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Hormone Replacement Therapy and Breast Diseases: A Matter of Concern for the Gynecologist

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ABSTRACT

Background: The carcinogenic effect of exogenous steroid hormones on the breasts is a matter of debate, causing confusion for physicians at the time of making prescriptions. This article, as part of a quadruple series about exogenous sex hormones and breast disorders, reviews the association of breast cancer and hormone replacement therapy (HRT) in the general population, women with benign breast disorders, women with personal or family history of breast cancer, and BRCA carriers.

Methods: We accomplished an extensive search of the literature by using relevant keywords to identify pertinent cohort studies, clinical trials, and reviews. Then, we extracted all points regarding the question.

Results: An extensive literature exists on the risk of breast cancer following HRT in the general population, and HRT has been mentioned as a risk factor for breast cancer, especially in recent, long-term users of combined formulations. However, there is still no consensus about it. Conversely, few studies have considered challenging issues like the use of HRT in breast cancer survivors and high-risk women.

Conclusion: HRT up to 5 years can safely be used for management of menopausal symptoms in healthy women, and those with low-risk benign breast disorders. On the contrary, its use in high-risk women should be limited to refractory menopausal symptoms after describing potential harms to the patient.

Introduction

Breast tissue is under the influence of endogenous sex hormones, and a definite association between breast cancer and these substances has been acknowledged.^{1, 2} Hormone replacement therapy (HRT), consumption of synthetic sex hormones for combating natural or iatrogenic menopause, is used by nearly 30% of women in the USA and the UK.^{3, 4} Although HRT was at first highly praised for its

positive effects on the cardiovascular system, osteoporosis, and other postmenopausal problems, it has subsequently been recognized as a risk factor for breast cancer (BC).^{5, 6}

The first author of this paper has practiced as a surgeon in women's hospitals for more than 18 years and has always been consulted by her colleagues and friends about breast-related issues associated with exogenous hormones. An extensive literature exists on the subject, but results and recommendations are extremely variable, with each work addressing only one of the topics regarding the breast, e.g., high-risk patients only, or BC survivors. A concise review of how various forms of exogenous sex hormones can affect the breasts of women with different conditions would probably help practitioners in this regard.

This perspective led to a series of reviews on the

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concerns of gynecologists about breast diseases while prescribing exogenous hormones. As the second part in a series of four papers on exogenous hormones and breast diseases (the first one considered oral contraceptives⁷), this article addresses concerns about the adverse effects of HRT on the breast in BC survivors, women at high risk for BC, the general female population, and those affected by benign breast disorders (BBDs). Some parts are updates of old studies and reviews, while results of recent works are summated in other parts.

Methods

We conducted a thorough literature search using the following keywords in different combinations: benign breast, *BRCA*, breast cancer, breast neoplasia, breast tumor, family history, fibroadenoma, fibrocystic, high risk, hormone replacement, neoplasia, risk factor, sex hormone, steroid hormone, and screening. We selected all relevant works including cohort studies, clinical trials, and reviews. Thereafter, all points regarding concerns of clinicians in prescribing HRT in abovementioned target groups were extracted and organized consistently.

Types of HRT

Estrogens can be prescribed alone for HRT, commonly referred to as estrogen replacement therapy (ERT), or in combination with synthetic progestins, known as combined HRT (CHRT). ERT was the first and predominating HRT used before 1975, but because of the revealed increased risk of endometrial cancer, CHRT was begun in order to oppose the adverse effects of estrogen.⁸ Both the progestin component and the type of estrogen vary by country. In European countries, estradiol and testosterone-like progestins are more prevalent, while the use of conjugated estrogens and medroxyprogesterone-acetate prevail in the USA.⁹

