Case Report



# Interdisciplinary Management of Transgender Individuals at Risk for Breast Cancer: Case Reports and Review of the Literature

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## Clinical Practice Points

- The estimated proportion of transgender adults in the United States has increased from 0.2% in 2007 to 1.8% in 2016.
- With increasing cultural and social acceptance, more transgender individuals are undergoing gender-affirming treatment.
- The effect of gender-affirming hormonal treatment on the risk of hormone-dependent malignancies in transgender individuals, including breast cancer, remains largely unexplored.
- In this report we present 2 cases: a 32-year-old trans woman with a family history of breast cancer and a germline BRCA1, DNA repair associated mutation and a 29-year-old trans man with a family history of male breast cancer who was incidentally diagnosed with ductal carcinoma in situ at the time of chest reconstruction surgery.
- Gender-affirming hormonal treatment is a lifelong therapeutic regimen. As a result, long-term observational studies are critically needed to assess the lifetime breast cancer risk in transgender individuals.
- Comprehensive and individually tailored screening programs for transgender individuals are crucial for determining the genetic risk, especially if family history points toward a hereditary predisposition.
- Future strategies to manage trans women might include gradual reduction of exogenous estrogen doses with age, thereby simulating natural menopause.
- In trans men, further studies are needed to assess the potential risks of constant testosterone exposure. Aromatase inhibitors could potentially prevent testosterone aromatization to estradiol, but have not yet been systematically studied in this context.

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**Keywords:** Breast cancer screening, Breast neoplasm, Gender-affirming hormonal therapy, Genetic Risk, Hormone-dependent malignancies

## Introduction

The umbrella term of "transgender" includes people who experience their gender identity as opposite to the gender assigned to them at birth and may include people who are nonbinary (not exclusively masculine or feminine). For gender transition, current standard of care regimens can include gender-affirming hormonal treatment (GAHT) and/or surgery. After the pioneering work of the endocrinologist, Dr Harry Benjamin, transgender individuals have been receiving GAHT since the early 1960s.[1] Trans women are assigned to the male gender at birth, but identify with the female gender (male-to-female). To acquire and maintain feminization they undergo estrogen therapy.[2]

Assigned female at birth, trans men identify as male (female-to-male). They frequently pursue testosterone therapy to induce masculinization.

There are almost 1 million transgender adults in the United States and the proportion has increased from 0.2% in 2007 to 1.8% in 2016.[3] A 2018 study by the Center of Expertise on Gender Dysphoria in the Netherlands also reported increased referrals to their clinic since 1972. For trans women, this number increased

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from 14.9 per year between 1972 and 1979 to 185.2 per year between 2010 and 2014. Similarly, the annual referral rate for trans men increased from 3.8 cases (1972-1979) to 103.6 cases (2010-2014).[4] As the number of transgender individuals increases, there is a growing need to understand the cancer risk in this population.

Breast cancer is the most frequently diagnosed cancer in women in the United States with 126 new cases per 100,000 women each year.[5] Male breast cancer only represents 1% of all breast cancer cases and <1% of cancers in men.[6] Certain predisposing risk factors are implicated in male and female breast carcinogenesis. Mutations in tumor suppressor genes BRCA1, DNA repair associated (*BRCA1*) and BRCA2, DNA repair associated (*BRCA2*) are 2 genetic aberrations that predispose an individual to breast cancer. They account for 5% to 10% of female and 5% to 20% of male breast cancer cases.[7] The frequency of breast cancer in transgender individuals, as well as the effect of GAHT on the risk of breast cancer, remains largely unexplored.

In this report, we present 2 cases: (1) a 32-year-old trans woman with a family history of breast cancer and a germline *BRCA2* mutation; and (2) a 29-year-old trans man with a strong family history of breast cancer who was incidentally diagnosed with ductal carcinoma in situ (DCIS) at the time of chest reconstruction surgery. We discuss these cases from a multidisciplinary perspective thereby summarizing the current knowledge about breast cancer in transgender individuals and reviewing the inherent risk of breast cancer while undergoing GAHT.

