Androgen therapy for loss of desire in women: is the benefit worth the breast cancer risk?

Leslie R. Schover, Ph.D.

Department of Behavioral Science, University of Texas M. D. Anderson Cancer Center, Houston, Texas

Objective: To contrast the limited evidence that androgen therapy is an effective treatment for low sexual desire in women with the extensive literature suggesting that androgens promote breast cancer.
Design: Evidence from population studies of women is reviewed on the association between endogenous androgen levels and sexual function or satisfaction. Recent randomized trials of testosterone therapy for low desire are critiqued in terms of methodology and generalizability. Research on endogenous testosterone levels and breast cancer risk in both premenopausal and postmenopausal women is summarized, as are recent studies of androgenic hormonal therapy and breast cancer risk.
Setting: Literature review.
Patient(s): Not applicable.
Intervention(s): Not applicable.
Main Outcome Measure(s): Not applicable.
Result(s): Endogenous androgen levels are not correlated with sexual desire in population-based studies of aging women. Factors that are strongly associated with low desire include pain with sexual activity, emotional distress, life stress, and relationship conflict. The efficacy of testosterone therapy for women's desire problems is modest. Expectancy effects were not adequately controlled in randomized trials. Epidemiological findings agree that higher endogenous serum androgen levels confer increased breast cancer risk both before and after menopause. Androgenic hormonal replacement regimens also increase the risk of breast cancer.
Conclusion(s): Testosterone supplementation should not be prescribed to women with low sexual desire unless long-term studies can demonstrate its efficacy and safety. Treatments for low sexual desire in women should address its common correlates: relationship distress, emotional distress, and dyspareunia. (Fertil Steril® 2008;90:129–40. ©2008 by American Society for Reproductive Medicine.)

Key Words: Testosterone, androgens, breast cancer, hypoactive sexual desire disorder, hormonal therapy

Recently, reporters and legislators have decried steroid use by amateur and professional athletes. Minimal attention has been given to potential health consequences of steroid use in our own bedrooms, however, as ordinary women turn to androgens to get in the mood for sex. Lack of desire for sex is a major problem for contemporary women. In several recent surveys, about a third of women in the United States (1–3) and 20% globally (4) label themselves as having abnormally low sexual desire.

Less than 20% of these women seek medical help (1, 4); however, with the advent of convenient methods of administering testosterone in gel or patch form, the pharmaceutical industry has been developing androgen supplements to enhance women's sexual desire. This process has been somewhat controversial. In December 2004, the Food and Drug Administration (FDA) declined to approve the female testosterone patch, Intrinsa® (Proctor & Gamble Pharmaceuticals, Cincinnati, OH), requesting more safety studies (5). In October 2006, the Endocrine Society published a guideline advocating further research before prescribing androgens for women in clinical practice (6). However, in July 2006, the European Commission approved Intrinsa® for marketing in the United Kingdom and throughout the European Union (7). Other pharmaceutical companies such as BioSante Pharmaceuticals (Lincolnshire, IL) and Vivus (Mountain View, CA) have testosterone products for women in stage 3 clinical trials (8, 9).

With or without the blessing of the FDA, women in the United States are using testosterone. In their Advisory Committee Briefing Document for the FDA, Proctor and Gamble noted that at least 21% of prescriptions of branded testosterone supplements in 2003 were written for women, contrary to approved usage. In addition, from 2000 to 2003, women filled 1,315,000 prescriptions for generic or compounded testosterone products such as genital creams (10). In a survey completed by 41% of practicing obstetrician/gynecologists in Tucson, Arizona, physicians wrote a mean of four prescriptions a week for testosterone. Seventy percent of the scripts were given to premenopausal women (despite minimal data on safety or efficacy in this group); 90% of those given to postmenopausal women were to treat "low libido" (11).

Statistics on testosterone prescriptions do not take into account similar usage of dehydroepiandrosterone (DHEA),

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Reprint requests: Leslie R. Schover, Ph.D., Department of Behavioral Science, Unit 1330, UT M. D. Anderson Cancer Center, P. O. Box 301439, Houston, TX 77230-1439 (FAX: 713-745-4286; E-mail: lschover@mdanderson.org).

a precursor of androgen and estrogen available in health food stores as an unregulated supplement. A political deal exempted DHEA from a bill passed in 2004 regulating other androgens (12). In 2003, the last year that sales figures were available, United States sales of DHEA totaled $47 million (10). Recently, DNA microarray technology has confirmed that DHEA has potent androgenic and anabolic steroid activity (13). In postmenopausal women, it is preferentially transformed into androgens rather than into estrogens (14).