Results and Discussion

1. HRT in the general population

Epidemiologic studies have been carried out since 1974 to assess the relationship between HRT and BC risk in menopausal women. First works did not show any association, except for one that reported a doubling in BC risk with 15 years or more of HRT. From 1980 onward, more studies pointed to an increase in BC risk with long-term use of HRT, although not very useful in clinical practice because of inconsistency. Thereafter, results of large-scale population-based works were gradually disseminated. Results from extensive studies published between 1985 and 1989 showed a wide range of relative risk (RR), from 0.6 to 5.3, for different lengths of use. Each study had its own limitations and biases, and the only confident inference was an increased risk of BC with long-term HRT.⁸

In 1993, the Women's Health Initiative (WHI) was launched as a national study in the USA, with multiple objectives regarding health issues in postmenopausal women, including BC prevention. The project enrolled more than 160,000 women between the ages of 50 and 79 years in several clinical trials or observational studies and has continued the follow-up of consenting participants through extension studies (<https://www.whi.org>). The announcement of WHI's results showing increased rates of BC secondary to HRT caused a great decline in HRT use among women in the USA and, after some time, other countries. This was generally followed by decreasing rates of BC, endorsing the HRT-BC relationship. Multiple studies have been performed using data from WHI since then, and parallel studies have been carried out in other centers. Also, multiple reviews have gathered and re-analyzed the results of previous works. Nonetheless, the huge bulk of published data is still awaiting reliable conclusive interpretation. While most researchers admit a definite increase in BC risk caused by HRT^{5,6,10-13}, albeit probably small, some question the association¹⁴, linking the decline in BC incidence to less frequent screening or other conditions.^{15, 16} Moreover, some studies have failed to demonstrate a significant difference between ever-users and non-users of HRT¹⁷ or any association between HRT and BC risk.¹⁸⁻²⁰ Still, there are studies that have shown HRT use to be associated with increased BC risk only for women older than 55 years.^{20, 21}

Regarding the type of HRT used, some studies demonstrated that ERT did not increase BC incidence^{15,22,23}, acknowledging an association exclusively for CHRT, or found a higher effect for CHRT compared with ERT.^{6,22,23} In contrast, a study in Mexico City found that only ERT increased BC risk in both Hispanic and non-Hispanic women.²⁴ Similarly, one study reported that formulations containing higher doses of estrogens were associated with higher BC risk¹⁰, and another one concluded that CHRT would reduce BC risk when used for 8 years or more.¹⁸

Higher duration of HRT has been associated with higher risk of BC.^{10,11,17,22,25} Nevertheless, some researchers reported no association between duration of HRT and BC risk.^{19,26}

Recent HRT use has also been suggested to be positively associated with the risk of BC^{13,19,21,27}. It was shown that in women who had stopped HRT for two,⁶ five,^{11,21,22} or ten years,¹⁷ the risk of BC had almost dissipated, although there is also evidence to the contrary.^{19,26}

Regarding the features of breast tumors developed in women undergoing HRT, most studies suggest that the tumors are more likely to have less aggressive biological behavior.^{6,28-31} However, some authors argue against this view.³² Also, breast tumors appearing in women who had undergone HRT have been shown to be associated with better survival^{31,33}, but this outcome has been linked to earlier detection due to stricter screening in women



receiving HRT than taking HRT itself.^{33, 34} On the other hand, some studies demonstrated similar^{34, 35} or worse¹² BC survival in previous HRT-users versus non-HRT-users.

Logically, if hormones are going to activate hormone-dependent cancer, they should generally affect tumors expressing receptors for those hormones. This notion has been validated through numerous studies reporting a higher frequency of hormone receptor-positive (HR+) tumors in HRT users.^{6, 13, 36, 37} A number of studies, however, have found similar tumor HR status in HRT users and nonusers,^{28, 30} or even less HR positivity in the former group.³⁵

Many studies have also attempted to define the pathologic type of tumors that were seen in women who had undergone HRT. They reported higher rates of invasive lobular carcinoma in HRT users versus nonusers.^{13, 28-30, 38}

