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.1

We have previously reviewed2 the article published by Chlebowski and his colleagues in the New England Journal of Medicine,3 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.4 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 reconsenting 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: we considered 31 reports (Références 11–16, 23, 29, 31, 32, 34, 36–41, 43–56 in our previous article).3 And while we regret having overlooked seven recently published reports,6–12 they do not explain the inconsistent findings reported from the same databases, or from the same countries.7 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”.5 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-up13 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,14 and detection bias was inevitable.

With regard to biological plausibility, we have previously reviewed the evidence from the WHI trial15 that [E+P] stimulates growth of already established breast cancers.16 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 detectable 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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REFERENCES


