Estrogen plus Progestin and Breast Cancer Mortality: Controversies Addressed

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The Women's Health Initiative (WHI) randomized trial observed an increase in both breast cancer incidence and mortality among users of estrogen plus progestin (E+P). (E+P is a type of hormone replacement therapy (HRT), used to alleviate postmenopausal symptoms.) In contrast, most observational studies had previously reported that the use of E+P was associated with an increased incidence of breast cancer, but decreased mortality. Some researchers have posited that E+P use is associated with breast cancers with a more favorable prognosis. It has also been suggested that differences between studies in rates of mammography, and/or the amount of time between menopause and initiation of E+P therapy, could explain the disparate findings.

Dr. Rowan Chlebowski (Harbor-UCLA Medical Center), Drs. Polly Newcomb and Ross Prentice (Public Health Sciences, FHCRC), and their collaborators addressed these questions using data from the WHI observational study. They assessed the relationship between E+P and breast cancer incidence, as well as mortality, comparing women who had used E+P with women who had no history of HRT. For the sake of comparability they selected a study sample which was similar to participants in the original randomized controlled trial. In both studies, women had to be postmenopausal, between the ages of 50-79 years at study entry, have at least a 3-year anticipated survival, have no record of prior hysterectomy or breast cancer, and have had a mammogram less than 2 years before study entry which was not suspicious for breast cancer. 41,449 women were included in this study, including 25,328 HRT non-users and 16,121 E+P users.

The investigators found that women using E+P were younger, more likely to be white, alcohol drinkers, and have a body mass index of less than 25 kg/m2 compared to HRT non-users. E+P users had been using E+P for an average of 5 years. During follow-up (mean: 11.3 years), 2,236 invasive breast cancers were diagnosed. E+P users had higher rates of breast cancer than non-users (0.6% vs 0.4% per year, respectively, HR 1.55, 95% CI 1.41-1.70). The sooner women had initiated use of E+P after menopause, the higher their risk of breast cancer. Among women diagnosed with breast cancer, survival from the time of diagnosis was similar in women who used E+P compared to non-users (HR = 1.03, 95% CI 0.79-1.35). The use of E+P was associated with a

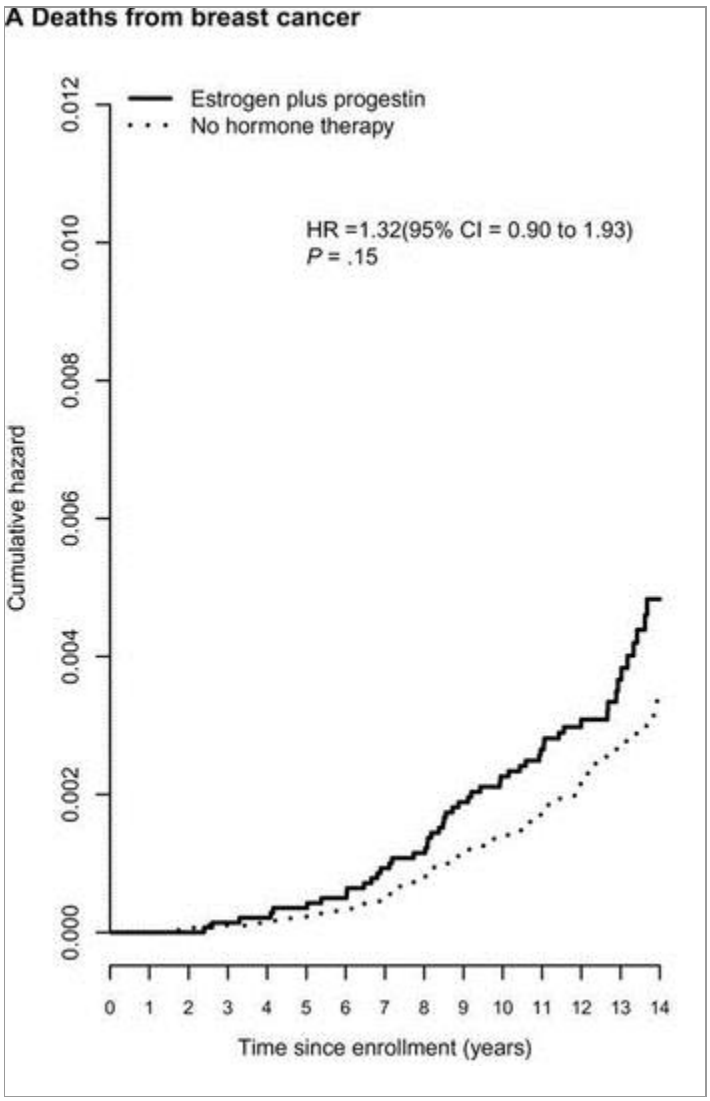
higher risk of death due to breast cancer (HR 1.32, 95% CI 0.90-1.93), and a higher risk of death from all causes (HR 1.65, 95% CI 1.29-2.12), compared to HRT non-use.

In this study, Chlebowski *et al.* were able to address some important questions about differences between findings of the WHI randomized trial vs. observational studies regarding the relationship between use of E+P and breast cancer mortality. The WHI randomized trial had observed an increased risk of death, but prior observational studies generally observed a decreased risk of dying of breast cancer associated with E+P use, leading to the hypothesis that E+P might cause breast cancers with a favorable prognosis. By creating an observational study with a similar population to the randomized trial in terms of eligibility requirements, the authors were able to demonstrate that certain differences between studies may indeed be responsible for the disparate findings in earlier studies. Specifically, there were differences in mammogram history between the observational studies and the randomized trials; women were required to have a recent negative mammogram to enter the clinical trial, and both arms of the trial (E+P vs non-users) received regular mammograms during study follow-up according to protocol. However, in observational studies, women using E+P tended to receive mammograms much more regularly than HRT non-users. Regular screening leads to the diagnosis of more early-stage, favorable tumors. Thus, differences in screening practices may have confounded the observational studies and created an apparent association between E+P use and better breast cancer survival.

These results, combined with the original randomized trial (also cited below), provide evidence that E+P increases risk of breast cancer incidence and mortality among postmenopausal women. In particular, initiation of E+P *soon after menopause* is more strongly associated with breast cancer incidence and mortality than delayed E+P inititation.

Chlebowski RT, Manson JE, Anderson GL, Cauley JA, Aragaki AK, Stefanick ML, Lane DS, Johnson KC, Wactawski-Wende J, Chen C, Qi L, Yasmeen S, Newcomb PA, Prentice RL. 2013. Estrogen Plus Progestin and Breast Cancer Incidence and Mortality in the Women's Health Initiative Observational Study. J Natl Cancer Inst. 105(8):526-35. doi: 10.1093/jnci/djt043. Epub 2013 Mar 29.

See also: Chlebowski RT, Anderson GL, Gass M, Lane DS, Aragaki AK, Kuller LH, Manson JE, Stefanick ML, Ockene J, Sarto GE, Johnson KC, Wactawski-Wende J, Ravdin PM, Schenken R, Hendrix SL, Rajkovic A, Rohan TE, Yasmeen S, Prentice RL; WHI Investigators. 2010. Estrogen plus progestin and breast cancer incidence and mortality in postmenopausal women. JAMA 304(15):1684-92. doi: 10.1001/jama.2010.1500.



Modified from Chlebowski et al.

Breast cancer mortality by estrogen plus progestin (E+P) use at baseline.