



Testosterone and Breast Cancer in Transmen: Case Reports, Review of the Literature, and Clinical Observation

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Clinical Practice Points

- Limited information exists regarding breast health in the transgender population.
- The incidence of breast cancer in transmen is very rare and only a few cases have been described in the literature. Nonetheless, a correlation between high dosage of testosterone and risk of breast cancer has been postulated. This is a very important issue within the health care of transgender people.
- Our experience is with 80 transmen who underwent top surgery to create an aesthetically pleasing male chest. Only in 2 of them we identified breast cancer. The first diagnosis was before top surgery, the second one was an occasional histological finding.
- It is important to bear in mind all of the complex relationships between testosterone therapy and breast cancer. It is necessary to inform transgender persons, especially those who have not yet undergone top surgery, of risk factors for breast cancer and the potential risk of developing a breast cancer, about the importance of selecting the most appropriate surgical technique according to the patient's risk and preferences, and to perform accurate postoperative surveillance.
- A multidisciplinary approach to these patients is strongly recommended, and large database creation and networking is warranted.

Clinical Breast Cancer, Vol. 19, No. 2, e271-5 © 2018 Elsevier Inc. All rights reserved.

Keywords: Breast cancer, Female to male (FtM), Testosterone, Top surgery, Transmen

Introduction

The term, “transmen” (or transgender men or female to male [FtM] person) describes individuals assigned female gender at birth but who later in life identify and live as men.^{1,2} Many, but not all transgender people, seek a social or a somatic transition to alleviate the significant distress (called gender dysphoria) resulting from the incongruence between the body and the gender identity.³⁻⁵ Somatic interventions—aimed at aligning the body with the perceived gender—might include a treatment with testosterone as well as the creation of an aesthetically pleasing male chest.^{2,6,7} These 2 steps

play a crucial role for many transmen in alleviating the experienced suffering.⁵⁻⁷ Despite few cases described in the literature of breast cancer (BC) in transmen, the relationship between exogenous (and endogenous) T levels and BC is still debated.⁸⁻¹¹ Indeed, a recent randomized clinical trial that evaluated adverse events after a 52-week treatment with T versus placebo in 814 postmenopausal women with hypoactive sexual desire, showed 3 new BCs in the T treatment arm, whereas no BC was reported in the placebo group.¹²

Conversely, there is consistent preclinical evidence of a protective role of T on the breast. Indeed, few studies have shown that T, through its cognate androgen receptor (AR), seemed to have a direct antiproliferative, proapoptotic, and estrogen receptor (ER) inhibitory effect on breast normal and neoplastic cells, as well as on BC cell growth.¹³ Moreover, BC AR positivity could represent a positive prognostic factor with respect to disease-free and overall survival.¹⁴

Considering that breast surgery is often delayed in transgender men (particularly in some countries such as Italy),¹⁵ BC risk should be carefully assessed, taking also into account that scheduling regular breast examination might represent an uncomfortable procedure for this population.²

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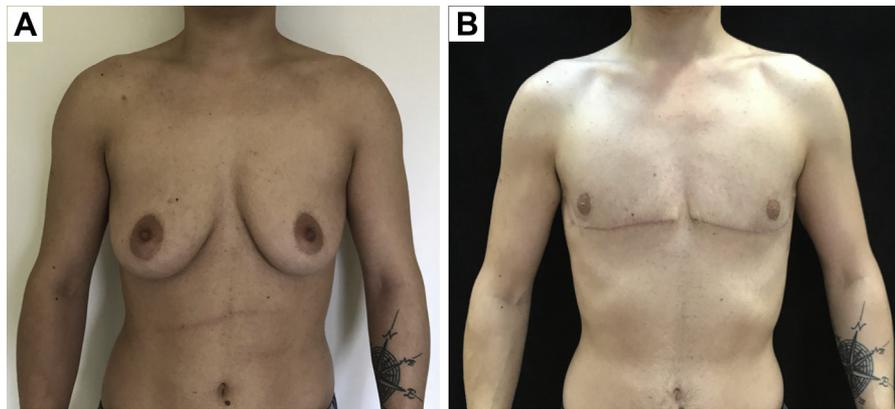
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Submitted: Jul 27, 2018; Revised: Oct 26, 2018; Accepted: Dec 4, 2018; Epub: Dec 20, 2018

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Figure 1 Clinical Case: Preoperative Frontal View of a 33-Year-Old Transman Who Reported Intramuscular Testosterone Undecanoate Therapy for 2.5 Years (A). Three Months Postoperatively After Double-Incision Mastectomy With Free Nipple-Areola Graft in Pendulous Breast (B)



We report on 2 cases of BC diagnosed in transmen who were treated with hormone-affirming therapy.

