COUNTERPOINTS

Current Controversies in Hematology and Oncology

Does Combination Menopausal Hormone Therapy Increase the Risk of Breast Cancer?

In 2002, researchers from the Women's Health Initiative (WHI) reported that menopausal hormone therapy (MHT) increases the risk of breast cancer. This widely publicized finding led to an immediate decline in the use of MHT for managing the symptoms of menopause. Since then, the study authors and other researchers have continued to monitor and analyze this population. Now, more than 22 years later, what do the data reveal about the relationship between MHT and breast cancer risk?

Yes, Combination MHT Increases the Risk of Breast Cancer

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There is continued interest in the use of MHT for relief of menopausal symptoms such as hot flashes and vaginal dryness. However, concerns remain regarding the effect of systemic hormone therapy on the development of breast cancer. This counterpoint addresses the use of combination therapy with systemic estrogen and a progestogen, which is the formulation that would be recommended for women with an intact uterus and has the strongest association with breast cancer risk. It does not address the effect on breast cancer risk of unopposed estrogen, which can be considered only in women without a uterus.

Breast Cancer Risk With Combination MHT

The WHI group recently reviewed the long-term follow-up data on their series of randomized trials evaluating the effect of a variety of interventions on the development of chronic disease, including MHT, supplementation with calcium plus vitamin D, and a low-fat diet.[1] The use of MHT therapy peaked in 1999 with 35 million annual prescriptions, despite a lack of randomized trial data demonstrating overall health benefits. The first results from the estrogen plus progestin (E+P) arm of the WHI were published in 2002, changing clinical practice. In 2003 through 2004, after 20 years of increasing rates of breast cancer, a large and substantial decline in the incidence of breast cancer occurred that was widely attributed to

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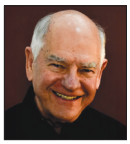
No, Combination MHT Does Not Increase the Risk of Breast Cancer



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The findings from the WHI, which were initially reported in a press conference on July 8, 2002,[1] and released in print on July 17, 2002,[2] have received mounting criticism for more than 22 years. The WHI investigators have walked back almost all of the initial negative claims that generated international alarm,[3] and they now report that CEE alone is associated with a decreased risk of breast cancer, a decreased risk of death from breast cancer, and a decreased risk of death from all causes.[4] Nonetheless, they continue to maintain that CEE plus MPA increases the risk of breast cancer, albeit with no increased risk of death from breast cancer.[5]

What the Evidence Says

In the original 2002 WHI report, the authors stated that the 26% increase in breast cancer in the E+P group "*almost* reached *nominal* statistical significance" [italics mine].[2] This is highly unusual wording that I have not seen in any other peer-reviewed, published medical report.

This misleading conclusion stands in stark contrast to WHI data showing no increase in breast cancer risk among women randomized to E+P who had not taken MHT before entering the study,[6,7] which reflects the majority of women so treated in the general population.[4,8] Furthermore, randomization of WHI participants was based upon the primary outcome of coronary heart disease, which has

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women stopping MHT in response to the WHI results.[2]

The E+P component of the WHI trials enrolled 16,608 postmenopausal women aged 50 to 79 years with an intact uterus and randomized them to either placebo daily (n=8102) or conjugated equine estrogen (CEE) at 0.625 mg daily plus medroxyprogesterone acetate (MPA) at 2.5 mg daily (n=8506).[3] The mean age at screening was 63.3 years (standard deviation [SD], 7.1). Most (74%) had never taken MHT before. Women with a prior history of breast cancer were excluded. Mammography rates were similar across the 2 arms. On May 31, 2002, after a mean follow-up of 5.2 years, the data and safety monitoring board recommended stopping the E+P arm of the trial on the basis of prespecified stopping rules that encompassed a variety of major outcomes, including breast cancer, coronary heart disease (CHD), stroke, hip fracture, pulmonary embolisms (PE), colorectal cancer, endometrial cancer, and death. All these outcomes were also summed together as a global index of potential benefits/risks. At the time the trial was stopped, the log-rank test statistic for breast cancer had crossed the prespecified boundary. Furthermore, the global index supported overall harm, driven mainly by increases in breast cancer, CHD, stroke, and PE. During the treatment phase of the trial, women assigned to E+P had a 24% higher breast cancer risk (95% CI, 1.01-1.53) in comparison with the placebo group. The breast cancer risk gradually increased with duration of use and by time since randomization (P=.005 for time trend).[4] Compared with breast cancers that developed in the placebo arm, breast cancers in the E+P arm were more commonly diagnosed at a later stage (P=.04) and were more likely to be node-positive (P=.02). Breast cancer mortality in the E+P arm was also numerically higher, but the difference was not statistically significant (hazard ratio [HR], 1.35; 95% CI, 0.94-1.95; P=.11).[5] With 20 years of follow-up, the breast cancer incidence in the E+P arm (annualized rate, 0.45%) was still elevated in comparison with placebo (annualized rate, 0.36%; HR, 1.28; 95% CI, 1.13-1.45). In terms of noncancer endpoints, even with longer term follow-up, E+P did not decrease the risk of CHD, stroke, or dementia in the WHI population.[1]

> In addition to the WHI randomized trial data, many epidemiologic studies have evaluated the association between MHT and the incidence of breast cancer, with similar findings.

