Combined Hormone Therapy and Breast Cancer
A Single-Edged Sword

Peter H. Gann, MD, ScD
Monica Morrow, MD

The Women’s Health Initiative (WHI) trial of estrogen plus progestin hormone therapy represents a major landmark in medical research. The study demonstrates that alteration of a woman’s basic hormonal physiology over decades in the interest of long-term disease prevention is fraught with hazard.1 The WHI investigators terminated the trial after an assessment of the overall risk-benefit ratio of this combined hormone therapy regimen failed to demonstrate a benefit. A statistically significant 26% increase in breast cancer incidence contributed to the overall negative effect of estrogen plus progestin.1

In the past, women and their physicians had been reassured that although combined hormone therapy increases breast cancer risk, this increase is observed in cancers of a favorable type,2,3 is associated with long duration of use,4 and does not result in increased mortality.3 In this issue of THE JOURNAL, the study by Chlebowski and colleagues6 provides more detailed information on breast cancer outcomes with estrogen plus progestin. With a mean (SD) follow-up of 5.6 years (1.3) (compared with 5.2 years [1.3] in the initial article), 349 invasive and 84 in situ breast cancers were available for this analysis. A 24% increase in breast cancer risk was observed in the estrogen plus progestin group, but this increased risk was not evident until the third year of the study.

This risk estimate is remarkably close to estimates derived from well-conducted observational research,7,9 such as the study by Li and colleagues,10 which is also reported in this issue. What is new here, apart from the strong confirmation that the association between combined hormone therapy and breast cancer is causal, and probably not due to unappreciated differences between combined hormone therapy users and nonusers? The expanded report from the WHI trial is significant because it strongly suggests that the breast cancers related to estrogen plus progestin use are not “good” ones, that they occur earlier than expected based on some previous studies, that there are no easily identified subgroups at higher risk, and that, to top it off, women using estrogen plus progestin experience a much higher rate of mammographic abnormalities leading to anxiety and further costly workups.

The use of combined menopausal hormone therapy has been documented to decrease both the sensitivity and the specificity of mammography, because of an increase in radiographic breast density.11,12 Changes in breast density in response to combined therapy appear to occur during a relatively short interval. In the Postmenopausal Estrogen/Progestin Interventions trial,13 the 16% to 26% of women taking estrogen plus progestin who experienced an increase in breast density did so within 12 months of initiating treatment. The finding by Chlebowski et al that significantly more women had an abnormal mammogram after 1 year is consistent with the results of case-control studies and is biologically plausible, given the well-documented effects of estrogen and progestin on the proliferation of normal breast epithelium.14 It is tempting to speculate that the findings of a delayed time to diagnosis as well as an increase in abnormal mammograms are because of an increase in breast density, but density was not measured in the WHI trial.

The ability of combined hormone therapy to decrease mammographic sensitivity creates an almost unique situation in which an agent increases the risk of developing a disease while simultaneously delaying its detection. Thus, the incidence curves presented in the report by Chlebowski et al6 show a striking crossover. The incidence of breast cancer diagnosis is actually lower in the estrogen plus progestin group for the first 2 years, after which the slope of the incidence curve for estrogen plus progestin begins to increase, leading to a crossover in cumulative breast cancer occurrence at year 4 and continuing divergence in risk at the end of follow-up. Given these nonproportional hazards over time, the summary risk ratio of 1.24 from the proportional hazards model is probably conservative. The authors, having anticipated this problem, also provide a weighted analysis that down-weights the importance of the early years of follow-up. A simplified but conservative analysis based on an a priori analysis plan is justifiable, particularly in an initial study.

See also pp 3243 and 3254.
The delay in diagnosis also complicates the analysis of the relationship between use of estrogen plus progestin and tumor size and stage. Breast cancers in the estrogen plus progestin group occur, as a whole, later in follow-up, and thus have had more time to grow and spread undetected. In fact, the tumor size difference between the groups is small (mean diameters of 1.7 cm and 1.5 cm in the estrogen plus progestin and placebo groups, respectively), and could be attributed to a small number of very large tumors in the estrogen plus progestin group. On the other hand, the difference in the percentage of cancers with regional spread is striking (25.9% vs 15.8%) and should translate directly into worse prognoses. Future secondary analyses are needed to clarify the association between estrogen plus progestin and tumor growth and spread by disentangling the effects of diagnostic delay. However, 2 points of interpretation can be made based on the current data. First, although there is some doubt that combined estrogen plus progestin therapy causes larger or more advanced tumors, it is very unlikely that the opposite is true, as reported in some previous studies. Second, the cancers occurring among women receiving combined hormone therapy are at least as invasive as those among women receiving placebo, if not worse.

The relatively early appearance of excess risk in the WHI trial is important for what it reveals about the possible risks of short-term exposure, despite several important nuances. For instance, women in the WHI trial were older (mean age at baseline, 63.2 years) than most women who start menopausal hormone therapy. Older women have a higher level of baseline risk than younger women and are potentially more likely to have preexisting, clinically occult tumors that, when stimulated by hormone therapy, would become detectable. In addition, more than a quarter of the women in the WHI trial had used menopausal hormones previously, and much of the excess risk of invasive breast cancer was observed in these women. These uncertainties, combined with the uncertainties regarding tumor size and stage, might lead some to speculate that short-term use of combination hormone therapy in younger, hormone-naive women for relief of menopausal symptoms might be safe. However, although the early appearance of breast cancer risk might be debatable, the risks of heart disease and pulmonary embolus associated with estrogen plus progestin use are apparent even in the first year of use.

