Androgens and Breast Cancer in Men and Women

Constantine Dimitrakakis, MD\textsuperscript{a,b,*}

There has been increasing focus recently on the importance of androgens in human physiology. Supplementation of testosterone in women with hypoactive sexual desire disorder is an area of great interest at present.\textsuperscript{1} Testosterone treatment in physiologic doses seems to improve sexual desire, responsiveness, and frequency of sexual activity, while at the same time it exhibits favorable effects on bone in postmenopausal women.\textsuperscript{2} However, the risk-benefit ratio for such treatment remains unclear.

Androgen receptors (AR) are found in virtually every tissue in women as well as in men, including breast, bone, and brain, indicating that androgens and their metabolites may play an important role in normal tissue homeostasis and possibly in pathologies, such as breast cancer, osteoporosis, decreased libido, and cognitive decline. A continuing area of concern is the notion that excess androgen exposure may increase the risk of breast cancer.\textsuperscript{3}

Over the past decade, there have been major advances in our understanding of the sources of endogenous sex steroids acting on mammary epithelium with the identification of tissue-specific expression of steroidogenic enzymes capable of converting circulating prohormones, such as dehydroepiandrosterone (DHEA), into potent androgens or estrogens. In addition, there have been great strides in the genetic elucidation of these steroidogenic enzymes and the steroid receptors.

Diverse clinical and experimental observations indicate that androgens moderate estrogenic effects on mammary proliferation and growth. Experimental data suggest
that conventional estrogen treatment regimens, both as oral contraceptives (OCs) and hormone therapy (HT), upset the normal estrogen/androgen balance and promote the unopposed estrogenic stimulation of mammary epithelial proliferation and, hence, potentially breast cancer risk.

The author compares literature evidence indicating that androgens augment the risk for breast cancer versus the evidence that androgens protect the mammary gland from hormone-induced stimulation, increased proliferation, and neoplasia.

**ACTION OF ANDROGENS IN BREAST PHYSIOLOGY: CLINICAL OBSERVATIONS**

Breast tissue is similar in prepubertal boys and girls, and steroid hormones begin to interact mainly through their specific receptors. It is generally accepted that estrogens stimulate and androgens inhibit breast development independently of genetic sex. Pubertal rises in estrogen levels cause breast growth in girls and frequently in boys (transiently). In girls with premature thelarche, estradiol levels are significantly higher than in normal prepubertal girls. A familial autosomal dominant syndrome of aromatase hyperactivity that increases estrone while decreasing testosterone levels presents as pubertal gynecomastia in boys. Decreasing testosterone levels may also trigger early breast growth, documented in girls that express a high activity isoform of the testosterone-metabolizing enzyme CYP3A4. Conversely, androgen excess caused by an adrenal tumor or hyperplasia suppresses normal breast development in girls, despite apparently adequate estrogen levels. In castrated male-to-female transsexuals, feminizing estrogen therapy stimulates breast growth with full acinar and lobular formation and estrogen-treated genetically male breast tissue exhibits normal female histology. Estrogens taken to treat prostate cancer also lead to breast development in men with suppressed gonadal function and reduced testosterone levels. Conversely, androgen use by female athletes and female-to-male transsexuals leads to breast atrophy.

Supporting the normal inhibitory role of endogenous androgens on breast growth, AR blockade with flutamide causes gynecomastia and rarely breast adenocarcinoma. In the androgen insensitivity syndrome, the inactive AR fails to counteract estrogenic stimulation, and genetic males with normal androgen levels eventuate with normal female breast development. Males may also develop gynecomastia when the estrogen/androgen ratio is increased because of decreased androgen production or increased aromatization.

