

Estetrol and mammary gland : friends or foes?

Anne Gallez, Françoise Lenfant, Elisabetta Marangoni, Jean-Michel Foidart, **Christel Péqueux**.

Hormonal treatments used to treat menopause symptoms increase the breast cancer risk. New formulations with a better benefit/risk profile are thus necessary. Estetrol (E4) is a native fetal estrogen that is currently approved for use as the estrogen component in a combined oral contraceptive. E4 is also being developed as a menopause treatment (MT) that abrogates hot flashes. E4 like the other estrogens activates the nuclear Estrogen Receptor alpha but antagonizes the membrane form of this receptor. This causes selective tissue actions, with limited impact on the normal and malignant breast. Here, we show that doses of E4 that are neutral on breast cancer growth and lung metastasis dissemination enhance endometrial proliferation. A progestogen should thus be combined to E4 to prevent endometrial hyperplasia and cancer. Through in vivo observations and transcriptomic analyses, our work provides evidence that combining a progesterone (P) or Drospirenone (DRSP) with E4 is neutral on breast cancer growth and dissemination, with very limited transcriptional impact. Our study provides new evidence that a therapeutic dose of E4 for MHT or COC, combined with P or DRSP may provide a better benefit/risk profile towards breast cancer risk compared to hormonal treatments currently available for patients.