

ORIGINAL RESEARCH—ONCOLOGY

Breast Cancer, Aromatase Inhibitor Therapy, and Sexual Functioning: A Pilot Study of the Effects of Vaginal Testosterone Therapy

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ABSTRACT

Introduction. Women with breast cancer have better cancer-related outcomes with the use of aromatase inhibitors (AIs), but the physiological suppression of estradiol can negatively affect sexual functioning because of unpleasant urogenital and vaginal symptoms. Local health care practitioners have observed that the benefits of vaginal testosterone in allaying these unpleasant symptoms in women with breast cancer are similar to the benefits of vaginal estrogen in women without breast cancer.

Aim. The aim of this study was to evaluate the effects of using a daily vaginal testosterone cream on the reported sexual health quality of life in women with breast cancer taking AI therapy.

Methods. Thirteen postmenopausal women with breast cancer on AI therapy and experiencing symptoms of sexual dysfunction were recruited from an oncology practice. The women were prescribed a 300 µg testosterone vaginal cream daily for 4 weeks. During the first study visit, a vaginal swab was obtained to rule out the presence of *Candida* species or *Gardnerella vaginalis* in participants. Women with positive vaginal swabs were treated prior to starting the vaginal testosterone therapy.

Main Outcome Measure. The Female Sexual Function Index (FSFI) survey, measuring female sexual health quality of life, was administered during the first study visit and at the final study visit, after completing testosterone therapy.

Results. Twelve patients completed 4 weeks of daily vaginal testosterone therapy. When compared with baseline FSFI scores, there was a statistically significant improvement for individual domain scores of desire ($P = 0.000$), arousal ($P = 0.002$), lubrication ($P = 0.018$), orgasm ($P = 0.005$), satisfaction ($P = 0.001$), and pain ($P = 0.000$). Total domain scores reflecting sexual health quality of life also improved when compared with baseline ($P = 0.000$).

Conclusions. The use of a compounded testosterone vaginal cream applied daily for 4 weeks improves reported sexual health quality of life in women with breast cancer taking AIs. **Dahir M and Travers-Gustafson D. Breast cancer, aromatase inhibitor therapy, and sexual functioning: A pilot study of the effects of vaginal testosterone therapy. Sex Med 2014;2:8–15.**

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Introduction

Breast cancer is the most common type of malignancy among women in the United States [1]. The advanced technology of mammography screening offers early detection and diagnosis of breast cancer. In the United States, about 75% of breast cancers are diagnosed in postmenopausal women, and 80% of them are estrogen receptor (ER) positive [2]. The recommended treatment for postmenopausal women with hormone receptor-positive cancers is estrogen deprivation through the use of adjuvant endocrine therapy, such as an aromatase inhibitor (AI). AIs inhibit the synthesis of estrogen by preventing the aromatase enzyme from converting androgens to estrogens [3]. Third-generation AIs suppress up to 98% of circulating hormones and are considered to be first-line treatment [4].

Women with breast cancer have better cancer-related outcomes with the use of AIs, but side effects from the medication can negatively affect sexual functioning because of the physiologic suppression of estradiol [4–6]. As a result, women taking AIs are more likely to experience a decreased sexual quality of life because of unpleasant urogenital and vaginal symptoms [7–9]. In 2008, Antoine et al. surveyed women with breast cancer for reported quality of life concerns during AI treatment. When compared with non-AI users, women taking AIs had significantly higher rates of vaginal dryness ($P = 0.01$), decreased sexual desire ($P < 0.02$), dissatisfaction with their sexual life ($P < 0.01$), and sexual dysfunction ($P < 0.001$) [7].

Baumgart et al. [8] reported in a population-based study that nearly 600,000 women in the United States currently take AIs and that these women are two times more likely than non-treated women to report symptoms of vulvovaginal atrophy and painful intercourse. Baumgart and colleagues evaluated subjective symptoms related to endocrine changes, such as estrogen deficiency, using the endocrine subscale of the Functional Assessment of Cancer Therapy-Breast tool. Fifty-eight percent of participants reported moderate to severe symptoms of vaginal atrophy, 42% reported vaginal dryness, and 62% reported pain or discomfort during intercourse [8].

