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EDITORIAL

Androgens, estrogens, and mammary epithelial proliferation

The growth of the breast is influenced by both androgens and estrogens. Breast tissue is similar in prepubertal boys and girls, but at puberty girls have an increase in breast mass, including both mammary epithelium and adipose tissue.[1] The stimulus to this growth is primarily estrogen. In most boys, puberty is marked by an enlargement of the breast, gynecomastia,[2] which is followed by regression of the tissue. This gynecomastia, as well as gynecomastia appearing at other times in men, is due to an imbalance in the androgen:estrogen ratio,[3,4] which is initially low, causing the gynecomastia, and then rises, resulting in disappearance of the gynecomastia and the loss of most glandular epithelium. In XY individuals who lack androgen receptors, the breasts develop as in essentially normal females, despite an androgen:estrogen ratio that is in the adult male range.[5] It has also been shown that testosterone and dihydrotestosterone can inhibit the action of estrogen in MCF-7 breast cancer cells.[6] Because breast tissue contains receptors for both androgens and estrogens,[7] it appears that the action of androgens to diminish the activity of estrogens was mediated by androgen binding to its receptor, although the detailed mechanisms for this action were unclear.

The paper by Dimitrakakis et al[8] in this issue of *Menopause* casts new light on a possible mechanism for the interplay of androgens and estrogens on breast growth. Their studies were done using normally cycling female rhesus monkeys treated with an androgen antagonist, flutamide, and with ovariectomized rhesus monkeys treated with estradiol (E_2), estradiol plus progesterone (E_2/P), or estradiol plus testosterone (E_2/T). At the end of each treatment, breast tissue was removed and stained for Ki67 as a marker of mammary epithelium proliferation (MEP). In addition, measurements of estrogen receptor α (ERα), estrogen receptor β (ERβ), and the MYC oncogene were taken by immunohistochemistry and also by in situ hybridization.

A marked increase in MEP was observed in the flutamide-treated monkeys, a recapitulation of the breast development seen in AR negative XY individuals.[9] No measurements of ERα or ERβ were made in these monkeys.

In the ovariectomized monkeys, E_2 administration resulted in a marked increase in MEP and MYC, whereas E_2/T resulted in lower levels of MEP and MYC. The expression of $E_{2\alpha}$ that followed E_2 administration was lowered by E_2/T, and $E_{2\beta}$ expression was increased by E_2/T compared with $E_{2\beta}$ expression after E_2. MYC expression and MYC mRNA expression were reduced by E_2/T compared with the expressions noted after E_2. MYC protein and RNA expression were similar after E_2/P as after E_2. The authors conclude that testosterone exerts its antiestrogenic effect through changes in ERα, ERβ, and MYC. In addition, they suggest that adding androgens to standard hormone therapy may reduce the risk of estrogenic cancer risk in women with ovarian failure.

These are very interesting findings that help to explain the complex interplay of androgens and estrogens on breast tissue. ERβ has been shown to inhibit ERα transcriptional activity,[10] and the authors postulate that the change in E2α:E2β ratio as a result of the testosterone administration can inhibit MYC expression and the resultant decrease in MEP, despite the high levels of E_2. It has been shown that MYC can increase MEP and that there is a correlation between MYC expression and breast cancer.[11,12] The authors grant that other mechanisms may help to explain how AR activation may inhibit mammary tumorigenesis.

Care was taken to maintain testosterone levels at a physiologic concentration of 0.4 ng/mL, important because it has been shown that supraphysiologic levels may bind to the estrogen receptor[13] and normal human breast tissue contains aromatase activity.[14] The peripheral tissue of rhesus monkeys can aromatize androgens to estrogens to the same extent as humans,[15] but the ability of rhesus breast tissue to aromatize is less clear. No measurements of aromatase activity were done in the present study, but it is unlikely that the amounts of estrogens so formed locally would have altered the results.

As noted above, the authors found that androgen increased ERβ expression and decreased the expression of ERα. They postulated that these changes decreased MYC, which in turn decreased MEP. Although androgens have been implicated in prostate cancer, a hormone-dependent cancer,[16] and ERα and ERβ have been noted in prostate tissue, the exact relationships between androgens, ERα, ERβ, and prostate cancer remain unclear. There is, however, some evidence that androgen-lowering therapy may reduce the levels of ERβ.[17,18]

There has been a great deal of interest in the use of androgens to increase libido in women with ovarian failure and as an additional agent to increase bone density.[19-23] There has been less attention paid to its possible role in reducing the risk of breast cancer. It will be of interest to determine whether any of the trials of androgen use in postmenopausal women have shown a decrease in breast cancer incidence. It may be too early to determine this, but the data should be examined.

There are certain caveats to the routine use, in postmenopausal women, of testosterone or other androgens, especially nonaromatizable androgens, because the latter may have less of an effect on bone. As noted, the amount of androgen to be administered should not be enough to raise the circulating level much above 0.4ng/mL because that could result in undesirable side effects. The level of E_2 that was achieved in the present study was one that occurs at ovulation, but it was far higher than noted at other times of the cycle, especially in rhesus monkeys.[24] Thus, it might be possible to inhibit the effect of estrogen on MEP with lower levels of androgen and lessen the risk of side effects.

Whether the rhesus monkey model is a suitable one to study androgen and estrogen effects could be debated, given that breast cancer is not common in rhesus monkeys.[25] However, the data relating androgens and MYC in humans is, in general, not too dissimilar to what was found in the present study.

In epidemiological studies, adrenal androgens, dehydroepiandrosterone (DHEA) and its sulfate (DHEAS),[26] as well as testosterone,[27] have been implicated in breast cancer. Although DHEA and DHEAS are characterized as androgens, they bind poorly to the one androgen receptor and could act by other means or as estrogens following aromatization. DHEA and DHEAS are more readily converted to androgens than estrogens, so the possible mechanism relating DHEA, DHEAS, and testosterone to breast cancer remains uncertain.

Although those studies suggest that testosterone may be deleterious for breast cancer, much conflicting data exist.[28] Androgens have been used as a treatment for breast cancer,[29] so the clinical and epidemiologic data are not in full agreement.

Because the role of hormone therapy in increasing the risk of breast cancer is still debated, it will probably be some time before any relationship between androgen use and reduction of breast cancer risk in postmenopausal women is established. However, the studies of Dimitrakakis et al should lead to further investigations into the use of androgens for women with ovarian failure.

Christopher Longcope, MD
Department of Medicine,
University of Massachusetts Medical School,
Worcester, MA, USA

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