EDITORIAL

Menopausal Hormone Therapy and Long-term Breast Cancer Risk
Further Data From the Women's Health Initiative Trials

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Reports from the Women's Health Initiative (WHI), first published in 2002,[1] have informed and complicated the narrative of the relative benefits and potential harms of menopausal hormone therapy (HT) over the past 20 years. Prior to the initiation of the WHI trials, hormone therapy had already experienced a tumultuous public stature. Initially heralded as the cure for menopause in the 1960s, unopposed estrogen therapy was vilified when its association with increased risk of endometrial hyperplasia and cancer emerged.[2] The discovery that the addition of progesterone to estrogen therapy mitigated this risk propelled hormone therapy back to mainstream use by the 1990s as the primary treatment of menopausal symptoms, with the prevention and treatment of osteoporosis and improved cardiovascular health as added purported benefits.[3]

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The initial results from the 2 WHI hormone therapy trials upended some of these assumptions. These 2 randomized placebo-controlled trials enrolled study participants from 1993 to 1998 and accrued a total of 27 347 postmenopausal women. One trial evaluated the efficacy of conjugated equine estrogen (CEE), 0.625 mg/d vs placebo, and included only women without an intact uterus, while the other trial randomized women with an intact uterus to CEE 0.625 mg/d plus medroxyprogesterone acetate (MPA) 2.5 mg/d vs placebo. The initial analyses of the intervention phase showed that combination hormone therapy increased cardiovascular disease risk, thromboembolic disease, and breast cancer but decreased colorectal cancer risk and hip fractures.[1] Given that the risks of combination therapy outweighed the benefits, the CEE-plus-MPA trial was stopped in 2002 after an intervention phase with a median of 5.6 years.[1] The CEE-alone trial was also stopped for safety concerns in 2004, after an intervention phase of 7.2 years.[4]

Since the termination of the randomized treatment phase of these trials, many of the women in these 2 studies have been followed up through an early postintervention phase and a late postintervention phase, generating data for multiple follow-up studies. In 2015, an analysis by Chlebowski et al[5] found that CEE-alone was associated with a lower breast cancer risk through the intervention and early postintervention phase, although the risk reduction was not observed in the late postintervention phase (hazard ratio [HR], 1.17; 95% CI, 0.73-1.87). The analysis also showed that CEE plus MPA, on the other hand, was associated with an increased breast cancer risk in the early postintervention phase and late postintervention phase (HR, 1.37; 95% CI, 1.06-1.77).[5] Previous survival analyses of these trials demonstrated that women in the CEE-group who developed breast cancer after the receipt of estrogen had significantly reduced breast cancer-specific mortality and all-cause mortality.[6] These findings contrasted with large observational studies that had demonstrated both combination hormone therapy and unopposed estrogen therapy were associated with a significantly higher risk of breast cancer mortality.[7]

In this issue of *JAMA*, Chlebowski et al[8] report the longer-term follow-up results of the WHI trials, focusing on the association of hormone therapy with breast cancer incidence and mortality. Among the 10 739 women in the CEE-alone trial, use of CEE, compared with use of placebo, was associated with a statistically significantly lower breast cancer incidence (238 cases [annualized rate, 0.30%] vs 296 cases [0.37%]; HR, 0.78; 95% CI, 0.65-0.93), and a significantly lower breast cancer-specific mortality (30 deaths [annualized mortality rate, 0.031%] vs 46 deaths [0.046%]; HR, 0.60; 95% CI, 0.37-0.97). This contrasted with the significantly increased breast cancer incidence among the 16 608 women who were randomized to receive CEE plus MPA compared with those randomized to receive placebo (584 cases [annualized rate, 0.45%] vs 447 cases [annualized rate, 0.36%]; HR, 1.28; 95% CI, 1.13-1.45), with no statistically significant difference in breast cancer mortality (71 deaths [annualized mortality rate, 0.045%] vs 53 [annualized mortality rate, 0.035%]; HR, 1.35; 95% CI, 0.94 to 1.95).

With regard to tumor subtype, the results suggest that use of CEE alone vs placebo was associated with a significantly lower risk of estrogen receptor (ER)-positive, progesterone receptor (PR)-negative breast cancer (HR, 0.44; 95% CI, 0.27-0.74) and erythroblastic oncogene B (*ERBB2*; formally *HER2*-negative breast cancer; HR, 0.74; 95% CI, 0.60-0.92), with no significant associations found between use of CEE plus MPA and tumor subtype. Despite the finding in earlier WHI analyses that a gap time (ie, the time between onset of menopause and the initiation of hormone therapy) of 5 years or more was associated with greater breast cancer risk reductions, with longer follow-up, gap time was not statistically significantly associated with breast cancer incidence.

