

## **Estetrol combined to progesterone for menopause or contraception indication has limited effect on breast cancer growth**

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Given the unequivocal benefits of menopause hormone therapies (MHT) and combined oral contraceptives (COC), there is a clinical need for new formulations devoid of any risk of breast cancer promotion. Accumulating data support that estetrol (E4) is a promising natural estrogen for medical indications. E4-based COC has been recently approved by EMA and FDA and phase 3 clinical studies are ongoing for MHT. Nevertheless, the assessment of these treatments on breast cancer risk in women can only be conducted during patient follow-up over decades. In this preclinical study performed on 3 in vivo models of breast cancer, we show that E4 is neutral on breast cancer development when administered at a therapeutic dose for MHT or COC. In addition, we also report that this dose of E4 remains active on endometrium. This implies that a progestogen should be combined to E4 to protect the endometrium of non-hysterectomized women from hyperplasia and cancer. Based on in vivo models and transcriptomic analysis, our works evidence that combining a progestogen to E4 remain neutral on breast cancer growth. Therefore, these data emphasize that the therapeutic dose of E4, for MHT and COC, combined with or without progesterone or drospirenone presents a better benefit/risk profile towards breast cancer risk.