ORIGINAL RESEARCH—EPIDEMIOLOGY

The Incidence of Invasive Breast Cancer Among Women Prescribed Testosterone for Low Libido

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ABSTRACT

Introduction. Although the efficacy of testosterone for the treatment of hypoactive sexual desire disorder is well established, the effect of testosterone therapy on breast cancer risk remains uncertain.
Aim. The incidence of invasive breast cancer among past and current testosterone users.
Methods. Retrospective cohort study of 631 women ever treated with testosterone between January 1989 and December 2007 in a clinical endocrinology practice.
Main Outcome Measure. The incidence of invasive breast cancer since first exposure, and the standardized incidence rate ratio (IRR) calculated using Australian age-specific incidence rates for 2005.
Results. The mean age of the women at first exposure to testosterone therapy was 49.1 ± 8.2 years, median treatment duration, 1.3 years, and mean follow-up of 6.7 ± 4.6 years, providing 4,015 woman-years of follow-up. Twelve cases of invasive breast cancer occurred among 599 women breast cancer-free before treatment, giving an age adjusted IRR of 1.35 (95% confidence interval 0.76–2.38). There was no evidence of an independent effect of duration of exposure on breast cancer risk.
Conclusion. In this study, testosterone use was not associated with a significant increase in breast cancer risk. **Davis SR, Wolfe R, Farrugia H, Ferdinand A, and Bell RJ. The incidence of invasive breast cancer among women prescribed testosterone for low libido. J Sex Med 2009;6:1850–1856.**

Key Words. Testosterone; Breast Cancer; Sexual Function; Androgens; Complications

Introduction

Testosterone therapy improves sexual function in women in randomized controlled trials [1–7]. Yet the use of testosterone as a therapy for women remains controversial due to the lack of long-term safety data, particularly with respect to effects on the breast [8,9].

In the United States, testosterone has most commonly been prescribed as methyltestosterone in a combination pill with esterified estrogen. In contrast to testosterone, methyltestosterone is not aromatized, with some evidence suggesting that it acts as an aromatase inhibitor [10]. Recent observational studies have provided inconsistent findings regarding the effects of esterified estrogen plus methyltestosterone on the breast [11,12]. Outside the United States, testosterone is more likely to be prescribed as a testosterone implant or as a transdermal cream [13], and, most recently, the transdermal testosterone patch has been approved for the use in surgically menopausal women in Europe. Exogenous testosterone may act directly or be aromatized to estrogen in the breast. Testosterone exhibits growth inhibitory and apoptotic effects in some, but not all, breast

cancer cell lines [14] and in rodent breast cancer models [14,15]. Human and primate studies indicate that testosterone serves as a natural endogenous protector of the breast and limits mitogenic and cancer-promoting effects of estrogen on mammary epithelium [16–18]. Older epidemiological studies of testosterone and breast cancer risk have significant methodological limitations [14], and whereas more recent observational studies have reported on the effects of oral methyltestosterone, less is known of the effects of parenteral testosterone and breast cancer risk [19].

To address this issue, we have determined the rate of invasive breast cancer in women treated with parenteral testosterone for low libido over 18 years in a single clinical practice. The study included premenopausal and postmenopausal women, past as well as current testosterone users, and all women provided follow-up data.

Methods

Study Population

Medical records and billing records of all women treated by SRD in her practice for loss of sexual desire from January 1989 to December 2007 were hand searched for documentation of treatment with testosterone. Treated women were both users and nonusers of postmenopausal hormone therapy, and were not excluded from treatment on the basis of characteristics such as cardiovascular risk factors, family history of breast cancer, or partnership status.

