3. An early exposition of the androgen-excess theory of breast cancer in 1994

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In the 1950s, Sommers demonstrated, in autopsy studies, that women with breast cancer had a high frequency of ovarian stromal and endometrial hyperplasia, and postulated that these women had chronic anovulation [2]. A few years later, Grattarola demonstrated that living women with premenopausal breast cancer had a high frequency of anovulatory hyperplasia of the endometrium (indicating that the anovulation was chronic) [3] and elevated testosterone excretion [4], a combination of characteristics that would now be described as pathognomonic of the polycystic ovary syndrome [PCOS] [5]; ovariectomy normalized the testosterone excretion [6], proving that the elevation was of ovarian origin. Interestingly, increased urinary testosterone levels reappeared in some of the women after ovariectomy had normalized excretion; in those cases, dexamethasone suppression of the adrenal cortex eliminated the excess testosterone [6], indicating that its source was the biotransformation of adrenal androgens, i.e., DHEA and DHEAS. Still later, studies from Secreto’s laboratory confirmed that a subset of women with breast cancer showed elevated urinary testosterone excretion,
that ovariectomy eliminated it, and that dexamethasone administration
eliminated recurrent hypertestosteronemia after ovariectomy [7].

That both premenopausal and postmenopausal women with breast cancer
have elevated testosterone levels has been found in a number of additional
studies [8, 9, 10-21], though some workers have not found this abnormality
[22-27]; the increased frequency of ovarian stromal hyperplasia in these
patients [2] is presumably the major source of hypertestosteronemia in both
groups. In addition, postmenopausal women with breast cancer have elevated
serum levels of DHEA and DHEAS [8, 28, 29], which can serve as a major
source of additional testosterone production.

The relationship of breast cancer to PCOS

The hallmarks of PCOS are hyperandrogenism and chronic anovulation.
Secreto and Zumoff reported in one study [9] that about 18% of their breast
cancer patients had elevated testosterone excretion, and in a second paper
[12] they reported a frequency of about 60%; the overall average was about
40%. Grattarola [3] found that about 40% of his breast cancer patients had
hyperplastic or atypical endometrium, indicative of chronic anovulation. It
seems reasonable that the hypertestosteronemic and anovulatory populations
may well be the same population, one whose characteristics are similar to
those of PCOS. Since the cumulative lifetime incidence of breast cancer in
Western societies is about 12% [30], it follows that women with breast cancer
who have high testosterone levels and chronic anovulation constitute some
5% of the overall female population, a figure about half the mid-range of
estimates of the prevalence of polycystic ovary syndrome [31-33]. Since
about 40% of women with pre-cancerous atypical breast-ductal hyperplasias
have likewise been found to have elevated testosterone levels [12], it is clear
that the proportion of PCOS patients who develop either precancer or full-
blown cancer of the breast may be very high indeed. Epidemiological studies
have directly demonstrated that PCOS is a major risk factor (RR 3.6) for
postmenopausal breast cancer [34, 35], the great majority of all breast cancer,
but not for premenopausal breast cancer [35, 36]. The absence of statistically
demonstrable risk with chronic anovulation in premenopausal breast cancer
in these latter studies is in contradiction to the demonstration by Grattarola of
a very high incidence of chronic anovulation in premenopausal breast cancer
patients [4]; a possible explanation is that many premenopausal women with
chronic anovulation receive treatment to lower their androgen levels.

PCOS is probably substantially determined by genetic factors [37], so
that the subgroup of premenopausal and postmenopausal breast-cancer
patients who have PCOS-like abnormalities of androgens and ovulation may
represent a second type of genetic predisposition in breast cancer, distinct from the genetic adrenal androgen deficiency that affects only premenopausal breast cancer patients [38].