Cases

Case 1

J.L. is a transman who began intramuscular (i.m.) testosterone undecanoate (TU) at age 33 years of age to induce masculinization. At age 36 years, he noted a mass in his left breast. Clinical examination revealed masculinization, with facial and body hair. He reported a strong family history for BC.

After a left breast ultrasound examination and a positive core biopsy, he underwent bilateral mastectomy with a sentinel lymph node biopsy. To create an aesthetically pleasing male chest a double-incision mastectomy was chosen and the grafts of the nipple-areola (NA) complexes were harvested from the healthy side.

Histologic specimen examination revealed a poorly differentiated invasive carcinoma of no special type. Sentinel node biopsy was negative. The ER expression was 90% positive; progesterone receptor (PR) was 20% positive; HER2 revealed a score of 2+, with no amplification in fluorescence in situ hybridization analysis; Ki-67 proliferative index was 30%. The AR expression was 60% positive. The right breast was densely fibrotic. Androgen therapy was discontinued. He received a total of 4 cycles of a chemotherapy regimen (docetaxel/cyclophosphamide, every 3 weeks), followed by endocrine therapy with nonsteroidal aromatase inhibitor (letrozole). He was treated with an LHRH analogue, while waiting for salpingo-oophorectomy. He tested negative for Breast Related Cancer Antigens (*BRCA*) mutations.

Case 2

C.A. is a 33-year-old transman who reported i.m. TU for approximately 2.5 years and no gynecological surgery. His family history was positive for BC; the mother died at an early age of BC.

He underwent top surgery with a double-incision mastectomy and NA grafts to create an aesthetically pleasing male chest (Figures 1 and 2).

Histological examination revealed a ductal carcinoma in situ Grade 3 in his right breast that measured 1.1 cm. The ER expression was 100% positive, PR was 5% positive, and AR was 80% positive (Figure 3). The left breast was densely fibrotic. Androgen therapy was discontinued.

This patient was evaluated by our BC multidisciplinary team; a clinical and instrumental follow-up as well as a genetic evaluation were planned. The salpingo-oophorectomy has been planned.

Discussion

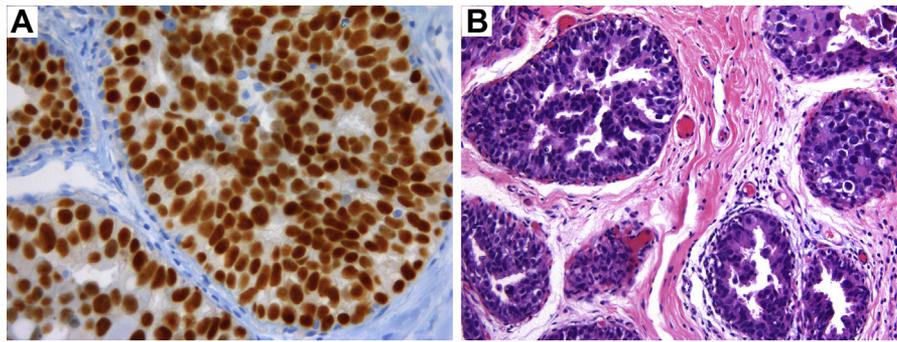
Therapy with T represents the milestone of hormonal gender-affirming treatment in transmen and is usually the first step to achieve and maintain the sexual characteristics of the desired gender.² Indeed, T has been shown to be effective in reducing general psychopathology, depressive symptoms, and body uneasiness levels in transgender men.³ It is generally assumed that transmen will not develop BC.¹¹ The typical clinical condition after systemic T therapy is the reduction of breast size and glandular tissue mediated by connective tissue shrinking and local fibrosis similar to involution changes observed in postmenopausal women.¹²

