Anti-estrogenic effect of estetrol in normal mammary gland

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Estetrol (E4) is a natural estrogen produced by the human fetal liver in both male and female foetuses. Due to its unique properties, E4 seems to be safer and suitable for oral contraception. Some preclinical data suggest a protective impact of E4 on breast cancer. The current study was designed to study the effect of E4 on normal mammary gland development. We investigated the impact of E4 alone or in association with estradiol (E2) on normal human breast epithelial cells (HBE) proliferation and on mouse mammary gland development.

Normal human breast samples were obtained from women undergoing reduction mammoplasty. Cells were then exposed ex vivo to increasing doses of E2 and/or E4. Moreover, five-week-old ovariectomized mice were treated orally with E2 and/or E4 for 14 days. The effects of these estrogen treatments on mammary gland development were then evaluated and quantified using a new unique computerized method.

We demonstrated that E4 stimulates the proliferation of human normal breast cells and promotes the growth of the mammary gland (total length, branching). The stimulatory effect of E4 on HBE cells proliferation can be prevented by the anti-estrogens ICI 182780 and tamoxifen. When E4 is administered concomitantly to E2, it significantly antagonizes the stimulatory effect of E2 in both HBE cells in vitro and in murine mammary glands in vivo.

Our data thus strongly support the hypothesis that E4 could contribute to prevent a role and/or to decrease the risk of breast cancer.