REPLY

Response to: Progesterone and breast cancer pathogenesis

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We make it clear in our review (Horwitz & Sartorius 2020) that it is important to distinguish between the natural hormone *progesterone*, and synthetic versions thereof we call *progestins*. We attempt to make the case that, in the breast, *progesterone* is not carcinogenic. We point out, however, that to be fair, the two major clinical studies of menopausal hormone therapies (MHT) – the Women's Health Initiative (WHI) which enrolled women in the 1990s and the Million Women Study (WMS) which began in 1996 – conclude that addition of a synthetic *progestin* to estrogens, increases the risk of breast cancer. We argue that this may reflect important functional differences between natural and synthetic progestational signaling, and that these differences require careful study.

In the commentary 'Progesterone and breast cancer pathogenesis' (published in this issue of *Journal of Molecular Endocrinology*, volume 66, pages C1–C2), Dr Bluming argues that the two MHT studies are statistically flawed, thus explaining the increased breast cancer incidence with the synthetic *progestins* (Bluming 2020).

That may be the case, but both MHT studies continue to be analyzed even today. Green *et al.* (2019) recently concluded that for the WMS, a key finding continues to be that 'Use of oestrogen-progestagen preparations causes much greater increases in the risk of breast cancer than oestrogen-only preparations'. Similarly, for the WHI, Chlebowski *et al.* (2020) reported last month that,

compared to placebo, estrogen plus medroxyprogesterone acetate (but not estrogen alone) 'was significantly associated with a higher breast cancer incidence, but no significant difference in breast cancer mortality'.

In summary, we stand by the points we raise in our review and are pleased that they may lead not just to further discussion, but more importantly, to further experimentation.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this article.

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