A possible protective effect of hormone therapy with estrogen on breast cancer: a commentary.

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The practice of hormone therapy (HT) witnessed a widespread application in the 1980s to control menopausal symptoms. In the 1990s, the speculation about HT's cardiovascular protective effect and bone loss prevention potential in the postmenopausal period increased its use. The lack of evidence about the risks and benefits of HT has led the Women's Health Initiative (WHI) group to conduct a series of randomized clinical trials aiming to answer some of these questions. The WHI Hormone Therapy trials included 27,347 women who were followed during the treatment. The subjects were randomized to take oral estrogen plus progestin or placebo, and women with prior hysterectomy were randomized to receive oral estrogen alone or placebo [1]

The outcomes of this randomized clinical trial published by the WHI abruptly changed the prescription of HT. The study aimed to evaluate the risks and benefits of HT; however, it was interrupted precociously due to the adverse effects. The study showed an increased relative risk of breast cancer (BC) development after an average use of combined HT for five years. The BC risk rate was 1.26 (CI 1.00–1.59) after an average of 5.2 years, and the risk raised to 2.3 (CI 1.12–3.94) when the use was extended to ten years. Thus, the WHI study indicated that the risks exceeded the benefits of combined HT usage after an average time of 5.2 years, despite the all-cause mortality being not affected in the study. One limitation of the study was the evaluation of only one combined hormonal therapy regimen, i.e., the conjugated equine estrogen 0.625 mg/d associated with 2.5 mg/d medroxyprogesterone acetate[1]. Nevertheless, despite this limitation of the study and the lack of specific mortality information, there was an unquestionable change-over after the WIH study. The 13 years of cumulative follow-up just corroborate these findings[1].

Another WHI publication assessed the use of estrogen alone in postmenopausal women who had undergone a hysterectomy. The primary outcome found was also the incidence of invasive BC; however, there was a decrease in the hazard ratio (HR) value to 0.77 (CI 0.59–1.01), suggesting a reduction in the risk of BC. Unfortunately, the study had to be interrupted due to an increased risk of cerebral vascular disease. The reduction in BC risk had no statistical significance according to this data. However, further investigation is warranted.[1]

These publications encouraged discussions regarding the risks and benefits of the use of HT, a topic that has been widely studied since then. It raised new questions, such as which type and duration of therapy and age of onset were related to the increased risk of BC. A recent meta-analysis answered some of these questions. The use of combined HT for five years in postmenopausal women, regardless of the age of onset, showed an increase in the risk of BC. Further, while evaluating the different types of therapies, no statistically significant differences between the estrogen therapies were observed. All HTs, except those given via vaginal route, increased the relative risk of BC.[2]

Remarkable data were presented at the "San Antonio Breast Cancer Symposium 2019" on the WHI Hormone Therapy trials. This 20-year follow-up of combined therapy group(>=5years) in postmenopausal women

confirmed the increased BC incidence and associated mortality (incidence BC HR: 1.29; CI 1.14 - 1.47; p< 0.001 and mortality after BC HR:1.29; CI 1.02-1.63, p 0.03). Mortality related to BC development in HT users was not assessed in previous literature, probably, due to shorter follow-ups. The second group of hysterectomized women using estrogen alone showed new data that resulted in a reduced incidence (HR: 0.77; CI 0.65-0.92; p=0.005) and mortality for BC (HR: 0.56; CI 0.34-0.92; p=0.005). Further studies are still needed to clarify this evidence, although, these impactful data on mortality come from a randomized clinical trial. [3]

The decreased risk of BC using estrogen alone in postmenopausal women might be due to an increase in estrogen-induced apoptosis in the breast cells [4]. The key point for estrogen-induced apoptosis is the selection of cell populations that can survive prolonged estrogen deprivation, comparable to long-standing menopause, and become sensitive to this apoptotic mechanism. These cells survive estrogen deprivation due to the activation of different types of receptors, and estradiol can bind to the receptors and trigger apoptosis [4]. The WHI hormone therapy trial selected women aged 50 – 79 years at baseline, many of whom probably have been in menopause for more than five years[1]. Therefore, we can hypothesize that this trial may have selected patients with long-standing menopause (with cells sensitive to this apoptotic mechanism) who were being benefited from the estrogen-induced apoptotic death of breast cells, thereby reducing the risk of BC.

The complexity of estrogen and BC is not completely understood. Another important randomized placebo-controlled trial, the International Breast Cancer Intervention Study I (IBIS I), showed an extended protection period of tamoxifen for BC risk in women deemed to be at an increased risk of developing BC with a hazard ratio of 0.69 (CI 0.53–0.91). The five-year use of 20 mg tamoxifen, a selective estrogen receptor modulator with antiestrogenic effects in the breast, reduced the incidence of BC in high-risk women[5]. So, there are trials that show that estrogen can protect from BC in some cases; however, medication with antiestrogenic effect has also demonstrated efficacy in BC prevention [3,5].

An interesting fact related to the effect of estrogen on breast cancer is the pathophysiology of HT in transgenders. Studies have demonstrated that testosterone therapy decreases the risk of BC in female to male transgenders, regardless of mastectomy. This probably is due to a decrease in estradiol-induced tissue proliferation resulting from a decrease in the expression of estrogen receptors and increase in the induction of epithelial breast cells apoptosis. All these alterations might prevent the effects of estradiol on inducing BC development[6]. It can be hypothesized that the basis for BC prevention lies on the estrogen receptors. Consequently, the decrease in estrogen receptors in breast induced by testosterone may lead to a reduction in BC cases in transgenders. The role of progesterone in this topic is still unknown. Despite these encouraging findings, further studies are required to assess the real effect of the therapy on this population and to understand the pathophysiology.

The rational use of HT is strongly based on evidence from randomized clinical studies related to the topic. Therefore, the gynecologist should provide information to their patients individually about benefits and adverse events, especially the risk of BC. It is important to note that the well-established time for safely using HT is five years. There is no evidence for the use of estrogen alone just for the prevention of BC in healthy postmenopausal hysterectomy patients. Therefore, the gynecologists must be updated regarding the use of HT unless these topics are fully understood. There is no doubt that the risk of BC should be individually discussed with the patients before initiation of HT, considering other individual risk factors for BC and other pathologies.

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