We performed a systematic literature search in the PubMed database between 1968 and 2018 and identified 2 population-based observational studies that reported the incidence of breast cancer in 3102 and 5135 transgender individuals.[8,9] Twenty cases of breast cancer in trans women and 16 cases in trans men have been reported (Table 1).[8,10-26] We also included a recent observational study on 3891 transgender individuals on the basis of its preliminary data published in early 2018.[27]

## Case 1: Trans Woman

A 32-year-old trans woman initiated estrogen therapy (6 mg estrogen daily) at the age of 26 years. She underwent genetic mutation screening because her 29-year-old sister was diagnosed with *BRCA2*—mutation-related breast cancer. The individual was determined to carry the same deleterious *BRCA2* mutation. She underwent bilateral orchiectomy and continued estrogen treatment. The family history revealed that her mother, mother's twin, and paternal aunt had been diagnosed with breast cancer. Her mother and mother's twin were premenopausal at the time of breast cancer diagnosis. Her father was also diagnosed with prostate cancer. The family history was negative for ovarian and pancreatic cancer. Because of the positive genetic screening result, she underwent high-risk screening mammography for hormone-mediated breast development. The exam was interpreted as 1 according to the Breast Imaging Reporting and Data System (ie, negative). A preoperative magnetic resonance imaging (MRI) scan was unremarkable. Because of her family history and *BRCA2* positivity, the individual opted for primary breast cancer risk reduction with bilateral skin-sparing mastectomies. Tissue expanders were placed at the time of surgery for implant-based breast reconstruction. The mastectomy specimen showed no evidence of malignancy in either breast.

## Case 2: Trans Man

A 29-year-old trans man had been receiving testosterone (testosterone cypionate 80 mg/wk intramuscularly) for 4 years and achieved a hormone profile consistent with menopause (high levels of follicle stimulating hormone, high levels of luteinizing hormone, and low levels of estradiol). He proceeded to chest reconstruction surgery and pathological assessment revealed estrogen receptor (ER)-positive (>90%), high-grade DCIS in the left breast. The right breast showed no evidence of malignancy. The individual had a strong family history of male breast cancer, which occurred in 2 paternal great uncles. He underwent genetic testing using a breast cancer screening panel consisting of 23 genes (*ATM*, *BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CDH1*, *CHEK2*, *DICER1*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *NBN*, *NF1*, *PALB2*, *PMS2*, *PTEN*, *RAD50*, *RAD51C*, *RAD51D*, *SMARCA4 STK11*, and *TP53*). No mutations or variants were detected. After chest reconstruction surgery, he underwent MRI to assess the presence of any residual breast tissue. Residual tissue was detected on both sides along with an enlarged lymph node in the left axilla. As a result, he underwent an ultrasound examination, which showed a mildly abnormal node with the cortex measuring up to 5 to 6 mm. The node was assessed using fine-needle aspiration, which was negative for malignant cells. He was offered adjuvant radiation therapy, which he declined.

## Discussion

### *Trans Women*

*Standard of Care.* Male-to-female transition is typically initiated during adulthood or late adolescence whereas the median age to start hormonal treatment is 30 years.[27] However, transgender adolescents (Tanner stage 2) might decide to suppress puberty with gonadotropin-releasing hormone analogues until age 16 years, after which they may be given GAHT.[28] GAHT regimens for trans women differ from hormone supplementation regimens for postmenopausal women. Aiming at achieving premenopausal serum levels (100-200 pg/mL), current protocols administer estrogen at substantially higher and fixed doses along with antiandrogens to suppress serum testosterone levels to the normal range of premenopausal women (<50 ng/dL).[2] Despite a potentially higher risk of breast cancer and cardiovascular events, additional progestin might be included in GAHT to aid in full breast development.[29] Table 2 provides a synopsis of clinical regimens and shows a comparison of the current GAHT dosing recommendations with postmenopausal hormone therapy.

Twelve months of hormonal therapy are recommended before breast augmentation and are imperative for genital surgery (orchiectomy, penectomy, vaginoplasty, clitoroplasty, labiaplasty).[30] However, all further aesthetic interventions (eg, facial feminization, thyroid cartilage reduction) do not require a defined period of previous GAHT according to the World Professional Association for Transgender Health guidelines published in 2011.[30]

In principle, GAHT is a lifelong procedure. However, it still remains unclear whether or not to induce menopause in trans women as they age to avoid the long-term side effects of high-dose estrogens. Many transgender individuals prefer to continue high-dose GAHT and dose adjustments remain at the discretion of caregivers who should discuss the benefits and the respective risks with the individual.[31]

