Menopause: The Journal of The North American Menopause Society
Vol. 11, No. 5, pp. 531-535
DOI: 10.1097/01.GME.0000119983.48235.D3

Breast cancer incidence in postmenopausal women using testosterone in addition to usual hormone therapy

Constantine Dimitrakakis, MD,[1] Robert A. Jones, MD,[2] Aiyi Liu, PhD,[3] and Carolyn A. Bondy, MD[1]

Abstract

Objective: There is now convincing evidence that usual hormone therapy for ovarian failure increases the risk for breast cancer. We have previously shown that ovarian androgens normally protect mammary epithelial cells from excessive estrogenic stimulation, and therefore we hypothesized that the addition of testosterone to usual hormone therapy might protect women from breast cancer.

Design: This was a retrospective, observational study that followed 508 postmenopausal women receiving testosterone in addition to usual hormone therapy in South Australia. Breast cancer status was ascertained by mammography at the initiation of testosterone treatment and biannually thereafter. The average age at the start of follow-up was 56.4 years, and the mean duration of follow-up was 5.8 years. Breast cancer incidence in this group was compared with that of untreated women and women using usual hormone therapy reported in the medical literature and to age-specific local population rates.

Results: There were seven cases of invasive breast cancer in this population of testosterone users, for an incidence of 238 per 100,000 woman-years. The rate for estrogen/progestin and testosterone users was 293 per 100,000 woman-years—substantially less than women receiving estrogen/progestin in the Women's Health Initiative study (380 per 100,000 woman-years) or in the "Million Women" Study (521 per 100,000 woman-years). The breast cancer rate in our testosterone users was closest to that reported for hormone therapy never-users in the latter study (283 per 100,000 woman-years), and their age-standardized rate was the same as for the general population in South Australia.

Conclusions: These observations suggest that the addition of testosterone to conventional hormone therapy for postmenopausal women does not increase and may indeed reduce the hormone therapy-associated breast cancer risk—thereby returning the incidence to the normal rates observed in the general, untreated population.

Key Words: Menopause – Hormone therapy – Estrogen – Androgen.

Received October 7, 2003; revised and accepted January 4, 2004.

From the [1]Developmental Endocrinology Branch, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD; [2]Memorial Medical Center, North Adelaide, South Australia; and the [3]Division of Epidemiology, Statistics and Prevention Research, National Institute of Child Health and Human Development, National Institutes of Health, Rockville, MD.

A limited grant for data collection and entry was provided by Organon (Aust) Pty.

Address correspondence to: Carolyn A. Bondy, Bldg. 10/10N262, 10 Center Dr., NIH, Bethesda, MD 20892 USA. E-mail: bondyc@mail.nih.gov.

The normal ovary produces larger amounts of testosterone than estradiol, and a variety of clinical and experimental observations suggest that androgens normally inhibit estrogenic effects on mammary growth.[1] Experimental data from rodents and nonhuman primates suggest that conventional estrogen treatment regimens, both as oral contraceptive[2] and hormone therapy in oophorectomized animals,[3] upset the normal estrogen/androgen balance and promote "unopposed" estrogenic stimulation of the mammary epithelium and, hence, breast can-

cer risk. This is because the suppression of gonadotropins by exogenous estrogen treatment results in globally reduced ovarian steroidogenesis, but only estrogens are provided by the treatment regimens. Moreover, commonly used oral estrogens stimulate the hepatic production of sex hormone binding globulin, which binds testosterone with high affinity, reducing androgen bioavailability. As a result of these dual effects, both total and bioavailable testosterone levels may be significantly reduced in women taking oral contraceptives or usual estrogen replacement for ovarian insufficiency. We recently provided evidence from a nonhuman primate model using an androgen receptor antagonist that endogenous androgens inhibit mammary proliferation in normal cycling animals,[4] supporting the concept of a normal, physiological protective role for androgens.

From these observations, one may conclude that it would be more physiological and possibly safer to administer testosterone together with estrogen/progestin regimens, but usual hormone therapy (HT) for ovarian failure consists only of estrogen and progestin for women with a uterus or estrogen therapy alone for hysterectomized women, although the risk of breast cancer is increased with such treatment.[5,6] In some countries, including Australia, testosterone is prescribed for some postmenopausal women in addition to usual HT. The rationale for testosterone supplementation in oophorectomized women is well-established,[7] but many postmenopausal women also experience a loss of libido and/or asthenic symptoms on usual HT,[8] possibly because of suppression of residual ovarian androgen production by estrogen treatment. One of us (RAJ) has been using testosterone to supplement standard HT for 25 years in the setting of a specialized menopause clinical practice in South Australia. After noting that women on testosterone in addition to usual HT rarely have abnormal mammograms compared with women on conventional HT, a systematic review of breast cancer incidence in this clinic population was undertaken. It is worth noting that these observations were collected for women on HT beginning in the 1980s and continuing until the end of the1990s. This was a time of great enthusiasm for estrogen therapy, not only to treat postmenopausal symptoms but also to prevent osteoporosis and coronary heart disease, as we thought at that time.

