DOI:10.1093/jnci/djt058
Advance Access publication March 29, 2013

EDITORIAL

The Effect of Estrogen Plus Progestin Hormone Therapy on Breast Cancer Mortality: Still Unresolved

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The article by Chlebowski et al. in this issue of the Journal (1) follows upon eight articles that have described the relationship between estrogen/progestin therapy and invasive breast cancer risk/mortality in studies from the Women's Health Initiative (WHI) (2–9). Although a previous analysis addressed relationships between estrogen plus progestin use and breast cancer incidence among participants in the WHI Observational Study (WHIOS) (5), a cohort noted to have characteristics similar to participants in the WHI Randomized Trial (WHIRT), this is the first presentation of data from the WHIOS related to mortality outcomes. A major goal of the Chlebowski et al. study was to explore discrepancies between the randomized trial, which noted increased breast cancer mortality and adverse tumor characteristics associated with estrogen plus progestin therapy, and previous observational studies, which have mainly found usage to be associated with favorable prognosis breast cancers.

Findings about increased breast cancer incidence associated with estrogen plus progestin therapy from the WHIRT were first published in 2002 after a mean follow-up of 5.2 years (2). Tumor characteristics were reported after a mean follow-up of 5.6 years; with 199 observed breast cancers in the estrogen plus progestin group (3), the invasive breast cancers were larger, more likely to be node positive, and diagnosed at substantially more advanced stages compared with the placebo group. In subsequent analyses, adverse tumor characteristics associated with the estrogen plus progestin group were primarily limited to those with prior hormone use (4) or to breast tumors diagnosed during the postintervention phase (8). After a mean follow-up of 11 years (9) and 385 breast cancers and 25 deaths due to breast cancer in the estrogen plus progestin group, considerably larger fractions of breast cancer patients were diagnosed with positive lymph nodes compared with the placebo group; in addition, breast cancer mortality was nearly doubled.

The latest analyses from the WHIOS were viewed as providing consistency with findings from the WHIRT, given observed increases associated with estrogen plus progestin use for breast cancer incidence and no relationship with prognosis, leading to expected increases in breast cancer mortality. In evaluating the results of the WHIOS in relationship to the WHIRT, Chlebowski et al. attempted to standardize eligibility criteria and focused on adjustment of incidence analyses for ongoing mammographic screening, gap time (the interval from menopause to first hormone treatment), and prior hormone usage.

There were, however, a number of differences between the WHIOS and the WHIRT that make it difficult to equate results. First, in the WHIOS, estrogen plus progestin users were not limited to the regimen taken during the clinical trial, and those with estimated survival of less than 3 years were not excluded (1). Moreover, in the WHIRT, subjects on estrogen plus progestin were considerably older than those in the WHIOS (21% vs 12% aged 70–79 years), more had hormone therapy initiated at least 5 or more years after menopause (83% vs 26%) (5), and more were overweight or obese (70% vs 48%) (2). Finally, the number of case subjects on estrogen plus progestin use in the WHIRT was considerably smaller than in the WHIOS (385 vs 1097), leading to questions about differences in precision of study estimates.

Despite efforts to standardize the entry criteria for this analysis with those of the WHIRT and to adjust for mammographic screening during the follow-up period, the findings with regard to tumor characteristics associated with estrogen plus progestin therapy were discrepant with those reported in the WHIRT. In general, tumors in estrogen plus progestin users in the WHIOS were not statistically significantly different from those in non–hormone users with regard to number of positive lymph nodes or tumor size but were more likely to be well differentiated and positive for hormone receptors, findings which are similar to those in other observational studies (10). Only in the small subgroup of 220 breast cancers diagnosed in women who began estrogen plus progestin therapy after study entry were the women more likely to have adverse tumor characteristics. These differences did not, however, translate into a survival difference between estrogen plus progestin users and nonusers.

Importantly, neither the WHIRT nor the WHIOS systematically addressed the issues of currency and duration of hormone use (including during the follow-up period) at time of diagnosis with regard to tumor characteristics and prognosis. In the article by Chlebowski et al. (1), hormone therapy use was classified at baseline and in exploratory analyses according to ongoing use, discontinued use, or use initiated during follow-up, which are, at best, crude estimates of patterns of use at time of diagnosis. One would expect that characteristics of study subjects and patterns of use of estrogen plus progestin that affect the degree of breast cancer risk (eg, body mass index, gap time, currency of use and duration of use at the time of diagnosis) might also have an impact on tumor biology and prognosis, independent of effects of mammography.

As currently presented, there remain some lingering questions about whether this analysis of data from the WHIOS resolves the issue of differences in tumor prognosis and tumor characteristics between the WHIRT and many observational studies. An analysis of

this dataset, perhaps in conjunction with other observational studies with updated information on hormone exposure and mammography screening during the follow-up period, that focuses on prognosis related to currency and duration of use and body mass index (to name a few characteristics of importance) might offer clues as to whether there are truly biological differences between tumors diagnosed in estrogen plus progestin users and those diagnosed in nonusers or whether all differences are because of mammographic screening behavior. In this regard, we note that only 41 449 (44%) of the 93 176 study participants originally enrolled in the WHIOS were included in the current analysis. Among those excluded were women who had not had a negative mammogram within 2 years of entry. It might be informative to include these women in a future analysis to further determine the potential impact of screening on breast cancer survival and mortality associated with estrogen plus progestin use.

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