

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

We thank Drs Chlebowski, Nikolaenko and Anderson for their comments.<sup>1</sup>

We have previously reviewed<sup>2</sup> the article published by Chlebowski and his colleagues in the *New England Journal of Medicine*,<sup>3</sup> and the claim that it documented that “mammography use was similar in the hormone-therapy and placebo groups ... before and after the intervention [i.e. the Women's Health Initiative (WHI) clinical trial]” is incorrect. Only the percentages of breast cancer that were detected by mammography were documented.

In a subsequent article Chlebowski *et al.*<sup>4</sup> stated that “mammography frequency was comparable in the two randomization groups during the original trial period ... (annualized percentage, 80% for hormone vs 80% for placebo). In the re-consenting population [i.e. women who consented for long-term follow-up after the protocol-specified trial period ended] ... the percentages of women with one or more mammograms were also comparable ... (86% for hormone vs 86% placebo [sic])”. However, the annual numbers, or the rates, of mammography among the women who stopped their treatments, either during the trial or thereafter, were not reported, and the likelihood that E+P [estrogen plus progestogen (progestin)] users who stopped received

more mammograms than placebo users who stopped was not excluded.

The statement that we “considered only three reports addressing the timing of [E+P] use and breast cancer incidence” is again incorrect<sup>5</sup>: we considered 31 reports (References 11–16, 23, 29, 31, 32, 34, 36–41, 43–56 in our previous article).<sup>5</sup> And while we regret having overlooked seven recently published reports,<sup>6–12</sup> they do not explain the inconsistent findings reported from the same databases, or from the same countries.<sup>5</sup> Nor do they necessitate any change in our conclusion that “a decline in breast cancer incidence should consistently have been observed in all or virtually all ... studies, and it has not been”. Nor do they change our further conclusion that “the decline should also have continued for several years, and it did not”.

Chlebowski *et al.* are once again incorrect when they quote us as having stated that participants were “dropped from follow-up when they discontinued study medication”.<sup>2</sup> We made no such statement.

Chlebowski *et al.* argue that “empirical ... evidence from the WHI trial undercuts [our] argument that unblinding ... due to bleeding may have caused detection bias” since in that case “one would have expected an increased risk during the first 2 years”, but a decreased risk was instead observed. That decrease could have been due to chance: in Years 1 and 2 of follow-up<sup>13</sup> the hazard ratios were 0.62 (based respectively on 11 and 17 E+P- and placebo-exposed cases) and 0.83 (26 and 30 cases); 95% confidence intervals were not given. In addition, E+P users subjected to the need to rule out endometrial cancer would also have become concerned about the possibility of breast cancer, especially since they were already informed at baseline that this was an outcome under study. With the passage of time they would progressively have become more concerned. The respective ‘unblinding’ rates were 44.4% and 6.8% in the E+P and placebo recipients,<sup>13</sup> and detection bias was inevitable.

With regard to confounding, consider a hypothetical clinical trial in which 100% of the participants soon become non-adherent to their assigned treatments, after which follow-up continues for years. As is obvious, an ‘intention-to-treat’ analysis would be absurd. In the WHI trial<sup>13</sup> the respective discontinuation rates of 42% and 38% in the E+P and placebo recipients

came more than one-third of the way to conforming with that absurdity. To minimise both detection bias and confounding the WHI investigators have repeatedly been challenged to publish an ‘as treated’ analysis confined to women who remained both ‘blinded’ and adherent.<sup>2 14</sup> Thus far they have failed to do so.

Chlebowski *et al.* express the opinion that it is incorrect to “apply a linear response criteria [sic] 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)”. If what is meant by that opinion is that increased breast tissue density among E+P users could have interfered with the detection of breast cancer, the increased density would also have augmented the likelihood of detection bias.<sup>2</sup> The plain fact is that a monotonic duration-response effect was not identified.

With regard to biological plausibility, Chlebowski *et al.* split hairs when they argue that the concepts of initiation and promotion are outmoded, and that he and his colleagues instead “suggested that [E+P] stimulates growth of already established breast cancers”. Exactly when a genetically damaged cell becomes an established breast cancer cell is unclear, but the hypothesis was that E+P accelerates the multiplication of such cells, and hence the onset of clinically detectible breast cancer. And there is no experimental evidence to support the speculation that the withdrawal of E+P may have effects similar to those of tamoxifen, aromatase inhibitors or oophorectomy.

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**Competing interests** Samuel Shapiro, John Stevenson, Henry Burger, Alfred Mueck and Anne Gompel presently consult, and in the past have consulted, with manufacturers of products discussed in this article. Richard Farmer has consulted with manufacturers in the past.

#### Provenance and peer review

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