Prior to 2002, treatment was with a testosterone 50-mg implant inserted subcutaneously [20]. All women had their testosterone level measured prior to treatment to ensure exclusion of any women with biochemical androgen excess, but not in order to diagnose androgen deficiency [21]. Subsequent implants were only inserted, usually every 4–6 months, if testosterone levels had fallen to the lower limit or below the normal range for young women. From 2002, treatment was also with transdermal testosterone cream (Androfeme, Lawley Pharmaceuticals, Subiaco, Western Australia, Australia), with the dose titrated to maintain total and free testosterone levels within the normal range for premenopausal women. In most cases, postmenopausal women used systemic estrogen alone or in combination with progestin therapy (HT). Premenopausal women were treated with testosterone alone, although some concurrently used hormonal contraception. Factors that might have affected the underlying risk of breast cancer of the women in this study include exposure to estrogen or estrogen plus progestin therapy, oophorectomy, and a family history of breast cancer. However, it was not possible to fully describe the studied sample in relation to these characteristics. The issue of characterizing HT exposure in terms of risk was complicated by women transiting menopause, commencing, changing, stopping, and recommencing a variety of hormonal preparations, undergoing hysterectomy, or switching to a progestin intrauterine device over the course of treatment and follow-up. For current patients and women who could be recontacted, we had self-reported oophorectomy status; however, for other women, this may have changed since their last consultation with SRD. In terms of family history of breast cancer, for women who were not current patients and could not be contacted, any change in family history since they were active patients would not have been documented.

All women aged 50 or more years were referred for biannual screening mammography as per Victorian guidelines. Younger women were referred for mammography if they had a family history of breast cancer or another clinical indication for mammography.

Study Methods

Duration of exposure to exogenous testosterone was established for current patients from their medical records. For past patients, a brief questionnaire was sent to all those for whom a current postal address was: (i) known, or (ii) established by linkage of names and birth dates against a recent version of the Victorian Electoral Roll provided by the Victorian Electoral Commission, or (iii) found in the white pages online (residential telephone numbers and addresses listed by last name and initials). If no response was received, a maximum of two reminder letters were sent. Past patients whose contact addresses were identified solely by searching the electoral roll were not sent reminder letters, in agreement with the Victorian Electoral Commission. For women who remained uncontactable, last exposure was designated as 6 months after the day on which they last had a testosterone implant inserted by SRD (the time by which testosterone levels would typically return to baseline), or 2 months after the date their last prescription for testosterone cream written by SRD was dispensed (the minimum period for use of one tube at the prescribed dose; all dispensing was from a single pharmacy).

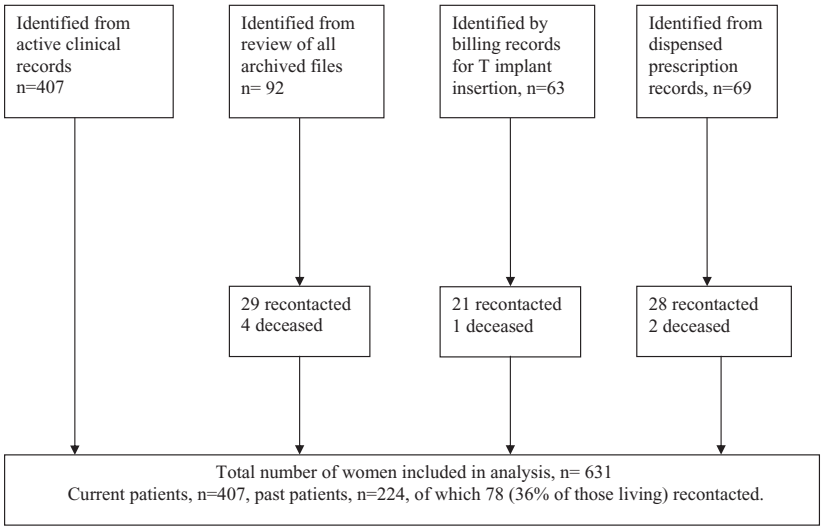

Figure 1 Identification of testosterone users.

Patients were matched to the Victorian Cancer Registry (VCR), which provided cancer diagnoses, including date of diagnosis, morphology, behavior, and grade, and, for deaths, whether death was caused by cancer.