The concurrent use of AIs with vaginal estrogen is generally not recommended because local estrogen may interfere with the drug's ability to suppress endogenous estrogen production [3]. The lack of treatment options is concerning because the number of women diagnosed with breast

cancer continues to increase; their longevity also continues to increase with the use of newer adjuvant chemotherapies [4,10]. The principal investigator (PI) has observed that the benefits of vaginal testosterone for sexual health in women with breast cancer are similar to the benefits of vaginal estrogen in women without breast cancer. Testosterone is a U.S. Food and Drug Administration (U.S. FDA)-approved drug, but currently, the U.S. FDA has not approved a vaginal testosterone medication for the treatment of vulvovaginal symptoms and negative sexual side effects related to AI use [11]. Testosterone is available off-label, by prescription, to women through compounding pharmacies that are licensed and regulated at the state level [12]. Pharmaceutical compounding requires sterile technique and a detailed process to ensure the right drug, weight, and dose; even distribution of the chemical throughout the base; and proper distribution of the compounded medication through the base, such as a cream.

Aim

This study aims to evaluate the effects of using a 300 μg testosterone vaginal cream daily for 4 weeks on the reported sexual health quality of life in women with breast cancer who take AI therapy. The authors hypothesized that vaginal testosterone therapy would improve sexual functioning in relation to desire, arousal, lubrication, orgasm, satisfaction, and pain.

Methods

The pilot study was approved by the Creighton University Institutional Review Board and registered with Clinicaltrials.gov. Participants were prospectively recruited from Nebraska Cancer Specialists in Omaha, Nebraska between January 11, 2013 and April 23, 2013. The target population was women with breast cancer who take AI therapy such as anastrozole, letrozole, or exemestane. Eligible participants included women who (i) were diagnosed with breast cancer and currently on AI therapy; (ii) had reported urogenital/vulvovaginal symptoms, such as vaginal dryness and pain with intercourse; (iii) had reported changes in sexual health quality of life/sexual functioning since starting AI therapy; (iv) were older than age 50 years; and (v) were postmenopausal (2 years since last menstrual cycle). The exclusion criteria included (i) the use of other treatments for breast cancer, such as chemotherapy or radiation, within the past 12

months; (ii) a known sensitivity to medications containing testosterone; and (iii) the use of exogenous hormone replacement therapy in the past 3 months, including systemic and local estrogen or testosterone therapy.

Study Setting and Procedures

Midwest Cancer Center Legacy in Omaha, Nebraska was the setting for conduct of the study, meetings with participants, and data collection. The PI procured initial and ongoing study consent and served as the sole educator throughout the study. Participants gave written informed consent prior to enrolling in the study.

During the first study visit, the PI conducted interviews and performed a physical examination. The PI procured a vaginal swab (Affirm, Becton Dickinson & Company, Franklin Lakes, NJ, USA) prior to prescribing testosterone therapy because women with suppressed estrogen levels have an increased risk of infection. A decrease in vaginal secretions reduces lactic acid production by lactobacilli, increases the vaginal pH, and predisposes the vulvovaginal area to infection [13–15]. In the clinical setting, the PI has observed that women who develop a yeast (*Candida* species) or bacterial (*Gardnerella vaginalis*) infection while using vaginal testosterone frequently report symptoms of vaginal itching, burning, or irritation.

Participants with a negative vaginal swab were prescribed a vaginal testosterone cream, and those with positive results were treated prior to starting the intervention. Participants who were treated for a vaginal infection did not have a repeat vaginal swab because a test of cure is not standard of care when the symptoms have resolved [16,17]. The vaginal testosterone cream was prepared by Precision, a licensed compounding pharmacy in Omaha, Nebraska, and given to the participants at no cost. The study drug was supplied in prefilled syringes, and each 0.5 mL dose delivered 300 µg of testosterone daily. The PI demonstrated proper application of the vaginal testosterone cream, and participants were instructed to apply 0.5 mL to the vaginal opening and clitoris once daily for 4 weeks (28 days). A treatment application protocol was followed to ensure consistency among participants in the application of the vaginal testosterone cream. A mirror was used to demonstrate application of the topical testosterone vaginal cream. After the physical examination, the patient was reinstructed on how to apply the vaginal testosterone cream using a diagram of the vulva.

