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Menopausal Hormone Therapy and the Breast: A Review of Clinical Studies

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Keywords
Hormone replacement therapy · Breast cancer risk · Recurrence risk · BRCA mutation · Ductal carcinoma in situ

Abstract

Background: Women in the peri- or postmenopause can experience symptoms related to the gradual degradation of ovarian function. Hormone replacement therapy (HRT) is the most effective therapy to treat common menopausal symptoms such as hot flashes and vaginal discomfort. However, safety concerns have been raised revolving, among others also, around the risk of breast cancer. ***Methods:*** This article is based on a selective literature search for relevant studies regarding HRT use and the risk of breast cancer in the general population or BRCA carriers, the risk of breast cancer recurrence, or the risk of breast cancer in situ. ***Summary:*** HRT can lead to little or no increase in breast cancer risk. The risk depends on the duration and composition of the HRT and decreases after stopping the treatment. Data assessing the oncological safety of HRT after breast cancer are inconsistent. According to current knowledge, HRT is fundamentally contraindicated after breast cancer but can be individually considered after a risk-benefit assessment and when non-hormonal therapies have failed. The same applies to HRT after DCIS, which should not be routinely offered but nonetheless can be considered in individual cases. HRT can be offered up to the age of natural menopause for BRCA mutation carriers who are undergoing risk-reducing bilateral salpingo-oophorectomy and do not have a personal history of breast cancer, but is contraindicated in BRCA mutation carriers who have already had breast cancer.

Introduction

The menopausal transition is the period that links a woman's reproductive years with full ovarian function in the premenopausal phase to a lack of estrogen synthesis in the postmenopausal phase. The start and duration of menopausal transition vary from woman to woman [1]. This hormonal change occurs naturally at an average age of 51, and symptoms such as hot flashes, night sweats, dyspareunia, hair loss, forgetfulness, depression, or sleep disorders can occur [2]. This constellation of symptoms is often referred to as the climacteric syndrome. Whether and to what extent women suffer from menopausal symptoms is individual. For some, menopausal transition is associated with a significant impairment of their quality of life [3].

The most effective treatment for menopausal symptoms is hormone replacement therapy (HRT) with estrogens and progestins. Vasomotor symptoms (VMS) such as hot flushes and atrophy of the vaginal mucosa and vulva are indications for HRT [4]. Counseling should include adequate information regarding the potential benefits and risks of HRT.

The misinterpretation of the Women's Health Initiative (WHI) study has led to an irrational fear of HRT among both the public and the medical community. For

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many physicians, the conclusion was that HRT should be avoided on the assumption that prescribing estrogen alone or with progestogens entails oncological and thromboembolic risks.

However, it is known that premature menopause and hypogonadism can reduce women's life expectancy through skeletal and cardiovascular effects, and this negative effect correlates with the length of the hypoestrogenemic period [5]. Therefore, rejection of HRT should also be supported by evidence and weighed against the potential benefits.

Rapid advances in medicine result in a growing population that lives long enough to either reach the natural age of menopause or experience cessation of gonadal function as a side effect of oncological therapy (e.g., ovarian removal, treatment with antiestrogens). More and more patients and physicians are confronted with the question of HRT which should be individually weighed against the risks.

Patients suffering from breast cancer who develop menopausal symptoms pose a major challenge as HRT may increase the risk of recurrence. The data for this are insufficient to derive a standardized procedure [6]. Individual advice is of particular importance in this case. Our aim was to present clinical studies that examine the correlation between HRT use and risk of breast cancer, breast cancer in situ (BCIS), or breast cancer recurrence and provide useful information for counseling patients.

Methods

This article is based on a selective literature search for relevant studies regarding HRT use and the risk of breast cancer in general population or BRCA carriers, risk of breast cancer recurrence or risk for BCIS.

