

Postmenopausal Hormone Therapy and Breast Cancer An Uncertain Trade-off

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IN 2002, THE WOMEN'S HEALTH INITIATIVE (WHI) RANDOMIZED TRIAL OF placebo vs hormone therapy with estrogen and progestin was stopped early because of evidence of harm.¹ Sales of combined estrogen-progestin plummeted 32% between the period immediately before the study's release and the analogous period 1 year later, as the WHI trial had shown that hormone therapy increased a woman's risk of breast cancer and myocardial infarction.² The finding contradicted decades of case-control and observational cohort studies that had suggested that hormone therapy was associated with strong protective effects on the cardiovascular system. The WHI results also undermined a long and successful campaign by hormone replacement advocates to present hormone therapy as a panacea against heart disease, loss of femininity, and other perils of aging. In the scientific community, the WHI results became "exhibit 1" for critics of observational studies, who argued that this latest upheaval of conventional medical knowledge proved (once again) that only randomized studies can yield useful insights into cause and effect.

Eight years hence, and many subgroup analyses later, a more nuanced explanation for the study's findings has emerged. Among the few women in the WHI who enrolled around the time of their menopause, hormone therapy with both estrogen and progestin did not increase the risk of cardiovascular disease and may have reduced it slightly. However, most women in the study were well past menopause at enrollment (the average age was 63 years), and the negative effects of hormone therapy, which increase with more elapsed time after menopause, exceeded any small benefits that might have been experienced by the younger women in the study.³ In addition, the WHI documented numerous other negative effects of hormone therapy, including an increased risk of stroke and pulmonary embolism,¹ which are not strongly associated with the timing of hormone therapy initiation. Ultimately, the only long-term benefit of hormone therapy that the US Food and Drug Administration

(FDA) allows the manufacturer to claim is reduction of risk of osteoporotic fractures.⁴

That breast cancer rates in the WHI increased among women receiving hormone therapy was not surprising. Epidemiological and biological studies had anticipated the effect,⁵ although the magnitude of risk was not known until the WHI, which showed that the effect of hormone therapy on breast cancer risk was about the same as the deleterious effect on cardiovascular health. In each case, 42 more of approximately 8000 women in the hormone therapy group than the placebo group experienced the adverse outcome. Put in a population perspective, this means that the absolute increase in risk was only approximately 0.5% over the course of the study. But what may seem like a small effect in the study apparently turned out to be an enormous effect in the population. Several years after use of hormone therapy plummeted in the United States, breast cancer incidence also declined.⁶

Other questions lingered. What, if at all, is the effect of hormone therapy on the type of breast cancer a woman develops? Are there differences in the aggressiveness or in the potential treatability of cancers caused by hormone therapy? Several observational studies suggested that hormone therapy had counterbalancing actions in that it caused more breast cancers, but on average those cancers were less advanced and had more favorable prognostic features, such as being more often estrogen receptor positive.⁷⁻⁹ This potential trade-off made the ultimate effect of the increase in incidence on the rate of death from breast cancer uncertain. Other questions involved the relation between duration of use of hormone therapy and increase in breast cancer risk. Would shorter periods of hormone therapy be associated with less risk? Would the risk decrease after cessation of hormone therapy or remain elevated for a sustained period?

In this issue of *JAMA*, Chlebowski et al¹⁰ report results of an 11-year follow-up of WHI estrogen-progestin trial participants that address many of these questions. The

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See also p 1684.

authors found that hormone therapy increases the frequency of breast cancer and that the breast cancers are on average more advanced and may be larger. The authors found no evidence that the cancers had favorable prognostic features, such as more frequently being estrogen receptor positive or lacking *HER2/neu* gene amplification. If anything, the results suggest a trend in the direction of less favorable cancers. In addition, the authors found strong evidence that the rate of breast cancer death is increased by hormone therapy.

The authors are circumspect about this last finding, perhaps because there was some loss to follow-up in their study, or perhaps because the confidence interval around the hazard ratio for death from breast cancer includes 1 (hazard ratio, 1.96; 95% confidence interval, 1.00-4.04) and the attendant *P* value is only marginally significant (*P* = .049). However, there is no evidence that loss to follow-up biased the study's findings (the characteristics of women who were lost to follow-up are similar between the 2 study groups), and using confidence bounds and *P* values is not a reasonable way of determining if an effect is present or not. Instead, it is probable that the increase in breast cancer deaths due to hormone therapy has been underestimated in the current study and that with longer follow-up, the deleterious effect will appear larger. This suggestion is based on several observations: the mortality curves appear to still be separating at the end of the current follow-up (Figure 4A in the article); the difference in cumulative breast cancer incidence between women in the hormone therapy and placebo groups is widening (Figure 2 in the article), which will ultimately lead to more deaths; and the breast cancers diagnosed among women who received hormone therapy are associated with a poorer prognosis.

Based on present data, the authors project that approximately 1.3 additional deaths from breast cancer per 10 000 person-years of follow-up have already occurred among the women who received hormone therapy in the study. Since this number is relatively small, clinicians might conclude that a brief period of hormone therapy for relief of menopausal symptoms is safe. Such a view would be consistent with some professional guidelines¹¹ and with the FDA-approved label for combined estrogen-progestin therapy.⁴ However, the study by Chlebowski et al¹⁰ does not address the effect of short periods of hormone therapy on breast cancer risk (or other disease risk), and the current estimate of the deleterious effects of hormone therapy may be underestimated.

Therefore, the available data dictate caution in the current approach to use of hormone therapy, particularly because one of the lessons from the WHI is that physicians are ill-equipped to anticipate the effect of hormone therapy on long-term health. Clinicians who prescribe brief courses of hormone therapy for relief of menopausal symptoms should be aware that this approach has not been proven in rigorous clinical trials and that the downstream negative con-

sequences for their patients are of uncertain magnitude. One option—discussing with patients the risk-benefit trade-offs in pursuit of an informed patient decision—may seem at first blush to be a reasonable approach given this lack of evidence. But the reality is that informed patient decisions are not valid when the information underlying the decision is itself speculative.

Given the substantial population of women who seek relief from menopausal symptoms and the large potential burden of disease that could be created if medications given to alleviate symptoms today cause cancer and other deaths tomorrow, it seems that additional randomized trials are needed specifically to determine whether lower doses or shorter durations of hormone therapy could alleviate menopausal symptoms without increasing cancer risk. Such a study would be ethically justifiable and could be based on determining the effects of hormone therapy on breast cancer incidence with shorter courses of treatment (as this study shows, incidence appears to be an adequate surrogate for mortality). Anticipating that shorter durations of hormone therapy are not risky simply because that treatment strategy has not been studied adequately would be less prudent, as would assuming that enough is known about how these agents modulate disease risk to infer confidently that a safe dose and duration of their use can be determined.

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