

Opinion

Adrenal androgens and human breast cancer: A new appraisal

... they are ill discoverers that think there is no land when they can see nothing but sea.

Sir Francis Bacon

The Advancement of Learning

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Summary

A clearer picture of the role of adrenal androgens in the etiology of breast cancer is beginning to emerge. Women who develop breast cancer in premenopausal years tend to have subnormal serum levels of adrenal androgens, while subjects who develop the disease in postmenopausal years have supranormal levels of these hormones. Androgens, by acting via the androgen receptor, oppose estrogen-stimulated cell growth in premenopausal years. In postmenopausal women, elevated adrenal androgen levels stimulate cell growth by the action of the unique adrenal androgen 5-androstene-3 β ,17 β -diol, also termed hermaphrodiol, via its combination with the estrogen receptor in a hormone milieu lacking, or having low concentrations of, the classical estrogen 17 β -estradiol.

Introduction

Within the broad field of hormones and breast cancer, perhaps no other area has had such a chequered and stormy history as that of the role of the so-called adrenal androgens in the etiology of the disease. The adrenal androgens are comprised of a group of C₁₉-steroids: dehydroepiandrosterone sulfate (DHEAS), dehydroepiandrosterone (DHEA), 5-androstene-3 β ,17 β -diol (ANDROSTENEDIOL), and 4-androstenedione (ADIONE). Despite the finding that DHEAS was secreted by the human adrenal by Beaulieu et al. in 1965 [1], and quantitatively is the most important steroid in human blood, the exact role of this hormone remains an enigma.

Studies aimed at establishing a possible link between adrenal androgens and human breast cancer first appeared in 1957 [2] when measurements of 11-deoxy-17-ketosteroids in urine were made; these being chiefly derived from metabolism of adrenal androgens. Many studies were reported over the subsequent decade. Some were aimed at determining a discriminant, based on the ratio of 11-deoxy-17-ketosteroids to 17-hydroxycorticosteroids in the urine of breast cancer subjects, as a guide to predicting results of hormone ablative procedures such as adrenalectomy and hypophysectomy. The results of these studies were discussed as part of an excellent review on hormone profiles and the epidemiology of breast cancer by Zumoff [3]. Suffice it to say the data on urinary steroid hormone metabolites

were very controversial and could probably be explained by distortions due to the non-specific effect of illness, or operative stress. As an example, operative stress, such as mastectomy prior to urine collection, was shown to alter the pattern of adrenal androgen metabolites. 16-hydroxylated-5-androstanes were formed in relatively large amounts, and, as these do not react with the Zimmerman reagent normally used in the assay of 17-ketosteroids at the time, incorrect interpretations of adrenal androgen production were made [4].

Problems such as those described above do not apply to prospective studies based on hormone assessment of urine collected from healthy subjects. Three such prospective studies, each involving 5,000 healthy women on the island of Guernsey, were carried out in a remarkable study by Bulbrook and his colleagues between 1961 and 1986 [5]. Urine, and later blood, samples were collected, stored frozen, and when breast cancer occurred in subsequent years, they were subjected to endocrine analysis and comparison made with a number of controls suitably matched for age, weight, parity, etc. In the first study, the main urinary metabolites of DHEAS, i.e. etiocholanolone and androsterone, were assayed in 110 women who subsequently developed breast cancer and 1335 women who did not. Results from women who developed the disease in the first 9 years of the study, and were mainly premenopausal, showed they had significantly lower levels of urinary androgen metabolites than age-matched controls. However, as the follow-up continued over 25 years, the results became less clear cut. Women with androgen metabolites at the lower end of the normal range generally had a diagnosis of their disease in the late-premenopausal period; those with higher levels developed breast cancer at older ages [5]. In analysing their overall data, Bulbrook and Thomas [6] concluded that low blood levels of androgens, as reflected in subnormal excretion of their metabolites, are markers for rapid tumor growth. Androgens may be acting to inhibit tumor growth and therefore time of onset of the actual appearance of a tumor, the hormone environment influencing the growth rate of a clone of neoplastic cells initiated by previous carcinogenic events.

