Conduct of the Women's Health Initiative randomised trial evaluating estrogen plus progestin: implications for breast cancer findings

In a recent commentary, Shapiro and colleagues¹ provided their perspective on the strength of the evidence relating the time-dependent decrease in combined menopausal hormone therapy use to a decrease in breast cancer incidence, examining three studies reporting on the trends in breast cancer incidence following declines in hormone therapy use. They concluded that “the ecological evidence is too limited to either support or refute the possibility that hormone therapy causes breast cancer”. Their conclusions were based mainly on the “lower reliability of data collected at the population level than analytic data collected at the individual level” and that “precise adjustment for the confounding effect of changes in mammography screening” was needed. In this regard, a report from the Women's Health Initiative (WHI) estrogen plus progestin (progestogen) (E+P) randomised clinical trial in the *New England Journal of Medicine* has directly addressed these issues² but was not cited in the Shapiro review. In the WHI report, individual use of mammography in the years immediately prior to and after E+P use was provided and no differences in mammography utilisation were seen comparing women in the E+P group to those in the placebo group. In addition, breast cancer incidence was seen to rapidly decline after intervention ended but only in the E+P group, directly addressing the two major concerns raised.² In addition, while the Shapiro review considered only three reports addressing the timing of E+P use and change in breast cancer incidence, a large number of more recently reported analyses addressing this issue found generally consistent associations between reduction in menopausal hormone therapy use and subsequent lower breast cancer incidence.^{3–10}

Addressing the topic of E+P and breast cancer risk, a prior commentary by Shapiro and colleagues on the WHI randomised, placebo-controlled clinical trial evaluating E+P challenged the

conclusion that combined hormone therapy increased breast cancer incidence and breast cancer mortality.¹¹ The authors suggested the WHI findings did not adequately satisfy the criteria for bias, confounding, statistical stability, the strength of the association, duration–response, internal consistency, external consistency or biological plausibility.

While it is appropriate for Shapiro and colleagues to review and comment on the findings of published literature, the omissions and inaccuracies in their report should be identified to permit fair-balance consideration of the available evidence. In this regard, the description of Shapiro and colleagues of the conduct of the WHI E+P trial, particularly with respect to mammography use and participant follow-up procedures, is inaccurate. In addition, the characterisation of the proposed explanation for the study findings misstates the published view of the WHI authorship.

This communication is not intended to point-by-point address all issues raised in the 2011 Shapiro commentary. Rather, it addresses the inaccurate description of critical components of the WHI trial conduct and provides clarification of our published description of the biological rationale underlying the study findings. However, we would be remiss not to point out that empirical published evidence from the WHI trial undercuts their argument that unblinding of women due to bleeding may have caused detection bias. Study gynaecologists (not the women) were unblinded in order to manage bleeding, most of the unblinding occurred in the first 2 years and if gynaecologist (or participant) concern about breast cancer played a role in ascertainment one would have expected an increased risk during the first 2 years – the opposite of what was actually observed.^{12–13} We also agree that discontinuation rates may bias trial results, and indeed this is why ‘intent-to-treat’ analyses are preferred over ‘on treatment’ analyses. Indeed, in our first publication we showed that breast cancer risk was higher when analyses were confined to adherent women.¹³

Much of the argument presented by Shapiro and colleagues¹¹ regarding the WHI E+P randomised trial results regarding breast cancer appears to be based on their understanding of the disposition of women in the trial who

stopped their assigned treatment. Shapiro and colleagues state that “those who did stop also stopped receiving annual study mammograms”. They then calculate what the mammography rates would be if all those who stopped study medication during the trial received no further mammograms (42% of E+P and 38% of placebo participants). On this basis they suggest that, as the trial progressed, mammography rates became low and could have been differentially utilised by E+P compared to placebo participants resulting in detection bias.¹¹

The description of Shapiro and colleagues regarding mammography utilisation in the WHI trial is inaccurate with respect to the actual trial conduct. Participants were not “dropped from follow-up when they discontinued study medication”.¹¹ Rather “participants were followed for clinical outcomes regardless of medical adherence”.^{12–13} This meant continual monitoring on an ongoing semi-annual basis for clinical outcomes and annual capture of information regarding mammogram frequency and findings.