Results

HRT and Breast Cancer Risk

The Million Women Study

The Million Women Study (MWS) was set up to investigate the effects of HRT on the incidence and mortality of breast cancer. It included women in the UK aged 50–64 who were eligible for mammography every 3 years from 1966 to 2001 and who were subsequently followed via questionnaire. Analyses were released in 2003, 2004, 2006, and 2011 and found significantly increased risk of breast cancer and fatal breast cancer; the effect was substantially greater for estrogen-progestogen combination therapy than for other types of HRT [7]. However, the credibility of the study and the ability to establish causality are questioned.

The Collaborative Reanalysis

In 1997, the Collaborative Group on Hormonal Factors in Breast Cancer brought together and reanalyzed about 90% of the worldwide epidemiological evidence on the relation between the risk of breast cancer and the use of HRT. Individual data on 52,705 women with breast cancer and 108,411 women without breast cancer from 51 studies in 21 countries were collected, checked, and analyzed. The risk of having breast cancer diagnosed was increased in women using HRT and was greater the longer the duration of use. This effect reduced after stopping the HRT and had largely, if not wholly, disappeared after about 5 years [8]. The collaborative reanalysis has also been criticized regarding credibility, and the satisfaction of the criteria for establishing causality has been questioned.

WHI Study

First data from the WHI study showed that the risk of breast cancer increased significantly after the use of estrogen-progestogen combination therapy (EPT) for five or more years [9, 10]. After a mean application time of 7.2 years of estrogen monotherapy (ET), the risk was not significantly reduced [11]. Since that time, more studies have looked at the topic with longer follow-up periods. The latest analysis of the WHI study in 2020 with more than 20 years of median cumulative follow-up showed that prior randomized use of ET (conjugated equine estrogens/CEE alone), compared with placebo, among women who had a previous hysterectomy, was significantly associated with lower breast cancer incidence and lower breast cancer mortality. However, prior randomized use of CEE plus medroxyprogesterone acetate (MPA), compared with placebo, among women who had an intact uterus was significantly associated with a higher breast cancer incidence but no significant difference in breast cancer mortality. Although the risk was statistically significantly higher, absolute numbers differed slightly over the course of 20 years. There were 584 cases of breast cancer in CEE+MPA users (annualized rate, 0.45%) versus 447 cases in the placebo group (annualized rate, 0.36%) [12].

The 2019 Collaborative Group on Hormonal Factors in Breast Cancer Meta-Analysis

The 2019 Collaborative Group on Hormonal Factors in Breast Cancer (CGHFBC) meta-analysis used individual

participant data from all eligible prospective studies from January 1, 1992, to January 1, 2018, that had sought information on the type and timing of HRT use. The authors conclude that if the associations in the studies are largely causal, then for women of average weight in developed countries, 5 years of HRT starting at age 50 years would increase breast cancer incidence at ages 50–69 years by about one in every 50 users of estrogen plus daily progestogen preparations; one in every 70 users of estrogen plus intermittent progestogen preparations; and one in every 200 users of ET. The corresponding excesses from 10 years of MHT would be about twice as great [13].

The French E3N Cohort Study

The goal of this cohort study was to assess and compare the association between different HRTs and breast cancer risk [14]. Invasive breast cancer cases were identified through biennial self-administered questionnaires completed from 1990 to 2002 during a mean follow-up time of 8.1 years. The association of estrogen-progestogen combinations with breast cancer risk varied significantly according to the type of progestogen: the relative risk was 1.00 (0.83–1.22) for estrogen-progesterone, 1.16 (0.94–1.43) for estrogen-dydrogesterone, and 1.69 (1.50–1.91) for estrogen combined with other progestogens. This latter category involves progestins with different physiologic activities (androgenic, non-androgenic, antiandrogenic), but their associations with breast cancer risk do not differ significantly from one another. This study found no evidence of an association with risk according to the route of estrogen administration (oral or transdermal/percutaneous). These findings suggest that the choice of the progestogen component in combined HRT is of importance regarding breast cancer risk; it could be preferable to use progesterone or dydrogesterone.