Main Outcome Measure

The primary end point of the study was to evaluate the impact of using vaginal testosterone cream on sexual health quality of life. Participants completed the Female Sexual Function Index (FSFI) questionnaire prior to starting testosterone therapy (pretest) and repeated the questionnaire after using the testosterone cream for 4 weeks (posttest). The FSFI is a 19-item multidimensional self-administered questionnaire and takes about 15 minutes to complete. The questionnaire assesses six dimensions of sexual functioning over the previous 4 weeks. The dimensions are related to desire, arousal, lubrication, orgasm, satisfaction, and pain; a total FSFI score less than 26.5 is suggestive of female sexual dysfunction.

The FSFI questionnaire was constructed by a group of experts in female sexual functioning to ensure face validity and that the questions were not biased, and to determine the ease of administration and scoring [18]. The questionnaire was revised, administered to a larger sample, and re-administered after 2–4 weeks to establish test-retest reliability. Reliability has been supported in numerous studies [19–21]. The original researchers granted permission to use the FSFI questionnaire free of charge and requested that publications using the FSFI questionnaire be emailed to them.

Statistics

The quasi-experimental pilot study involved a one-group pre–posttest design using the FSFI questionnaire and participants serving as their own controls. The data were collected, recorded, and analyzed using SPSS 21.0 for Macintosh (SPSS, Inc., Chicago, IL, USA). The demographics and characteristics of participants were analyzed by descriptive statistics. The FSFI scores were analyzed by paired *t*-test and presented as mean, standard deviation, *t*-score, and probability (*P*) values. The *P* value was considered statistically significant if $P < 0.05$. A power calculation was not used because the intention for this pilot study was to collect preliminary data and expand for future research.

Results

There were no participant reports of serious adverse events to vaginal testosterone therapy. Of the 13 women enrolled in the study, one withdrew because of recurrent *G. vaginalis*. Per study protocol, her bacterial vaginal infection was treated prior to starting testosterone therapy, and the par-

Table 1 Demographics of project participants

	N = 12	Percentage (%)	Mean
Age (years)			59.67
Body mass index			
18.5–24.9 (normal)	2	16.7	
25–29.9 (overweight)	5	41.7	
30.0 and above (obese)	5	41.7	
Marital status			
Married	12	100	
Not married	0	0	
Sexually active prior to study*			
Yes	7	58.3	
No	5	41.7	
Sexually active during study*			
Yes	11	91.7	
No	1	8.3	
Time from breast cancer diagnosis to enrollment in study			4.6
Years			
Education			
High school degree	3	25	
Associate's degree	3	25	
Bachelor's degree	4	33.3	
Master's degree	2	16.7	

*Participants who engaged in sexual intercourse within the past four weeks.

participant used the study drug for 2 weeks. After 2 weeks, the participant reported symptoms of a recurrent vaginal infection and burning discomfort with application of the testosterone cream.

Table 1 shows the participant demographics. The participants were between the ages of 50 and 69. The mean age of participants was 59.67 years of age, and all of the participants were married. Most of the participants were overweight (41.7%) or obese (41.7%) by body mass index criteria, and all participants were high school graduates. The mean time frame from diagnosis of breast cancer to enrollment in the study was 4.6 years, and the time frame ranged from 2.2 years to 18.6 years. Prior to enrolling in the study, 58.3% of participants had engaged in sexual intercourse within the past 4 weeks. After completing 4 weeks of vaginal testosterone therapy, 91.7% of participants had engaged in sexual intercourse. Two of the participants shared their thoughts about participating in the study. One participant stated, "I did not tell my husband about the study because I did not want to get his hopes up. He has been patient and I feel bad for him. I hope you can help me." Another participant stated, "My husband doesn't know I am here today. I want to surprise him on Valentine's Day."

