast cancer represents 11.7% of all cancer cases, and is the most incident type of cancer among women in 159 countries.[5] Specifically, in women, breast cancer accounts for 25% of diagnoses of cancer and 15.5% of deaths, and is the leading cause of cancer deaths in 110 countries.[5] Breast cancer is very heterogeneous, comprising a number of distinct histological tumors, to the extent that some authors claim it can be considered a group of different diseases.[6] This fact may be a barrier in fully understanding its etiology. Earlier menarche, a family history of breast cancer, alcohol consumption, menopause at an older age, and mutations in certain genes are some of the environmental risk factors positively associated with this cancer.[6,7]

Experimental research regarding the role of intermittent hypoxia on breast tumor cells supports the potentially negative impacts of OSA on cancer.[8] To date, the directionality of the association between breast cancer and OSA is not yet known. The intermittent hypoxia produced by the disruptions in air flow provoked by OSA induces the production of reactive oxygen species (ROS). Combined with the implications of sleep deprivation caused by the high frequency of arousals during sleep, ROS stimulate alterations in the metabolism, making a significant impact on physiological processes, including the emergence of cancer.[8] The inflammation state of the body and high levels of proinflammatory cytokines (tumor necrosis factor α [TNF-α], interleukin [IL]-1, and IL-6), common characteristics of chronic OSA, should be considered as other variables that may affect the tumor development, as this is one of the hallmarks of cancer.[9] As an example, the mitogen-activated protein kinase (MAPK) pathway is crucial for the inflammatory signaling pathways, particularly p38 MAPK, which plays a role in the synthesis of proinflammatory molecules, including TNF-α,[10] and MAPK family genes may be mutated in several breast tumors.[6]

There are types of breast cancer that are sustained by endogenous and exogenous hormones, and the growth of these tumors depends on the expression of estrogen receptor (ER+) and/or progesterone receptor (PR+), which are associated with hormonal replacement therapy.[6] This demonstrates the endocrine dependency of some types of breast cancer and highlights the importance of mammography screening in women aged between 40 and 69 years,[5] as major endocrine alterations occur during and after menopause.[11]

Although observational studies have suggested that OSA itself may be associated with breast cancer,[12–14] the findings are still inconclusive. Longitudinal prospective studies should be undertaken to evaluate the incidence of breast cancer in postmenopausal women with and without OSA. The risk factors for both disorders, such as age, body mass index, alcohol and cigarette use, physical activity, and family history of breast cancer, should be controlled for in the analysis, and the OSA should be diagnosed by polysomnography.[15] This may shed light on the real effect of OSA on breast cancer incidence and the appropriate therapy for the management of OSA, while providing valuable data in relation to the risks of breast cancer in women with this sleep-related breathing disorder.

We strongly suggest that oncologists and gynecologists carefully investigate OSA in patients by using specific questionnaires for OSA (including the Berlin questionnaire,

STOP-Bang, and NoSAS scores) and polysomnography to confirm this sleep disorder, especially after menopause. This can guide health professionals to ensure a low risk of development of breast cancer by providing better approaches to improving sleep, with positive effects on quality of life.

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