



Breast Cancer in Transgenders: Narrative Review

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Abstract

The molecular pathogenesis of breast cancer (BC), the second most common cancer, varies significantly between sexes, with minimal data in the transgender population. The overall prevalence of BC in transgenders is estimated to be 0.02%. Besides experiencing social disparities, transgenders have to face a lot of discrimination in the healthcare system. Adversities faced, along with the urge to identify with physical attributes to the gender felt by them, forces transgenders to use non-prescribed hormones. Gender affirming hormone therapy (GAHT) is a key feature of transition-related care, rehabbing mental health, and the quality of life of transgenders, but at the expense of their health. Studies have reported that GAHT is associated with severe health conditions such as cancer in transgenders. Estrogens and testosterone are associated with a moderate risk of developing BC. The types of BC diagnosed in transgenders after cross-sex hormone therapy include invasive ductal and neuroendocrine carcinoma, in addition to tubular adenocarcinoma. Although diagnosed at an age earlier compared with ciswomen, BC screening recommendations for transgenders are the same as for ciswomen. This review studies in detail the types of transgenders, their characteristics, different types of breast cancers associated, issues faced while treatment, and their best possible solutions. We also hope to have well-designed research in the future, which will fill the existing gaps in knowledge and provide scientific insight into the transgender population and issues related to their health. There are no international guidelines on screening and management of transgender patients but it appears that breast screening before cosmetic mastectomy, exposure to hormonal therapy for more than 5 years, and as per natal women screening guidelines should be offered to the patient with detailed discussion on the harms and benefits of the same.

Keywords

- ▶ transgenders
- ▶ breast cancer
- ▶ transwomen
- ▶ transmen
- ▶ gender-affirming hormone therapy

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Introduction

Transgenders are the ones who have a gender individuality that is different from the sex at the time of birth.¹ It is estimated that from 8 to 25 million individuals worldwide now identify as transgenders.² The census of 2011 in India revealed the total population of transgenders to be around 4.88 lakh.³ These people experience unique disparities in terms of social, hormonal, or surgical transition and are the subject of limited focused health research.^{4,5} As a consequence, little is known regarding the medical and mental health of transgender individuals.⁶ Transgender people face psychological stress due to the uncomfortable feeling of living in a discordant gender role.⁴ To reduce this distress, these people opt for various measures such as cross-sex hormone therapy (CSH) or gender-affirming hormone therapy (GAHT) apart from surgical transitions, which are reported to be associated with serious conditions such as breast and prostate cancers.^{7,8}

Breast cancer (BC) is the second most common cancer overall and the most common cancer in females with a lifetime risk of 12% and 0.1% in males.^{2,9,10} The molecular pathogenesis of BC differs between sexes.² The proportion of transgender affected with BC is not known accurately although one study reported the overall prevalence of BC in transgenders to be 200 per 1,00,000 patients after years of CSH treatment in a cohort study.¹⁰ In transgenders, the first two cases were reported in 1968 in two male to female (MtF) patients.¹¹ Among transgenders, transwomen (male to female) are at a higher risk of BC, as reported by de Block et al in a retrospective study.¹⁰ In this report, we try to gain more

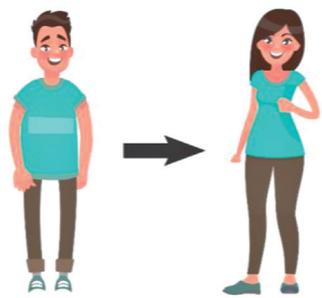
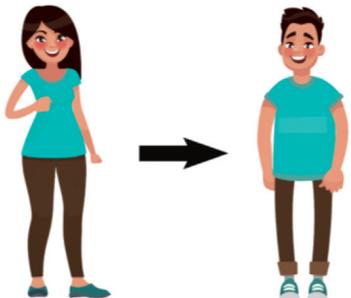
insights into types of transgenders, GAHT, the risk associated with GAHT, patient presentation, and the dilemmas faced by this population in our society. We would also discuss the paucity of standard international guidelines on the screening and management of transgender individuals and possible solutions. Relevant clinical articles (published in the English language) included in this narrative review are selected from PubMed, Google Scholar, and appropriate websites (keywords: transgender, breast cancer, transwomen, transmen, female to male, male to female, hormone therapy). Also, transgender is a heterogeneous entity and consists of transmen and transwomen with different clinical characteristics and hormonal profiles. Below is a brief description of the types of transgenders and **Table 1** shows the differences between them.