Why are American women reluctant to take estrogens and progesterone after publicity about the Women's Health Initiative (15) yet eager to use androgens? Neither the public nor the scientific and medical communities involved in reproductive health seem aware of the growing literature in oncology and epidemiology journals documenting a strong association between androgens and risk of breast cancer. The safety concerns in the Intrinsa® hearings at the FDA focused mainly on cardiovascular risk (5). The Endocrine Society Clinical Practice Guideline also only cites one observational study that suggests an antiproliferative impact of androgens on breast tissue (6). The public education pamphlet for Intrinsa® in the United Kingdom mentions unknown risks of breast cancer with long-term use (12), and advises women who have had hormone-sensitive malignancies not to use Intrinsa®. However, the publication states that the only common side effect is a skin reaction to the patch itself.

This review compares the evidence that testosterone therapy is an effective treatment for women's lack of sexual desire versus the findings that such treatment could promote the risk of breast cancer either as a first malignancy or as a recurrence or second primary.

LOW SEXUAL DESIRE IN WOMEN: WHEN IS IT A SEXUAL DYSFUNCTION?

In Western societies, a sexually healthy woman is expected to experience frequent, spontaneous desire for sex (16). Researchers have tried to define "hypoactive sexual desire disorder" (HSDD) in women in a manner that would transcend cultural values. A consensus committee convened by the American Urological Association recommended that any diagnosis of female sexual dysfunction include the criterion that a woman has "personal distress" about her sexual problem (17). Hypoactive sexual desire disorder is only diagnosed when a woman reports absent desire before sexual activity, states that desire is not triggered during sexual experiences, and rates herself as distressed about the problem. This leads to the paradox that with aging the percentage of women reporting lack of desire increases greatly, but because older women are less distressed about their desire for sex, the prevalence of HSDD as a diagnosis remains constant with age (18). Few women are aware of these complexities, however. Many label themselves as abnormal because they, or their partners, do not believe their desire for sex meets standards portrayed in popular media, even if such "norms" are unrealistic according to population studies.

WHEN IS LOW DESIRE A MEDICAL SYNDROME?

Although HSDD is officially a psychiatric diagnosis, it also is frequently assumed to be a medical problem caused by abnormally low serum androgen levels. In 1995, Sands and Studd (19) coined the term "female androgen insufficiency" (FAI) to describe this syndrome. In 2002, after transdermal testosterone patches and gels had been approved for men, the pharmaceutical industry funded a consensus conference on female androgen insufficiency syndrome (FAIS) (20). This condition was characterized by low values of free serum testosterone along with complaints of low desire, loss of well-being, and depressed mood. Researchers acknowledged a lack of normative data on levels of free serum testosterone in women as well as a problem finding reliable, low-cost assays to measure it. Nevertheless, they maintained that FAIS existed because women with the diagnosis improved on testosterone (21).

A fundamental problem with FAIS is that studies of endogenous testosterone do not show a correlation of hormonal levels with women's sexual function or satisfaction. Conventional wisdom is that testosterone acts in the brain to promote women's desire for sex, so women in a "deficient" state will have no interest in initiating sex, will have difficulty feeling excitement or pleasure, and also will have trouble reaching orgasm (20, 21).

Table 1 lists six population-based surveys (one represented by two publications) on hormone levels and sexual function in women. Despite differences in methodology, they largely agree that mean levels of endogenous androgens are not correlated with women's sexual desire or with sexual pleasure and function (3, 22–27), although two studies found that very low levels of DHEAS were associated with sexual dysfunction in some women (3, 26). Changes in androgen levels during transition to menopause or after menopause were not associated with loss of sexual desire (2, 22–25, 27). Rather, vaginal dryness and dyspareunia from vaginal atrophy (28, 29), relationship conflict, life stress, and depression are strongly associated with low desire for sex in women.

Although women's endogenous androgen levels vary widely across the adult lifespan, perhaps FAIS only exists in extremely deficient states. Table 2 summarizes several recent studies comparing women undergoing surgical menopause versus hysterectomy alone or surgical versus natural menopause. A survey of 1345 European women aged 20 to 70 years, all in sexual relationships, found that women who reached menopause due to surgery had twice the rates of hypoactive sexual desire disorder as premenopausal women or women who had natural menopause (30). A parallel study conducted in the United States reported the same finding (31). The researchers concluded that the hormone impact of oophorectomy caused the HSDD.