The statement in the Shapiro commentary that women who stopped study medication “also stopped receiving annual study mammograms”¹¹ is also incorrect. While mammograms were mandated on an annual basis, the vast majority of mammograms for WHI participants were performed in the community at more than 3000 clinics, hospitals and practice settings.^{13–14} Regardless of continuation of study medication use, women were questioned annually regarding whether a mammogram was obtained. The mammogram reports were obtained, reviewed and results coded. As a result, the values provided in our publications for mammography use, which were balanced between randomisation groups and high throughout the study intervention and follow-up periods, are accurate as published.^{2–13–15} They reflect the findings from the 95.9% of randomised participants who provided recent (within 18 months) follow-up information regardless of their adherence to study medications.¹³

Similarly, the statement from the Shapiro commentary that “mammography rates among women who discontinued their assigned treatments were not compared and is likely that they were higher in women originally assigned to E+P”¹¹ is inaccurate. The

percentages for mammography use in E+P versus placebo users in the WHI report of the trial^{2 13 14} was based on comprehensive assessment of mammography from all sources regardless of adherence to the study medication (E+P or placebo) in the indicated number of participants continuing follow-up.

We follow with selective comments regarding the Shapiro commentary conclusions on the relationship of the E+P findings to criteria supporting causal inference.

The major thrust of the rejection by Shapiro and colleagues that the conduct of the WHI E+P trial did not meet confounding criteria was that there was differential early detection of breast cancer in E+P participants due to unbalanced mammography. However, this was simply not correct. We have published the year-by-year frequency of mammography by randomisation assignment both during^{13 15} and after the combined hormone therapy intervention ended.² In addition, the consequence of early detection of breast cancers should be diagnosis at earlier stage and reduced breast cancer mortality related to early medical intervention. In fact, the breast cancers in the E+P group were diagnosed at more advanced stage and there was a statistically significant increase in breast cancer mortality.^{14 15} Just the opposite of what would be expected from a bias related to early detection.

The Shapiro commentary also questions whether results from the WHI E+P trial identified a duration response relationship since there was a reduced hazard ratio for breast cancer with E+P use during the first 2 years of follow-up. In fact, we have published analyses indicating that E+P use significantly interfered with breast cancer detection by mammography and delayed breast cancer diagnosis.¹⁴ Consequently it would be incorrect to apply a linear duration response criteria on an intervention that not only increased the endpoint (breast cancer) but decreased the chance of identifying that endpoint (by interfering with breast cancer detection).

With respect to biological plausibility, the Shapiro commentary incorrectly projects a hypothesis never stated in any WHI publication, namely that WHI investigators felt that E+P acted as a promoter of breast cancer. We have never addressed the outmoded concepts of initiation and promotion in our discussions. Rather, we suggested that E+P

stimulates growth of already established breast cancers, which could occur at any size tumour and could be manifest after even short duration exposure.

Finally, with respect to biological plausibility of a rapid drop in breast cancer after stopping E+P use the Shapiro commentary states “there is no pathological evidence to support the suggestion that withdrawal of E+P leads to regression of preclinical cancers”.¹¹ However, in fact in the WHI trial breast cancer incidence substantially decreased in the years immediately following discontinuation of E+P but not placebo use.² The WHI hypothesis was that rapid withdrawal of the hormones represented a hormonal treatment equivalent to oophorectomy in premenopausal women or estrogen receptor-targeted therapy like tamoxifen or estrogen reduction with aromatase inhibitors. In that setting rapid regression of breast cancers are routinely seen. In primary prevention trials comparing tamoxifen or exemestane to placebo, separation of the incidence curves was seen beginning early in the second year of the trials.^{16–18}

Readers are free to interpret the published findings from the WHI randomised trial evaluating E+P as they wish. However, they should not base their judgements on inaccurate description of the trial conduct or the misrepresentations of the biological rationale underlying our findings.