The study was approved by the Monash University Human Research and Ethics Committee, Clayton, Victoria, with special information access granted by the Victorian Electoral Commission, Medicare Australia, and the VCR.

Analysis

Follow-up commenced on the date treatment started and ended on either December 31, 2007, the date of diagnosis of invasive breast cancer, or the date of death for women without breast cancer. Only cases of invasive breast cancer were considered in the calculation of risk with testosterone, with 28 women with invasive breast cancer prior to testosterone treatment and four women with ductal carcinoma in situ excluded.

Within-cohort comparisons of breast cancer (BC) cases and noncases used Wilcoxon rank sum tests and *t*-tests as appropriate. Poisson regression was used to calculate the standardized incidence rate (morbidity) ratio (IRR), and separately to assess the effect of duration of exposure to testosterone on risk of developing BC. Standardization used age-specific incidence rates for invasive BC in Victoria for 2005 [22]. The incidence of invasive BC in women in Victoria has been stable since an increase in 1993/1994 after the introduction of screening mammography for women aged 50–69 in 1992 [23]. The BC diagnoses made in the cohort of women in this study were all made in the years between 2002 and 2007, except for one, which was made in 1994. The participation rate of women aged 50–69 years in mammographic screening is about 60% [23]. As the comparator population was all women over 18 years in the state of Victoria, no adjustments for menopausal status, other exogenous hormone use, or family history of BCs were made.

Results

Six hundred thirty-one women, of whom 407 were current patients, were identified as being treated with testosterone between January 1989 and December 2007 (Figure 1). The mean age of the women at start of therapy was 49.1 years, women used testosterone for a median of 1.3 years, and were followed for an average of 6.7 years, with a total of 4,015 woman-years of follow-up (Table 1).

Twelve cases of invasive BC occurred during follow-up, and their median duration of testosterone therapy (1.1 years) was not different from that of noncases ($P = 0.79$) (Table 2). The mean age at first exposure of cases (55.1 ± 6.4 years) was greater than that of noncases (mean difference 6.2 years, 95% confidence interval [CI] 1.6–10.9; $P = 0.009$). All women who developed BC during follow-up were also past users of systemic estrogen and only one woman was a current user of testosterone at the time of her BC diagnosis.

The incidence rate of invasive BC in the cohort was 299 cases/100,000 person-years, with an age-standardized IRR of 1.35 (95% CI 0.76–2.38) (Table 3). There was no evidence that

Table 1 Study cohort characteristics

Age* in years, n = 624†	
Mean ± SD	55.8 ± 9.0
Oophorectomy	
Yes	109 (17.3%)
No	438 (69.4%)
Not known	84 (13.3%)
Current testosterone user, n (%)	168 (26.9%)
Past testosterone user, n (%)	456 (73.1%)
Treatment type, n (%); n = 631	
Testosterone implant	268 (42.5%)
Testosterone cream	270 (42.8%)
Implant and cream	91 (14.4%)
Nandralone injections	1 (0.2%)
Oral testosterone undecanoate‡	1 (0.2%)
Age at commencement of treatment in years, n = 631	
Mean ± SD	49.1 ± 8.2
Duration of treatment years,* n = 631	
Mean ± SD	2.6 ± 3.2
Median, range	1.3, 0.03–18.6
Duration n (%)	Absolute cumulative, n (%)
Use <12 months	267 (42.3%)
Use 12 to <24 months	113 (17.9%) 380 (60.2%)
Use 24 to <36 months	67 (10.6%) 447 (70.8%)
Use 36 to <48 months	40 (6.3%) 487 (77.2%)
Use 48 to <60 months	36 (5.7%) 523 (82.9%)
Use 5 to <10 years	88 (13.9%) 611 (96.8%)
Use >10 years	20 (3.2%) 631 (100.0%)
Person years of follow, n = 599§	
Total person years	4,015
Mean person years ± SD	6.7 ± 4.6
Median	5.5
Range	0.0–20.6

*Cut-off date: December 31, 2007.
†Seven women deceased.
‡Treated prior to referral to SRD.
§Excludes 32 women treated after breast cancer diagnosis. For women who developed breast cancer or died, person-years are from treatment commencement to date of diagnosis or death.
SD = standard deviation.

the risk of BC was related to duration of exposure in years (IRR per year of exposure = 1.00, 95% CI 0.86–1.17), or to use for 5 or more years when adjusted for age (compared with less than 5-year duration, IRR = 1.16, 95% CI 0.31–4.33).

