Menopausal hormone therapy and breast cancer risk: 21 years from the WHI clinical studies

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ABSTRACT

This article analyzes relevant studies that associate the relative risk of suffering from breast cancer with the use of menopausal hormone therapy, which have appeared since the publication of the Women's Health Initiative (WHI) study in 2002 and have been in permanent discussion. Based on both the WHI study updated 20 years after its first publication, and the 2019 meta-analysis published by the Collaborative Group on Hormonal Factors in Breast Cancer in The Lancet, the authors conclude that up-to-date information shows that exogenous estrogens reduce the risk of breast cancer and that today's combined menopausal hormone therapy (which excludes medroxyprogesterone acetate) does not increase the relative risk of breast cancer. Contemporary knowledge has revealed that not all progestins are the same, and that natural progesterone and tibolone do not report a significant increase in the relative risk of breast cancer. The relative risk of breast cancer is a partial aspect of the problem, with no real impact (absolute risk), and it is clinically not the most important issue for climacteric women who are on menopausal hormone therapy. Cardiovascular disease is the real cause of death among climacteric women, and the protection against it (excluding strokes) provided by menopausal hormone therapy when used during the window of opportunity is unquestionable. This therapy has proven to maintain and improve the quality of life of the symptomatic women.

KEYWORDS

Breast cancer, menopausal hormone therapy, estrogens, progestins, Women's Health Initiative.

Introduction

Every now and then, the controversy rises again, inexhaustible, on whether menopausal hormone therapy (MHT) increases the relative risk (RR) of suffering from breast cancer (BC). It is an old idea that has often been disproved, and it is still brought up in scientific journals with the consequent social alarm and the consecutive maladjustment in the treatment plans of hundreds of thousands of women during their menopausal transition.

The objective of this document is to review and analyze the relevant studies that relate MHT use with the RR of suffering from BC, that have emerged to date since the first publication of the Women's Health Initiative study in 2002 [1]. This is because since the first WHI publication, the use of MHT among women has significantly decreased, as evidenced up to date by the decline in prescriptions.

Analysis of risk factors for breast cancer

An article published in 2019 by the Collaborative Group on Hormonal Factors in Breast Cancer (CGHFBC) [2], that has revived the previously mentioned controversy, deserves attention mainly because the comments of the writing group are based on a meta-analysis. At the beginning of the article, it is recognized that MHT is currently used in much less than a third of women that received it in the year 2000, going from 38 million women to less than 12 million currently [3]. The study would have real relevance if the data was new or derived from unpublished updated studies, but the majority comes from research that has been previously assessed, and that has reported equally confusing and contradicting findings for historical series like the ones analyzed in 1997 [4].

While classifying the types of MHT, dosages and therapeutic sequences, the same article by the CGHBFC presents several contradictions. The first issue that draws attention is that its appendix 4 [2] shows that the study that provides more data to be analyzed is the Million Women Study with 43,022 subjects, over an included total of 82,734 in the prospective studies [5]. Therefore, it is inevitable that both studies report several similar findings.

Secondly, of a total of 864 cases of invasive BC presented in table S18 from the supplementary material of the CGHFBC article [2], 757 come from the WHI st udy; this represents an 87.61% of the total number of BC cases. Furthermore, the mean age of the participants exceeds 63.6 years [1,6], a figure that has resemblance to the mean age of women at the initiation of MHT.

As for the highest quality of scientific evidence, it is widely known that it can be obtained from prospective randomized studies. Therefore, in the case of MHT and BC risk, the highest quality

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of scientific evidence would correspond to the WHI study published in 2004 [6], which demonstrates that 7.2 years of estrogen-only MHT reduce the RR of BC by 23% (RR 0.77). The foregoing information is confirmed by the analysis published in 2020 [7] by the same authors, that includes a 20-year follow-up from the first publication and shows a 40% reduction in BC mortality (RR 0.6). All of this is in contradiction with what is observed in the meta-analysis, in particular the authors do not mention this absolute reduction of the RR of BC, not even in the discussion section. Moreover, regarding the 40% increase of RR with the use of combined MHT for a period of 5 years stated by the authors of the meta-analysis [2], when translating the data to absolute risk (AR), the increase is 0.08% per year (0.40% after 5 years), which remains without modifications after a 20-year follow-up from the WHI study [1]. To put this into context, the mentioned figure does not surpass the AR of BC associated to alcohol or tobacco consumption, obesity and even women's height. These are all minor risk factors for BC. Furthermore, combined MHT does not increase BC mortality [7].

