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
dependencies of the E + P hazard ratio on both gap time and
time from E + P initiation, when the combined cohort anal-
yses were restricted to women without prior hormone ther-
apy. However, as noted in the Discussion, the clinical trial
included few women who were without prior hormone ther-
apy 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 demon-
strate 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.

ACKNOWLEDGMENTS

Conflict of interest: none declared.

REFERENCES

1. Langer RD. Re: “Estrogen plus progestin therapy and breast
cancer in recently postmenopausal women” [letter]. Am J
progestin therapy and breast cancer in recently postmenopausal
equine estrogens and breast cancer risk in the Women’s Health

Ross L, Prentice1, Rowan T, Chlebowski2, Marcia L.
Stefanick3, Jacques E. Rossouw4, and Garnet L.
Anderson1 (e-mail: rprentic@fhcrc.org)
1 Division of Public Health Sciences, Fred Hutchinson
Cancer Research Center, Seattle, WA 98109
2 Los Angeles Biomedical Research Institute at Harbor-
UCLA Medical Center, Torrance, CA 90502
3 Stanford Prevention Research Center, School of Medicine,
Stanford University, Stanford, CA 94305
4 National Heart, Lung, and Blood Institute, Bethesda, MD
20824

DOI: 10.1093/aje/kwn423; Advance Access publication February 10, 2009