Table 2 Summary of 12 women with invasive breast cancer diagnosed after treatment with testosterone started

Age in years when treatment started	
Mean; range	55.1, 46.9–70.7
Age in years at diagnosis	
Mean, range	63.5, 56.9–74.6
Time of diagnosis from commencement of treatment in years	
Mean, range	8.4, 2.3–13.6
Method of treatment	
Testosterone implant	9
Transdermal testosterone cream	1
Implant and cream at some time	1
Nandrolone decanoate injections	1
Duration of treatment	
Median, range	1.1, 0.2–13.8
Use ≥5 years, n (%)	3 (25%)

Table 3 The incidence rate of invasive breast cancer in the cohort and Victorian population by age

	Study cohort				Victorian population 2005 [22]				
Age group	Observed	Expected	Women-years	Rate per 1,000 women-years	Number of breast cancer cases	Number of women	Rate per 1,000 women-years	IRR	95% CI
25–29	0	0.00	4	0	11	170,863	0.06	—	—
30–34	0	0.02	67	0	48	192,883	0.25	—	—
35–39	0	0.13	203	0	122	189,961	0.64	—	—
40–44	0	0.47	431	0	206	190,832	1.07	—	—
45–49	0	1.28	665	0	349	181,133	1.93	—	—
50–54	0	2.04	898	0	376	165,369	2.27	—	—
55–59	3	2.37	910	3.3	398	152,872	2.60	1.27	0.26–3.73
60–64	6	1.58	520	11.5	348	114,733	3.03	3.80	1.39–8.37
65–69	2	0.68	210	9.5	316	98,150	3.22	2.96	0.36–10.78
70–74	1	0.25	79	12.7	271	84,098	3.22	3.93	0.10–22.07
75–79	0	0.06	22	0	225	78,206	2.88	—	—
80–84	0	0.01	5	0	187	61,838	3.02	—	—
85+	0	0.00	1	0	176	55,174	3.19	—	—
Total	12		4,015		3,033	1,736,112		1.35	0.76–2.38

IRR = incidence rate ratio; CI = confidence interval.

There were seven deaths during the follow-up period, with only one due to BC in a woman who had a single testosterone implant 7 years prediagnosis.

Discussion

Among a cohort of women who were past or current users of parenteral testosterone for low libido, and who provided 4,015 women-years of follow-up, we observed an incidence of invasive BC that was 35% higher than the background population incidence rate, possibly due to increased case detection. There was no sufficient evidence to conclude the existence of a real effect of testosterone treatment in increasing BC risk in that our finding was not statistically significant, and our data are consistent with the true risk of testosterone treatment being anywhere within the range of being moderately elevated (up to 2.4-fold) through to modestly diminished (0.8-fold) compared with the risk in the general population. The overall incidence rate we observed, 299 cases /100,000 women years, was comparable with that reported for HT nonusers in the Nurses Health Study [24] (295/100,000 women-years) and the Million Women Study [25] (283/100,000 women-years), and lower than the rate reported for estrogen users for the Nurses Health Study (345/100,000 women-years) [24].

Only one BC was diagnosed among current users, and there was no evidence from our analysis that duration of exposure was independently associated with the risk of BC, although with relatively few cases of BC in the analysis, there was limited power to assess this.