Table 2 shows additional characteristics of the participants. One-third of the participants were surgically postmenopausal (surgical removal of

ovaries). Regarding breast tumor characteristics, 91.7% of participants were ER positive, 83.3% were progesterone receptor positive, and one participant (8.3%) was human epidermal growth factor receptor 2 positive. Anastrozole was the most commonly prescribed AI therapy (91.7%), 8.3% were taking letrozole, and none of the participants was taking exemestane. Twenty-five percent of the participants were positive for *G. vaginalis* at the initial screening, treated successfully prior to study intervention, and none of them was positive for *Candida* species. Upon completion of the study, 91.7% of the participants decided to continue use of vaginal testosterone therapy, and several participants offered qualitative feedback (see Table 3).

All FSFI domain scores increased after using the testosterone vaginal cream, and the findings were statistically significant. The individual mean pretreatment to posttreatment domain scores were as follows: desire: 1.35 to 2.65, $P = 0.000$; arousal: 1.2 to 2.83, $P = 0.002$; lubrication: 1.18 to 2.68, $P = 0.018$; $P = 0.005$ for orgasm; $P = 0.001$ for satisfaction; and $P = 0.000$ for pain (see Table 3).

The total FSFI posttest scores improved for all participants when compared with baseline FSFI scores. Two of the participants had a total posttest

Table 2 Participant characteristics

	N = 12	Percentage (%)
Oophorectomy		
Yes	4	33.3
No	8	66.7
Estrogen receptor (ER) status		
ER+	11	91.7
ER-	1	8.3
Progesterone receptor (PR) status		
PR+	10	83.3
PR-	2	16.7
Human epidermal growth factor receptor 2 (HER2) status		
HER2+	1	8.3
HER2-	11	91.7
Aromatase inhibitor		
Anastrozole (Arimidex, Astra Zeneca, Wilmington, DE, USA)	11	91.7
Letrozole (Femara, Novartis Pharma, New York, NY, USA)	1	8.3
Exemestane (Aromasin, Pfizer, New York, NY, USA)	0	0
Vaginal swab test		
No vaginal infection	9	75
<i>Gardnerella vaginalis</i>	3	25
<i>Candida</i> species	0	0
Continued vaginal testosterone upon completion of study		
Yes	11	91.7
No	1	8.3

Table 3 Qualitative feedback from participants

- I never knew I had options. I hope you can help more women like me.
- After using the cream I was almost pain free—thank you for that.
- I no longer use Vagisil and I feel like my vaginal tissues have healed.
- I have noticed an increase in desire, but I still have pain.
- I feel like things opened up after using the testosterone cream.
- The testosterone cream caused moisture in my vagina within 24 hours of use. Prior to using the cream, there was no moisture.
- I thought there was no hope for me. Now I have moisture in my vagina and hardly any pain.
- I was really happy I did this. I always enjoyed cuddling with my husband, but I feel like I am more alert and aware about sexual thoughts. I have noticed increased clitoral sensitivity. I still have tenderness around my vaginal opening, but I am hoping it will get better.

Table 4 Female Sexual Function Index (FSFI) questionnaire results

FSFI Domains	Mean score pretreatment (SD) N = 12	Mean score posttreatment (SD) N = 12	t score	P value*
Sexual desire (score range 1.2–6)	1.35 (0.37)	2.65 (0.87)	–5.117	<0.001
Arousal (score range 0–6)	1.2 (0.68)	2.83 (1.26)	–4.113	0.002
Lubrication (score range 0–6)	1.18 (0.62)	2.68 (1.93)	–2.770	0.018
Orgasm (score range 0–6)	1.73 (1.77)	2.93 (2.05)	–3.518	0.005
Satisfaction (score range 0.8–6)	2.3 (1.31)	4.2 (1.29)	–4.857	0.001
Pain (score range 0–6)	0.93 (0.88)	3.5 (2.28)	–4.960	<0.001
Total FSFI score[†] (score range 2–36)	8.69 (3.80)	18.78 (7.05)	–5.790	<0.001

