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Dose-dependent effect of estetrol (E4) on mammary gland and breast cancer: an opportunity for new menopause treatments

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Context: Estetrol (E4) is the first Native Estrogen acting Selectively in Tissues (NEST™). It is produced by the human fetal liver during pregnancy. Several evidences highlight that E4 is a promising compound for a new generation of menopause treatment. It is thus mandatory to clearly define its impact on mammary gland and on breast cancer, one of the major side effect of hormone replacement therapy (HRT).
Objective: The aim of this study is to characterize the dose-dependent effect of E4 on mammary gland and on breast tumor development.
Results: We report preclinical data showing that E4 is less efficient than 17?-Estradiol (E2) to induce mammary gland growth. In addition, we observed that E4 used at 0.3 mg/kg/day did not modify neither mammary primary tumor, intratumoral vessel density nor lung metastasis. This dose (0.3 mg/kg/day) matches to the therapeutic dose that could be used in human and already prevents hot flushes in animal models. Thus, E4 has a minimal impact on breast cancer growth. It acts as a weak estrogen and stimulates the growth of ER?-positive breast cancer only at concentration exceeding therapeutic needs. Interestingly, we also observed through in vitro and in vivo experiments that E4 was able to antagonize the action of E2. This dual weak-estrogenic/anti-estrogenic feature of E4 resulted from differential activation of ER? expressed either by cancer cells or by their microenvironment.
Conclusions: In conclusion, E4 exhibits both weak estrogenic and anti-estrogenic effects that are dose dependent and related to ER? signaling. Since E4 has a limited impact on breast cancer, it may offer a safe therapeutic window for the treatment of menopausal symptoms.

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