As in frank PCOS, elevation of serum testosterone (particularly free testosterone) is a regular finding in abdominal (“android”) obesity in women [39,40]; such women, who often have ovulatory disturbances too [41], are clearly at increased risk for breast cancer [42]. Precise distinction of classical PCOS from the PCOS-like syndrome of women with abdominal obesity can be accomplished only retrospectively, when obese women lose weight: if they resume ovulation, they are called PCOS-like syndrome of obesity [41], and if they don’t, they are called true PCOS.

**Mechanisms by which hypertestosteronism could favor the development of breast cancer**

Secreto and Zumoff [9] found that women with operable breast cancer who had elevated testosterone levels preoperatively were more likely to develop recurrences or metastases (a finding more recently confirmed by a separate study from Secreto’s laboratory [43]), and also that women with recurrent or metastatic breast cancer who had elevated testosterone levels were more likely to undergo remission after ovariectomy than women without elevated testosterone levels. The most reasonable explanation for this apparent paradox is that there exist in breast cancers substantial numbers of cells that are testosterone-dependent; such cells would be stimulated to grow and metastasize if elevated levels of testosterone were present, but would regress if the excess testosterone were removed. Support is given to this concept by the finding that testosterone receptors are demonstrable in 50-90% of breast-cancer specimens [44, 45].

Since breast-tissue levels of delta-4 androstenedione are higher than those of serum [46], and testosterone is present in substantial amounts in breast-duct fluid aspired from the nipple [47], it is clear that the testosterone-androstenedione oxidoreduction pair can gain access to the interior of the breast. This may be even more so in women with apocrine cysts of the breast, which show high levels of testosterone [48]; women with such cysts are at high risk for the development of breast cancer [49,50]. Once within breast tissue, testosterone could stimulate the growth of breast-cancer cells by at least three mechanisms: one is by binding to testosterone receptors on testosterone-dependent cells and directly stimulating their growth; a second is by stimulating the formation of epithelial growth factor [EGF] [51, 52], which can in turn stimulate the growth of breast-cancer cells [53]; the third is by aromatization to estradiol (a process that one study shows is
more active in adipose tissues [54], though another study [55] fails to confirm this), with consequent estrogenic stimulation of the growth of breast-cancer cells.

The last of these mechanisms, in which testosterone exerts a tissue effect via aromatization to estradiol, seems strange at first glance, but there exist two striking, well established examples of such a process: 1. Masculinization of the perinatal rodent brain by testosterone requires aromatization of testosterone to estradiol, which then binds to estrogen receptors in the brain; non-aromatizable androgens do not have the masculinizing effect [56, 57]; administered estradiol does not have the masculinizing effect either—only the estradiol formed in situ from testosterone does. 2. Suppression of pituitary gonadotropin secretion by testosterone requires its prior aromatization, as documented by the fact that an aromatase inhibitor prevents the suppressive effect [58]. Thus it is possible that high blood testosterone levels can cause an estrogenic stimulation of breast-cancer cells that high blood estrogens themselves cannot cause.

Finally, PCOS and other hyperandrogenemic states, including that of abdominal obesity, regularly feature marked hyperinsulinemia [59] and elevated levels of one or more insulin-like growth factors [IGFs] [60, 61], and it may well be that the elevated levels of insulin and/or IGFs, are a major, or the major, cause of the hyperandrogenemia, either through their ability to directly stimulate ovarian stromal secretion of testosterone [62, 63] or by increasing intracellular estradiol levels: insulin and IGF-1 stimulate aromatase [64], which is responsible for the aromatization by which testosterone exerts its estrogenic intracellular effects, as described in the preceding paragraph; they also stimulate the reductive activity of estradiol 17-beta hydroxysteroid dehydrogenase [65], which converts estrone to estradiol and thereby increases the effective estrogenicity of a given amount of estrogen.

References

7. Secreto, G., Oriana, S., and Recchione, C. Ovariectomy Alone or in Combination with Dexamethasone in Patients with Advanced Breast Cancer and High Levels of Testosterone or Androstanediol Excretion. 1984, Rev. Endocrine-Related Cancer, Suppl 14, 55.
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