*Derived from paired t-test

[†]A total FSFI score less than 26.5 suggests female sexual dysfunction
FSFI = Female Sexual Function Index; SD = standard deviation

score greater than 26.5 (a total FSFI score less than 26.5 is suggestive of sexual dysfunction) (see Figure 1). The total mean FSFI scores improved from pretreatment to posttreatment (8.69 to 18.78, $P = 0.000$). Although this finding was statistically significant, the mean posttreatment score was less

than 26.5 and suggests continued female sexual dysfunction (see Table 4).

Discussion

Testosterone is an important hormone for female sexual functioning because it facilitates sexual

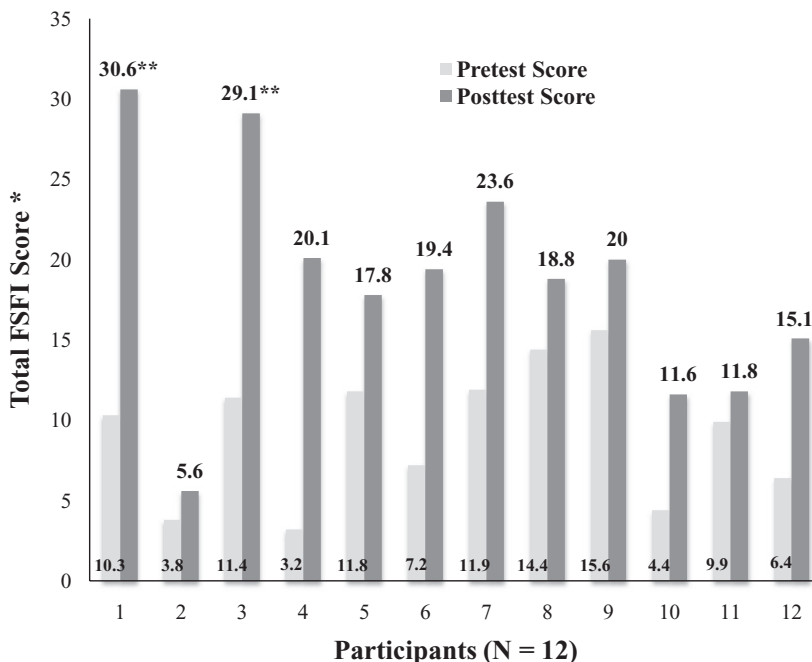


Figure 1 Total FSFI scores for individual participants.
*A total FSFI score less than 26.5 suggests female sexual dysfunction.
**Participants with a total FSFI score greater than 26.5.
FSFI = Female Sexual Function Index.

response through increased blood flow, vaginal and clitoral engorgement, sensation, and lubrication [22,23]. Testosterone therapy has been prescribed off-label for women since the early 1900s. At the turn of the last century, little safety data existed on the use of testosterone in women, and health care providers prescribed testosterone based on professional observations in the clinical setting [24].

There is limited research regarding the safety and efficacy of using local vaginal hormones to alleviate symptoms associated with AI treatment. Available evidence suggests that the use of topical vaginal testosterone may be an appropriate alternative to vaginal estrogen treatment in women with breast cancer who take AIs [25,26]. At the American Society of Clinical Oncology Breast Cancer Symposium, Glaser [25] reported findings from a proof-of-concept study using testosterone/anastrozole subcutaneous implants in women with breast cancer. The study included 43 women with breast cancer, 40 of whom had ER-positive cancers. Serum estradiol and testosterone levels were drawn 2 weeks after each insertion, and about 93% of serum estradiol levels were less than or equal to 30 pg/mL (the normal range of serum estradiol levels is less than 41 pg/mL in postmenopausal women) [27]. All women reported relief of vulvovaginal symptoms related to hormone deficiency, there was no recurrence or progression of breast cancer over 3 years, and no associated adverse events were reported. The researcher concluded that subcutaneous implants of anastrozole/testosterone provide therapeutic levels of testosterone and do not cause elevated estradiol levels [25].