In contrast to these two cross-sectional studies, prospective studies of women undergoing surgical menopause suggest a different etiology. The impact of bilateral oophorectomy was investigated by Aziz et al. (32), who followed 217

TABLE 1

Population-based studies relating androgen levels to female sexual function.

Citation	N	Design and inclusion criteria	Hormonal assessment	Sexual assessment	Significant findings
Cawood and Bancroft, 1996 (22)	141	Prospective study over 5 weeks; healthy community volunteers, aged 40–60 years, no hormones last 3 months, with sex partner.	Four weekly blood samples (time of day or day of menstrual cycle varied, but midcycle samples were excluded), averaged 4 samples; measured T, SHBG, A, DHEA, DHEA-S, E_2, E_1, progesterone, FSH, LH, FAI.	Five structured interviews over 5 weeks; Frenken Sexual Experience Scale.	Hormones and menopausal status not significantly correlated with sexual function. Sexual function better if adequate vaginal lubrication, good relationship, higher socioeconomic status, lower BMI, and normal mood.
Gracia et al., 2004 (23)	326	Prospective study over 4 years; random population sampling of Philadelphia women aged 35–47, intact uterus and $\geq$1 ovary, menses at baseline.	Blood sample on days 1–6 every 8 months; T, DHEAS, E_2, FSH, LH.	One question on ''decreased libido'' in last month and one on vaginal dryness.	Only 27% of women had low desire. No difference in their mean hormone levels, but had greater fluctuation of total T over time. Low desire related to depression, vaginal dryness, and having children at home.
Gracia et al., 2007 (3)	313	Penn Ovarian Aging Study; 3-year prospective data of equal samples of African-American and Caucasian women aged 35–47 years at baseline and still menstruating, no hysterectomy or hormone replacement.	Blood sample on days 1–6 of menstrual cycle in two consecutive cycles once a year; E_2, FSH, LH, SHBG, DHEAS, total T.	Female Sexual Function Index.	Sexual dysfunction did worsen as menopause progressed. Although low DHEAS was correlated with vaginal dryness, pain, and orgasmic dysfunction (odds ratio 1.59), much stronger relationship of sexual dysfunction was found with lack of a partner (OR 11.2) and high anxiety (OR 3.8).

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TABLE 1

Continued.

Citation	N	Design and inclusion criteria	Hormonal assessment	Sexual assessment	Significant findings
Dennerstein et al., 2002, 2005 (24, 25)	336	Prospective study over 8 years; random population sampling of Australian women aged 45–55 years, menstruating at baseline, no hysterectomy; 56% response rate and 88% retention rate.	Yearly fasting morning blood sample days 4–8 of menstrual cycle or after 3 months of amenorrhea; FSH, E_2, T, SHBG, DHEA-S, inhibin, FAI; used RIA. T assay may have lacked sensitivity at low levels.	Personal Experiences Questionnaire validated for Australian women; Sexual response score included desire, arousal, pleasure, and orgasm.	Androgens had no impact on sexual function. Most important factors were previous sexual function, losing a partner (negative) or getting a new partner (positive), and satisfaction with current relationship. E_2 level impacted sexual desire/arousal and dyspareunia.
Davis et al., 2005 (26)	1021	Cross-sectional study in Australia; random selection from community, aged 18–75 years; only 9% response rate.	One fasting morning blood sample; if premenopausal cycle day 8 to onset of menses; T (direct RIA), FAI, DHEA-S and SHBG immunometric assays; A (direct RAI); FSH, TSH, LH, and prolactin using automated machines.	Profile of Female Sexual Function, validated questionnaire for measuring sexual desire and other aspects of sexual function.	No significant relationship between androgen levels and sexual function, unless DHEAS below 10th percentile, but most women with low DHEAS did not report sexual problems. No serum androgen level definitive for female sexual dysfunction.
Santoro et al., 2005 (27)	2961	Longitudinal study of multi-ethnic community-based samples of women aged 42–52 years at baseline, menstruating, and having uterus and $\geq$1 ovary, and off all hormones. Not diabetic.	Blood drawn after 10-hour fast on days 2–7 of follicular phase. Serum E_2 measured with immunoassay. T with polyclonal anti-T antibody binding, SHBTG and DHEAS with commercial binding assay. FAI calculated. Assays were calibrated for low levels of T in women.	Questionnaire designed for the study asked about frequency of desire for sex and about arousal during sex.	Androgen levels were only weakly associated, if at all, with sexual desire, sexual arousal, or mood but were associated with having the metabolic syndrome.