With the advent of radioimmunoassay techniques, serum concentrations of adrenal androgens were able to be determined in breast cancer subjects and controls. Although no general conclusions were reached, the trend was towards a lower concentration of these hormones in breast cancer cases, but again stress of operation was not considered, nor was menopausal status recorded, in many cases [3]. In one carefully controlled study, DHEA and DHEAS were measured in pooled 24 hr serum samples, collection being made every 20 min. Subjects were 11 women with primary operable breast cancer aged 31 to 78 years and controls were 37 normal women aged 21 to 75 years. In contrast to the marked decline in adrenal androgens with age in the blood of normal women, the concentrations of both steroids were age invariant in the cancer patients; the premenopausal patients had subnormal while the postmenopausal patients had supranormal levels of each steroid hormone [7].

More recently, the results of two prospective studies have been published wherein analyses were determined on serum samples stored in blood banks. In the first of these, serum was obtained from the Washington County, Maryland, serum bank, which holds specimens from 25,620 volunteers collected in 1974. Such banks are unique and the policy is to allow analyses of 30 cases and appropriate controls; if statistically significant results are achieved, the study stops. Gordon et al. [8] measured serum levels of DHEA and DHEAS in 30 postmenopausal women who subsequently, at least 9 years later, developed breast cancer, and in 59 matched controls. Significantly elevated serum DHEA levels were found among cases prior to diagnosis compared to controls. DHEAS levels were slightly increased among cases. In a parallel investigation involving 15 women who developed breast cancer while still in their premenopausal years, the risk ratio for women in the highest tertile, compared to the lowest tertile of serum DHEA, was 0.4 with a suggestion of a dose-response trend with increasing levels. No consistent association between serum DHEAS and risk of premenopausal breast cancer was evident [9].

In a very recent study, Dorgan et al. [10] measured DHEAS, DHEA, and ANDROSTENE-

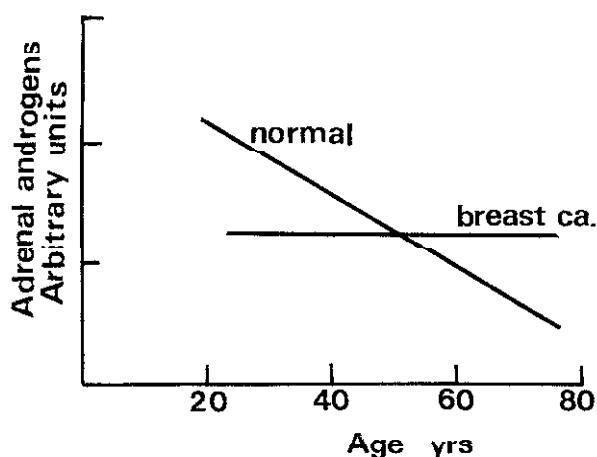


Figure 1. The decrease in serum levels of adrenal androgens with advancing age in normal women is contrasted with the age invariant behaviour seen in women with breast cancer, or at higher risk of developing the disease.

DIOL in serum samples from the Columbia Missouri Breast Cancer Serum Bank. Seventy one healthy postmenopausal volunteers, not taking replacement estrogen when they donated blood, subsequently developed breast cancer up to 10 years later. Two randomly selected controls, who were also postmenopausal and not taking estrogen, were matched to each case on exact age (date \pm 1 year) and time (\pm 2 hours) of blood collection. Significant gradients of increased risk of breast cancer were observed for increasing concentrations of DHEA and ANDROSTENEDIOL. Women whose serum levels of these hormones were in the highest quartiles were at significantly elevated risk compared to those in the lowest. The relationship of DHEAS to breast cancer was less consistent, but women with levels in the highest quartile also exhibited a significantly elevated risk ratio.

