RE: Estrogen Plus Progestin and Breast Cancer Incidence and Mortality in the Women's Health Initiative Observational Study

In their report of increased risks of breast cancer and mortality in estrogen plus progestin (E+P) users after 11.3 years of follow-up (1), the Women's Health Initiative investigators failed to consider the likelihood of bias, despite quantitative evidence of its presence. The incidence was higher in the observational study than in the clinical trial (1,2), and bias would inevitably have been present among users who had declined to participate in the trial but who nevertheless agreed to be followed; who were informed of a possibly increased risk of breast cancer when recruited; and who were also notified of an increased risk when the trial ended (2).

The mortality data (1) are further evidence of bias: for all deaths and for breast cancer deaths the respective hazard ratios (HRs) were 1.65 and 1.32. The preponderance of the epidemiological evidence suggests that E+P reduces all-cause mortality (3), as well as the breast cancer case-fatality rate.

Women who had "a mammogram not suspicious for breast cancer less than 2 years before entry" were studied, and the data were censored "for a greater than 2-year interval without a mammogram." The investigators claim that doing so minimized residual confounding. That claim is not defensible: in the 2 years before recruitment, E+P users aware of breast lumps could selectively have participated. During follow-up, users could have told the mammographers that they had used E+P, and breast cancer could selectively have been diagnosed.

The observational findings were also discordant with the Million Women Study and the Collaborative Reanalysis (4), in which the relative risks declined to baseline within 2 to 5 years. In an earlier analysis of the Women's Health Initiative observational data (5), after 6.9 years of follow-up that ended in 2005, "before 2002 the … HR was nearly 2.0, and within 2 years the HR declined to 1.00, when the use of E+P had declined by 66% (6). Yet after 11.3 years of follow-up that ended in 2010 (1), the hazard ratio remained elevated, even though the use of E+P had declined by 66% at least 5 years previously.

Finally, estrogens and progestins vary in their metabolic effects, and a class effect cannot be assumed. The observational study predominantly evaluated conjugated equine estrogens plus medroxyprogesterone acetate (CEE+MPA). Even if the worst case assumption is made that CEE+MPA causes breast cancer, that assumption cannot be generalized. Preparations currently in use are taken at low doses; they are commonly identical to endogenous hormones, new products now exist, and in the E3N cohort study (7) the risk of breast cancer varied according to the preparation used.

To conclude, whether or not CEE+MPA increases the risk of breast cancer remains controversial, and if it is assumed that it does, the findings cannot be generalized to all products. It is also likely that the use of E+P reduces all-cause mortality, as well as the case-fatality rate among users who develop breast cancer.

SAMUEL SHAPIRO
TOBIE J. DEVILLIERS
AMOS PINES
DAVID W. STURDEE
DAVID F. ARCHER
ROD J. BABER
NICK PANAY
RICHARD D. T. FARMER
JOHN C. STEVENSON
ALFRED O. MUECK
HENRY G. BURGER
ANNE GOMPEL

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Affiliations of authors: Department of Public Health and Family Medicine, University of Capetown, Cape Town, South Africa (SS); Department of Obstetrics and Gynecology, Stellenbosch University, Cape Town, South Africa (TJD); Department of Medicine, Tel Aviv University,Tel Aviv, Israel (AP); Department of Obstetrics and Gynecology, Solihull Hospital, Solihull, UK (DWS); Department of Obstetrics and Gynecology, East Virginia Medical School, Norfolk, VA (DFA); Department of Obstetrics and Gynecology, University of Sydney, St. Leonards, Australia (RJB); Department of Obstetrics and Gynecology, Queen Charlotte's and Chelsea and Westminster Hospitals (NP), National Heart and Lung Institute (JCS), Imperial College, London, UK; Women's Hospital, University of Tubingen, Tubingen, Germany (AOM); Departments of Endocrinology and Medicine, Prince Henry's Institute, Melbourne, Australia (HB); Department of Gynecology, University Paris Descartes, Paris, France (AG).

Correspondence to: Samuel Shapiro, MB FCP(SA), FRCP(E), Department of Public Health and Family Medicine, University of Capetown, Anzio Rd, Observatory, Cape Town, South Africa 7925 (e-mail: samsap@mweb.co.za).

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