CLIMACTERIC
https://doi.org/10.1080/13697137.2023.2292073

Taylor & Francis
Taylor & Francis Group

LETTER TO THE EDITOR

Progesterone and not estrogens or androgens causes breast cancer

H. J. T. Coelingh Bennink[a] and F. Z. Stanczyk[b]

[a]Pantarhei Bioscience BV, Zeist, The Netherlands; [b]Department of Obstetrics and Gynecology, University of Southern CA, Keck School of Medicine, Los Angeles, CA, USA

Dear Editor,

The article 'Lack of evidence that progesterone in ovulatory cycles causes breast cancer' by Gompel et al. [1] is an extensive comment on our Perspective Review paper 'Progesterone from ovulatory menstrual cycles is an important cause of breast cancer' [2] by Herjan J. T. Coelingh Bennink, Iman J. Schultz, Marcus Schmidt, V. Craig Jordan, Paula Briggs, Jan F. M. Egberts, Kristina Gemzell-Danielsson, Ludwig Kiesel, Kirsten Kluivers, Jan Krijgh, Tommaso Simoncini, Frank Z. Stanczyk and Robert D. Langer. It makes sense to mention all authors here since all of us agreed on the text and the implications for the use of reproductive hormones as drugs for human conditions. All authors also agreed on the text of this Letter. To provide context to the statements made by Gompel et al. [1], we first summarize our key observations, findings and conclusions, and subsequently comment on the issues raised.

Distinguish between cause and stimulation of breast cancer

Our objective when reviewing the literature on the role of sex hormones, especially estradiol (E2), progesterone (P4) and testosterone, as a cause of breast cancer was to try to distinguish between causing breast cancer or stimulating the growth of already existing breast cancer [2]. This differentiation is often not made, as demonstrated by Gompel et al., who have also confused these matters in their comments [1]. Essential for this differentiation is to look at the effect of sex hormones on normal breast epithelium and not on breast cancer. Two questions with major clinical implications are especially relevant: can the sex hormones E2, P4 and testosterone cause mutations in normal breast epithelium; and what is the lag time between the induction of a mutation and the diagnosis of breast cancer?

Non-hormonal causes of breast cancer can be genetic or environmental, as briefly discussed in the Perspective Review [2]. The approximate 10% of breast cancers that are due to genetic causes are generally caused by DNA repair mutations [3], and it would be interesting to know what would happen in women with such repair mutations if no menstrual cycles occurred. The environmental factors related to breast cancer are in most cases stimulatory factors, as shown by the fact that breast cancer does not seem to occur without P4, independent of the presence of environmental factors. Indeed, toxic factors and irradiation can induce mutations, as shown by the early age of breast cancer in atomic bomb survivors in Japan [4] mentioned by Gompel et al. [1].

The mutagenicity of sex hormones

During the menstrual cycle, P4 has a strong proliferative effect on normal breast epithelium, whereas E2 and testosterone have only minimal effects. We agree with Gompel et al. that P4, just like estrogens and androgens, does not induce mutations, but P4 is carcinogenic for the breast since it stimulates the synthesis of several strong mutagens in normal breast epithelium [1]. We have summarized in our Perspective the mutagenicity of several of those factors including the paracrine factors receptor activator of nuclear factor-κB ligand (RANKL) and WNT4, and the DNA mutator APOBEC3B [2].

There is no convincing evidence that natural and synthetic estrogens and androgens or their metabolites are able to cause mutations in normal breast epithelium. We have supported our pathophysiological molecular considerations concerning the essential role of P4 with clinical data and we searched the literature for the relationship between the occurrence of breast cancer and exposure to P4. In summary, we found that breast cancer does not occur in women without menstrual cycles, who have not been exposed to reproductive hormones due to genetic abnormalities. We also found a strong correlation between the total lifetime number of menstrual cycles and the occurrence of breast cancer in physiological, pathological and genetic circumstances affecting the number of cycles a woman experiences, which we illustrate with extensive data in our Perspective [2]. Although there is no proof of ovulation in every cycle in all these studies, there is no reason whatsoever to question that, in general, most cycles will have been ovulatory with luteal phase P4.

The essential role of P4 and not E2 or testosterone is supported by clinical situations with estrogens and normal breasts but without P4, where breast cancer does not occur (e.g. complete androgen insensitivity syndrome) or where the risk is very low as in male to female transgender persons. The female to male transgender transition demonstrates that

CONTACT Herjan J. T. Coelingh Bennink hcb@pantarheibio.com Pantarhei Bioscience BV, P.O. Box 464, Zeist, AL 3700, The Netherlands