Other Studies

Vinogradova et al. [15] conducted a nested case-control study using the two largest UK primary care databases, QResearch and Clinical Practice Research Datalink (CPRD) GOLD in 2020. The authors came to the conclusion that, compared with never use, in recent users (<5 years) with long-term use (≥5 years), estrogen-only therapy and combined estrogen and progestogen therapy were both associated with statistically significant increased risks of breast cancer. For combined progestogens, the increased risk was highest for norethisteron. In accordance to other studies, the lowest risk was for dydrogesterone. Past long-term use of estrogen-only therapy and past short-term (<5 years) use of estrogen-progestogen were not associated with increased risk. However, contrary to other studies, the risk associated with past long-term estrogen-progestogen use remained increased. In recent estrogen-only users, between three (in younger women) and eight (in older women) extra cases per 10,000 women years would be expected, and in estrogen-progestogen users, between nine and 36 extra cases per 10,000 women years. For past estrogen-progestogen users, the results would suggest between two and eight extra cases per 10,000 women years.

A cohrane meta-analysis in 2017 including 22 studies involving 43,637 women showed that in relatively healthy postmenopausal women, continuous combined HRT increased the risk of breast cancer after 5.6 years of use from 19 per 1,000 to between 20 and 30 per 1,000 [16]. Although the WHI study showed a reduction of breast cancer risk with ET, other randomized controlled trials (RCTs) did not confirm this tendency between placebo and ET users. Nevertheless, these studies had significantly fewer participants and shorter application times [17–19].

Regarding the vaginal ET, there are fewer concerns. The vaginal ET can initially lead to a slight increase in systemically active estrogens, which decrease after multiple dosing [20]. Ultra-low dosages of vaginal estrogens have good therapeutic results, and it is unlikely that they have an impact on breast cancer risk even after chronic application [21, 22].

HRT after Breast Cancer

Hormonal Replacement Therapy after Breast Cancer – Is It Safe? Study

The Hormonal Replacement Therapy after Breast Cancer – Is It Safe? (HABITS) study, an open randomized clinical trial with allocation to either HRT or the best treatment without hormones, started in Scandinavia and addressed whether HRT is safe for women with previous breast cancer. The main endpoint was any new breast cancer event. After 6 years of recruitment until September 2003, 434 women were recruited; 345 had at least one follow-up report. After a median follow-up of 2.1 years, 26 women in the HRT group and 7 in the non-HRT group had a new breast cancer event. These findings indicated an unacceptable risk for women exposed to HRT in the HABITS trial, and the trial was terminated on December 17, 2003 [23].

Stockholm Study

The Stockholm trial was another study in Scandinavia designed to minimize the dose of progestogen in the HRT arm. Disease-free women with a history of breast cancer were randomized to HRT (n = 188) or no HRT (n = 190).

The trial was stopped in 2003 when the HABITS trial reported increased recurrence risk in the HRT group. However, data from the Stockholm trial showed no excess risk after 4 years of follow-up [24]. In the long-term follow-up from Fahlen et al. [25], the number of new events did not differ significantly between groups after 10.8 years.

Other Studies

A qualitative review of 2007 systematically analyzed the safety of HRT in breast cancer patients [26]. Twenty studies were included. Most of them were uncontrolled retrospective, ten were prospective, and two were randomized (HABITS and Stockholm trial). These were characterized by heterogeneity in the study population, tumor characteristics, prognostic factors, and treatments. Some studies reported a reduced relative risk for recurrence, some reported lowered breast cancer mortality rates in HRT users, and one randomized study reported an increased rate of new breast cancer events in HRT users (HABITS). The authors conclude that there are currently no reassuring data indicating the absence of a harmful effect of HRT and that more randomized trials assessing the safety of HRT after breast cancer are needed.

LIBERATE Study

The LIBERATE study assessed the safety of therapy with tibolone for the treatment of menopausal symptoms. The study showed that the use of tibolone led to an increase in the risk of recurrence [27]. A later study reported additionally on the effects of tibolone on climacteric symptoms, vaginal dryness, and health-related quality of life in the study population of the LIBERATE trial with positive results [28].