METHODS

Postmenopausal and ovariectomized women on usual HT were referred to this clinic for evaluation of testosterone supplementation because of the practitioner's expertise in this treatment. Reasons for referral included persistent complaints of emotional lability, fatigue and loss of stamina, impaired concentration and memory, breast tenderness, loss of libido, sleep disturbance and/or muscle weakness. In addition, some women were referred because of osteoporosis despite estrogen treatment. Medical and family histories and physical exams were obtained for all participants. Baseline mammograms were done before initiation of testosterone treatment and at 2-year intervals thereafter. Study participants received implants containing 50 mg to 150 mg testosterone every 5 months, in addition to conventional estrogen or estrogen plus progestin treatment. The testosterone dose was titrated to alleviate symptoms, improve bone mineral density, and minimize adverse effects such as hirsutism or acne; it was most commonly 100 mg. Initially, most women were on oral estrogens (conjugated estrogens 0.625 mg, or estrone sulfate in a dose of 1.25 mg daily). In more recent years, most women were treated with estradiol implants in a dose of 50 mg at 5- to 15-month intervals. Women with a uterus were treated with medroxyprogesterone continuously (2.5 mg-5 mg) or cyclically (5 mg-10 mg) or with norethisterone (0.3 mg-2.5 mg).

TABLE 1. *Participant characteristics in the Adelaide, South Australia, study*

	Total (n = 508)	E/T (n = 161)	E/P/T (n = 347)
Menarche age	13 ± 1.6	13 ± 1.7	13 ± 1.6
Menopause age	46 ± 6	43 ± 7	46 ± 7
Parity	2.4 ± 1.3	2.6 ± 1.3	2.3 ± 1.3
Years on E	8.1 ± 5.1	7.9 ± 5.4	8.1 ± 5
Years on T	5.8 ± 2.5	5.4 ± 2.5	5.9 ± 2.5
Family Hx	29%	28%	30%
Cases (%)	7 (1.4)	1 (0.6)	6 (1.7)
Cases per 100,000 woman-years	238	115	293

E/T, estrogen + testosterone; E/P/T, estrogen + progestin + testosterone; E, estrogen; T, testosterone; Hx, history.

TABLE 2. *Breast cancer cases in women using testosterone compared with major studies*

	N	Age	Cases/100,000 woman-years	Years observed
Schairer et al[10] (E/P)	1,854	57.4 y	628	10.2
WHI[6] (E/P)	8,506	63.2 y	380	5.2
Million Woman[5] (E/P)	142,870	55.9 y	521	2.6
Million Woman[5] never-users	392,757	55.9 y	283	2.6
Adelaide (E/P/T)	347	57 y	293	5.9

Current E/P users are analyzed in comparison with never-users (from the Million Woman Study) and E/P/T users from Adelaide, South Australia. Citations refer to the "References" section at the end of the article. WHI, Women's Health Initiative; E/T, estrogen + testosterone; E/P/T, estrogen + progestin + testosterone.

TABLE 3. *Age-specific breast cancer cases observed and cases expected*

	Age groups									
	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84
Observed cases (cases/total)	0/2	0/19	0/63	1/119	3/132	1/80	1/59	0/23	1/9	0/2
Total observed years	4.74	89.7	285.3	625.9	757.6	536.8	397	153	66.9	15.4
Percentage	0	0	0	0.8	2.3	1.2	1.7	0	0	0
Expected cases (A) (cases/total)	0/2	0/19	0/63	1/119	2/132	1/80	1/59	1/23	0/9	0/2
Expected cases (B) (cases/total)	0/2	0/19	1/63	1/119	2/132	1/80	1/59	1/23	0/9	0/2
Expected cases (C) (cases/total)	0/2	0/19	0/63	1/119	2/132	2/80	2/59	1/23	0/9	0/2

Cancer statistics: A, 1982-1986; B, 1987-1991; C, 1992-1996. Total is the number of women in each age group. Data from Australia's Breast Cancer Statistics, 2002, Table A9, available at http://www.nbcc.org.au.