All of the above prospective studies are then in general agreement; lowered levels of adrenal androgens being associated with risk of breast cancer in premenopausal years and elevated levels with risk of developing breast cancer in postmenopausal years (Figure 1).

Both DHEA and ANDROSTENEDIOL are mainly derived by peripheral conversion from DHEAS [11] secreted by cells of the zona reticularis of the human adrenal [4]. Although ANDROSTENEDIOL is a member of the adrenal androgen

family, it was shown to possess unique estrogenic properties by Huggins et al. in 1954 [12]. At physiological concentrations, it is estrogenic in a wide variety of experimental systems, including the stimulation of growth of human mammary cancer cells in culture. This action occurs by combination with the estrogen receptor (ER) and without prior conversion to estradiol [13–16]. There are some other remarkable similarities between ANDROSTENEDIOL and estradiol which need to be mentioned. These involve the transformations which the two hormones undergo when exposed to human mammary cancer cells in culture. Firstly, both steroids are converted to biologically inactive esters by combination with a variety of long-chained fatty acids. These esters, which are retained within the cell, then undergo a slow transformation to release the biologically active free hormone. In this manner, occupancy of the ER can be maintained – a process thought to be necessary for hormone-stimulated DNA synthesis and cell replication. Secondly, elimination of hormone from the cell, necessary for signal termination, occurs mainly by formation of water-soluble sulfate esters catalysed by two separate sulfotransferase enzymes. One is specific for phenolic estrogens such as estradiol, and the other for hydroxysteroids such as ANDROSTENEDIOL. Both enzymes are under estrogen control, have a very high affinity for their respective steroid substrates, and show cooperativity in their binding. These enzymes may serve to eliminate the hormone from the cell after processing of the ligand-charged receptor [17].

Rochefort and Garcia [18] demonstrated that high concentrations of potent androgens such as Δ^4 -dihydrotestosterone (DHT), could act as estrogens via combination with ER. The concentrations required to induce estrogenic effects were far higher than those required to saturate the androgen receptor (AR). Such results were of paramount importance in acceptance of the proposal that the specificity of response to steroid hormone, in a defined target tissue, is determined by interaction of charged receptor with nuclear components, and not by the nature of the hormone complexed to this receptor. Estrogenic and antiestrogenic activities of androgens in female target tissues were the subject of