Witherby et al. [26] also recognized the need for an alternative to vaginal estrogen to treat vaginal atrophy in women with breast cancer who take AIs. Uncertainty about whether the use of vaginal estrogen with AIs decreases the efficacy of breast cancer treatment led to this phase I/II pilot study. Two groups of patients (N = 20) received different daily dosages of testosterone in a compounded vaginal cream. Ten study participants received a daily 300 µg dose of testosterone, and 10 participants used a 150 µg dose of testosterone daily. The researchers concluded, per participant report, that a 4-week course of vaginal testosterone improved symptoms of vaginal atrophy without increasing estradiol or testosterone levels [26].

Health care providers, regardless of their specialty, should proactively assess sexual health in women with breast cancer who are taking AIs

because they may experience a decrease in quality of life and sexual functioning because of side effects from adjuvant endocrine therapy, typically AIs [7–9]. However, AIs are currently the first-line treatment for hormone receptor-positive tumors in postmenopausal women because of better cancer-related outcomes [4,28]. Research regarding the use of testosterone replacement in women with breast cancer who take AIs is limited, and the findings from this pilot study suggest the use of 300 µg testosterone vaginal cream daily for 4 weeks reduces unpleasant urogenital and vaginal symptoms and improves related sexual health quality of life in women with breast cancer on AI therapy. However, these results should be viewed with caution because the small sample size may not accurately reflect statistical significance. Next, the pilot study revealed an unexpected secondary outcome regarding the discovery of *G. vaginalis* in several participants during the baseline assessment. The clinical assessment findings align with prior research suggesting that women with compromised ovarian functioning have an increased risk for developing a vaginal infection; as such, the presence of any vaginal infection must be ruled out prior to starting testosterone therapy [13–15]. Finally, vaginal testosterone may be a safe and efficacious alternative to estrogen in women suffering from the negative sexual side effects related to the use of AIs [25,26].

Limitations of this pilot study included the narrow time frame for enrollment and follow-up, the exclusion of surgically menopausal women under the age of 50, and the presence of recurrent *G. vaginalis*. The small sample size was another limitation; however, the purpose of conducting a pilot study is to critique the study procedure, identify problems with data collection, and improve the design for an expanded study [29]. Some patients declined participation in the study because of the traveling distance for study visits. Other patients declined participation because they identified situational factors that would likely inhibit sexual activity during the 4-week study. The situational factors included caring for a daughter with poor health, no sexual activity due to a long-distance relationship, and a second surgery for breast reconstruction had been scheduled during the enrollment time frame. The following potential threats to validity were identified: participants may not represent women with breast cancer who take AIs in the general population; sexual functioning may have been affected by history or events such as relationship conflict, stress, or vacation; and non-adherence

with using the vaginal testosterone cream as demonstrated and prescribed.

Conclusions

Sexual health is a state of physical, emotional, mental, and social well-being [30]. The domains of sexual functioning (desire, arousal, lubrication, orgasm, satisfaction, and pain) often do not occur as a single diagnosis [18]. Rather, each domain seems to have a “domino effect” in which multiple problems with sexual functioning can coexist [31]. It is not professional, compassionate, or ethical for health care providers to ignore or dismiss sexual functioning, and doing so omits total disease management [31,32]. In closing, women with breast cancer who experience symptoms of sexual dysfunction due to AI therapy need to know about evidence-based treatment options and possible unknown risks. Results from the current pilot study suggest that daily topical testosterone treatment may be an effective therapy to support sexual health quality of life for women with breast cancer who are on AI therapy. Future prospective studies with larger sample sizes and more age-inclusive criteria are needed to establish the safety and efficacy of testosterone use in women with breast cancer who take AIs and how it relates to sexual dysfunction.

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Conflict of Interest: Melissa Dahir is a speaker for Warner Chilcott.

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Category 3

(a) Final Approval of the Completed Article

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