Limited information exists regarding breast health in the transgender population. Historically, transgender individuals have had poor access to medical care; perceived and real discrimination in the health care setting is well documented by several studies and often leads to inadequate preventative health care and delayed presentation to treatment.^{15,16}

Breast cancer is the most common cancer in women and the second leading cause of cancer mortality, with a 1 in 8 lifetime risk for natal female individuals. Breast tumors in transmen are relatively rare.^{16,17} The estimated incidence rate of BC in these individuals was 5.9 per 100,000 person-years. For comparison, the expected incidence of BC would be 154.7 per 100,000 person-years for cis women and 1.1 per 100,000 person-years for cis men.¹⁷

At the present time there are no randomized studies on the effects of long-term T use on BC risk.¹⁰ The effects of T on breast tissue are still uncertain. There are 2 proposed hypotheses of T effects in

Figure 2 (A) Ductal Carcinoma in Situ of Intermediate Nuclear Grade With Micropapillary and Solid Patterns (Hematoxylin and Eosin). (B) Immunohistochemistry for Androgen Receptor Shows Positivity in Most of the Tumor Cells



the breast (or in BC). In the first, aromatase converts T to estradiol (E2), which stimulates breast-cell proliferation by activating ER; in the second, 5 α -reductase converts T to dihydrotestosterone, which directly affects the AR.^{8,11} The available literature shows conflicting results: some epidemiological and clinical studies suggest that high levels of circulating androgens might increase the risk of developing BC,^{11,18,19} whereas others do not.²⁰⁻²³

Unlike in cis women, the cases of BC observed in transmen occurred at a younger age (transmen median age of 44.5 years vs. cis women median age of 62 years) and after relatively short spans of estrogen exposure and showed similarities to BC in men.^{16,24}

Transmen are an ideal model to examine the effects of T on the breast tissue because they are biologically female individuals subjected to long-term exposure to exogenous T.⁸

A recent study revealed a significant histological finding in 51/68 cases (75%) of cases of transmen gender-affirming breast surgery. The main histological effect was a benign breast disease, in particular a fibrocystic change with marked reduction of glandular

mammary gland tissues and increased fibrous connective tissue,²⁵ followed by gynecomastoid change, fibrotic stage 22 cases (32.4%), and fibroadenomatoid change 11 cases (16.2%) including 1 case (1.5%) of flat epithelial atypia.²⁰ All of this evidence indicates that T acts on the breast tissue in some way.^{8,26}

Reports of BC in transgender men have been described in the medical literature since the 1960s; to date the literature reports 17 transgender men with BC.^{8,10,11,17,24,27-30}

The 17 FtM patients with BC had a median age at diagnosis of 44.5 (range, 27-76) years. There were 8 cases of invasive ductal carcinoma, 2 tubular carcinomas, and 7 unrecorded types of BC. Twelve of the 14 known ER status tumors were positive, of which 9 were also progesterone-positive. Three patients had a recorded positive family history and none were BRCA-positive. Patients presented in several ways unique to FtM transformation. Six patients presented with palpable masses: 4 patients presented post masculinizing chest surgery with palpable masses, 1, 5, 7, and 12 years postoperatively, respectively, and 2 had no previous masculinizing breast surgeries. Three BCs were incidentally found in gender affirmation surgery mastectomy specimens upon routine pathology. One patient presented with axillary lymphadenopathy. All but 2 patients underwent testosterone hormonal therapy with a treatment span between 18 months and 15 years as part of their gender-affirming treatment.¹⁶

Our experience is on 80 transmen and only in 2 of them we identified BC (2.5%). The first diagnosis was before top surgery, the second one an occasional histological finding. No cancer was diagnosed after top surgery.

Our cases have some common characteristics with those described in the literature: young age, BC hormone receptor-positive status, and BC family history. Both cases described in this report are in a quite uncommon age range (between 30 and 40 years).^{8,9} All individuals had family histories of BC but did not have prophylactic mastectomy while receiving hormonal manipulation.