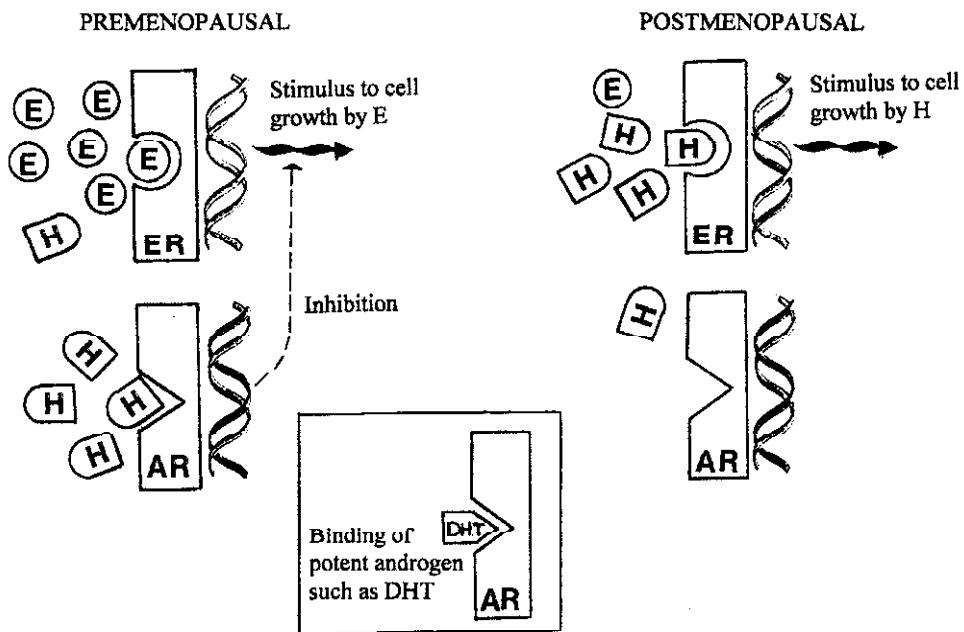


Figure 2. Diagrammatic presentation of binding of sex hormones to ER and AR in transformed mammary epithelial cells. In premenopausal women, high concentrations of estradiol (E) bind with high affinity to ER resulting in a stimulation of cell growth. ANDROSTENEDIOL, also known as hermaphrodiol (H), has a lower affinity for binding to ER compared to E, and is shown binding to AR. In postmenopausal women, when secretion of E from the ovaries ceases, H is able to bind to ER for which it has higher affinity compared to AR. More potent androgens such as DHT, though present at lower concentration, can bind with high affinity to AR (inset) but with negligible affinity to ER at these physiological concentrations.

a masterly review by these workers [19]. They emphasise that several lines of evidence show that anti-estrogenic effects of androgens are mediated via the AR. The dosages of androgen which antagonise estrogen action are lower than those generally required for interaction with ER, but are in the range required to occupy AR. Furthermore, the antiestrogen effects of androgens are inhibited by antiandrogens, again supporting the concept that AR is involved in this antagonism of estrogen response. They concluded that the major difficulty in understanding the mechanism of action of androgens in hormone-regulated tumors, is that androgens can inhibit or stimulate tumor growth through different receptor mechanisms depending on the nature of the androgens, their concentration and metabolism, the concentration and nature of the different cellular receptors in the tumors, and on the endocrine status of the patient.

If we turn to human breast cancer, it has been established that growth of some human breast cancer cell lines in culture is inhibited by physiological con-

centrations of DHT via action on the AR [20, 21]. Bocciuzzi et al. [22] found that although ANDROSTENEDIOL stimulated growth of the human mammary cancer cell line MCF-7 at physiological concentrations, at these same concentrations it inhibited cell growth if estradiol was present. The fully active androgen DHT also inhibited estrogen-stimulated cell growth at physiological concentrations, but only stimulated cell growth at pharmacological concentrations in the absence of estradiol. They suggested that this data has clinical relevance to breast cancer; in premenopausal women, ANDROSTENEDIOL may partially counteract estradiol-stimulated growth by effects mediated through the AR, but upon withdrawal of estradiol at menopause, then ANDROSTENEDIOL is able to activate growth via combination with the ER.

So, after some 40 years, a picture is starting to emerge concerning the role of adrenal androgens in the development of breast cancer. The key component appears to be ANDROSTENEDIOL which, alone among the group of adrenal androgens, can

act as an estrogen at the concentration found in the blood of Western women. In postmenopausal women, when production of estradiol from the ovaries ceases, elevated serum ANDROSTENEDIOL levels could stimulate growth of a clone of neoplastic, or preneoplastic, cells transformed by carcinogenic events occurring some years earlier. High serum concentrations of ANDROSTENEDIOL derived from DHEAS, and other adrenal androgens derived from ADIONE, would oppose estradiol-stimulated cell growth in premenopausal subjects; subnormal levels of these androgens being manifested in the appearance of tumors at an early age. ANDROSTENEDIOL is then a novel hormone possessing both estrogenic and androgenic action at physiological concentrations. The name 'Hermaphrodiol' conferred on it is appropriate to describe its unique features (Figure 2).

The lower incidence of breast cancer in postmenopausal Japanese women in Japan compared to Western women, and the rise of incidence in migratory Japanese populations, run parallel to serum DHEAS levels measured in these groups of women [23]. These data are then in harmony with the above interpretation of the role of adrenal androgens in the etiology of the disease.

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