**Table 1** Synopsis of Breast Cancer Cases in Trans Women (n = 20) and Men (n = 16 + 1)

| Reference | Age, y | Breast Tumor Type | GAHT (Duration of GAHT, y) | BRCA Mutation | Family History | Hormone Receptor Status | Therapy |
|---|---|---|---|---|---|---|---|
| **Women** | | | | | | | |
| Symmers[10] | 30 | Adenocarcinoma | E (NA) | NA | NA | NA | Death before treatment |
| | 30 | Adenocarcinoma | E (6) | NA | NA | NA | Radical mastectomy |
| Pritchard et al[11] | 35 | Ductal carcinoma | E (10) | NA | Yes | $ER^-$, $PR^+$ | Modified radical mastectomy, progesterone |
| Ganly and Taylor[12] | 36 | Ductal carcinoma | E (14) | NA | NA | $ER^-$ | Wide local excision, continue GAHT, tamoxifen |
| Grabellus et al[13] | 46 | Secretory breast carcinoma | E (NA) | NA | Yes | $ER^-$, $PR^-$ | NA |
| Dhand and Dhaliwal[14] | 58 | Adenocarcinoma | E (9), break (17), E (2) | NA | Yes | $ER^+$, $PR^+$ | Radiotherapy with tamoxifen and zoledronic acid |
| Pattison and McLaren[15] | 43 | Ductal carcinoma | E and CA (7), break (3) | NA | No | $ER^-$, $PR^-$, $HER2^-$ | Neoadjuvant chemotherapy, radiotherapy |
| Gooren et al[8] | 57 | Ductal carcinoma | E (36) | NA | NA | $ER^+$, $PR^-$, $HER2^-$ | NA |
| | 56 | NA | E (NA) | NA | NA | NA | NA |
| Maglione et al[16] | 55 | Ductal carcinoma | E (30) | NA | NA | $ER^-$, $PR^-$, $HER2^+$ | Neoadjuvant chemotherapy |
| | 65 | DCIS | E (13) | No | Yes | $ER^+$ | Bilateral mastectomy |
| Sattari et al[17] | 60 | Ductal carcinoma | HT (7) | No | No | $ER^+$, $PR^+$, $HER2^-$ | Radical mastectomy with reconstruction, GAHT discontinued, tamoxifen |
| Gooren et al[18] | 46 | Ductal carcinoma | E (approximately 14) | NA | Yes | $ER^+$, $PR^+$, $HER^+$ | Radical mastectomy, adjuvant radiotherapy and chemotherapy, tamoxifen |
| | 52 | Adenocarcinoma | CA and E (30) | No | No | $ER^+$, $PR^-$ | Adjuvant chemotherapy, aromatase inhibitor, GAHT discontinued |
| Teoh et al[19] | 41 | Ductal carcinoma | E and AA (14) | No | NA | $ER^-$, $PR^-$, $HER2^-$ | Wide local excision, SLNB, adjuvant chemotherapy, continue GAHT |
| Brown[20] | 54 | NA | NA | No | NA | $ER^-$, $PR^-$ | Death before treatment |
| | 54 | Ductal carcinoma | NA | NA | Yes | $ER^+$, $PR^-$, $HER2^+$ | NA |
| | NA | NA | E (7) | No | NA | $ER^+$, $PR^-$ | NA |
| Gondusky et al[21] | 51 | DCIS | E (14) | No | Yes | $ER^-$, $PR^-$, $HER2^-$ | Adjuvant chemotherapy, discontinued GAHT |
| Corman et al[22] | 46 | Ductal carcinoma | CA and E (7) | BRCA2 mutation | Yes | $ER^+$, $PR^+$ $HER2^-$, $AR^+$ | Simple mastectomy and SLNB, declined tamoxifen, local relapse: radiotherapy and adjuvant chemotherapy |
| **Men** | | | | | | | |
| Burcombe et al[23] | 33 | Ductal carcinoma | T (13) | NA | NA | $ER^+$, $PR^+$ | Mastectomy, level II axillary node clearance |
| Gooren et al[8] | 27 | Adenocarcinoma | T (3) | NA | NA | $ER^+$, $PR^+$ | Incidentally detected during sex reassignment surgery |
| Gooren et al[18] | 48 | Ductal carcinoma | T (approximately 9) | NA | NA | $ER^-$, $PR^-$, $HER2^-$ | Adjuvant chemotherapy |
| | 41 | Ductal carcinoma | No | No | NA | $ER^+$, $PR^+$, $HER2^-$, $AR^+$ | Radiotherapy, chemotherapy, tamoxifen |
| | 41 | Adenocarcinoma | T (approximately 6) | NA | NA | $ER^+$, $PR^+$, $HER2^-$ | Incidentally detected during mastectomy, low-dose T |
| Brown (2015)[20] | 74 | Ductal carcinoma | T (approximately 3) | NA | NA | $ER^+$, $PR^-$, $HER2^+$ | Simple mastectomy, chemotherapy |
| | 47 | NA | No | NA | No | $ER^+$, $PR^+$ | Mastectomy |