Note: A: androstenedione; DHEA: dehydropiandrosterone; DHEA-S: dehydroepiandrosterone-sulfate; E_1: estrone; E_2: estradiol; FSFI: Female Sexual Function Index; FSH: follicle-stimulating hormone; LH: luteinizing hormone; RIA: radioimmunoassay; SHBG: sex-hormone–binding globulin; T: testosterone.

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Swedish women choosing to have hysterectomy alone for benign indications such as heavy bleeding, compared with 106 opting to have a bilateral prophylactic oophorectomy at the time of hysterectomy. Hormones and sexual function were assessed before surgery and at 1-year follow-up. Women were prescribed estrogen replacement if they were menopausal after surgery so that vaginal atrophy was not a factor in sexual function. Androgen levels did decrease after bilateral oophorectomy, but sexual function and satisfaction remained stable. Psychological well-being improved in both groups.

One caveat is that the women who chose prophylactic oophorectomy were significantly more anxious at baseline, and their sexual function/satisfaction, though still within the normative range for Swedish women, was significantly lower than that of the hysterectomy-alone group (33). A similar pattern was observed in a 3-year prospective study in New Zealand comparing 257 women who had hysterectomy alone with 57 who also had bilateral oophorectomy (34). At baseline, the oophorectomy group was less sexually active, more depressed, and reported more pelvic pain. Both groups of women had significant improvements in mood and pain after hysterectomy and neither noted a decline in sexual activity or problems with vaginal dryness (as in the Swedish study, women were offered estrogen replacement after surgery). Baseline differences in sexual interest and emotional distress, rather than hormone changes, may be responsible for postsurgical differences in sexual satisfaction or function between women who choose ovarian conservation versus oophorectomy.

In general, women who have hysterectomies are more psychologically distressed before surgery than women who go through a natural menopause transition (35, 36). Unlike erectile dysfunction, sexual dysfunction in women is not closely linked to aging or poor health status. Rather, it is associated with lower educational attainment, relationship conflict, emotional distress, and living in societies that do not value egalitarian gender roles in dyadic relationships (1, 2, 28, 37, 38). The Endocrine Society's Clinical Practice Guideline recently recognized the limited evidence for FAIS as a medical cause of low sexual desire and recommended against using it as a diagnosis (6).

ESTABLISHING NORMS FOR ANDROGENS IN WOMEN

One chronic problem with measuring androgens is that assays designed for male values lack the sensitivity to measure the low levels of free and total testosterone that are normal in women (6, 39–41). Advocates of the FAIS typically use the Free Androgen Index, a calculated ratio of total testosterone to sex-hormone&binding globulin (SHBG), to diagnose androgen deficiency (42). This ratio is clinically meaningless, however. Less than 3% of testosterone in women is unbound and free to act in target cells, although 30% or 40% is loosely bound to albumin and thus bioavailable, as opposed to the fraction bound to SHBG. However, bioavailability depends on the target tissue (6). The best studies not only sample blood at a standard time of day and point in the menstrual cycle for younger women but also measure free testosterone directly using experimental and expensive methods based on chromatography followed by tandem mass spectrometry (40, 41). Samples should be batched and analyzed in one run per hormone to avoid interassay variability.

Three recent cohort studies provide normative data for total and free androgen levels in healthy premenopausal and postmenopausal women (42–44). They agree that testosterone levels are highest in women in their 20s, falling sharply during the years from 30 to 39. Testosterone does not automatically decline with menopause (6, 43, 44). These findings cast even more doubt on the importance of androgens in women's desire for sex because it is precisely women in their 20s who have the highest rates of sexual dysfunction in population surveys (1). Their difficulty in enjoying sex is statistically significantly correlated with lack of knowledge about sexuality and with having unstable, unsatisfying intimate relationships.