The women's characteristics are presented as mean with SD for continuous variables and as percentage for binary variables. Breast cancer incidence rates are expressed as number of cases per 100,000 woman-years. The direct standardization method[9] was used to calculate age-standardized rates.

RESULTS

Breast cancer status was ascertained by mammography before commencing HT and biannually thereafter, with mean duration of follow-up equal to 5.8 ± 2.5 (SD) and range of 0.07-11.4 years. Observations began in 1987 and ended in 1999. The mean age of the women at the start of observation was 56.4 years; additional demographic data are reported in Table 1. The average duration of estrogen therapy was about 8 years; it was about 5 to 6 years for testosterone. There was a rather high rate of positive family history for breast cancer in this group of women (147/508, Table 1). In more than half of them (75/508, 15%), a first-degree relative (mother, sister, or daughter) was affected.

Within this observation period, seven invasive breast cancer cases were diagnosed among these women, resulting in an incidence of 238 per 100,000 woman-years for the combined (E/T and E/P/T) groups (Table 1). Notably, six of seven cases and the only death occurred in the E/P/T group. Thus, the incidence for this group was considerably higher than the group as a whole: 293 cases per 100,000 woman-years. The rates for estrogen plus progestin users reported in three major studies are compared with our group's rates in Table 2. Note that the rates were considerably higher in estrogen plus progestin users in all three comparison studies. Remarkably, the breast cancer rate closest to that seen in our E/P/T users was 283 cases per 100,000, reported in the never-users from the "Million Women" study (Table 2).

Age-specific incidence rates for women in our study are shown in Table 3. Using the incidence rates of breast cancer in South Australia for 1982 to 1986, 1987 to 1991, and 1992 to 1996,[10] we calculated the expected incidence for each age group and found that the expected number of cases in our study group is about the same as that actually observed for each of the three time intervals. Because women in the general population are expected to have a lower incidence rate than current HT users, these observations suggest that testosterone treatment suppresses the expected HT-induced increase in cancer rates. The Australian Breast Cancer Statistics[10] also provide age-standardized incidence rates of breast cancer in South Australia for each year from 1982 to 1996. Notably, the age-standardized cancer incidence rate noted in our group is 72.8 per 100,000 woman-years, lower than the reported incidence rates of breast cancer in South Australia for any year from 1989 to 1996.

DISCUSSION

The breast cancer rates noted in the present study of women taking testosterone in addition to estrogen with or without progestin are substantially lower than those reported for women of similar age receiving conventional HT. For example, Schairer et al report a rate of 453 cases per 100,000 woman-years in women receiving estrogen alone and 628/100,000 for estrogen plus progestin.[11] The Women's Health Initiative study reports a rate of 380 per 100,000 woman-years in women receiving estrogen plus progestin,[6] although the average age at the start of follow-up in this study was somewhat higher than in our group (63.2 vs 56.4 y). The "Million Woman" study reported 430 cases per 100,000 woman-years for current HT users, compared with 283/100,000 for never-users over a 2.6-year observation.[5] These three study groups are the largest and most similar to our group in terms of demographic characteristics supporting cross-study comparison. One difference, however, is that for the latter half of the treatment period, most study participants were on estradiol as well as testosterone implants, whereas most of those in the referenced studies from the United States

and the United Kingdom were on oral regimens. However, the "Million Women" study had enough participants to allow subgroup analysis, which showed that the women on transdermal estrogen exhibited a similar cancer rate to those on oral estrogen.[5] Our data confirm the increased risk in estrogen plus progestin compared with estrogen only groups noted in previous studies. The rather high prevalence of a positive family history in our group indicates these women were at a relatively high risk for breast cancer at baseline,[12] making the present observations of breast cancer rates similar to untreated postmenopausal women all the more remarkable. There was no apparent increase in the prevalence of venous thrombosis or acute coronary syndromes among these testosterone-treated women, although there was no systematic data collection to document the observation.