The report by Chlebowski and colleagues[8] reflects the commitment of the investigators to continue collecting long-term data on more than 10 000 participants from the WHI trials, with a median of 20.3 years of follow-up and mortality data available for more than 98% of study participants. However, many questions still remain on whether (and how) a hormone therapy intervention that occurred many years earlier may continue to affect breast cancer risk and mortality at

20 years. Even though the assumption is that the innumerable biological, genetic, environmental, clinical, and behavioral confounders that affect risk over time are balanced between treatment groups in a large, randomized clinical trial, it is impossible to isolate the degree of influence of exposure to hormone therapy and subsequent, late outcomes. Furthermore, the authors acknowledge the suboptimal adherence to treatment—with 54% discontinuing CEE alone and 42% discontinuing CEE plus MPA during the course of the trial—questioning the true treatment exposure of women during the randomized treatment phase of the study. Nevertheless, the enduring data on the health outcomes associated with unopposed estrogen therapy among women without a uterus remains compelling.

Although the decrease in breast cancer–specific mortality among patients who received CEE alone is modest, with 4 breast cancer–related deaths prevented per 10 000 person-years, on a population level, the number of breast cancer deaths avoided could be substantial. With these findings, it is tempting to suggest that CEE may be another possible chemoprevention strategy, especially because despite significant decreases in breast cancer incidence among women in tamoxifen groups of the large randomized chemoprevention trials, no corresponding decreases in mortality have been reported. However, the relative populations in question are different from the high-risk participants in the International Breast Cancer Intervention Study (IBIS)[9] and the National Surgical Adjuvant Breast and Bowel Project P-1 study[10] (defined in IBIS as meeting specific family history criteria, having lobular carcinoma in situ, or atypical hyperplasia, and defined in P-1 as having at least a 1.66% predicted 5-year risk of breast cancer, a history of lobular carcinoma in situ, or atypical hyperplasia).

In the current WHI analysis,[8] the greatest risk reduction was seen among women without a history of benign breast biopsy and those without a family history of breast cancer—2 important factors in widely used risk scoring systems such as the Gail risk score[11] and Tyrer-Cuzick model.[12] The fact that CEE-alone has been shown to decrease breast cancer incidence despite its association with increased mammographic breast density,[13] a breast cancer risk factor in both normal-risk and high-risk populations,[14,15] is a noteworthy observation and highlights the limitations of current understanding of the factors and mechanisms that predispose women to breast cancer. The interplay of risk factors and interventions in high-risk populations is complex, and teasing protective factors from hazardous ones will require large-scale evaluation. While the WHI data may not directly inform the effect of CEE among high-risk women, it can be indicative of protection among normal-risk women and could, when counseling selected women with a history of a hysterectomy regarding hormone therapy, tip the scales for estrogen therapy.

In reality, despite the reassuring data from Chlebowski and colleagues[8] and the availability of multiple agents to lower breast cancer risk in the average- or high-risk setting, decisions to initiate these medications remain complex. Clinicians will likely remain hesitant to prescribe unopposed estrogen for most women, with low utilization of hormone therapy for years to come.[16] Factoring in these most recent data into clinical decisions will require clinician time and expertise in understanding the evidence base; after all, breast cancer risk is only one of myriad factors that women and their clinicians must weigh when deciding to initiate hormone therapy.

For postmenopausal women with a history of hysterectomy, estrogen alone may confer a lower risk of the development of breast cancer and improved breast cancer–specific survival, but age, severity of menopausal symptoms, and the woman's individual risk of developing other conditions, such as cardiovascular disease, thromboembolic disease, osteoporosis leading to hip fracture, and colorectal cancer, may also be considered in the decision. Given this multifactorial decision, these latest WHI data are unlikely to lead to use of hormone therapy for the sole purpose of breast cancer risk reduction but can provide some reassurance to women taking estrogen-alone that they are not elevating their breast cancer risk over time. Facilitating a high-quality decision is never a short conversation and for a choice such as this one, which involves consideration of conflicting evidence and multiple relevant factors, decision aids could be extremely helpful. As nuanced as this conversation may be, one point is clear: more than 20 years after the start of accrual, the WHI trials have not ceased to be an integral part of women's health and will continue to generate research and clinical conversations for years to come.

ARTICLE INFORMATION

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