Another thorny issue is whether serum levels of androgens reflect hormonal action in the brain, where sexual desire and pleasure presumably originate, or inside target cells in general. Labrie et al. (45) have suggested that serum levels of androgens are not reflective of their intracellular activity. In human females, peripheral tissues synthesize large amounts of androgens from DHEA, never releasing these hormones into the circulation. However, because all androgens are metabolized to androgen glucuronides, measuring serum levels of androsterone glucuronide (ADT-G) may give a more accurate assessment of androgenic activity in women. Although Labrie et al. (45) found that ADT-G levels did not correlate with serum androgens in a large sample of women, a relationship between the metabolite and supposed symptoms of FAIS has yet to be demonstrated. Two recent large surveys of postmenopausal women have found that DHEAS was the only hormone that correlated with sexual function (3, 26).

ANDROGENS, OBESITY, AND FITNESS IN WOMEN

A gender difference in the relationship of androgens to health also may be relevant to their role in sexual function. In men, testosterone not only declines with aging, but obesity, smoking, and a sedentary lifestyle are clearly associated with lower hormonal levels (46). In women, conversely, total and free testosterone are elevated with obesity and SHBG levels are decreased, especially in women who have the abdominal fat distribution associated with cardiac risk or who meet criteria for the metabolic syndrome (27, 47, 48). Estrogens and some androgens, including free testosterone and androstenedione, were elevated in the most obese and sedentary women in a sample of 300 randomly chosen from the Woman's Health Initiative (49). Women who exercise and lose weight actually decrease their androgen levels (50). The potential negative impact on cardiac health of chronic

TABLE 2

Studies of oophorectomy, hormones, and sexual function.

Citation	N	Design and inclusion criteria	Hormonal assessment	Sexual assessment	Significant findings
Dennerstein et al., 2006 (30)	1345	European women aged 20–70 years with sexual partners.	None.	Profile of Female Sexual Function, Personal Distress Scale.	Women with surgical menopause were twice as likely as premenopausal or naturally postmenopausal women to have HSDD. Women with low desire often had difficulty with sexual pleasure and orgasm.
Leiblum et al., 2006 (31)	952	Cross-sectional study of American women aged 20–70 years with a partner, premenopausal, postmenopausal, or surgically menopausal. 22% participation rate.	None.	Profile of Female Sexual Function, Personal Distress Scale.	Surgically menopausal women aged 20–49 years were about twice as likely to have HSDD as premenopausal controls; but after menopause, no difference in HSDD between surgically and naturally menopausal women. Women with HSDD also had significantly higher rates of marital distress and had lower mental and physical health scores on a measure of health-related quality of life.
Aziz et al., 2005 (32)	323	Prospective study, Sweden; women aged 55–65 years before surgery and 1-year follow-up; 217 elected hysterectomy alone vs.106 hysterectomy plus bilateral oophorectomy; menses in past year, and sex in past 6 months.	Time of day or menstrual cycle varied for blood samples: T, E_2, SHBG (time-resolved fluoroimmunoassay with commercial kit); A and DHEA-S (RIA); FAI and FEI calculated. Estrogen given after surgery to 26% hysterectomy group and 98% bilateral oophorectomy group.	McCoy Female Sex Questionnaire; Psychological General Well-Being Index.	Only 1 out of 98 correlations significant between changed hormonal levels and changed sexual function. No difference between groups in hormonal levels at baseline. Hysterectomy-alone group slightly better sexual function at baseline than women who chose bilateral oophorectomy. Advantage same at follow-up. At 1-year follow-up BSO group had significantly lower T, A, FAI, higher SHBG.

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TABLE 2

Continued.

Citation	N	Design and inclusion criteria	Hormonal assessment	Sexual assessment	Significant findings
Farquhar et al., 2006 (34)	314	3-year prospective study compared 257 women <46 years with FSH <40 mmol/L choosing hysterectomy alone vs. 57 choosing bilateral oophorectomy.	Baseline FSH and annual FSH for women with conserved ovaries.	Questionnaire written for the study and the CES-D to measure depression.	Women who had bilateral oophorectomy had more problems at baseline, less sexually active, more depressed, and more likely to have pelvic pain. Sexual frequency and vaginal dryness stable in both groups after surgery (all offered estrogen replacement). Both groups improved mood and less pelvic pain after surgery.

Note: A: androstenedione; BSO: bilateral salpingo-oophorectomy; CES-D: Center for Epidemiologic Studies Depression Scale; DHEA-S: dehydroepiandrosterone-sulfate; E_2: estradiol; E_1: estrone; FAI: free androgen index; FEI: free estrogen index; FSH: follicle-stimulating hormone; RIA: radioimmunoassay; SHBG: sex-hormone–binding globulin; T: testosterone.