Types of Transgenders

Male To Female Patients

Male to female (MtF) or transwomen are persons assigned male sex at birth but have a longing to live as a female.^{5,10,12} The important physical features of a female body are breast growth, wider hips, less fat in the abdominal region, decreased hair growth on the body, and softer skin.^{7,8} To develop these characteristics, transwomen require surgical transitions including breast augmentation and orchiectomy or vaginoplasty^{10,13} and exogenous hormones or GAHT including estrogens and anti-androgens.⁵⁻⁷ Also, therapy should be able to reduce the number of spontaneous erections and sperm production, which are characteristics of a male body.^{7,8} The surgical interventions such as breast

Table 1 Difference between MtF and FtM transgenders

Male to Female (MtF)	Female to Male (FtM)
	
Transwoman	Transman
Assigned male sex at birth	Assigned female sex at birth
They require predominant hormone manipulation with estrogen and progesterone	They require predominant hormone manipulation with testosterone
To develop female characteristics, they usually undergo orchiectomy, vaginoplasty, breast augmentation	Surgical intervention required is hysterectomy, oophorectomy, and phalloplasty, and subcutaneous mastectomy
Estrogens given exogenous increase the risk of prolactinoma and breast cancer	Exogenous testosterone increases the risk of breast and endometrial cancer

augmentation and placements of implants may give rise to rare type of lymphomas of the breast such as implant-associated anaplastic large cell lymphoma.

Female to Male Patients

Female to male (FtM) or transmen are persons born as female at the time of birth but associate themselves to male sex.^{2,6,12} Transmen require testosterone preparations in their GAHT regimens to stimulate virilization, to emulate male-like body hair growth and contours, along with surcease of menstruation, diminished glandular tissue, and increased fibrous connective tissue.^{2,13} Progestational agents are administered when transdermal or oral testosterone is used as they are unable to cease menstruation and to prevent endometrial hyperplasia.^{2,14} Surgical transition in transmen includes subcutaneous mastectomy, which is primarily done to achieve aesthetic masculine thorax and uterus extirpation and/or oophorectomy, and phalloplasty.^{10,18}

Dilemmas Faced by Transgenders in the Healthcare System and Transgender Care

Apart from society, transgenders have to face a lot of discrimination in the healthcare system.⁵ Although the standard treatments for transgenders are available, they still face many barriers.¹⁵ According to the Virginia Transgender Health Initiative Study, the social stigma of being transgender is the basis of poor health status, resulting in alienation that accumulates throughout their life.¹⁵ Various studies reported that transgenders were either denied medical care or have faced some form of harassment in the healthcare system.^{15,16,18} The doctors refuse to provide treatment to them either because they feel insufficient to care for them⁵ or due to their low financial status.^{7,14,17,18} As a consequence, to avoid harassment, these people either hide their gender identity from doctors, which is important for getting correct advice regarding their breast health or avoid seeking medical attention.^{5,15} These difficulties and a serious urge of confirming their physical attributes to the gender felt by them incite them to use alternatives to the standard treatments such as non-prescribed hormones (NPH).^{5,18}

