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Estrogen-dependency of breast cancer after menopause

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The fact that the majority of breast cancers detected after menopause is estrogen receptor positive and dependent on estrogen for growth is at odds with the known concentrations of estradiol in serum after menopause. There are a number of observations that lead us to hypothesize that estradiol concentrations in the breast are regulated and maintained at relatively constant levels by enzymes within the breast. While serum estradiol declines to 30 pg/ml or less after menopause from levels that may exceed 300 pg/ml during the menstrual cycle, the concentrations in nipple aspirate fluid (NAF) of the breast decline non-significantly by 20 to 50% from concentrations present in premenopausal women. Similar results have been reported for measurements of estrogens in breast tissue. Fluctuations in serum levels of estradiol during the menstrual cycle are also not reflected in NAF, and the correlation is poor with R^2 values of 0.15 or less. The reason for the poor correlation relates, in part, to the different patterns of estradiol in serum and NAF during the menstrual cycle. In a cross-sectional study conducted in our laboratory serum estradiol was highest in the mid-cycle period as expected but NAF estradiol was highest in the follicular phase of the cycle and lowest at mid-cycle. Current data from a longitudinal study confirm these observations. Evidence for local formation of estradiol in the breast of premenopausal women has been obtained by many investigators. In one such study reported from this laboratory the concentration of estradiol was estimated from its precursor concentrations in the breast by a multiple regression analysis. The model correlation was 0.85. That the estradiol measured in NAF was biologically active was shown by the fact that estradiol and its precursors in NAF also related closely to the concentration of the estrogen response protein cathepsin D with a model correlation of 0.93. A similar study has not been conducted in postmenopausal women at this time but one would assume that the relationship would be as good or better because the availability of estradiol from serum is greatly decreased, and biosynthesis from precursors within the breast must be increased to maintain tissue concentrations.

Recent results from this laboratory show that polymorphisms in several genes of steroid transport, biosynthesis and metabolism result in significant alterations in the concentrations of the products in NAF of human subjects. A SNP in the steroid sulfate transporter SLCO2B1, known to decrease its activity, resulted in a decrease in both estradiol and testosterone in NAF but not in serum. Similarly, a SNP in CYP19A1, known to increase aromatase activity, resulted in a decrease in the precursor DHEA in NAF but not in serum. A SNP in CYP1B1, which has activity in 4-hydroxylation of estrogens and 6β-hydroxylation of neutral steroids, was found to increase progesterone in both serum and NAF. The latter is consistent with observations on the relatively good correlation between serum and NAF progesterone. The increase in serum progesterone is undoubtedly due to decreased metabolism in the liver, and this produced a decrease in progesterone in the breast. Also, a SNP in AKR1C3 resulting in increased 17β-hydroxysteroid dehydrogenase activity resulted in an increase in serum androstenedione and an associated increase in NAF estrone. All of the evidence presented here indicates that enzyme systems in the breast are capable of increased activity to support estrogen levels in the breast. On the other hand, increases in availability of estradiol either by administration of estrogens, as in women receiving hormone replacement, or indirectly, as in women taking tamoxifen, does not appear to increase the clearance of estrogen from the breast. A greater than 7-fold increase in NAF estradiol was found in postmenopausal women taking hormone replacement, and a greater than 2-fold increase was observed in women taking 20 mg of tamoxifen per day. The latter result is similar to the increase in estradiol in serum.

The question of how lower concentrations of estrogens in the breast stimulate production from within the breast is largely unknown. If the activity of steroidogenic enzymes is greatest in the absence of estradiol, and increasing concentrations of estradiol inhibit its biosynthesis, this could explain the results discussed above. Certainly, there are many genes that are down-regulated by estradiol, but a systematic study of potential effects on biosynthesis of estradiol has not been conducted. Estrogen biosynthesis within the breast is an important aspect of tumor growth in postmenopausal women, and inhibitors that are specific to the breast could be effective without sacrificing the beneficial effects of estrogens in other organ systems of the body.

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