The above review contains contradictory points, but, overall and for practical use, it is most probable and most prudent to consider HRT as a risk factor for BC, while being more cautious about CHRT. Accordingly, the National Institute for Health and Care Excellence (NICE) guidance states that, depending on the length of treatment, CHRT may increase the risk of BC, while ERT does not, or causes a slight increase (<http://pathways.nice.org.uk/pathways/menopause>). It must be emphasized, however, that the risk associated with HRT is not as serious as that associated with inherent or lifestyle elements such as high BMI, late first full-term pregnancy, and high mammographic breast density.³⁹ Then again, although the risk imposed on an individual woman would be low, physicians should be aware that frequent use of HRT would lead to high increments of BC incidence in the population.^{25, 40} Also, decision regarding prescription of HRT must be balanced against the efficacious control of menopausal adverse effects, while prescribing short-term HRT should be preferred.⁴¹ According to the British Menopause Society consensus statement, short-term (5 years or less) use of HRT for management of menopausal symptoms in the general population surpasses its adverse effects regarding BC.⁴²

2. HRT in benign breast disorders

BBDs are heterogeneous lesions with varying levels of risk for BC, including fibrocystic changes (FCC) (no risk), fibroadenomas (FA) (very low risk), and papillomas and precancerous lesions like atypical hyperplasias (AH) (moderate risk to high risk). Overall, the most common benign lump of the breast is FA, while the most frequently seen BBD is FCC. Both of these disorders are hormone dependent and undergo cyclic changes in concord with normal breast tissue.⁴³

AH includes atypical ductal hyperplasia (ADH) and atypical lobular hyperplasia (ALH). These are borderline lesions which are differentiated from in

situ carcinomas by quantitative histologic criteria. Both are infrequent lesions, and their main concern is about a 3- to 5-fold increase in the risk of cancer.⁴⁴⁻⁴⁶

The association of HRT with any of these benign lesions has not been studied extensively. One study mentioned a lower frequency of BBD in women taking HRT.⁴⁷ Among studies investigating benign proliferative epithelial lesions, two detected an increased incidence^{48, 49}, and one found no association.⁵⁰

The effect of HRT on FCC has been assessed slightly more than other BBDs. A positive association has been reported with ERT^{4, 51}, which grows stronger with long-term use — a 5-fold increment was seen for 10 years or more of ERT.⁵¹

Research about the influence of HRT on FAs is rare. Only two studies, published in the 1980s, were found that showed an increased incidence of FA with ERT.^{52, 53}

AH, a high-risk lesion of the breast, has been studied for potential association with HRT. HRT was shown to stimulate epithelial hyperplasia of breasts with atypia⁵⁴, and one study reported a strong association between HRT and AH incidence.⁵⁵ Conversely, another study failed to demonstrate this relationship for any type of HRT and use for any length of time⁵⁰, and a more recent study showed a reverse association between HRT and AH.⁴⁸ Importantly, HRT did not increase the risk of subsequent BC in AH or other BBDs.⁵⁶

In summary, HRT might induce FCC and FA, but benignity of these lesions does not make them an obstacle toward HRT use when necessary. Association of HRT with AH has not been proved, and increases in malignancy rates have not been reported to date. Nevertheless, because these lesions are high-risk, and probably hormone-dependent, it seems wise not to prescribe HRT to patients with AH.

3. HRT in breast cancer survivors

Many women who have undergone treatment for BC suffer from hot flashes and other menopausal symptoms. This can be secondary to natural menopause, which is happening more frequently because of better survival. Also, menopausal symptoms can happen much sooner, and perhaps more severely, because of antiestrogen therapy in hormone-positive tumors, or for the cessation of menstrual cycles subsequent to chemotherapy. Nevertheless, because of hormone-dependency of BC, physicians are concerned that prescribing HRT to BC survivors may activate dormant cancer cells or induce new primary tumors in the ipsilateral or contralateral breast.^{31, 57-59} A survey of BC patients showed that around 70% feared BC recurrence and did not want to undergo HRT despite high frequency of menopausal symptoms.⁶⁰