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testosterone supplementation was a major concern for the FDA panel evaluating Intrinsa® (5).

DOES TESTOSTERONE IMPROVE WOMEN'S DESIRE FOR SEX?

Five large randomized, double-blinded trials of a transdermal testosterone patch for women have been published (51–55). Four included only women who had bilateral oophorectomy for benign indications and were already taking stable dosages of unopposed estrogen after surgery (51–53, 55). In one study (55), the estrogen was transdermal. The most recent trial recruited naturally menopausal women who were on stable doses of estrogen or estrogen plus progesterone (if they still had a uterus) and complained of loss of desire for sex (54). Abnormal baseline total or free testosterone was not an entry criterion for any of the trials, although oophorectomized women were presumed to have abnormally low testosterone because the ovaries produce about 50% of serum levels. Dosage levels included 150-μg/day, 300-μg/day, and 450-μg/day, but only the 300-μg/day dose improved sexual function significantly more than placebo. The failure of the highest dose is puzzling. It cannot be explained by increased side effects because the 450-μg/day group did not have more adverse events or dropouts from the study (53). Testosterone may influence sexual desire and pleasure on a "threshold model." Once the level of bioavailable hormone is adequate, giving more has no incremental effect (56). However, one would not expect a higher dose to be *less* effective than an adequate dose.

The results of these trials also raise other questions. Women attained median levels of total testosterone by 24 weeks at the 300-μg/day dosage that exceeded the normal range for premenopausal women in all five trials (51–55). The researchers discount the importance of these findings, however, because free or bioavailable testosterone remained within the premenopausal reference range. These ranges are based on values in premenopausal women, however, and may not be "physiologic" for women over the normal age of menopause.

A sizable placebo effect was observed in all trials, although it was less marked in the trial of women on transdermal estrogen (55). For example, in the third trial with oophorectomized women, those on placebo had a 48% increase in sexual desire scores compared with a 67% increase in the 300-μg/day dosage group (53). The 300-μg/day dosage group had a 79% increase in the frequency of satisfying sex compared with 43% in the placebo group (53). The improvement from testosterone therapy translated into a rather modest increase from three to five satisfying episodes of sex across a 5-week period, although women's sexual satisfaction also rose significantly (53, 54). Women in these trials consistently reported at least two satisfying episodes of sex per month, which is quite discrepant from women who come to sex therapy clinics for treatment of HSDD. These women typically have not enjoyed sex in many months (30, 31). The criteria for diagnosing HSDD in the clinical trials were not as strict as those proposed by the consensus committee (4), leaving doubt as to generalizability of the results.

Despite the double-blinded design, expectancies could account for the between-group differences. If women could accurately identify whether they were receiving the active drug versus the placebo, those who believed they were taking testosterone may have "expected" it to work and therefore perceived more improvement. Assessing whether participants can guess their randomization condition is crucial when subjective, self-report end points such as ratings of pain or desire for sex are used in clinical trials (57, 58). However, no data of this type were reported for any of the trials. In fact, women could have been alerted to their treatment group by a series of questions they were periodically asked about adverse effects, that is, if they had noticed deeper voice timbre, altered patterns of facial and scalp hair, excess body hair, or skin reactions (53, 55, 56).

In summary, testosterone replacement has a significant impact on sexual desire in menopausal women, but the clinical magnitude of the improvement remains questionable. Positive changes only occur at a dose that achieves a supraphysiologic total testosterone level in most women. Placebo effects cannot be ruled out as the source of the improvement. Because transdermal testosterone has only been studied in combination with estrogen replacement, its applicability is currently limited to women who do not have contraindications to taking estrogen. Nevertheless, many physicians are prescribing testosterone for women who do not use estrogen, creating a hormone environment that is unnatural and entails unknown risks.

TESTOSTERONE USE BY FEMALE CANCER SURVIVORS

Diminished sexual desire and arousal is the most common sexual problem for women after cancer treatment, reported by at least half of women whose cancer therapy causes sudden ovarian failure (59–62). In the early 1990s, the influential sex therapist Helen Singer Kaplan was diagnosed with breast cancer and became interested in this problem, asserting that loss of desire after chemotherapy was a direct result of androgen deficiency (63, 64). Kaplan suggested that testosterone supplementation was safe for breast cancer survivors because it had been used as a treatment for breast cancer before the advent of selective estrogen receptor modifiers. Of course, the impact of a hormone given in a very high dose is far different from a chronic, low dose. Nevertheless, Kaplan's legacy has continued long after her tragic and premature death. Many breast cancer survivors are using testosterone without estrogen, convinced it is far safer than other forms of hormone replacement. It is ironic that the only two cohort studies measuring androgen levels and sexual function in breast cancer survivors found no evidence that low testosterone is linked to sexual dysfunction (65, 66).