Interesting is the fact that the same study suggests that the influence of obesity and the long-term MHT use are similar and comparable risk factors [2]. It suffices to recall the maintenance and improvement of the quality of life among women who use MHT with medical indication, and the impairment of quality of life, and the increase of multiple risks that overweight and obesity confers during the years of the menopausal transition. In the case of overweight, the RR of developing BC for the four age groups (50-54, 55-59, 60-64, 64-69 years) were 1.33, 2.66, 4.29 and 6.29 respectively. For obesity, these rose to 1.52, 3.03, 4.89 and 7.17 [2]. There is no mention regarding the fact that weight has at least as much influence on the increase in RR as MHT used for more than 10 years [8]. Anecdotally, according to what epidemiologists have proven years ago, divorce as a RR generator for BC would present similar risks as the long-term use of MHT [9].

The study at issue presents a shallow analysis that does not pretend to be exhaustive from the statistical point of view. Furthermore, it presents other peculiarities, such as the statement that the RR of BC after using combined MHT (estrogens plus progesterone) increases as the dosage decreases. Well then, whether conjugated equine estrogens (CEE) or estradiol (E2) is implemented, the RR grows progressively as the dosage decreases, as shown on table S9 from the CGHFBC article: 1.94 for a 0.3 mg CEE dosage, 1.34 for 0.625 mg and only 1.32 if the dosage was >0.625 mg [2]. This contradicts the biological plausibility that the higher the dose, the greater the effect and perhaps the more side effects.

Equally, for E2, the presented RR is greater as the dosage decreases (RR 1.34 for 1 mg), when compared to the standard dose (1.29 for 2 mg) [2]. The present article will not comment on the type of therapy employed, since the drafting group recognized the significative heterogeneity (with p= 0.0001) for each type of MHT when comparing the data from prospective and retrospective studies [2]. At least, this allows the affirmation that it is not the same to administer one treatment than another and that grouping them together in the analysis only increases confusion.

The same article also presents a biological incoherence when it approaches the influence of the age factor —the most influential in developing BC in men and women [2]— in the variation of the RR. On table S3 of the appendix included in the CGHFBC article [2], the RR difference between users and nonusers is an increase of 0.07% in the 50-54 age group, it is similar in the 55-59 age group; it increases a meager 0.08% against users between ages 60-64 and up to 0.10% in the 65-69 age group [2]. These differences are barely imperceptible when translated into AR. What is most notable is that the RR remains invariable at 1.40% both in the 50-54 and the 50-59 age groups. Given the facts, an unsolved question remains: does this occur due to the damping of the increase in risk with age, precisely due to the use of MHT?

To delve further into the biological inconsistencies that seem to arise in this study specifically whenever it addresses the age factor, when figures S5 to S9 from the supplementary material of the CGHFBC article [2] are analyzed altogether, it appears as if the estrogen-only treatment (due to the lack of a uterus) as a form of MHT is a progressively protective factor for BC as women age. Nevertheless, this goes manifestly against what is biologically expected, which is that as you age, the risk of developing any type of cancer increases.

Another peculiarity between what is biologically expected and what was statistically obtained in the study results from the analysis of the effect of age and MHT use. Among those who were never users, figure S12 from the supplementary material of the CGHFBC article [2] shows that the RR of BC increases with age (for the age groups 50-54, 55-59, 60-64 and 64-69, a RR of 1.33, 1.33, 1.63 and 1.99 respectively). However, among MHT users, the RR decreases to 1.86 in the 55-59 years interval and remains at 1.36 between 60-64 and 64-69 years [2]. Once again arises the question of it being a consequence of the damping caused by the age factor when using MHT.