Vaginal HRT after Breast Cancer

A special case is vaginal ET after breast cancer. A number of studies could confirm both the efficacy in vaginal atrophy and the increase in serum estrogen concentrations after local application [20–22]. Nevertheless, therapy with ultra-low doses of estrogen (e.g., estriol 0.03 mg, 3 applications per week) seems to be justifiable in women with significant suffering after breast cancer [29].

HRT and DCIS

The correlation of HRT to BCIS has not been so extensively investigated as the correlation of HRT to invasive breast cancer. However, there are some cohort studies and some case-control studies reporting on HRT use and BCIS risk. A prospective cohort study with a follow-up of 11 years revealed no association between the use of HRT and the incidence of DCIS [30]. The latest relevant published study from 2012 also showed no association between DCIS and previous or ongoing use of HRT (ET or EPT) [31]. However, a meta-analysis of 2012 concerning the risk of BCIS after HRT reported a statistically significant higher risk of BCIS after ET or a non-significant relative risk/odds ratio of <1 after EPT [32]. Luo et al. [33] in 2013 used the WHI study's data to assess the effects of HRT on DCIS risk in two groups (CEE+MPA users or CEE-only users vs. non-users). CEE+MPA users had a higher risk of developing DCIS over a mean period of 11 years compared to non-users, which was not statistically significant. Corresponding observational studies supported an increased risk for DCIS in CEE + MPA users compared to women who were non-users (HR = 1.65; 95% CI: 1.25–2.19). CEE-alone data of the WHI population showed that the risk of DCIS was non-significantly lower in the treatment than in the placebo group, while analysis of the corresponding observational studies showed a non-significantly higher risk of DCIS in the CEE-alone users than in non-users. All in all, this analysis suggests that combined estrogen plus progestin use in postmenopausal women may increase the risk of DCIS [33]. Whether estrogen use alone is associated with DCIS requires further investigation. Data on the use of HRT after DCIS are lacking, so no evidence-based recommendation can be derived.

HRT after Risk-Reducing Bilateral Salpingo-Oophorectomy

A special group are women who have an increased risk of breast and ovarian cancer due to a BRCA1 or BRCA2 mutation. A risk-reducing bilateral salpingo-oophorectomy (RRSO) is recommended for premenopausal healthy women. In the general population, premature menopause is associated with poorer quality of life and cognitive function as well as an increased risk of bone and cardiovascular disease, so HRT is recommended until the average age of menopause. However, for BRCA mutation carriers, potential augmentation of already elevated breast cancer risk is of great concern. Though evidence is limited, HRT after RRSO has a number of reported benefits and does not appear to impact breast cancer risk reduction in BRCA mutation carriers [34].

The non-increased breast cancer due to HRT use after PBSO in BRCA mutation carriers is also confirmed in the meta-analysis by Marchetti et al. [34]. Comparing the different HRT regimens, it is suggested that estrogen alone is associated with the lowest risk of breast cancer [34, 35].

Discussion

This article is based on a selective literature search for relevant studies and guidelines regarding HRT use and breast cancer risk or recurrence risk and provides a broad overview of current research. Several studies have assessed the safety of HRT regarding breast cancer risk, risk of recurrence, or risk of BCIS. As part of the consultation, patients should be adequately informed about the various benefits and risks of the HRT.

HRT and Breast Cancer Risk

In the 1990s, two of the largest studies regarding HRT users were undertaken: the WHI study and the MWS. The published results of these two studies raised concerns regarding the safety of HRT and so did the results of the collaborative reanalysis [7–10]. However, these studies have been criticized, and their ability to causally link HRT with breast cancer has been questioned over the course of time.

The Shapiro group explored the credibility of the three studies – the MWS, the WHI study, and the collaborative reanalysis (CR). It was evaluated whether the evidence in the studies was consistent with generally accepted principles of causality: time order, information bias, detection bias, confounding, statistical stability, duration-response, internal consistency, external consistency, and biological plausibility. Shapiro and colleagues found the studies did not adequately satisfy the above criteria to establish causality [36–38].

