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Estradiol concentration in breast tissue obtained during surgery in women taking oral contraceptives or adjuvant endocrine therapy.

PROF. DR. H. DEPYPERE

Menopauze kliniek en borstkliniek, Universitair Ziekenhuis, Gent. No conflict of interest
Relative Levels of Estrogen in Breast Cancers and Circulation

Premenopausal

- Estrogen concentration in the breast

- Peripheral estrogen production

Postmenopausal

- Estrogen concentration in the breast

- Peripheral estrogen production

Blood vessels

O = Ovulatory
L = Luteal
F = Follicular

Miller W et al.
Glandular tissue was isolated by meticulous dissection avoiding contamination from the surrounding fat and connective tissue. The actual 17β-estradiol concentrations in breast epithelial cells of patients treated with tamoxifen or with an aromatase inhibitor, or healthy controls, were quantified using ELISA.
Normal breast tissue was obtained during 68 operations for aesthetic or reconstructive indications in women with and without breast cancer. Our study included six different groups of women.

Normal cycling women (n=24)
Women taking oral contraceptives (n=12)
Postmenopausal women (n=16)

These women wanted a breast reduction for aesthetic reasons

Premenopausal women currently taking tamoxifen treatment (n=6)
Postmenopausal women currently taking tamoxifen treatment (n=4)
Postmenopausal women currently taking an aromatase inhibitor (n=6)

The latter three groups of needing contra-lateral corrective aesthetic surgery.
Findings:

In normal cycling women, there was a strong correlation \((r=0.853; P<0.0001, n=24)\) between \(17\beta\)-estradiol concentrations in serum \((median: 42.2 \text{ pg/mL}; CI: 13.8-80.6 \text{ pg/mL})\) and in breast epithelial cells \((36.6 \text{ pg/g}; CI: 21.5-139.9 \text{ pg/g})\).

Women taking oral contraceptives had both low serum and breast tissue levels of \(17\beta\)-estradiol. Postmenopausal controls had low serum and breast tissue \(17\beta\)-estradiol concentrations \((r=0.813; P=0.0001, n=16)\).

Six premenopausal women taking tamoxifen had very high concentrations of \(17\beta\)-estradiol in both serum \((277.9 \text{ pg/mL}; CI: 69.3-641.3 \text{ pg/mL})\) and epithelial cells \((251.9 \text{ pg/g}; CI: 115.0-426.5 \text{ pg/g})\), being respectively 6.6 times and 6.9 times higher than those observed in premenopausal controls.

Four postmenopausal women taking tamoxifen had low concentrations of \(17\beta\)-estradiol in serum \((7.0 \text{ pg/mL})\) and in epithelial cells \((14.6 \text{ pg/g})\). Six women treated with aromatase inhibitors had extremely low concentrations of \(17\beta\)-estradiol, in both serum and epithelial cells.
Box and whiskers plots of the concentration of 17β-estradiol in breast epithelial cells of women taking aromatase inhibitors (AI, n=6), premenopausal women taking oral contraceptives (EE2, n=12), postmenopausal controls (CTL post, n=25), premenopausal controls (CTL pre, n=24), premenopausal women taking tamoxifen (TAM pre, n=6), and postmenopausal women taking tamoxifen (TAM post, n=4).
The median serum and breast tissue $17\beta$-estradiol concentrations of premenopausal women taking tamoxifen were resp. 6.6 and 6.9 times higher than those measured in normal cycling women.

Tamoxifen effectuates its protective activity in premenopausal women, despite extremely high levels of $17\beta$-estradiol in epithelial breast cells. This sustains the hypothesis that the affinity of tamoxifen for the estrogen receptor is so strong to even compete with high intracellular estrogen concentrations.

Lowering circulating $17\beta$-estradiol concentrations by concomitant LHRH analogs may, therefore, remain ineffective as far as breast cancer relapse and mortality are concerned, in low risk women.
Our study may also explain why two studies on hormonal replacement therapy after breast cancer had different outcomes. The Habits trial was stopped after 2.1 years due to the 3.5 increased risk of relapse in women receiving hormone replacement.

In the Habits trial only 21% patients were taking tamoxifen, whereas it can be estimated that at least 60% of breast cancers were estrogen receptor positive.

In the Stockholm trial the risk of relapse was not increased even after 10 year of follow up. In the latter study, 52% of women were treated simultaneously with tamoxifen.
Conclusion:

This study shows that serum levels of estradiol affect the estrogen levels in breast tissue. Adjuvant anti-estrogen tamoxifen treatment in premenopausal women is associated with high concentrations of 17β-estradiol in breast epithelial cells.

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