FIVE AUTHORS REPLY

We thank Dr. Langer (1) for his views on the data reported in our paper (2). In that paper on estrogen plus progestin (E + P) and breast cancer incidence, we describe a dependence of the breast cancer hazard ratio for E + P use on time from menopause to first use of postmenopausal hormone therapy or ''gap'' time, with higher hazard ratios among women having short gap times. Acknowledgment of this dependence provides an explanation not provided by other time scales or by other study subject characteristics for the higher hazard ratios in the Women's Health Initiative observational study compared with the clinical trial.

Dr. Langer expresses concern that the E + P hazard ratio dependence on gap time may be biased by differential control for confounding factors between the clinical trial and the observational study in these analyses, or by confounding by age or by duration of hormone therapy use. On the first point, our observational study analyses took into account a range of baseline breast cancer risk factors, with separate regression coefficients according to prior hormone therapy status and with provision for the type and duration of hormone therapy use among prior users of this therapy. Additionally, we included an E + P observational study/clinical trial hazard ratio in combined cohort analyses, toward controlling any residual confounding in the observational study. Although corresponding risk factor modeling could be included in the clinical trial component of our analyses, it is unnecessary to do so because randomization assignment (E + P vs. placebo) is independent of all baseline risk factors (regardless of whether they are recognized as such). In choosing not to include such modeling, we avoided the exclusion of clinical trial women who had missing data for these variables, thereby also preserving the independence just mentioned.

We interpret Dr. Langer's concern about confounding by age or duration of hormone therapy as pertaining to the modeling of the E + P hazard ratio function (i.e., effect modification), rather than standard confounding. Table 4 in our paper (2) shows some results from analyses in which the E + P hazard ratio depends on prior hormone therapy status, years from E + P initiation, and gap time. Under this model, women who begin E + P at menopause experience elevated hazard ratios within the subsequent few years, in both the clinical trial and observational study and in combined analyses.

As described in the Results section narrative (2, p. 1211), the hazard ratio dependence on gap time remained highly significant and essentially unchanged, in combined clinical trial and observational study analyses, when the E + P hazard ratio was additionally allowed to depend on age or on further refinements of time since E + P initiation, while dependence of the hazard ratio on these latter factors was comparatively minor. Our Figure 1 shows strong

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dependencies of the E + P hazard ratio on both gap time and time from E + P initiation, when the combined cohort analyses were restricted to women without prior hormone therapy. However, as noted in the Discussion, the clinical trial included few women who were without prior hormone therapy and had short gap times, so that these analyses do rely substantially on observational study data.

Although modeling exercises of this type necessarily have some uncertainty as to whether all relevant effect-modifying factors have been considered, and although hazard ratios within some subgroups are estimated with limited precision, it is noteworthy that hormone therapy hazard ratios demonstrate a strong dependence on 2 basic time variables: 1) time from menopause to first use of hormone therapy and 2) time since hormone therapy initiation. It is also noteworthy that consideration of these variables, but not other potential effect-modifying factors, is sufficient to bring together breast cancer hazard ratios from the Women's Health Initiative clinical trial and observational study, not only for E + P (2) but also for estrogen alone as shown in our companion paper (3), which used the same methodology.

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REFERENCES

1. Langer RD. Re: ''Estrogen plus progestin therapy and breast cancer in recently postmenopausal women'' [letter]. *Am J Epidemiol*. 2009;169(6):784–785.
2. Prentice RL, Chlebowski RT, Stefanick ML, et al. Estrogen plus progestin therapy and breast cancer in recently postmenopausal women. *Am J Epidemiol*. 2008;167(10):1207–1216.
3. Prentice RL, Chlebowski RT, Stefanick ML, et al. Conjugated equine estrogens and breast cancer risk in the Women's Health Initiative clinical trial and observational study. *Am J Epidemiol*. 2008;167(12):1407–1415.

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