For instance, the MWS study did not exclude breast cancers that were already present when the women were recruited. Also, HRT users who were already aware of breast lumps or suspected that they had cancer were likely to selectively choose to participate, thus increasing the number of cancers in this group. Such detection bias could also have been present during follow-up, since those on HRT were advised to have mammography more frequently than those not on HRT. Nor did the MWS researchers adequately control for confounding, since factors such as menopausal status, time since menopause, age at menopause, and BMI changed during follow-up, but such data were missing for 57–62% of women by the third report [36].

The data from the WHI and CA were similarly processed and have been proven inadequate [37, 38]. All in all, HRT may or may not increase the risk of breast cancer, but neither of the studies can establish that it does.

The 2019 CGHFBC meta-analysis noted a duration-dependent increase in the risk of breast cancer diagnosis with both unopposed estrogen and combined HRT, the risk with the latter being greater. This differs from the randomized WHI study's result, where a decreased risk of diagnosis was reported with unopposed CEE [12]. These apparent opposing effects of unopposed estrogen on the risk of diagnosis can be explained by the estrogen deprivation hypothesis, in which the duration of a woman's endogenous estrogen depletion determines whether apoptosis of pre-existing, occult breast cancers occurs upon estrogen re-exposure with unopposed HRT. Short-term estradiol depletion is not associated with apoptosis upon reexposure, whereas long-term estradiol deprivation is [39]. Moreover, the review concluded that the risk is higher with continuous combined MHT regimens compared with cyclical, and the risk of breast cancer remains elevated more than 10 years after discontinuing HRT. The meta-analysis showed no estrogen dosage effect on the risk of breast cancer diagnosis with HRT and that vaginal estrogen exposure did not increase the risk of breast cancer diagnosis. However, there are a number of limitations in the methodology of the CGHFBC meta-analysis that need to be considered when interpreting the data according to the BMS, IMS, EMAS, RCOG, and AMS Joint Statement on menopausal hormone therapy (MHT) and breast cancer risk in response to EMA Pharmacovigilance Risk Assessment Committee recommendations in May 2020 [40]. Some of the studies included in the CGHFBC meta-analysis had methodological limitations. The meta-analysis only included a very small number of women on micronized progesterone, and it did not include data from the French E3N study. In addition, the CGHFBC meta-analysis did not report on breast cancer mortality.

The findings from the CGHFBC meta-analysis should be explained to women when discussing the benefits and risks of HRT. However, discussions on the risk of breast cancer with MHT should also include the findings from the WHI placebo-controlled randomized trials and the large E3N observational studies, which reported on the risk of breast cancer in users of micronized progesterone compared with other progestogens. Neither of the last two studies was included in the CGHFBC meta-analysis. Women who took combined estrogen and progestogen HRT had an increased risk of breast cancer compared to placebo but showed no significant difference in breast cancer mortality compared with placebo. The E3N observational studies suggested a lower breast cancer risk in users of micronized progesterone compared to users of more androgenic progestogens.

The meta-analysis noted a duration-dependent increase in the risk of breast cancer diagnosis with both unopposed estrogen and combined HRT, the risk with

the latter being greater. The review concluded that the risk is higher with continuous combined MHT regimens compared with cyclical, and the risk of breast cancer remains elevated more than 10 years after discontinuing HRT. The meta-analysis showed no estrogen dosage effect on the risk of breast cancer diagnosis with HRT and that vaginal estrogen exposure did not increase the risk of breast cancer diagnosis.