If the real risk of BC was higher in our group compared with the general population, it cannot be assumed that the increase in risk should be attributed to testosterone exposure. The universal use of screening mammography in the cohort would have resulted in greater case finding than in the general population, and exposure of postmenopausal women in the cohort to hormone therapy would independently increase the risk of BC in this group. Any detection bias would be in the direction of overestimating the incidence of BC in the women in our study. About one in five women in our cohort had a history of oophorectomy, which may offer some protection against BC. However, among women for whom both oophorectomy status and use of HT were known, 98% had also received HT. Ever use of HT by 69.5% of study patients was greater than the use by postmenopausal women in the general community (about 40%) [26,27], potentially increasing BC risk.

There has been one prior follow-up study of BC incidence in postmenopausal women exposed to parenteral testosterone. Dimitrakakis and others, in a similar-sized study conducted in South Australia, reported no increase in the risk of invasive BC among postmenopausal women while being treated with testosterone implants (293/100,000 women-years for E + P + T, and 115/100,000 women-years for E + T over an average of 5.9 years) [19].

There have been three recent U.S. studies reporting on the effects of methyltestosterone combined with esterified estrogen and BC risk. The first of these reported an increased rate of invasive BC among current users over and above that of postmenopausal estrogen users [24]. Use of methyltestosterone by this study cohort was often for management of mastalgia, as opposed to low libido, with methyltestosterone users more likely to have had benign breast disease [24]. Investigators for the Women's Health Initiative Observational Study compared the incidence of invasive BC among estrogen plus methyltestosterone users vs. nonusers of hormone therapy, and found that users of fewer than 12 months had a twofold increase in risk, whereas users for more than 12 months had no increase in risk [12]. In contrast, in a large case-control study, no increase in risk of BC was observed for users of estrogen alone or esterified estrogen plus methyltestosterone, whereas an increase in BC risk was seen for users of estrogen plus progestin with and without concurrent methyltestosterone use [11]. These data, taken together with studies of the effects of testosterone on mammographic density and breast cell proliferation in users of estrogen plus progestin [16,28], would suggest that the addition of exogenous testosterone confers no additional invasive BC risk to that of the concurrent postmenopausal estrogen–progestin regimen. The most important clinical difference between the various studies is the increase in risk among current users reported in the U.S. studies involving methyltestosterone use [12,24], which was not seen in the present study or that of Dimitrikakis and colleagues [19].

Strengths of this study are that it was community based, past and current users were included, complete follow-up was achieved, and cases and deaths were identified by a cancer registry. Furthermore, treatment involved parenteral testosterone, with close monitoring of the doses during treatment.

The main limitations are that the study was observational and the cohort was not large. Confounding is a potential limitation of any cohort or case-control study, and this is clearly an issue for the observational studies, which have examined the issue of exposure to testosterone therapy and BC. The characteristics of women who seek treatment with testosterone for low libido are likely to be different from those who do not seek such treatment in ways that could affect their underlying risk of BC. Also, as stated earlier, women who seek such treatment also enter a medical surveillance system (of regular clinical examination and mammographic screening), which increases the chances that any BC they develop will be diagnosed. Despite the fact that some of the women were premenopausal at the time of treatment, the vast majority of follow-up for all of the women was during their postmenopausal years. Although no cancers occurred in women under the age of 55 years, this data does not provide evidence of safety in younger women.

Our study also does not inform the issue of the safety of long-term testosterone use, with most women using testosterone for less than 5 years and nearly one half of the women using testosterone for fewer than 12 months. However, the finding of only one BC among current users in a clinical practice environment, and the pattern of use being mainly short term, is somewhat reassuring. The relatively short-term safety of testosterone will be further informed by the findings of phase III safety trials of a testosterone currently underway [29].

In summary, this study suggests that the past and current use of parenteral testosterone therapy by women in the community is not associated with a statistically significant change in BC risk. Although a moderate increase in risk cannot be excluded, if such a real increase existed, then it cannot simply be attributed to testosterone exposure.

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Conflict of Interest: Dr. Davis has received honoraria from and has been an investigator for Proctor and Gamble Pharmaceuticals, Acrux Australia, Astra Zeneca, Novartis Oncology Australia, Bayer Schering, and Organon.

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Category 3

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