Estrogen-Progestin Therapy Raises Breast Cancer Risk

BY KURT SAMSON

Postmenopausal women with an intact uterus who undergo combination therapy with estrogen and progestin have significantly elevated risk of developing and dying from breast cancer for at least a decade after completing treatment, while monotherapy with estrogen appears to have the exact opposite effect, according to long-term, follow-up analysis of outcomes from two large observational trials.

The review of data of from two Women’s Health Initiative (WHI) trials showed that menopausal hormone therapy using only estrogen decreased breast cancer incidence and death with persistent results after discontinuation of use, while estrogen plus progestin increased breast cancer incidence with persistent results after discontinuation of use, according to researchers at the University of California Los Angeles Harborside Medical Center during a press conference at the San Antonio Breast Cancer Symposium (Abstract GS5-00).

Both therapies are used by millions of women worldwide, yet after nearly half a century, the influence of hormone therapy on breast cancer incidence and mortality “remains unsettled, with discordant findings from prospective observational studies compared to findings from randomized clinical trials,” said Rowan T. Chlebowski, MD, PhD, Chief of the Division of Medical Oncology and Hematology at Harbor-UCLA Medical Center, and an investigator at The Lundquist Institute.

He told reporters that, earlier this year, findings published by the Collaborative Group on Hormonal Factors in Breast Cancer—from a meta-analysis of 58 observational studies—showed estrogen plus progestin as well as estrogen alone were both associated with significantly increased risk of breast cancer incidence, while the Million Women Study found that both were significantly associated with increased breast cancer mortality.

The new findings update earlier data from two randomized WHI clinical studies on breast cancer incidence and mortality in women randomly assigned to conjugated equine estrogens (CEE) plus medroxyprogesterone acetate (MPA), CEE alone, or placebo, and included more than 19 years of cumulative follow-up.

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—Rowan T. Chlebowski, MD, PhD, Chief of the Division of Medical Oncology and Hematology at Harbor-UCLA Medical Center

Although participants in past observational studies may not have had the same clinical characteristics and treatment regimens as women in the WHI, the difference between those results and the randomized WHI findings regarding estrogen monotherapy “are difficult to reconcile,” Chlebowski added.

Methodology

The WHI investigators recruited postmenopausal women, with no prior breast cancer, between 50 and 79 years of age into one of two randomized clinical trials at 40 U.S. centers from 1993 to 1998. To evaluate long-term outcomes, the women were followed through September 2016.

Subjects with an intact uterus received CEE and MPA (8,506) or a placebo (8,102) for a median of 5.6 years, while postmenopausal women who had undergone hysterectomy were treated with estrogen monotherapy (5,310) or placebo (5,429) for a median of 7.2 years.

Chlebowski reported that after 16.1 years of follow-up, there were 520 incident breast cancers during the post-intervention period among women who had been treated only with CEE. Compared with their counterparts given the placebo, treated women were 23 percent less likely to have developed breast cancer and 44 percent less likely to have died from the disease.

“These positive outcomes are in agreement with the earlier findings from this trial during the intervention period,” he noted.

Among the women who underwent therapy with both CEE and MPA, there were 1,003 incident breast cancers during the post-intervention period after 18.3 years of cumulative follow-up. Compared with women who had received placebo, those who had received combination therapy were 29 percent more likely to have been diagnosed with breast cancer, a rate that was similar to earlier findings from the trial during the intervention period. In addition, there was an increased risk of death from breast cancer among the combination group in the extended analysis; however, it did not reach statistical significance.

According to Chlebowski, one of the more important limitations of the study is that breast cancer mortality analyses did not specify the other treatment protocols that the women underwent. Moreover, the trials evaluated one dose and schedule of CEE plus MPA, or CEE alone, respectively, and therefore the findings may not be applicable to other preparations, doses, or schedules, he noted.

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Kurt Samson is a contributing writer.