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Breast cancer survivals and hormone therapy: estrogen and melatonin

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Climacteric is a period of transition between reproductive and non-reproductive periods. It is filled with fears and anxieties. Although many women go through this age phase without any symptoms or significant challenges, others suffer with intense vasomotor symptoms (hot flashes), which can cause perspiration and interfere with sleep if they occur at night[1]. Also, approximately 80% of breast cancer patients are above 50 years old, which matches with the mean age of menopause[1,2]. However, the behavior and prognosis of this malign neoplasia may be related to the estrogen status[3]. It is a concern for menopausal hormone treatment.

Estrogen hormone therapy is known for its benefits, such as alleviating vasomotor symptoms arising from the state of hypoestrogenism. However, long-term use can provide an increased risk of breast cancer, which brings fear for both physicians and women[4]. This relative risk (RR) of estrogen associated with progestin to develop breast cancer is around 1.25[5], which is a weak factor. The progestin is important to avoid endometrial proliferative lesions that may progress to cancer[6]. However, this unopposed estrogen breast cancer RR is not significant in hysterectomized women[7].

Regarding the RR of cancer, the values over 1:50 are considered relevant for any event. At this point, hormone therapy would have no relevant impact on the onset of breast cancer compared to familial or genetic risk[8]. However, the fear is still very great in the perception of women in relation to breast cancer. Non-hormonal therapy could be an alternative, but side effects and lack of improvement are the main reasons for non-adherence to patients[8]. Therefore, estrogen therapy is still more effective for this treatment.

Some breast cancer survivors experience hot flashes without improvement when treated by the non-hormonal drugs, mainly serotonin reuptake inhibitors, as well as the inhibitors of reuptake of noradrenaline and serotonin and other substances[9]. It is a great concern to alleviate these symptoms, which affect sleep patterns, professional activities, and quality of life[1,2]. The hormone therapy with estrogen is a controversial question: it decreases the symptoms, but may impact the prognosis of the patient[1-3,8]. The HABITS trial showed 2.4 times more risk of new breast cancer events in breast cancer survivors with a cumulative incidence of 22.2% in the group taking hormone replacement versus 8% in the control arm at 5 years[10].

Recently, Mendoza et al.[11] reported a new view in the use of hormone therapy in the climacteric, including classifying it into categories, which is similar to hormonal contraceptive during the reproductive period by the World Health Organization[11]. In addition, the authors suggest that hormone therapy with estrogen could be indicated in women with triple negative breast cancer[11], but the evidence supporting this conduct is few and the prognosis of this type of breast tumor is lower than that with positive receptor[11]. These findings were supported by Poggio et al.'s[12] meta-analysis of four clinical trials with 4050 patients randomized to receive estrogen/progestogen or tibolone against placebo or no hormone therapy. The hormone replacement increased the risk of breast cancer recurrence by 46%, ranging from 12 to 91% according to the confidence interval, but only in the hormone receptor positive subgroup analysis (HR 1.8, 95%CI 1.15–2.82, p=0.010). The triple negative group had no risk (HR 1.19, 95% CI 1.15–1.77, p=0.39). For these reasons, this proposal is still controversial. However, the North American Menopause Society states that if the patient has decreased quality of life and has tried other non-hormonal treatments without adequate results, hormone therapy should be discussed with the patient[13].

In general, estrogen has its proliferative effect on breast tissue due to intracellular signaling after activation of the alpha receptor on the cell membrane, whose pathway involves the

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mitogenic protein[14]. In this process, there is interaction with the activation of cyclic AMP and PKA, which are also the target of melatonin signaling[15], and this could interfere with the estrogenic mitogenic action in the breast tissue[14].

Melatonin has oncostatic actions that are exerted through different mechanisms: indirect effects by reducing ovarian estrogen production; direct anti-estrogenic actions at the level of tumor cells; induction of apoptosis; antioxidant effects; increased anti-neoplastic immunity; reduction of telomerase activity; inhibition of fatty acid uptake and metabolic pathways of fat; and inhibition of angiogenesis[16].

Regarding its anti-angiogenic effects, melatonin reduces the expression of vascular-endothelial growth factor (VEGF) mRNA in MCF-7 cells and inhibits proliferation, invasion, and migration of endothelial cells and formation of tubular networks induced by VEGF[16-18]. Similarly, melatonin indirectly inhibits angiogenesis through the repression of IGF, EGF, and ET-1 (tumor growth factors and tumor angiogenesis enhancers) and decreases the production of ROS, which has an important function in the stabilization of the hypoxia-inducing factor-α during hypoxia[16].

In patients with estrogen receptor (ER) positive breast cancer, melatonin appears to have an inhibitory action on estrogen-mediated cells. It presents an anti-cancer effect because of two membrane protein named MT1 receptor and MT2 receptor. The oncostatic effect in breast cancer is achieved by the suppression and inhibition of ER mRNA. Besides that, melatonin also regulates the metabolism of other steroid hormone and nuclear receptor family members, which interferes with the effect of the estrogen on breast tissue[19].

Melatonin acts on the sleep of postmenopausal women with breast cancer, but without improvement in vasomotor symptoms[20]. Furthermore, it seems to have a synergic effect with other anti-neoplastic treatments, with the reduction of toxicity[19]. Perhaps, a combination of estrogen and melatonin could be beneficial for women with intense vasomotor symptoms. However, there is a need for studies, and perhaps this is the great challenge of the future: optimal hormone replacement in women who have had breast cancer.

AUTHORS' CONTRIBUTIONS

JMSJ: Conceptualization, Writing – original draft, Writing – review & editing. **BSM:** Conceptualization, Writing – original draft, Writing – review & editing. **GBN:** Writing – original draft. **JRF:** Writing – review & editing. **ICES:** Writing – review & editing. **ECB:** Conceptualization, Writing – original draft, Writing – review & editing.

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