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Letters to the Editor

FOUR AUTHORS REPLY

In response to the letter by Dr. Shapiro (1), we would like to reiterate that a major motivation for our joint analysis (2) of Women's Health Initiative (WHI) clinical trial and observational study data on conjugated equine estrogens and breast cancer incidence, as well as for our companion paper on conjugated equine estrogens plus medroxyprogesterone acetate and breast cancer (3), is the elucidation of differences between clinical trial and observational study results. The WHI provides an ideal context for such comparisons, because clinical trial and observational study subjects were drawn from the same populations, over essentially the same time period, with much commonality in data collection, protocol, and procedures. We see this as an excellent setting for assessing the reliability of observational study results and for identifying needed analytical procedures under either study design. To declare such formal joint analyses to be ''illegitimate,'' as Dr. Shapiro does (1, p. 1213), seems tantamount to suggesting that WHI investigators should not analyze their data!

Dr. Shapiro argues that study subject knowledge of their hormone therapy exposure status invalidates the large body of observational data on conjugated equine estrogens and breast cancer. However, our analyses indicate good overall agreement between the WHI clinical trial and observational study after controlling for confounding in a standard fashion and after acknowledging hazard ratio dependencies on two basic epidemiologic variables, namely, time from menopause to first use of hormone therapy and time since the initiation of conjugated equine estrogen use (duration of use among adherent women). This agreement argues for the absence of important biases due to a woman's knowledge of her hormone therapy exposure. Hazard ratios were about null in our joint analyses among women who started hormone therapy within a few years of the menopause, but these were not precisely determined. The large body of well-conducted observational studies (4, 5) provides a useful source for more precise hazard ratio estimates among such women.

Our analyses (3) also indicate good agreement between clinical trial and observational study effects of conjugated

equine estrogens/medroxyprogesterone acetate on breast cancer, and they indicate substantially elevated hazard ratios within a few years of initiating this therapy, among women who begin such use soon after the menopause. In his letter and in other forums, Dr. Shapiro argues that doubt is cast on the clinical trial finding of an elevated breast cancer risk with conjugated equine estrogens/medroxyprogesterone acetate, since some women may have become unblinded because of persistent vaginal bleeding. In response, we further analyzed the post 1-year trial data by separately estimating hazard ratios for women assigned to active conjugated equine estrogens/medroxyprogesterone acetate according to whether or not they experienced persistent bleeding throughout the first year from randomization. Hazard ratios were elevated ($P < 0.05$) both among women with and among women without persistent vaginal bleeding. Control for baseline breast cancer risk factors had little effect on these analyses.

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