The discussion regarding the risk of MHT and BC is clarified with the data of the 20-year follow-up from first publication of the WHI study [7], the only great randomized prospective study, hugely criticized due to superficial analysis and systematic exposure to media that should have never happened with a well-developed scientific article, but with a surely biased analysis. The data is conclusive after 20 years: exogenous estrogens (used for 7.2 years) reduce the risk of developing BC in a 32% (RR 0.68) and reduce BC related mortality in a 40% (RR 0.60). Also, combined MHT (CEE + medroxyprogesterone acetate [MPA]) —the only therapy measured in the WHI study— when used for 5.6 years increased the RR of BC in a 28% (RR 1.28), without increasing mortality caused by BC [7].

Influence of the type of progestin

Regarding the increase of the RR observed with MPA in combined MHT [1], it is currently known that different progestogens act differently on the possibility of apoptosis or, adversely, on the proliferation of BC epithelial cells in the presence of growth factors derived from the stroma as a stimulator. Current data shows that unlike the effects of MPA in the breast, natural micronized progesterone (NMP) does not increase the risk of BC in women that used combined MHT with NMP for five years [10,11]. The absence of BC risk is also noticed during the use of pure progesterone agonists [12]. Finally, when observing another compound used as MHT such as tibolone, similar data is registered. A meta-analysis by Formoso *et al*. [13] found that the use of

tibolone displayed a 48% reduction (*p* non-significant) of developing BC in women that have not been previously diagnosed.

It must be emphasized that endogenous levels of estrogens do intervene in the genesis of BC, which manifests clinically in a higher risk of BC in women with dense breasts. Nevertheless, this is not valid for exogenous estrogens used in MHT that result in a totally inverse effect [14,15].

Aversely, in the genesis of BC, MHT with estrogens and combined MHT CEE+MPA present opposite effects regarding the incidence of BC, without statistically significant interactions by ethnicity or by body mass index (BMI). Therefore, the observational studies must not combine these two different regimens in the analysis that examine the risk of BC [16].

Expert opinion

The present article seeks to emphasize that the findings of the WHI study (2002, 2004 and 2020) —the largest prospective randomized clinical trial of MHT (using CEE and MPA)— regarding the RR of MHT on BC is categoric by noting that estrogens reduce the risk of BC [6,7] and that combination therapy reports a minimal increase in RR [1,7].

Additionally, the RR of BC is a very partial aspect of the issue with an insignificant real impact (that is to say, absolute risk), and it is not the most relevant matter for our climacteric patients using MHT from an epidemiological perspective, nor from a clinical one.

Cardiovascular disease is the real cause of death among climacteric women, and the protection against it (excluding strokes) that MHT provides to women when used during the window of opportunity is unquestionable [17-19].

Moreover, when considering the risk of other pertinent pathologies like deep vein thrombosis, this risk primarily rises within the initial year of MHT use, particularly when administered orally. Nonetheless, such an escalation is not witnessed with its transdermal alternative [20].

There is clear evidence regarding the fact that not all progestins are the same and that natural progesterone shows no increase of the RR of BC [21]. The studies that were referenced in this article have also demonstrated that it is not the same to use any type of MHT when analyzing their relation to developing BC [22].

Finally —and surely the most important conclusion—, MHT has already demonstrated that it is able to maintain and improve the quality of life of symptomatic women [8], who are the true target of such treatment.

To ensure the success of our treatments, we must provide our patients with comprehensive and accurate information, free from statistical bias or incomplete analysis. This approach will guarantee that menopause is no longer seen by women as the onset of an irreversible decline in their quality of life [23]. That is and will continue being the objective of the management of the climacteric.

Reflecting on the above, it is concluded that to decide whether MHT is or is not a risk factor of real importance for BC, twenty years ago the overall scientific community did not consider the hard data of the WHI study; this is summarized in the final phrase of first publication of the results of the 2002 WHI study [1]: *"This trial tested only 1 drug regimen, CEE, 0.625 mg/day, plus MPA, 2.5 mg/day, in postmenopausal women with an intact uterus. The results do not necessarily apply to lower dosages of these drugs, to other formulations of oral estrogens and progestins, or to estrogens and progestins administered through the transdermal route. It remains possible that transdermal estradiol with progesterone, which more closely mimics the normal physiology and metabolism of endogenous sex hormones, may provide a different risk-benefit profile"*.

Unfortunately, 20 years after the publication of the first data from the WHI study, women in the climacteric stage lack the attention and treatments they deserve and need to maintain their quality of life in this period that currently represents a third of their lives.

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