**Table 1** Continued

| Reference | Age, y | Breast Tumor Type | GAHT (Duration of GAHT, y) | BRCA Mutation | Family History | Hormone Receptor Status | Therapy |
|---|---|---|---|---|---|---|---|
| | 64 | NA | E (approximately 2.5) | NA | NA | $ER^+$, $PR^+$ | Lumpectomy and chemotherapy and tamoxifen |
| | 42 | NA | T and E (2) | NA | Yes | $ER^+$, $PR^+$ | Nipple-sparing bilateral mastectomy |
| | 57 | NA | E and MP (approximately 2) | NA | No | NA | Lumpectomy and radiotherapy |
| | 42 | NA | T (3) | NA | No | NA | Bilateral total mastectomy and subsequent reconstruction |
| | 48 | NA | No | NA | NA | $ER^+$, $PR^+$ | Mastectomy |
| Shao et al[24] | 53 | Ductal carcinoma | T (5) | No | Yes | $ER^+$, $PR^-$, $HER2^{+++}$ | Bilateral mastectomy and adjuvant chemotherapy and trastuzumab, aromatase inhibitor, T (topical) |
| | 27 | Ductal carcinoma | T (6) | No | Yes | $ER^+$, $PR^+$, $HER2^{+++}$ | Bilateral mastectomy, adjuvant chemotherapy, trastuzumab (recommendation: bilateral salpingectomy, tamoxifen or aromatase inhibitor), resumed T |
| Nikolic et al[25] | 42 | Ductal carcinoma | T (1.5) | NA | No | $ER^-$, $PR^-$, $HER2^{+++}$, $AR^+$ | Neoadjuvant chemotherapy, radical mastectomy and axillary dissection, adjuvant chemotherapy and trastuzumab |
| Katayama et al[26] | 41 | Neuroendocrine carcinoma | T (15) | NA | No | $ER^+$, $PR^+$, $HER2^-$ | Residual mammary gland was removed, SLNB, aromatase inhibitor, adjuvant radiotherapy |
| Current study | 29 | DCIS | T (4) | No | Yes | $ER^+$ | Intensive screening |

Abbreviations: AA = antiandrogen; AR = androgen receptor; CA = cyproterone acetate; DCIS = ductal carcinoma in situ; E = estrogen; ER = estrogen receptor; GAHT = gender-affirming hormone treatment; HT = hormonal treatment; MP = medroxyprogesterone; PR = progesterone receptor; SLNB = sentinel lymph node biopsy; T = testosterone.

*Breast Cancer Incidence.* Numbers on the incidence of breast cancer in trans women receiving GAHT remain vague. As of 2018, 2 population-based studies assessed the breast cancer risk attributable to GAHT. Both studies were limited by small numbers of breast cancer cases and a lack of genetic risk stratification.[8,9] Thus, their data must be interpreted with caution. The first study by Gooren and colleagues consisted of 2 breast cancer cases among 2307 Dutch trans women undergoing androgen deprivation and estrogen administration.[8] They reported an estimated rate of breast cancer of 4.1 per 100,000 person-years. This was lower than expected for women (170 per 100,000) but above the expected frequency of male breast cancer (1.2 per 100,000). Table 3 provides a synopsis of the calculated breast cancer risk, noting that numbers vary as incidence per 100,000 patient years in this study had been normalized to trans women and trans men specimens, respectively.[8] The second study by Brown and Jones was conducted using the United States Veterans Administration database of 3556 trans women with 3 breast cancer cases. There were 22.1 breast cancer cases per 100,000 patient-years of estrogen therapy between 1996 and 2013.[9] It must be noted that only 1386 (39%) of all trans women received previous GAHT and that all 3 patients with breast cancer detected did not receive any hormonal treatment before diagnosis. Both studies concluded that there is no increased incidence in breast cancer in trans women.

A preliminary 2018 investigation by de Blok and colleagues identified 18 cases of breast cancer (80% were ER-positive) in a cohort of 2567 trans women receiving GAHT for a median duration of 222 months.[27] In this cohort, the median age of trans women diagnosed with breast cancer was 51 years compared with a median of 61 years among the general female Dutch population (Table 3). The incidence of breast cancer in trans women was considered higher than the risk in Dutch men (0.4 cases expected) but below the expected reference for Dutch women (72 cases expected). The authors concluded that trans women taking GAHT are at an increased risk of breast cancer compared with the male Dutch population.