**ENDOCRINE AND INTRACRINE MODES OF ACTION**

Mammary cell proliferation in both normal and malignant tissues is critically regulated by the dynamic balance between stimulatory effects of the estrogens and inhibitory effects of the androgens. A specific estrogen/androgen ratio, predictive of breast stimulation or inhibition, that would be safe for breast tissue has not been identified for several reasons. Estradiol and testosterone assays have been neither very sensitive nor accurate in the lower ranges because both hormones bind to SHBG and total values are not as informative as free or bioavailable hormones. Moreover, single hormone measurements may not be very informative about tissue exposure over time. Steroid levels vary hourly in response to diurnal rhythm, diet, stress, and exercise, so a single value may be inadequate to assess true tissue exposure. In addition, estradiol and testosterone may be synthesized locally in peripheral tissues from circulating precursors, such as the sulfate of DHEA (DHEA-S) and androstenedione. According to intracrinology, breast tissue has the ability and the enzymatic background to produce estrogens, to metabolize
androgens precursors to active forms, and to respond to minimum hormonal concentrations. In this way, the breast controls steroid concentrations and homeostasis independently of circulating estrogen and androgen levels. The conjugated products of steroid metabolism find their way into the circulation after peripheral action and provide evidence as to the proportion of the precursor pools of steroids used as androgen or estrogen. Analysis of these metabolites by Labrie and colleagues and Sasano and colleagues suggested that the major proportion of androgen effectors in women derive from such an endocrine mode of action, which will not be detected by assays of circulating testosterone or dihydrotestosterone (DHT). Although circulating levels of testosterone and DHT are 5- to 10-fold higher in men than in women, the abundance of androgen metabolites is less than 2-fold higher in men, suggesting that the local tissue production and the action of androgens in women may be more significant than historically suspected.

All the steroidogenic enzymes necessary for the formation of androgens and estrogens from steroid precursors (steroid sulfatase, 17\(\beta\)-hydroxysteroid dehydrogenases [17\(\beta\)-HSDs], 3\(\beta\)-HSDs, 5\(\alpha\)-reductases, and aromatase) have been reported in normal mammary tissues, breast cancer specimens, or cell lines. Androgens stimulate or inhibit the growth of breast cancer cells in vitro depending on the cell line and the clone under study according to former data. Breast cancer cell lines and tissue specimens express the enzymes involved in DHT as well as estradiol synthesis. In a histochemical study, expression of 5\(\alpha\)-reductase was significantly correlated with AR expression and 17\(\beta\)-HSD and 3\(\beta\)-HSD immunoreactivities, and the abundance of this androgenic molecular assembly was inversely correlated with tumor size, histologic grade, and proliferative index, suggesting an inhibitory role for DHT in tumor growth.

**ANDROGEN RECEPTOR: ASSOCIATIONS WITH BREAST CANCER RISK**

The cellular response to steroid hormones requires their conjunction to a membrane-bound or to an intracellular receptor. The human AR is a member of the nuclear receptor superfamily that includes receptors for steroid hormones, vitamin D, rhodopsin, and other agents. Normal mammary epithelium, but not stromal or myoepithelial cells, coexpress AR and estrogen and progesterone (PR) receptors. The coexpression of estrogen receptors (ER) and AR in mammary epithelial cells suggests that the effects of estrogen and androgen on mammary epithelial proliferation are integrated within the mammary epithelial cell. AR expression is abundant in normal mammary epithelium and in the majority of breast cancer specimens and cell lines. There is emerging evidence that the androgen-signaling pathway plays a critical role in breast carcinogenesis.

Binding of testosterone or DHT triggers a cascade of signaling events, including phosphorylation and conformational changes in the receptor, which dissociates from cytoplasmic proteins and migrates to the cell nucleus. Ligand-activated AR regulates gene expression through binding to AR elements located in a gene’s enhancer or promoter region. As with other similar receptors, the AR functions in transcriptional regulation in concert with a host of nuclear proteins, which may serve as coactivators or corepressors. Interestingly, the BRCA1 gene product has been identified as an AR coactivator. The BRCA1 protein binds to the AR and potentiates AR-mediated effects, suggesting that BRCA1 mutations may blunt androgen effects. However, other studies have not confirmed these findings.

The AR gene is located on the X chromosome with no corresponding allele on the Y, so it functions solely as a single copy gene, as shown by the complete loss of androgen effect in XY individuals with an inactivating mutation of the AR. AR has
a highly polymorphic CAG repeat in exon 1 that encodes a polyglutamine stretch. The CAG polymorphisms have become the point of interest to a series of studies with various results. There is evidence that longer CAG repeats are associated with breast cancer onset earlier in life, especially among women using oral contraceptives or menopausal hormone therapy and probably among male patients with breast cancer. However, another study found no association with breast cancer risk. In a study nested within the Nurses’ Health Study cohort, no relation was found between AR genotype and breast cancer risk among postmenopausal Caucasian women overall, but an increased risk was observed when analysis was limited to those individuals with a first-degree family history of breast cancer. Another study provides evidence that the association of breast cancer with the long AR-CAG was observed only in postmenopausal and not in premenopausal women, which may explain the insignificant results in studies restricted to young women. In other studies, reduced risk was observed with another trinucleotide repeat, GGC, in young women. AR-CAG repeat length was inversely associated with testosterone levels in both premenopausal and postmenopausal normal women. On the level of AR-protein expression, some germline mutations in the AR gene confer variable degrees of androgen insensitivity and have been associated with the occurrence of breast cancer in men.