Guidelines regarding the use of HRT and breast cancer risk do not differ around the world. In June 2017, the North American Menopause Society updated its guidelines on using HRT. For women aged younger than 60 years or who are within 10 years of menopause onset and have no contraindications, the benefits of HRT outweigh the risks when treating bothersome VMS [41]. In the guideline program of the DGGG (German Society of Gynecology and Obstetrics), OEGGG (Austrian Society for Gynecology and Obstetrics), and SGGG (Swiss Society for Gynecology and Obstetrics), it is recommended that women considering HRT be informed that a combined HRT (EPT/ET) can lead to low or no increase of breast cancer risk. The possible increase depends on the composition of the HRT and the duration of treatment and reduces after stopping the HRT [29]. Regarding the vaginal ET, there are fewer concerns. The vaginal ET can initially lead to a slight increase in systemically active estrogens. However, ultra-low dosages of vaginal estrogens have good therapeutic results, and it is unlikely that they have an impact on breast cancer risk even after chronic application [21, 22].

In summary, HRT (ET, EPT) can lead to little or no increase in breast cancer risk. This fact must be taken into account in the benefit-risk assessment when concerning a HRT for climacteric symptoms. The risk depends on duration and composition of the HRT and decreases after stopping treatment. A vaginal ET can be administered with less concern.

HRT after Breast Cancer

Results from studies regarding the use of HRT by women who already have breast cancer are conflicting, and there are currently no reassuring data indicating the absence of a harmful effect of HRT. On the one hand, the HABITS Trial (RCT) has shown a significant increase in the risk of recurrence through HRT. On the other hand, other studies, including the Stockholm study, have not shown an increased risk of recurrence after treated breast cancer in HRT users. Statistically significant difference in the rate of recurrence was observed between the two studies (HABITS and Stockholm), indicating that chance may not be the only explanation. The increased recurrence in HABITS has been attributed to higher progestogen exposure. Moreover, the heterogeneity in the assessed patients (for instance, a higher number of patients in an advanced tumor stadium) could explain the different results. As both trials were prematurely closed, data do not allow firm conclusions. Both studies found no increased mortality from breast cancer or other causes from HRT. Current guidelines typically consider HRT contraindicated in breast cancer survivors. Findings suggest that in some women, symptom relief may outweigh the potential risks of HRT [25]. There is a need for randomized trials assessing the safety of HRT after breast cancer. In the meantime, patients should be informed about the absence of safety data.

In this context, according to the guideline program of the DGGG, OEGGG, and SGGG, HRT can increase the risk of recurrence after treated breast cancer and should generally not be carried out in women after breast cancer. However, it can be considered individually when non-hormonal therapies have failed and the quality of life is significantly impaired due to climacteric symptoms [29].

HRT and BCIS

The correlation of HRT to BCIS has not been so extensively investigated as the correlation of HRT to invasive breast cancer. The above recommendations relate to invasive breast cancer and not to the preliminary stages such as DCIS.

The presented studies contribute to a small literature regarding HRT use and the risk of BCIS that remains inconclusive. As long as it is not clear how HRT correlates with the risk of DCIS, it should not be routinely suggested to women after DCIS. Nonetheless, the benefits of HRT may outweigh the risks after benefit-risk assessment in individual women [42]. Data on the use of HRT after DCIS are lacking, so no evidence-based recommendation can be derived [43].

Women who have an increased risk of breast and ovarian cancer due to a BRCA1 or BRCA2 mutation are a special group when it comes to HRT counseling. Potential augmentation of already elevated breast cancer risk is of great concern in this group. Though evidence is limited, HRT can be offered up to the age of natural menopause for BRCA mutation carriers who are undergoing RRSO and do not have a personal history of breast cancer, but it is contraindicated in BRCA mutation carriers who already have breast cancer [33].

Conclusion

In summary, the risk of breast cancer or breast cancer recurrence depends on the type of HRT, the dose, the

duration, and the individual health history of the patient. The decision should be made after consultation with the informed consent of the patient. Counseling should include adequate information regarding potential benefits and risks of HRT, which should be individually weighed against each other.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

The authors confirm contribution to the paper as follows: study conception and design and analysis and interpretation of results: M. Sourouni and L. Kiesel; data collection and draft manuscript preparation: M. Sourouni. All authors reviewed the results and approved the final version of the manuscript.

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