ENDOGENOUS TESTOSTERONE AND THE RISK OF BREAST CANCER

It is crucial that clinicians and the public become aware of the evidence linking women's androgen levels with breast cancer risk (67). Epidemiological research demonstrates that higher endogenous androgen levels increase breast cancer risk in postmenopausal women. The only controversy is the mechanism (68): Is the association due to aromatization of androgens to estrogen in peripheral fat tissues? Is testosterone binding to SHBG and leaving more estradiol in circulation? Or does testosterone have a direct proliferative effect on breast cancer cells? Most have androgen receptors (68). Androgens appear to have antiproliferative effects in some tumors but proliferative effects in others (69). Androgen blockade or reduction of circulating DHEAS levels may be therapeutic in some subsets of women (69).

A meta-analysis of nine prospective studies in postmenopausal women concluded that endogenous testosterone increases breast cancer risk even after adjustment for estradiol levels (70). The odds ratio of breast cancer for women with total testosterone in the top quartile compared with those in the bottom quartile was 1.73 (1.16–2.57). Since that publication, two large prospective studies have confirmed the association. In one, both cases and controls were drawn from the Nurse's Health Study. Hormone levels were compared in 322 postmenopausal women who developed breast cancer and 644 matched controls (71). Endogenous estrogens and androgens (testosterone, androstenedione, DHEAS) contributed independently and significantly to the risk of breast cancer. Another nested case-control study used the Women's Health Study registry, comparing 297 women who developed breast cancer with 563 controls (72). Endogenous androgens were significantly higher in women who developed breast cancer, but the association decreased when adjusted for levels of estrone, the estrogen most strongly linked to breast cancer risk. The investigators concluded that androgens contribute to risk mainly by being converted to estrogens. A recent case-control study suggested that an interaction of high circulating levels of both androgens and insulin-like growth factor 1 (IGF-I) could act synergistically to increase the risk of hormone-dependent breast cancer in postmenopausal women (73).

Evidence has also increased for a link between premenopausal breast cancer and endogenous androgen levels. Within a cohort participating in a prospective study of hormones and diet in breast cancer, 65 women who developed breast cancer before menopause were compared with 243 matched controls (74). All had a blood sampled on days 20 to 24 of the menstrual cycle. The odds ratio for breast cancer was 2.85 (1.11–7.33) in women whose free testosterone was in the highest tertile compared with the lowest tertile. In contrast, higher levels of progesterone were associated with decreased breast cancer risk.

A similar pattern was seen in a nested case-control study of women in the European Prospective Investigation into Cancer and Nutrition (75). A total of 370 premenopausal women developed breast cancer and were matched to 726 controls. The phase of the menstrual cycle at blood collection was not standardized, but was matched between cases and controls. Levels of testosterone, androstenedione, and DHEA-S were statistically significantly higher in women who developed breast cancer. When women under age 40 were followed for 10 years, 2.6% of those with testosterone in the highest quartile developed breast cancer compared with 1.5% of women with hormones in the lowest quartile. Again, higher progesterone was associated with decreased cancer risk. The most likely explanation is that breast cancer risk is elevated among women who have an excess of ovarian androgens and produce reduced amounts of progesterone.

Most recently, in a nested case-control study within the Nurses' Health Study II, higher endogenous levels of total and free testosterone, androstenedione, and follicular total and free estradiol were all significantly associated with breast cancer risk, particularly for risk of invasive and hormonally positive tumors. Adjustment for estradiol did not decrease the association between androgen levels and breast cancer risk (76).

Higher androgen levels are also associated with risk of breast cancer recurrence in postmenopausal women (8, 77). A group of 115 breast cancer survivors free of disease at study entry were followed for 5.5 years. Serum testosterone, estradiol, and glucose were significantly higher, as was body mass, for the 31 who either had a cancer recurrence or new primary breast tumor. The hazard ratio for recurrence/new breast cancer was 7.2 (2.4–21.4) for women whose testosterone was in the upper tertile compared with those in the lowest tertile.

