Estrogen Decreases Breast Cancer Incidence in Postmenopausal Women, Estrogen Plus Progestin Has Opposite Effect

Jason Harris

Rowan T. Chlebowski, MD, PhD

Updated findings from Women's Health Initiative (WHI) studies involving more than 27,000 patients demonstrated that estrogen alone as menopausal hormone therapy (MHT) decreased breast cancer incidence in postmenopausal women. In contrast, estrogen plus progestin was associated with increased incidence and death.[1]

In both cases, the result continued after discontinuation said Rowan T. Chlebowski, MD, PhD, chief of the Division of Medical Oncology and Hematology at Harbor-UCLA Medical Center. He presented the data during a press briefing at the San Antonio Breast Cancer Symposium.

"Use of estrogen alone and use of estrogen plus progestin have opposite effects on breast cancers," he said. "[Estrogen] alone after use for 7.2 years, now with 19.2 years follow-up, resulted in a 23% reduction in breast cancer use, which was statistically significant. The [estrogen plus progestin] use ended up increasing breast cancer by 29%."

Postmenopausal women aged 50 to 79 years with no prior breast cancer were recruited into 1 of 2 randomized clinical trials at 40 U.S. centers from 1993 to 1998. Those with an intact uterus received estrogen plus progestin (n = 8506) or placebo (n = 8102) for a median of 5.6 years. Women who had undergone hysterectomy received estrogen alone (n = 5310) or placebo (n = 5429) for a median of 7.2 years.

Investigators observed 231 breast cancers in women assigned to estrogen alone compared with 289 for those assigned to placebo (HR, 0.77; 95% CI, 0.65-0.92; $P = .005$). Estrogen alone patients also had a reduced risk for disease-specific death (HR, 0.56; 95% CI, 0.34-0.92; $P = .02$) and for deaths after breast cancer (HR, 0.75; 95% CI, 0.56-1.01; $P = .06$).

There were 572 breast cancers diagnosed among women among women assigned to the combination compared with 431 for those assigned to placebo (HR, 1.29; 95% CI, 1.14-1.47; $P < .0001$). These patients also had an increased risk for disease-specific death (HR, 1.45; 95% CI; $P = .06$) and deaths after breast cancer (HR, 1.29; 95% CI, 1.02-1.63; $P = .03$).

Chlebowski added that the reduced risk for incidence associated with estrogen continued after the study period (HR, 0.83; 95% CI, 0.57-1.20). Similarly, the increased risk continued with estrogen/progestin (HR, 1.30; 95%

CI, 0.99-1.70). In both cases, the effect continued over decades.

“The use of the drug was only for 5.6 years, but you can see that the increased [risk] is continuing for up to 20 years,” he said. “A woman takes estrogen plus progestin for 5 year and she is exposed to a 20 year increased breast cancer risk. [The risk] doesn't seem to be leveling off, so one can speculate it will be a lifetime risk for short-term use.”

These data directly contradict findings published this year by the Collaborative Group on Hormonal Factors in Breast Cancer and the Million Women Study.

The Collaborative Group conducted a retrospective analysis of 58 trials involving 108,647 postmenopausal women developed breast cancer at mean age of 65 years. Half the patients had used MHT. Mean MHT duration was 10 years in current users and 7 years in past users.

Among current users, there was a clear risk for breast cancer 5 to 14 years after treatment for estrogen/progestin (RR, 2.08; 95% CI, 2.02-2.15) and estrogen alone (RR, 1.33; 95% CI, 1.28-1.37).[2]

The Million Women Study included 907,162 postmenopausal women who were breast cancer-free at recruitment. Among them, about a third were current users of MHT, one-sixth were past users, and half were never-users.

Women who were on either estrogen alone or estrogen/progestin preparations at recruitment had significant excess breast cancer mortality risks (P <.0001). While there was no increased mortality found for patients who used MHT for about 5 years, those on therapy for roughly 8 years had a significant excess breast cancer mortality over the next 20 years (HR, 1.24; 95% CI, 1.12-1.38; P = .0005).[3]

Chlebowski said patients and physicians considering hormone therapy would have to weigh the data, but based on these findings from his group, estrogen and estrogen/progestin clearly do not have the same effect.

“Women who are considering estrogen alone should know that it's safer and there may be a breast cancer benefit associated with its use,” he said. “Women considering estrogen plus progestin have a little bit more difficult dilemma because they have to be willing to accept the maybe 20 year, and maybe lifetime, increased breast cancer risk.”

References

1. Chlebowski RT, Anderson GL, Aragaki AK, et al. Long-term follow-up shows estrogen alone and estrogen plus progestin have opposite effects on breast cancer incidence in postmenopausal women. Presented at:

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2. Collaborative Group on Hormonal Factors in Breast Cancer. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. *Lancet*. 2019;394(10204):1159-1168. doi: 10.1016/S0140-6736(19)31709-X.
3. Beral V, Peto R, Pirie K2, Reeves G, et al. Menopausal hormone therapy and 20-year breast cancer mortality. *Lancet*. 2019;394(10204):1139. doi: 10.1016/S0140-6736(19)32033-1.

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