Emphasis should be given to the fact that none of these studies had sufficient statistical power to implicate or exclude specific AR defects in breast cancer risk. A recent epidemiologic meta-analysis concludes that there is no association between AR genetic variations and breast cancer risk among Caucasian women.

Mammographic density is a potent risk factor for breast cancer. It has been reported that postmenopausal carriers of a less active AR treated with estrogen/progesterone therapy, presented with a higher mammographic density than carriers of the more active AR. This finding means that AR genotype modifies hormone-induced proliferation as reflected in mammographic density and may explain the mechanism by which estrogen/progesterone use increases breast cancer risk. However, the exact mechanisms and metabolic paths in which AR participates in normal tissues are still obscure. The role of AR in oncogenesis or breast tumor proliferation remains unclear. Experimental data suggest that breast cancer growth is inhibited primarily directly through AR stimulation or indirectly via downregulation of other receptors, such as PR or ER. It seems that AR presence is sometimes adequate to block ERα-related growth stimulation of breast cancer cells, and overexpression of AR decreases ERα-related transcriptional activity. Other preclinical data indicate that androgens, like antiestrogens, may act by promoting apoptosis in human breast cancer cell lines. However, it is possible that the steroid receptor contributes differently in healthy compared with cancerous breast tissue; thus, several unanswered questions remain, and further studies are needed before safe conclusions are drawn.

The hypothesis that androgens are directly involved in breast carcinogenesis is based on the presence of ARs in the majority of breast cancers. It is proposed that androgens, through binding to their receptors, act independently to produce tumors with specific clinical behaviors. A significant number of poorly differentiated breast carcinomas are ER negative and PR negative but AR-positive. On the other hand, hormone-dependent tumors with poor AR expression are connected to an increased risk of cancer-related-death. Tumors classified as AR negative are usually characterized by poor prognosis, associated to larger tumor size, higher grade, and frequent lymph node metastasis. Some investigators have proposed that AR expression may be lost during the development process of more aggressive and larger tumors and that AR expression in both ER-positive and ER-negative tumors is an independent
prognostic factor associated with improved recurrence-free survival. These associations constitute important clinical and pathologic prognostic information. Recently, AR expression in a tumor is considered as an indicator of lower malignancy potential; this provides a new range of therapeutic targets for poorly differentiated cancers.

**EPIDEMIOLOGIC DATA**

Long-term treatment with estrogens increases the risk of breast cancer in both men and women primarily through estrogenic stimulation of mammary epithelial proliferation, although additional carcinogenic effects by estrogen metabolites have been proposed. The most widely accepted risk factor for breast cancer is the cumulative dose of estrogens that breast epithelium is exposed to over time. However, it has been difficult to correlate breast cancer risk with isolated serum estrogen levels in epidemiologic studies, probably secondary to problems using single random hormone levels for the evaluation of tissue-specific exposure as previously discussed.

Correlation of adrenal precursor steroids with breast cancer incidence has been consistent, perhaps reflecting the importance of local tissue conversion. Interest in a potential role for adrenal androgens in breast carcinogenesis began in the late 1950s, with the demonstration of reduced 17-ketosteroid excretion in the urine of premenopausal women with breast cancer. This observation has been repeatedly confirmed in subsequent studies showing reduced DHEA-S in the serum of premenopausal patients with breast cancer. In the first prospective study in this field, levels of androgen metabolites in urine were found to be abnormally reduced in premenopausal women who subsequently developed breast cancer, indicating a protective role of androgens on the breast. In contrast, in more recent prospective studies of premenopausal women, no association was found between plasma adrenal androgen levels and the risk of breast cancer. Interestingly, in the Nurses’ Health Study II, among premenopausal women there was a positive association, especially for tumors that express both ERs and PRs. Also, among premenopausal women, higher levels of testosterone and androstenedione were associated with the increased risk of invasive ER+/PR+ tumors, although with a nonstatistically significant increase in the overall risk of breast cancer. In a recent study, levels of testosterone and DHEA-S in saliva (where the unbound fraction of hormones is measured) were statistically significantly lower in patients with breast cancer compared with controls and these differences were more profound in postmenopausal women. Patients with breast cancer, when compared with controls, presented with an androgen insufficiency and a relative imbalance of sex steroid hormones in favor of estrogens.

