Short-term Use of Unopposed Estrogen
A Balance of Inferred Risks and Benefits

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When recruitment for the Women's Health Initiative (WHI) began in 1993, hormone therapy (HT) was prescribed for a variety of reasons that ranged from the management of menopausal symptoms to the prevention of chronic disease, and the WHI focused on documenting the risks and benefits of HT use for chronic disease prevention. In 2004, one of the first publications from the WHI reported the balance of risks and benefits during active intervention with unopposed estrogen among women with previous hysterectomy.[1] Based on data collected through the end of the trial's intervention phase, women randomly assigned to estrogen had a significantly increased risk of stroke and reduced risk of hip fracture and possibly breast cancer compared with women receiving placebo. There was no overall effect of estrogen on a global index of risks and benefits[1] including coronary heart disease. These findings were revolutionary and changed practice.[2,3]

Today, indications for HT are narrow, and many physicians take pause before performing elective bilateral salpingo-oophorectomy during hysterectomy.[4,5] Short-term unopposed estrogen therapy is still a mainstay in managing menopausal symptoms among women with previous hysterectomy, although questions remain regarding the safety of this treatment,[3] including whether there is a safe duration of estrogen use and whether there are long-term risks and benefits of estrogen therapy that persist after cessation. Once again, data from the WHI study[6] in this issue of *JAMA* help to provide guidance.

To assess the long-term effects of unopposed estrogen therapy and the balance of risks and benefits over time, LaCroix and colleagues[6] report follow-up of women who completed the intervention phase of the WHI estrogen-alone study. Seventy-eight percent of eligible women gave consent for continued observational follow-up through a mean of 10.7 years from baseline. During follow-up, the increased risk of stroke observed previously did not persist after cessation of estrogen therapy, whereas the previously observed significant reduction in hip fractures was eliminated. Other risks and benefits associated with estrogen therapy during the intervention phase were not maintained; however, the reduced incidence of breast cancer persisted. This finding is inconsistent with a longstanding, corroborated body of evidence[7,8] and raises the possibility that other important factors modify documented risks and benefits of estrogen therapy among these long-term WHI participants.

Building on previous evidence[9,10] that highlights the importance of age at HT initiation, LaCroix and colleagues[6] postulate that an age effect may also underlie some of their findings. For example, the authors expected fewer adverse effects among women who initiated estrogen at the time of menopause, and they found that for every 10 000 women aged 50 to 59 years taking estrogen, there were 12 fewer myocardial infarctions, 13 fewer deaths, and 18 fewer adverse events compared with those taking placebo, and they conclude the overall benefits of estrogen therapy may be greater among younger women. In contrast, a recent report by Beral et al[10] from the Million Women Study demonstrates an adverse effect of postmenopausal estrogen use on breast cancer risk, with a significantly increased risk among women beginning therapy within 5 years of menopause and little or no increased risk among those beginning therapy 5 or more years after menopause. These findings derive from an analysis of 15 759 incident breast cancer cases diagnosed during 4 million patient-years of follow-up.[10] Sixty-eight percent of women enrolled in the WHI were older than age 60 years at randomization. Given this fact and the findings from the Million Women Study, an important question that emerges is whether the WHI population is appropriate for reaching definitive conclusions regarding younger women and the risk of breast cancer associated with HT.

In addition to a potential age effect on the risk-to-benefit profile of HT, overall duration of HT use remains a major concern. The median adherent time (defined as women taking ≥80% of study pills) among women in the WHI estrogen-alone group was 3.5 years. Thus, the WHI results do not address the balance of risks and benefits associated with longer-term estrogen use. Longer unopposed estrogen use may

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increase the risk of breast cancer as was demonstrated in a meta-analysis that combined data from 16 studies,[8] and in an analysis of combined data from 52 705 women with breast cancer.[7] In these studies, leaner women had an even higher risk of breast cancer with long-term estrogen use. Data from the WHI estrogen-alone group do not demonstrate a significant interaction with body mass index despite consistent evidence from other studies demonstrating this effect.[8,10,11]

Overall, results from the WHI suggest that adverse event rates are low and largely limited to current use of unopposed estrogen. The results show no substantial benefit when comparing women who use HT with those who do not. Risks may be lower among women aged 50 to 59 years than among older women. Short-term use appears safe with rapid decline of risks and benefits after cessation of use. Balancing these risks and benefits at the population level suggests no overall harm or benefit; however, for individual patients this balance will vary. Continued surveillance of long-term HT users is necessary to refine the assessment of risks and benefits among women who choose to continue therapy beyond 5 years. The lack of an adverse effect of unopposed estrogen when used for a short period in the WHI does not counter the larger body of evidence of an elevated risk of breast cancer with increasing duration of use,[8] the greater adverse effect among leaner women,[10] and randomized controlled trial evidence that estrogen agonist/antagonists (eg, tamoxifen) reduce the incidence of estrogen receptor–positive breast cancer by more than 50%.[12,13] This body of evidence has led the International Agency for Research on Cancer to conclude that unopposed estrogen HT[14] and combination HT are carcinogenic.[15]

Despite the evidence linking unopposed estrogen HT use to breast cancer, many clinicians and patients make decisions to use HT. Clinicians must be aware of the implications of these decisions. They must interpret new and existing data, and must understand the value and limitations of the data when making recommendations. Prevention trials are difficult to implement, yet findings from the WHI have been an important guide for clinicians on the overall risks and benefits of HT. However, to optimize safety in routine clinical care settings, physicians must take caution when extrapolating results from the WHI to the risk profile of women in routine care.[16] In general, extrapolating safety data from prevention trials is difficult, due in part to the lack of participant adherence to preventive interventions over time, which may introduce bias. The precision of measures of actual exposure to HT may be greater in observational settings in which participants report their use. When exposures are refined in analysis to measure the same intended dose, timing, and duration, observational studies and trials agree.[17,18]

There may still be a role for short-term use of unopposed estrogen for treating some women with menopausal symptoms, but this role may be vanishing as existing and emerging data continue to be better understood in terms of application to patients. In the meantime, the symptoms of menopause can be significant and require thoughtful management. This would include careful consideration and discussion of the long-term risks and short-term benefits of HT as well as thorough discussion of other treatment strategies and optimization of lifestyle to ensure the best outcomes for women in the many years they should enjoy postmenopause.

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