Transgender Care

Prevalent inequity and neglect threaten the health and well-being of the transgender population, making them one of the most marginalized populations in medicine.¹⁸ Therefore, as per the Endocrine Society's updated clinical practice guidelines 2017, the medical team dealing with transgenders should involve a psychiatrist having the knowledge to diagnose gender dysphoria, and GAHT should be trained and experienced in assessing psychopathology and should be willing to participate in ongoing care.¹⁹ The involvement of a psychiatrist helps by supporting access to care to the transgender population that may benefit from treatment.¹⁸ For optimum care, pretreatment education and assessment, customized dosing, continuous monitoring, and standard screening for BC and prostate cancer are important.²⁰

For children and adolescents who qualify for gender dysphoria, standards of care have been developed that

involve puberty suppression, appropriate mental health support, and hormonal interventions, which may make future affirmation easier and safer.^{20,21} The development of undesired secondary sexual characteristics in transgender adolescents can be prevented by drugs that either suppress the sex hormone production or block its action.²¹ Drugs such as GnRH agonists for pubertal suppression, progestins for the reduction in biologic hormone production, and androgen receptor antagonists are useful.²¹ The best treatment regimen for adolescents is the use of a GnRH agonist for complete suppression of puberty starting at tanner stage 2, followed by the introduction of cross-sex hormones in later adolescence.²¹

Gender Affirming Hormone Therapy

Gender affirming hormone therapy is the standard treatment used along with surgical transitions in transgenders to develop secondary sexual characteristics that align with their felt gender.⁸ Transgenders have been receiving GAHT since the early 1960s.⁶ GAHT is a key feature of transition-related care, rehabbing mental health, and the quality of life of transgenders.⁵ The treatment regimens of GAHT are different for MtF patients and FtM patients.^{2,6,10,13}

GAHT for Transwomen

The GAHT regimen for transwomen includes estrogen and anti-androgen drugs such as spironolactone.⁵⁻⁷ Cyproterone is given as adjunctive therapy for lowering testosterone concentrations in the body and adds to curb testosterone production or to deter the androgen receptor.⁷ This therapy helps in developing female secondary sex characteristics (breast development, redistribution of fat, reduction in body hair) and minimizing male characteristics (reduced number of spontaneous erections, reduced sperm production, slowing of scalp alopecia).^{7,8,18} The use of progestin along with these drugs is controversial. According to a study, adding progestin to estrogen does not alter breast size,^{2,22} rather it increases the risk of BC.¹⁵

In guidelines, estrogen also has caveats to its use as serum concentrations of conjugated equine estrogens cannot be accurately measured, conferring dose adjustments difficult.⁵ Additionally, two studies reported that estrogens use in MTF individuals might put them at risk of BC due to high levels of circulating androgens and increased estrogen exposure.^{1,2} The length and dosage of estrogen treatment also play a role in the propagation of neoplastic breast epithelium.¹¹ Oral ethinylestradiol, an estrogen preparation, is not advised owing to the associated increased risks of blood clots and cardiovascular (CV) morbidity and mortality. However, transdermal estradiol patches or gel are safer to use as the risk of blood clotting is low. The use of transdermal estradiol has been suggested and employed predominantly in older TW.⁵

After the administration of GAHT, breast development is modest in transwomen.⁸ Mean breast-chest difference increase ranged from 3.7 cm (95% CI: 3.3–4.2) to 4.16 ± 2.9 cm at baseline to 7.9 ± 3.1 cm after 1 year of CHT.⁸ Additionally, anatomical differences in the thoracic bone structure

compared with ciswomen may result in breast size appearing smaller than the objectively measured volume.⁵