Researchers have studied the effects of HRT in BC survivors. HABITS was a randomized trial which was ended well in advance of its design because of high frequency of recurrence. The extended follow-up that



took place later confirmed this finding.⁶¹ However, the mortality of BC survivors was not shown to be augmented by HRT in the participants, and data about recurrence were not enough to provide accurate conclusion because of early closure.⁶² In contrast, several other studies demonstrated that HRT did not worsen the prognosis of BC, in terms of recurrence⁶²⁻⁶⁵ or mortality^{63, 64, 66} in BC survivors. Interestingly, a few studies have even mentioned a more favorable outcome in BC survivors who had received HRT.^{67,68}

Two meta-analyses also found conflict between the results of observational studies, which displayed no increased risk, and randomized trials, which revealed increased rates of recurrence with HRT, in BC survivors.^{69,70}

Given the contradictory findings of the studies, it is advisable that caution be exercised in prescribing HRT to BC survivors. Accordingly, the NICE guidance recognizes personal history of BC as a contraindication to HRT.⁷¹ Somewhat less strict, Health Canada's Canadian Breast Cancer Initiative and the British Menopause Society do not recommend routine HRT in BC survivors and encourage the use of alternative nonhormonal treatments in symptomatic women, recommending short-term, low-dose HRT only for retractable symptoms after informing the patient about the potential hazards.^{42,72}

4. HRT in groups at higher risk of breast cancer

4.1. Family History of Breast Cancer

A family history of BC is one of the most important risk factors of the disease. Using HRT in these women is challenging as it may increase the BC risk. While having a first-degree relative with BC has been associated with a higher risk of BC in women

undergoing HRT²⁶, results presented by some researchers are not in favor of any additive effect of HRT on the risk conferred by family history.^{57,73}

The British Menopause Society recommends that menopausal symptoms of women with a family history of BC should be managed with nonhormonal options in the first place and that short-term, low-dose HRT should only be used in intractable cases who have been informed about possible risks.⁴² Also, NICE guidance recommends that women with a family history of BC should become aware of the increased risk of BC with treatment duration before undergoing HRT.⁷⁴

4.2. BRCA mutations

Carrying mutated BRCA1 or BRCA2 genes is a very strong risk factor for BC. Whether HRT can further increase the risk in these women is of utmost importance because many undergo bilateral oophorectomy as a risk reduction measure and suffer from hot flashes or other menopausal symptoms thereafter. The few studies that have evaluated the question have not shown any increment in BC risk due to HRT in BRCA carriers.^{75,76} More recent works have confirmed the safety of short-time ERT but have been more guarded about CHRT.^{75,76}

Although primary results are reassuring, data are insufficient to yield convincing conclusions; and further study is necessary in order to allow safe prescription of HRT in defective gene carriers. For the time being, NICE guidance interdicts HRT in women with mutated BRCA genes.⁷¹

Table 1 summarizes the existing knowledge about the restrictions of HRT use in different breast conditions.

Table 1. Recommendations for hormone replacement therapy in various breast conditions

Breast condition	Action to take about HRT
Normal	Yes
BBD	Yes for low-risk lesions; No for high-risk lesions* except for short-term, low-dose HRT only in intractable cases, and the patient must know about potential risks.
BC survivor	No
FH	Yes, but the patient must know about potential risks.
Mutant BRCA	No, except for short-term, low-dose HRT only in intractable cases, and the patient must know about potential risks.

In all cases, HRT is recommended to be used for management of symptoms and not as a preventive measure.

* Like atypical hyperplasia of the breast. BBD= benign breast disorder, BC= breast cancer, FH= family history, HRT= hormone replacement therapy

In conclusion, despite numerous studies about HRT in general women, no definite conclusion can be reached about the actual effects on BC risk. Short-term (up to 5 years) HRT for managing menopausal symptoms is reasonable in these women, as well as in women with low-risk BBDs. For groups at higher risk, including women with a personal or family history of BC, carriers of BRCA mutations, or lesions with high-risk pathology in the breast, HRT is

not advisable.

Conflict of Interest

None

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