In recent years, several epidemiologic studies have examined the correlation between circulating androgens, such as testosterone, and breast cancer risk. A major limitation of such studies is that the androgen assays used were developed primarily to measure the higher levels found in men and lack reliability in the low ranges found in normal women. Moreover, testosterone and androstenedione levels demonstrate substantial variability from day to day and even from hour to hour, influenced by diurnal rhythms, diet, exercise, and stress; however, most of the epidemiologic data are based on a single blood sample collected at nonstandard times. Another problem using serum testosterone levels to gauge androgenic effects at the tissue level is that most of the circulating testosterone is tightly bound to SHBG although only the free hormone is bioactive. SHBG, and thus total testosterone levels, vary widely based on genetic, metabolic, and endocrine influences, and it is now accepted that measurement of free or bioavailable testosterone
predicts androgenic effects more accurately than total testosterone levels. Finally, as discussed previously, the major proportion of androgenic activity in women originates from the peripheral conversion of precursors, such as DHEA, into androgens within the cells of target tissues, and this activity will not be detected by the measurement of circulating androgens.

Several studies have revealed, however, that adrenal androgens are increased in postmenopausal women with breast cancer. A possible explanation regarding the divergence between premenopausal and postmenopausal findings is that one adrenal androgen, androstenediol (also known as hermaphroditol), is a weak ER agonist. In the presence of high estrogen levels in premenopausal women, androstenediol could exhibit antiestrogenic effects, while in the hypoestrogenic postmenopausal milieu, the agonist effect may predominate. This view remains speculative and other possibilities still exist. It is possible that the high-estrogen environment in premenopausal women promotes androgenic enzyme and AR expression in mammary tissue, allowing androgenic effects by DHEA metabolites, whereas in postmenopausal women, an estrogen-deficient tissue microenvironment may favor estrogenic effects. Also, genetic variation in CYP19 and SHBG genes was found to contribute to the variance in circulating hormone levels in postmenopausal women, but none was statistically significantly associated with breast cancer risk.

In some prospective epidemiologic studies, age-adjusted mean values of total and free testosterone and estradiol were significantly higher prediagnostically in postmenopausal breast cancer cases compared with controls, and estradiol and total testosterone were elevated in other case-control studies of postmenopausal breast cancer. It was observed that elevated serum levels of both estrogens and androgens contribute to a greater risk of breast cancer, and a meta-analysis of 9 prospective studies revealed that breast cancer risk increases with increasing concentrations of almost all sex hormones.

None of these studies, however, adjust for estrogen levels and this constitutes a serious bias. As a result, they do not manage to disconnect the risk associated with increased estradiol levels from the androgen component, and because androgens are the obligate precursors for estradiol synthesis, this is a major confounding factor in assessing the role of androgen independently of the known cancer-promoting estrogen effect. Some epidemiologic data indicate that serum concentrations of estrogens, but not of androgens or sex-hormone binding globulin, are associated with breast hyperplasia in postmenopausal women, suggesting that estrogens may be implicated early in the pathologic process toward breast cancer. In line with these observations, a recent study concluded that increased breast cancer risk with increasing body mass index among postmenopausal women is largely the result of the associated increase in estrogens. The association of androgens with breast cancer risk did not persist after adjustment for estrone, the estrogen most strongly associated with the risk. Other investigators conclude that conversion of DHEA to estrogens, particularly estradiol, is required to exert a mitogenic response. These results suggest that the conversion of androgens to breast cancer risk is largely through their role as substrates for estrogen production. Other studies have found no association between androgens and breast cancer.

The previous observations indicate the difficulty in separating potential direct effects of circulating testosterone from its potential to be aromatized into estradiol. It would be more interesting to investigate levels of testosterone and DHT metabolites in these studies to more directly assess tissue exposure to androgens.