GAHT for Transmen

Testosterone preparations are the standard treatment to stimulate virilization, emulate male-like body hair growth and contours, along with surcease in menstruation, diminished glandular tissue, and increased fibrous connective tissue.^{2,13} Testosterone is administered in the form of injectable, gels, and transdermal patches.¹⁴ Androgens are usually administered 6 months prior to reassignment surgery and continued thereafter.¹³ Progestational agents are administered when transdermal or oral testosterone is used as they are unable to cease menstruation and prevent endometrial hyperplasia.^{2,14} In transmen, serum testosterone levels are in the mid to normal range.² The removal of breasts in sex reassignment surgery (SRS) reduces the risk of BC in transmen by around 90%.¹⁵ However, a few studies have reported BC in transmen. One study reported BC in the residual mammary cells of transmen after 10 years of mastectomy.¹⁴ Another study reported a total of four cases of BC in transmen, three of which were diagnosed several years after subcutaneous mastectomy and the other at the time of mastectomy.¹⁰ A large retrospective study conducted at the U.S. Veterans Affairs medical health system identified seven cases of BC in transmen.²² Various studies reported that the aromatization of the circulating testosterone into estradiol by the aromatase enzyme was the reason for BC in transmen.^{2,14,23}

Self-Use of Hormone Therapy

The widespread use of NPH has been documented in several studies.^{17,18} In Washington, DC, 58% of transgenders reported the use of NPH once in their lives.¹⁷ A report in Virginia suggested that around 60% of MTFs and 22% of FTMs patients were using NPH.⁵ Similar reports were obtained from Chicago, California (San Francisco),²⁶ and Europe.^{27,5} The majority of patients taking NPH were transwomen.¹⁷ The major sources to obtain NPH were friends and online purchasing.^{18,27} In rare cases, people have performed surgeries on themselves as they were unable to afford SRS.¹⁷ Opting for such dangerous measures indicates pre-existing mental conditions such as depression, psychiatric comorbidity, social distress, and body dissatisfaction.¹⁷

Risks associated with GAHT

Gender affirming hormone therapy certainly improves the QOL of transgenders, but at the expense of their health. Various studies have reported that GAHT use is associated with severe health conditions such as cancer in transgenders.^{10,28–30} Many benign and malignant tumors are known to be associated with CSH therapy as different organ-specific malignancies express sex hormone receptors.³¹ It is seen that breast tumors develop rapidly in transgenders after short-term exposure to hormone therapy (median duration: 18 years).¹⁰

International guidelines published by the World Professional Association for Transgender Health in 2012 and the

Endocrine Society in 2017 suggest estrogens presents a moderate risk of prolactinoma and BC development³¹ and testosterone therapy is associated with a moderate risk of breast and endometrial cancer.²² The proposed mechanism of BC development in transwomen is the binding of exogenous estrogen to the estrogen receptor (ER) in the breast tissue and stimulating carcinogenesis via increased cell proliferation, decreased apoptosis, and elevated production of oxidative metabolites that result in DNA damage.³² For transmen, the aromatization of testosterone to estrogens in peripheral tissues, and the activation of androgen receptors leads to cellular growth and proliferation, particularly in mammary tissues leads to BC development.³³ Other risks associated with estrogens use in transwomen are myocardial infarction, thrombosis,²⁵ and ischemic stroke.³⁴ Conversely, transmen receiving testosterone did not suggest the increased probability of cardiovascular or cerebrovascular disease.³⁴

Patient Presentation

The most common clinical feature of BC is a lump in the breast, which may be painful or painless.^{33,35} Other symptoms of BC are bloody nipple discharge,¹¹ enlarged lymph nodes in one of the axilla,⁶ dense breast tissues, or subareolar masses¹¹ on mammographic screening. In a systemic review by Fledderus et al, 7 out of 23 FtM transgenders were diagnosed to have breast cancer incidentally on routine histological examination after they underwent a cosmetic mastectomy. Genetic testing in transgenders has shown that the use of CSH therapy is also associated with the upregulation of various oncogenes.^{10,35} Studies have reported that these symptoms are noticed after long-term use of CSH therapy.^{6,37} The types of BC diagnosed in transgenders after CSH therapy were variable, including invasive ductal carcinoma, neuroendocrine carcinoma, and tubular adenocarcinoma.³⁵ Most of these tumors are hormone receptor-positive. The development of BC affects the GAHT regimen in transgenders. Most patients were put on low doses of exogenous hormones or even their CSH therapy was discontinued.^{35,38}