TESTOSTERONE SUPPLEMENTATION AND THE RISK OF BREAST CANCER

Does supplementing a woman's testosterone have the same impact on risk for breast cancer as having high endogenous testosterone? High endogenous testosterone may be a marker for obesity or high-fat diet rather than a direct promoter of breast cancer. However, the convergence of hormonal factors in breast cancer etiology is striking. Early menarche, late menopause, nulliparity, obesity after menopause, and postmenopausal estrogen therapy with a progestin all increase the breast's lifetime exposure to hormones as well as elevating the risk of breast cancer. It is plausible that hormone therapy regimens producing chronically supraphysiologic levels of free and total testosterone would increase breast cancer risk.

Although estrogen use after breast cancer had not been linked to recurrence in observational studies, two recent randomized trials suggest that taking estrogen directly increases recurrence rates with a pooled relative risk of 3.41 (1.59–7.33) (78). Because androgens are converted in vivo to estrogen, these data should increase women's caution about any type of hormone replacement (79).

Advocates of testosterone replacement cite an observational, retrospective study reporting lower rates of breast cancer in 508 Australian postmenopausal women who used testosterone in addition to other hormonal replacement therapy compared with a group taking hormones without testosterone (80). However, three prospective, case-control comparisons nested within very large cohort studies recently have found that androgen supplementation increases breast cancer risk. A case-control comparison within the Danish Nurse Cohort Study revealed that the more androgenic the hormone replacement regimen and the more extensive the use, the higher a woman's risk of breast cancer (81). Current users of tibolone had a fourfold relative risk of breast cancer. Tibolone increased breast cancer rates by 50% in the British Million Women Study (82). In the United States, researchers performed a nested case-control comparison including women from the Nurses' Health Study who were using a variety of postmenopausal hormone regimens (including estrogen alone or estrogen plus progestins). Free and total estradiol were significantly higher in women over 60 years old who developed breast cancer. A trend was also seen for free testosterone to be associated with breast cancer risk in this group (83).

Most recently, a longer, prospective case-control study evaluated women in the large Nurses' Health cohort from 1978 to 2002 (84). Results confirmed that among women who reached natural menopause, each year of using estrogen plus testosterone hormone replacement produced a 17.2% increase in breast cancer compared with women who did not use any hormone therapy. Their risk of breast cancer was also significantly higher than women using estrogen alone and tended to be higher than the risk of women on combined estrogen and progesterone therapy (84).

It is worth noting that the endogenous serum testosterone levels associated with elevated breast cancer risk in various studies are in the range of $\geq$51 to 58 ng/dL (74, 75) in premenopausal women or $\geq$20 to 26 ng/dL in postmenopausal women (70, 71). In the Intrinsa® trials, median total serum testosterone ranged from 54 to 102 ng/dL after 24 weeks of treatment (51–55).

RECOMMENDATIONS

We suggest that women offered testosterone supplementation be informed of the probable increased risk of breast cancer. Given that the average woman in the United States has one chance in seven of developing breast cancer in her lifetime (85), a significant increase in relative risk translates into a substantial increase in absolute risk. A conservative estimate is that the odds ratio for breast cancer increases to 1.75 for women with high levels of serum testosterone. Some women under age 40 might be willing to trade a 2.6% versus 1.5% risk of breast cancer in the next 10 years for better sexual desire (75). However, would 40 year olds with a 4.18% chance of breast cancer by age 59 (85) be willing to tolerate increasing that risk to 7.32%?

Androgen supplementation is particularly undesirable in women with a history of breast cancer. Other cancer survivors at increased risk for breast cancer as a second malignancy should also be warned not to use androgens. This category includes women treated for Hodgkin disease with mantle irradiation (86), survivors of chest irradiation for pediatric cancer, or young women with a history of bone or soft tissue sarcoma (87). The risks of hormone therapy for more than a short period may also be exacerbated for women carrying BRCA mutations (88). Because the link between androgens and sexual desire has been so salient, clinicians forget that behavioral therapies may be more effective than hormonal treatment if they target the factors that repeatedly predict HSDD such as dyspareunia, life stress, psychological distress, and relationship conflict (89).

The FDA should reevaluate the over-the-counter status of androgenic steroids such as DHEA (6, 12, 13). Off-label testosterone prescriptions should also be discouraged because their dosage and safety profiles are unknown (90). If products such as Intrinsa® are to gain FDA approval, safety studies should be required with adequate power and duration of follow-up to ascertain breast cancer risk.

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