In addition to the WHI randomized trial data, many epidemiologic studies have evaluated the association between MHT and the incidence of breast cancer, with similar findings. These studies addressed one of the key issues regarding the generalizability of the WHI results because the epidemiologic studies included younger women who initiated hormone therapy close to the age of menopause. The most comprehensive effort was conducted by the Collaborative Group on Hormonal Factors in Breast Cancer, which published an individual participants' meta-analysis that encompassed 108,647 postmenopausal women worldwide from 24 prospective studies.[6] Unlike in the WHI, the mean age for starting hormone therapy was 50 years (SD, 6), better reflecting the real-world use of MHT for symptom relief at the time of menopause transition. The results of this meta-analysis were similar to those of the WHI, with E+P use associated with an increased breast cancer risk that increased with duration of use. The relative risk (RR) of breast cancer was 1.60 (95% CI, 1.52-1.69) for years 1 to 4 and 2.08 (95% CI, 2.02-2.15) for years 5 to 14. Regardless of the age at the initiation of hormone therapy, the RRs were similar across age groups, at 2.22 (95% CI, 1.96-2.52) for those aged 40 to 44, 2.14 (95% CI, 2.03-2.24) for those aged 45 to 49, 2.10 (95% CI, 2.01-2.21) for those aged 50 to 54, and 1.97 (95% CI, 1.81-2.15) for those aged 55 to 59 years.

In sum, multiple epidemiologic studies and large-scale randomized trial data provide level 1 evidence that E+P is associated with an increase in breast cancer incidence among women 50 years of age or older. However, several criticisms have been raised regarding the generalizability of the WHI findings. The mean age at screening of 63.3 years[3] is an older age than is typical at the initiation of MHT, and breast cancer incidence is well known to increase with age.[7] However, the increase in breast cancer incidence with age would change the absolute difference in the number of cases, but the relative effect/HR should be the same regardless of age. For example,

screening mammography has larger absolute benefits as women age because of the larger number of cases, but the RRs of benefits are relatively similar across decades of age.[8] Furthermore, the Oxford meta-analysis, which encompassed women with a mean age of 50 years, showed results similar to those of the WHI.[6] Another issue that has been raised to support the use of E+P is that although the incidence of breast cancer in the WHI was higher with E+P than with placebo, the mortality difference was not statistically significant. However, the HR was numerically higher, and the WHI trial was underpowered to detect a difference in breast cancer mortality, with only 71 deaths in the E+P group and 53 deaths in the placebo group.[5] Finally, it should be noted that the WHI evaluated only a single formulation of CEE and MPA. However, the Oxford meta-analysis encompassed a large variety of formulations and demonstrated increases in risk similar to those in the WHI. For example, among users of combination E+P with varying progestin components, the RRs were similar regardless of formulation, at 2.12 (95% CI, 1.99-2.25) for levonorgestrel, 2.20 (2.09-2.32) for norethindrone acetate, and 2.07 (1.96-2.19) for MPA.[6]

Conclusions

Combination oral E+P was associated with an increased incidence of breast cancer in a large-scale randomized trial and multiple epidemiologic studies. The magnitude of risk increased with the duration of E+P use, and the absolute risk of breast cancer also increased with age. On the basis of the observed associations with breast cancer, the long-term use of E+P should be discouraged among postmenopausal women because of an increase in breast cancer risk. Only a limited duration of 1 to 2 years of E+P should be considered for symptom relief in perimenopausal women without a history of breast cancer.

Disclosures

Dr Chen has no disclosures.

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No, Combination MHT Does Not Increase the Risk of Breast Cancer *(cont)*

different risk factors than those for breast cancer. According to the WHI investigators, adjustment for breast cancer risk factors—including family history of breast cancer, age, and age at first birth—"did not substantially alter the risk estimate" of E+P. The risk fell from 1.24 (CI, 1.02-1.50)[3] to 1.20 (CI, 0.94-1.53),[6] however, and was no longer statistically significant.[6]

Finally, the increase in the HR for breast cancer for women randomized to CEE+MPA vs the increase in those randomized to placebo is attributable to the unexplained extremely low rate of incident breast cancer in the women who had taken estrogen in the past, before being randomized to the placebo arm, rather than to an increased breast cancer risk among those randomized to CEE+MPA. When these *prior* estrogen users were eliminated from the analyses, mirroring the experience of most women starting MHT during perimenopause or early menopause, the remarkably low incidence of breast cancer observed in the placebo group returned to its expected level, and the increase in the HR disappeared. The key point is that any explanation for the low incidence in the placebo group does not change the fact that this low rate is responsible for the observed elevation in the HR, which the WHI continues to misleadingly interpret as an increase in breast cancer risk.[5]

> In the original 2002 WHI report, the authors stated that the 26% increase in breast cancer in the E+P group "*almost* reached *nominal* statistical significance."