Screening Recommendations for Transgenders

Breast cancer in transgenders is diagnosed at an early age as compared with ciswomen.³⁹ The median age of diagnosis of BC in transwomen is 51 years and for transmen, it is 47 years.^{6,10} There are no guidelines defined especially for transgenders. However, BC screening recommendations for the cis population have been extrapolated for them.³⁹ The annual mammography screening is advised in transwomen older than 50 years of age and continuously undergoing GAHT, having greater than 5 years use of estrogen and progestin, a body mass index >35, or a positive family history.^{6,10,15} For transwomen with implants, ultrasound serves as the first-line imaging technique because mammographic screening becomes less sensitive in the presence of implants.⁵ Magnetic resonance imaging (MRI) should be performed, if there is concern about intracapsular rupture not visible by ultrasound.^{5,40} Because the SRS does not

include removal of the prostate, prostate cancer screening should also be performed annually in transwomen after the age of 40 years.⁶

The current guidelines suggest the regular monitoring of the hormone profile of transwomen under estrogen therapy to minimize the risk of thromboembolism, hypertension, and cholestasis.^{6,22} For transmen, who have undergone chest reconstruction surgery, annual examinations of the sub- and peri-areolar breast by MRI or ultrasound, together with chest wall and axillary examination remain the key screening tool.^{10,15} Transmen who retain their physical characteristics should opt for routine annual screening using mammography starting at the age of 40 years.^{10,15,41}

Treatment Recommendations: Differences?

There is a scarcity of data regarding the plan of management of BC in transgenders and so is the lack of data regarding the survival of these patients. The review of literature also suggests management from a case-to-case basis with the management in line with breast cancer in women. The plan of management involves surgical resection, hormone status, and further management as per the stage of the patient. Most of the patients reported were hormone positive thus receiving hormone therapies as a part of their BC treatment. Individual hormonal profiles of the patient including serum estradiol, luteinizing hormone, follicle-stimulating hormone, and testosterone levels should be tested before deciding about the choice of hormonal therapy and whether LHRH analogs are required in addition to aromatase inhibitors.

The basic difference comes in the treatment outcome as there are a lot of social reasons for the delay in reaching the healthcare systems and further bias after reaching hospitals. Special clinics may be needed in the major cancer centers where their medical needs may be met and these patients visit at the earliest after detecting a lump in the breast.

Conclusion

This review article highlights that transgenders are at the margins of the healthcare system. This is attributed to their low financial status and the negligence of the clinicians. These factors are responsible for NPH use, which is assuredly deleterious for them. Therefore, a need to develop the skills essential for the safe management of transgenders has been felt. This will improve patient interaction and will ensure the rational use of exogenous hormones and appropriate screening. Rational usage of GAHT is necessary as it is reported to be associated with reproductive organ cancer risks. Contradictory to this, a study by Hambree et al did not report any increased risk of BC.²² The duration after which these symptoms appear in a person on GAHT is also contrasting in different studies. A few authors have suggested that the BC develops rapidly after short-term exposure to hormone therapy, while some studies have indicated that these symptoms are noticed after long-term use of CSH therapy. Because many of these cancers are diagnosed incidentally after cosmetic mastectomy, preoperative breast cancer screening

should be advocated to decide about the type of surgery. Epidemiology of transgenders in low-to-middle income group countries such as India will be different from the developed countries as not many transgender individuals take hormonal therapy or undergo advanced surgeries and access to tertiary care centers is lesser thereby more advanced disease on presentation. Follow-up of patients after cosmetic mastectomy is also important as few of these histopathology specimen are positive for malignancy and can be missed if not followed. Also, over time we need better screening guidelines and treatment recommendations. For a concrete opinion on this, further research is required, until then it is recommended to follow the screening recommendations designed for the normal population strictly as early detection can increase the chances of survival.

Conflict of Interest

None declared.

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