Currently, there are no formal recommendations regarding timing for mastectomy and the suggested screening program is the same as for the cis gender people.^{8,9,16,31}

There are no data about the timing between T therapy and mastectomy, but we hypothesize that the risk of developing tissue

Figure 3 Double-Incision Mastectomy Involves the Surgical Removal of All Breast Tissue Including the Excess Skin and the Nipple Areola Complex With a Rapid and Radical Mastectomy. A Circular Full-Thickness Graft Is Harvested in the Context of Native Areola and a Smaller Portion of the Nipple Is Harvested Separately From the Areola as a Full Graft to Create a Nipple Areola Complex With Masculine Characteristics



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alterations increases with increasing duration of T therapy. There is insufficient evidence to recommend a specific age requirement; clinicians could determine the timing of breast surgery for transgender male individuals on the basis of the physical and mental health status of the individual.²

Various surgical procedures have been reported. To date, in our surgical practice we used only 2 techniques: the periareolar mastectomy for small-sized breast and a double-incision mastectomy with NA graft for medium to large sized breast, but sometimes also in small breast.⁶ Double-incision mastectomy involves the surgical removal of breast tissue and excess skin with a rapid and radical mastectomy, as well as resizing and placement of the areolas as skin grafts to a more masculine position (Figure 3). The periareolar technique is similar to a nipple-sparing mastectomy and the breast tissue is removed through a small incision at the bottom of the areola, carefully leaving sufficient subareolar glandular tissue to avoid NA complex ischemia and necrosis.

We usually sent all specimens for pathological analysis to ensure incidental BC is not missed.^{16,25}

Breast cancer is a notable risk associated with incomplete removal of breast tissue. When natal female individuals undergo bilateral nipple-sparing mastectomies, their risk of BC is reduced. However, any residual breast tissue, including the nipple-areolar complex, remaining after a mastectomy is at risk for development of breast carcinoma, as was highlighted by 3 FtM patients who presented with BC post mastectomy.¹⁶

Hence, if transmen subjects desire top surgery, technical characteristics must be carefully selected and risk status assessment is essential in making a surgical decision. Personal characteristics including age, race, reproductive history, and personal history of atypia/malignancy are all important when assessing risk. For all patients, a detailed family history should be obtained, including history of breast and ovarian cancer and age at diagnosis.²⁴ In the absence of formal guidelines, the communication between patient and clinician regarding relative risk and benefits of each procedure must occur for informed surgical decision-making, and postsurgical surveillance should be performed on the basis of risk status and surgical selection.⁹

There are several challenges regarding the management of our patients. T use is contraindicated in women with a history of BC but the decision of a patient to resume therapy should be respected and the risk of recurrence clearly explained.^{8,11}

Standard therapy with antiestrogens and antiaromatase drugs is effective against increased estrogen production but quite ineffective against androgen excess.¹⁰ Adequate androgen replacement is necessary to preserve masculinity; this benefit must be balanced against the theoretical risk that androgen therapy might promote recurrence of their BC. Another option can be ER modulators but they induce feminization and are strongly avoided in these subjects.¹¹ As an alternative, the use of an aromatase inhibitor might mitigate the deleterious effects of exogenous T by inhibiting aromatization to inhibit the conversion of T to E2 (the indirect mechanism).⁸

Conclusion

The correlation between T supplementation and BC risk is still not clear. Because the number of transgender people accessing

health care is still relatively low and BC has complex etiologies, the incidence of BC in transmen might be underestimated.³²

For health care providers working with transgender people, it is important to bear in mind all of the complex relationships between T therapy and BC.¹⁰ Indeed, it is necessary to inform transgender persons who have not yet undergone chest surgery about the potential risk of developing BC, about the importance of selecting the most appropriate surgical technique according to the patient's risk and preferences, and to perform an accurate postoperative surveillance. To our knowledge, at present there are no randomized studies on the effects of long-term T use on BC risk. We believe that a multidisciplinary approach to these patients is strongly recommended, and large database creation and networking is warranted.

Disclosure

The authors have stated that they have no conflicts of interest.

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