As previously noted, a single serum hormone measurement seems unlikely to be informative about a woman’s true long-term exposure to that hormone or her specific
risk of developing breast cancer; nor does it seem to be a biologically plausible mecha-
nism that androgens acting as androgens could promote breast cancer because virtually all clinical data suggest just the opposite. If elevated androgen levels directly contribute to breast cancer, then women with clinically evident long-term hyperandrogenism (for example, polycystic ovary syndrome and congenital adrenal hyperplasia) should experience increased rates of breast cancer, but this is not the case. Moreover, androgen levels are chronically elevated in men, who have a breast cancer risk less than 1% of that of women. Male breast cancer is a rare disease, but genetic syndromes explanation is not sufficient for the majority of the cases and other risk factors with hormonal impact have been implicated. In Klinefelter syndrome, a 50-fold increase of breast cancer risk has been observed, and other hypogonadal situations share a percentage of new cases of male breast cancer. In these conditions, the patients have normal estrogen levels in the lower percentage, but they lack the protective androgenic effect of testosterone. Bone fractures in men, in contrast to women, are associated with an elevated risk for breast cancer. The interpretation for that fact also implicates testosterone deficiency advancing the age, which may be the causal factor for reduced bone density and strength. Conditions, such as obesity or liver cirrhosis, that increase estrogen conversion and metabolic maintenance while reducing androgens bioavailability alter the estrogen/androgen ratio and are also correlated to increased breast cancer risk in men, as in women. Epidemiologic studies in men indicate that low urinary androsterone and serum-free testosterone levels are related to the early onset of breast cancer, a much higher relapse rate, and a worse response to endocrine therapy.

**HORMONE THERAPY, ANDROGENS, AND BREAST CANCER**

Both endogenous and exogenous estrogen exposure is thought to contribute to increased breast cancer risk. Since the introduction of combined OCs, many changes in doses and their biochemical structures have taken place; however, the impact of OCs on breast cancer remains controversial. Epidemiologic studies provide inconclusive results, whereas a recent meta-analysis reports increased premenopausal breast cancer risk with the use of OCs. However, because pill users are young, this represents a very small increase in absolute risk. It is not yet known if lower dose and variable OC formulations are associated with a similar increase in risk, making comparisons very difficult.

There are many lines of evidence supporting a causal relationship between the use of HT and breast cancer. Recent and long-term users of HT are associated with higher risk. The effect of concurrent progestin use appears to further increase risk greater than that with estrogens alone. The most important randomized clinical trial providing information about this issue is the Women’s Health Initiative (WHI) study. The results from observational studies are generally consistent with those of the WHI trial, reporting increased but no significant variation in the risk of breast cancer with use of different estrogens, progestins, doses, or routes of administration. A group of postmenopausal participants in the WHI study used testosterone combined with estrogens. In this group, the testosterone addition for a period of 1 year had no statistically significant effect on breast cancer occurrence, suggesting at least that androgen induction did not increase the number of breast cancer cases in this trial. In the same study, rates of breast cancer were lower in longer-term compared with shorter-term users of estrogen plus testosterone. On the other hand, in a prospective study of more than 1 million person-years with 24 years of follow-up within the Nurses’ Health Study, current users of estrogen plus
testosterone have shown a 2.5-fold increased risk of developing breast cancer compared with menopausal women who used estrogen-only therapy or to women who never used postmenopausal hormone formulations. However, in a recent study, adrenal androgens, such as DHEA and its sulfate, combined with an aromatase inhibitor to ensure that the androgenic maintenance has shown an inhibitory effect on human breast ER-negative breast cancer cell lines with a strong AR expression. Specifically, DHEA acting as an AR agonist presented apoptotic action on these cell lines augmenting the cell death rate.