Apart from women with previous exposure to hormone therapy, the WHI trial analyses do not reveal any subgroups with particularly increased or decreased risk due to estrogen plus progestin use. Family history of breast cancer is one potentially interesting risk modifier, but this was not presented in the WHI analysis. There is a suggestion in the WHI data that obese women, who already have higher endogenous estrogen levels, might have a lower risk of estrogen plus progestin–induced breast cancer, but the statistical power for detection of this phenomenon was quite low. This finding is consistent with the observations of Schairer et al7 that women with a body mass index of less than 24.4 had an increased risk of breast cancer than did women with a higher body mass index after exposure to combination hormone therapy.

Another finding of major concern in the WHI report by Chlebowski et al is the sharp increase in mammographic abnormalities among women in the estrogen plus progestin group. The anxiety produced by such results is easily understood and well documented.16 Perhaps less well documented but no less important is the likelihood that some women who have experienced false-positive mammographic findings might turn away from breast cancer screening altogether. The unusually high compliance with annual mammography in the WHI trial (nearly 90%) is worth noting for several reasons. First, it no doubt limited the harm caused by estrogen plus progestin exposure in the trial, and it raises the possibility that in a group of women less adherent to screening mammography recommendations, the potential hazards of estrogen plus progestin use could be considerably worse. Second, the high-level and equal compliance with mammography screening in both treatment groups minimizes the risk of bias in both the breast cancer results and the abnormal mammography results due to increased mammographic surveillance in the estrogen plus progestin group. This protection against bias is especially important given that more than 40% of women receiving estrogen plus progestin became unblinded because of persistent vaginal bleeding.

The role of mammographic density is important for both biological and clinical reasons. It is possible that women who develop an increase in mammographic breast density in response to combined hormone therapy are the same ones who experience an increased risk for breast cancer. The finding that selective estrogen receptor modulators, such as tamoxifen and raloxifene, which decrease breast cancer risk, also decrease breast density17,18 make this an attractive hypothesis. The WHI investigators indicate that they are planning an ancillary study to address this question and help determine whether physicians can use a change in breast density as a cue for recommending termination of menopausal hormone therapy. The reasons some women respond to hormone therapy in this way remain unknown, although some recent investigations involving genetic determinants appear promising.19,20 Identification of the biological mechanism for the breast density response to combined hormone therapy has the potential to clarify the role of breast density and the response to endogenous estrogens and progestins in the larger population of women with breast cancer.

Experienced observers hesitate to label any biomedical research study as “definitive,” especially in an area as historically controversial as the study of menopausal hormone therapy. Nevertheless, the WHI trial of estrogen plus progestin therapy is as close to definitive as can be expected. The effort and commitment of the investigators, funding agency, and participants were prodigious. Although the...
results are clear enough to discourage any future attempt at replication, further research certainly is necessary. For instance, the risks and benefits of short-term use of hormone therapy for menopausal symptoms need to be clarified in rigorous investigations, and studies examining lower dosage formulations and alternative delivery methods, such as skin patches, would be useful. Moreover, the WHI trial of estrogen-only use among women who have had their uterus removed is still ongoing. If the observational studies are again correct, estrogen-only use could have much less impact on breast cancer risk than estrogen plus progestin use. The findings related to heart disease in the estrogen-only use will be of particular interest. If estrogen-only use reduces the risk of heart disease and has little impact on breast cancer risk, a reanalysis of the risk-benefit ratio of estrogen-only use in women with an intact uterus would seem warranted.

In the meantime, the message for physicians caring for menopausal patients is clear. The increased risk of breast cancer and the mammographic abnormalities among women in the WHI study provide further compelling evidence against the use of combination estrogen plus progestin hormone therapy.

REFERENCES

Smallpox Immunization in the 21st Century
The Old and the New

Mary E. Wright, MD MPH
Anthony S. Fauci, MD

Just over 6 months ago a decision was made to re-institute smallpox vaccination for selected segments of the US population. This decision to implement a pre-event smallpox vaccination program was based on the concern that smallpox could be used as an agent of bioterrorism; however, certain questions about the risk of smallpox vaccination in a 21st-century setting arose. Among these was the possibility that the current United States population might be more vulnerable to serious adverse effects of the smallpox vaccine due to a relative increase—compared with 3 to 4 decades ago—in conditions affecting the immune system such as the use of immunosuppressive drugs and the presence of human immunodeficiency virus infection in the community. A consequence of this change in population profile could be an increased incidence of established adverse events as well as the emergence of herefore unrecognized adverse events. At the same time that

Author Affiliations: National Institute of Allergy and Infectious Diseases, National Institutes of Health, Department of Health and Human Services.

Corresponding Author and Reprints: Anthony S. Fauci, MD, NIAID/National Institutes of Health, Bldg 31, Room 7a03, MSC 2520, Bethesda, MD 20892 (e-mail: fauci@nih.gov).

See also pp 3278, 3283, 3290, and 3295.