To reinforce this inaccurate conclusion, the WHI investigators often cite the Collaborative Group on Hormonal Factors in Breast Cancer[11] and the Million Women Study (MWS).[12] Unfortunately, they ignore widely published critical comments questioning the validity of these studies and dismiss the glaring, contrasting findings between these studies and those of the WHI.[13]

Consider these issues regarding the re-analysis of the Collaborative Group:

1. No increase in breast cancer was observed among women who had taken MHT in the past, no matter how long they had taken it. In contrast, the WHI has reported a persistently elevated risk of breast cancer among past users,[10] even after 20 years of follow-up.
2. The reported increase in breast cancer was 6 per 10,000 women-years, hardly a strong or compelling finding.
3. More than 80% of the women were on estrogen alone yet were reported to have an increased risk of breast cancer—precisely the opposite of the WHI finding of a decreased risk for women on estrogen alone.[7]

And consider these challenges to the MWS:

1. Although called a study, it consisted of just 2 questionnaires separated by approximately 3 years. The questionnaires were sent to a million women, of whom only 44% responded to both surveys.
2. The total incidence of breast cancer was 1.0% among users of estrogen alone and 1.4% among users of estrogen plus a progestogen.
3. Of that 1.0% to 1.4%, the increased risk was identified only in current—not past—users, even if past use had exceeded 15 years.
4. The authors of the MWS did not discuss the possibility that breast cancer may have been present in a significant number of the study participants before they joined the study. Women were invited to participate on the basis of having received a mammogram, which represents a fundamental selection bias.[14,15] In support of that interpretation, the average time from joining the study to a diagnosis of breast cancer was only 1.2 years, and the median time from diagnosis to death from breast cancer was only 1.7 years. Given that breast cancer requires 9 to 16 years to become clinically identifiable,[16,17] it is more likely that the breast cancers were not directly related to MHT use but were already present at the time the women were enrolled.

Although these 2 profoundly flawed and contradictory studies continue to be cited as if they confirm the WHI position, a thorough review of the evidence shows that they do not.

Additionally, the risk of breast cancer with combination MHT should be most apparent when MHT is administered to patients at the highest risk for breast

cancer. However, a review of published studies reporting the risk of breast cancer recurrence among breast cancer survivors receiving MHT found that only one of 25 studies identified an increased risk. That one discordant study, *which did not mandate baseline breast imaging*, reported that the increase was only for local or contralateral recurrence and was not associated with an increased risk of distant metastases or breast cancer death.[18]

Furthermore, although pregnancy increases the body's levels of estrogen and progesterone, pregnancy after breast cancer has been shown not to increase the risk for breast cancer recurrence. This applies even to estrogen receptor–positive (ER+)[19] and *BRCA*-mutated breast cancer.[20] In 2023, Partridge and colleagues reported an international study of 497 women treated for ER+ breast cancer. The women were, per the usual procedure for treating breast cancer, receiving therapy designed to suppress the effects of estrogen. However, the authors allowed them to suspend that treatment for 2 years if they wished to become pregnant. Nearly half of them also had in vitro fertilization, which of course greatly elevates estrogen and progesterone levels, and 507 pregnancies occurred in the ensuing 3 years. Partridge and colleagues then compared these women with breast cancer patients, matched for stage of the disease, who continued their estrogen-suppressing treatment. After 3 years, no difference was found between the 2 groups of women in risk of breast cancer recurrence.[21]

The assertion that the WHI 2002 report resulted in a precipitous drop in MHT prescriptions accompanied by a decrease in breast cancer incidence contains 3 fundamental flaws. First, according to Centers for Disease Control and Prevention statistics, the decline in breast cancer incidence was evident as early as 1999 in the United States, 3 years *before* the release of the WHI initial results.[22] Second, the incidence of breast cancer in the United States has increased by roughly 0.5% annually since the premature termination of the WHI trial in 2002,[23] even though the rate of hormone use has remained low.[24] And third, as mentioned earlier, breast cancer usually takes from 9 to 16 years to become clinically identifiable.[16,17] How, then, could a drop in the rate of breast cancer be related to stopping HRT 6 months to 1 year prior?

Conclusion

Our opinion will evolve, as it should, with the availability of additional data. Today, however, the fear of increasing the risk of de novo or recurrent breast cancer by administering MHT should not automatically overrule the benefits of this therapy.

Disclosures

Dr Bluming has no disclosures.

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