Rowan T Chlebowski, MD, PhD

Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA, USA; rowanchlebowski@gmail.com

Liana Nikolaenko, MD

Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center, Torrance, CA, USA; liananik@gmail.com

Garnet Anderson, PhD

Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA; garnet@whi.org

Competing interests None

Provenance and peer review Not commissioned; internally peer reviewed.

J Fam Plann Reprod Health Care 2013;**39**:226–228. doi:10.1136/jfprhc-2013-100642

REFERENCES

- Shapiro S, Farmer RDT, Stevenson JC, *et al*. Does hormone replacement therapy (HRT) cause breast cancer? An application of causal

principles to three studies. Part 5. Trends in breast cancer incidence in relation to the use of HRT. *J Fam Plann Reprod Health Care* 2013;**39**:80–88.

- Chlebowski RT, Kuller L, Prentice RL, *et al*. Breast cancer after estrogen plus progestin use in postmenopausal women. *N Engl J Med* 2009;**360**:573–587.
- Farhat GN, Walker R, Buist DS, *et al*. Changes in invasive breast cancer and ductal carcinoma in situ rates in relation to the decline in hormone therapy use. *J Clin Oncol* 2010;**28**:5140–5146.
- Renard F, Vankrunkelsven P, Van Eycken L, *et al*. Decline in breast cancer incidence in the Flemish region of Belgium after a decline in hormonal replacement therapy. *Ann Oncol* 2010;**21**:2356–2360.
- De R, Neutel CI, Olivetto I, *et al*. Breast cancer incidence and hormone replacement therapy in Canada. *J Natl Cancer Inst* 2010;**102**:1489–1495.
- von Euler-Chelpin M. Breast cancer incidence and use of hormone therapy in Denmark 1978–2007. *Cancer Causes Control* 2011;**22**:181–187.
- Sprague BL, Trentham-Dietz A, Remington PL. The contribution of postmenopausal hormone use cessation to the declining incidence of breast cancer. *Cancer Causes Control* 2011;**22**:125–134.
- Rusner C, Bandemer-Greulich U, Engel J, *et al*. Population-based hormone receptor-specific incidence trends of breast cancer in Germany. *Maturitas* 2012;**73**:152–157.
- Hofvind S, Sakshaug S, Ursin G, *et al*. Breast cancer incidence trends in Norway – explained by hormone therapy or mammographic screening? *Int J Cancer* 2012;**130**:2930–2938.
- Zbuk K, Anand SS. Declining incidence of breast cancer after decreased use of hormone-replacement therapy: magnitude and time lags in different countries. *J Epidemiol Community Health* 2012;**66**:1–7.
- Shapiro S, Farmer RD, Mueck AO, *et al*. Does hormone replacement therapy cause breast cancer? An application of causal principles to three studies. Part 2. The Women's Health Initiative: estrogen plus progestogen. *J Fam Plann Reprod Health Care* 2011;**37**:165–172.
- Rossouw JE, Anderson GL, Prentice RL, *et al*. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative. *JAMA* 2002;**288**:321–333.
- Chlebowski RT, Hendrix SL, Langer RD, *et al*. Estrogen plus progestin influence on breast cancer and mammography in healthy postmenopausal women: the Women's Health Initiative randomized trial. *JAMA* 2003;**289**:3243–3253.
- Chlebowski RT, Anderson G, Pettinger M, *et al*. Estrogen plus progestin and breast cancer detection with mammography and breast biopsy. *Arch Intern Med* 2008;**168**:382–391.

- 15 Chlebowski RT, Anderson GL, Gass M, *et al.* Influence of estrogen plus progestin on breast cancer incidence and mortality. *JAMA* 2010;304:1684–1692.
- 16 Fisher B, Costantino JP, Wickerham DL, *et al.* Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst* 2005;97:1652–1662.
- 17 Cuzick J, Forbes JF, Sestak I, *et al.* Long-term results of tamoxifen prophylaxis for breast cancer – 96 month follow-up of the randomized IBIS-I trial. *J Natl Cancer Inst* 2007;99:272–282.
- 18 Goss PE, Ingle JN, Ales-Martinez J, *et al.* Exemestane for breast-cancer prevention in postmenopausal women. *N Engl J Med* 2011;364:2381–2391.