There are plausible biological mechanisms that could explain testosterone's apparent suppression of breast cancer in estrogen-treated women. Androgens function by binding to the intracellular androgen receptor (AR), which is abundant in normal mammary epithelium.[3] We have previously shown that testosterone treatment inhibits estradiol-induced mammary epithelial proliferation in the rhesus monkey[3] and, more recently, that this suppressive effect is correlated with AR-induced down-regulation of estrogen receptor-α (ERα) and up-regulation of estrogen-receptor-β (ERβ) expression, resulting in reversal of the ERα dominant receptor ratio found in the mammary epithelium from estradiol-treated animals.[4] We found that an important consequence of this alteration in ER ratio was down-regulation of estradiol-induced MYC expression.[4] Because the MYC oncogene induces mammary tumorigenesis, this may be an important mechanism whereby androgens reduce not only estrogen-induced proliferation but also suppress tumorigenesis. Finally, it is worth noting that in the past, androgens have been used with success comparable to that of other hormonal therapies in treating breast cancer.[13]

A major weakness of the present study is that the women were not randomly assigned to receive testosterone; thus it is possible that there may have been an unknown bias favoring the prevention of breast cancer in our study group. It is difficult to think of any likely preventive bias, however. The primary reason for referral to this particular menopause clinic was that women were dissatisfied with usual HT, with the most common complaints being emotional lability, asthenia, and deficient libido. It does not seem likely that these characteristics protect women from breast cancer. There is one source of bias in this group, however, that would put these women at greater rather than lesser risk for breast cancer. It seems likely that some women with a positive family history of breast cancer were referred to the specialist clinic by primary care practitioners who were uncomfortable in treating such women with HT, accounting for the relatively high prevalence of this history in our group. Another weakness of our study is the relatively small size of the study groups and the absence of a concurrent HT group not receiving testosterone. However, this was not planned as a randomized, controlled study at the outset, and women came to this clinic because they or their primary caregivers thought they would benefit from testosterone therapy. Thus, control data were gleaned from the public Breast Cancer Registry for Australia and from published studies reporting breast cancer rates in similar-aged women followed for a similar length of time.

Despite methodological limitations, our clinical observations in the present study, taken together with many other types of evidence that androgens suppress breast growth,[1,13] support the concept that a balanced formulation of ovarian hormones—including estrogen, androgen, and progesterone—may be advantageous in treating women with ovarian failure. We think the aim of HT should be to recreate as closely as possible the physiological steroid milieu found in normal cycling women, using a parenteral route to avoid pharmacological first-pass effects upon the liver. This type of approach is particularly important when treating young women with premature ovarian failure, for whom the term hormone "replacement" treatment is justified. The indications for treating young women are more clear-cut than those for postmenopausal women, and they usually need to take HT for decades.

CONCLUSIONS

The present observations suggest that the addition of testosterone to conventional HT for postmenopausal women does not increase, and may indeed reduce, the HT-induced breast cancer risk, thereby returning the incidence to the normal rates observed in the general, untreated population. Rigorous, randomized, and placebo-controlled studies will be necessary to establish the point.

Acknowledgments: The authors are grateful for the able assistance of Mrs. Christine Causby.

REFERENCES

1. Dimitrakakis C, Zhou J, Bondy CA. Androgens and mammary growth and neoplasia. *Fertil Steril* 2002;77(Suppl 4):26-33.
2. Jayo MJ, Register TC, Hughes CL, et al. Effects of an oral contra-

ceptive combination with or without androgen on mammary tissues: a study in rats. *J Soc Gynecol Investig* 2000;7:257-265.
3. Zhou J, Ng S, Adesanya-Famuiya O, Anderson K, Bondy CA. Testosterone inhibits estrogen-induced mammary epithelial proliferation and suppresses estrogen receptor expression. *FASEB J* 2000; 14:1725-1730.
4. Dimitrakakis C, Zhou J, Wang J, et al. A physiologic role for testosterone in limiting estrogenic stimulation of the breast. *Menopause* 2003;10:292-298.
5. Beral V. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet* 2003;362:419-427.
6. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321-333.
7. Braunstein GD. Androgen insufficiency in women: summary of critical issues. *Fertil Steril* 2002;77:94-99.
8. Davis SR, Burger HG, McCloud P, Strauss BJ, Burger H. The rationale for physiological testosterone replacement in women *Baillieres Clin Endocrinol Metab* 1998;12:391-405.
9. Fleiss JL, Kingman A. Statistical management of data in clinical research. *Crit Rev Oral Biol Med* 1990;1:55-66.
10. Australia's Breast Cancer Statistics, 2002. National Breast Cancer Center. Available at: http://www.nbcc.org.au. Accessed July 25, 2003.
11. Schairer C, Lubin J, Troisi R, Sturgeon S, Brinton L, Hoover R. Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. *JAMA* 2000;283:485-491.
12. Gail MH. The estimation and use of absolute risk for weighing the risks and benefits of selective estrogen receptor modulators for preventing breast cancer. *Ann N Y Acad Sci* 2001;949:286-291.
13. Labrie F, Simard J, de Launoit Y, et al. Androgens and breast cancer. *Cancer Detect Prev* 1992;16:31-38.