Suppression of normal endogenous androgen may be an adverse consequence of pharmacologic estrogen therapy, if androgens are indeed protective against estrogen-induced mammary proliferation. Conventional HT and OCs may promote breast cancer not only by increasing estrogen exposure but also by decreasing endogenous androgen activity. Oral estrogen therapy reduces free androgens by stimulating hepatic production of SHBG and by suppressing LH, thus inhibiting ovarian androgen production. Testosterone levels are normally maintained at high levels throughout a woman’s lifespan by uninterrupted ovarian and adrenal production. This continuous androgenic action may serve as a protective antiproliferative factor for breast tissue. Thus, institution of pharmacologic estrogen therapy at menopause may result in a drastic reduction in the testosterone/estradiol ratio, and increased risk for breast cancer (Fig. 1). Studies in ovariectomized rhesus monkeys have shown that the addition of low physiologic doses of testosterone (producing serum levels in the mid-normal range for women as well as rhesus monkeys) to estrogen therapy significantly inhibits HT-induced mammary epithelial proliferation (Fig. 2). Additionally, testosterone treatment significantly reduced mammary epithelial ER expression, thus, suggesting a potential mechanism for the growth inhibitory effect. Moreover, treatment of intact cycling monkeys with the AR antagonist flutamide resulted in a significant increase in mammary epithelial proliferation, adding to the burden of evidence that endogenous androgens normally limit mammary proliferation and, hence, cancer risk. Other studies on primates also suggest that inclusion of testosterone with estrogen/progesterone use may counteract breast cell proliferation. In a recent randomized, double-blind, placebo-controlled study, testosterone use inhibited exogenous estrogen-induced breast tissue proliferation in postmenopausal women. There is also evidence that

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**Fig. 1.** Average estradiol (E2) and testosterone (T) levels across the female lifespan. Dash lines represent changes in T and E2 levels resulting from hormone therapy beginning at menopause.
testosterone does not influence mammographic breast density like conventional HT, a risk factor for breast cancer.66,67 Pertinent to these observations, a prospective study in 508 postmenopausal women in Australia receiving testosterone in addition to usual HT regimen68 provides important information on this topic. The incidence of breast cancer in testosterone users was substantially less than in women receiving estrogen/progestin in the WHI study and in the Million Woman Study.69 Breast cancer rates in the testosterone users was closer to that reported for HT never users, and their age-standardization rate was the same as for the general population in South Australia. These observations suggest that the addition of physiologic doses of androgen to OCs and HT could protect the breast from unopposed estrogenic effects.

Men with prostate cancer receiving antiandrogenic treatment present with gynecomastia and are at higher risk for male breast cancer. In the limited population of males-to-female castrated transsexuals that use estrogen/progesterone regiments, several cases of breast cancer have been documented.70,71 These breast tumor cases presented after relatively short periods after exposure (5–10 years) and at an earlier age at diagnosis.23 In contrast, no case of hormone-dependent cancer is documented at present for the female-to-male transsexual population.72

Women, and particularly postmenopausal women, have been treated with testosterone for female sexual dysfunction for decades. The main safety concern for women who have undergone years of this therapy has been the breast and endometrial cancer risk related to androgens. In a recent trial of 814 sexually hypoactive women, the results for breast cancer risk were inconclusive.1 Nevertheless, current experience does not confirm a positive correlation between testosterone use and breast cancer occurrence (Table 1); thus, androgens can have a place in female sexual dysfunction treatment.
SUMMARY

Measurement of circulating sex steroids and their metabolites demonstrates that androgen activity is normally abundant in healthy men and women throughout their entire lifetime. Epidemiologic studies investigating testosterone levels and breast cancer risk have major theoretical and methodological limitations and do not provide consensus. The molecular epidemiology of defects in pathways involved in androgen synthesis and activity in breast cancer hold great promise, but investigation of these is still in the early stages. Clinical observations and experimental data indicate that androgens inhibit mammary growth and neoplasia, and they have been used in the past with success to treat breast cancer. It is of concern that current forms of estrogen...
treatment in OCs and for ovarian failure result in suppression of endogenous androgen activity considering that the addition of testosterone to the HT regimen ameliorates the stimulating effects of estrogen/progestin on the breast. Further research is needed to address the role of androgens in breast cancer prevention and the efficacy and safety of hormonal supplementation.

Mammary gland growth and differentiation is under hormonal regulation, and it is now accepted that estrogens stimulate and androgens inhibit breast growth and proliferation independently of genetic sex. Experimental and molecular data, clinical observations, and epidemiologic studies, although not conclusive, indicate a breast cancer protective effect of androgens. Exposure to exogenous estrogens upsets the normal estrogen/androgen balance and promotes unopposed estrogenic stimulation of proliferation and, hence, breast cancer risk. Further research is needed for the potential preventive role of androgens in breast cancer and the safety of testosterone supplementation.

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REFERENCES