*Effect of GAHT and Genetics on Breast Cancer Risk.* Because of the limited clinical experience in transgender medicine, hormonal treatment in postmenopausal women might provide an approximation to estimate the risk of breast cancer in trans women. In the Million Women Study on 1,084,110 British postmenopausal women receiving hormonal treatment, 66% showed an increased risk of breast cancer, noting that the highest risk was in women taking estrogen-progestogen combinations (100% increased risk).[32] Another study of 52,705 women with breast cancer and 108,411 matched controls reported that for each year beyond 5 years of hormonal treatment, the risk of breast cancer increases by 35%.[33] It is important to note that GAHT in trans women is given at significantly higher doses and for longer periods compared with postmenopausal hormonal treatment (Table 2). Because GAHT is nowadays initiated at increasingly younger ages and continues into senescence, individuals are subjected to far longer exposure periods

**Table 2** Hormone Regimens in Trans Women (vs. Postmenopausal HT) and Men

| Class | Drug | Formulation | Dose Recommendation | |
|---|---|---|---|---|
| **Women** | | | **In Male-to-Female Transition** | **In Postmenopausal HT** |
| Estrogen | Estrogen | Oral | 2.0-6.0 mg/d | 0.5-2.0 mg/d |
| | Estradiol patch | Transdermal | 0.025-0.2 mg/d | 0.0025-0.1 mg/d |
| | Estradiol valerate | Intramuscular | 5-30 mg biweekly or 2-10 mg weekly | Not recommended |
| Antiandrogen | Spironolactone | Oral | 100-300 mg/d | Not recommended |
| | Cyproterone acetate | Oral | 25-50 mg/d | Not recommended |
| GnRH agonist | Goserelin | Intramuscular | 3.75 mg monthly or 11.25 mg every 3 mo | Not recommended |
| **Men** | | | **In Female-to-Male Transition** | **In Breast Cancer Patients** |
| Testosterone | Testosterone enanthate/ cypionate | Intramuscular Subcutaneous | 100-200 mg biweekly 50-100 mg weekly | Not recommended |
| | Testosterone undecanoate | Intramuscular | 1000 mg every 12 wk | Not recommended |
| | Testosterone gel 1.6% | Transdermal | 50-100 mg/d | Not recommended, but a single case observation suggests feasibility[23] |
| | Testosterone patch | Transdermal | 2.5-7.5 mg/d | Not recommended |
| GnRH analogues | | Intramuscular | NA | Not recommended |
| Progesterone | Medroxyprogesterone | Intramuscular | NA | Not recommended |

Abbreviations: GnRH = gonadotropin-releasing hormone; HT = hormone therapy.

than previously reported.[4] Therefore, it is important to follow and document the effect of long-term estrogen exposure on the mammary epithelium in trans women and to determine the risk of breast cancer. In this context, breast tissues from trans women (retrieved during breast augmentation) and trans men (retrieved during chest reconstruction surgery) might provide a valuable proxy to study how exogenous hormones influence breast carcinogenesis.

Genetic predisposition has to be taken into account when initiating feminization in trans women. The lifetime breast cancer risk for women is 12%, whereas 72% of women with a *BRCA1* mutation and 69% of women with a *BRCA2* mutation will develop breast cancer by the age of 80 years.[5,34] Male breast cancer cases are more often associated with *BRCA2* than *BRCA1* mutations.[35] Male *BRCA2* carriers have a 6.8% lifetime risk compared with 0.1% in the normal male population.[36] Ninety percent of male breast cancer cases are ER-positive and progesterone receptor-positive.[37]

*General Screening Recommendations.* Phillips et al recently proposed guidelines to screen for breast cancer in trans women receiving GAHT. Annual mammography screening is recommended in trans women who are: (1) older than 50 years of age; (2) continuously undergoing GAHT; and (3) have additional risk factors such as estrogen and progestin use for more than 5 years, a body mass index >35, or a positive family history.[38] The age cutoff of 50 years is on the basis of the diagnostic limitations of mammography, because mammography sensitivity and specificity increase with age.[39] Consequently, in younger trans women, the predictive value and benefits of mammography might not outweigh the costs, inconvenience, and emotional distress associated with the procedure. As of yet, these guidelines are not on the basis of comprehensive long-term data but may be used to direct clinical care.

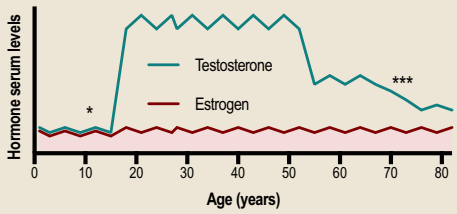
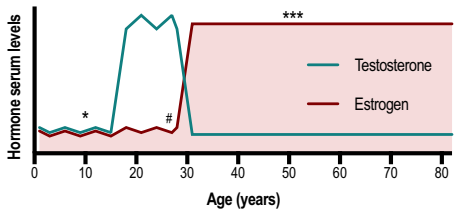
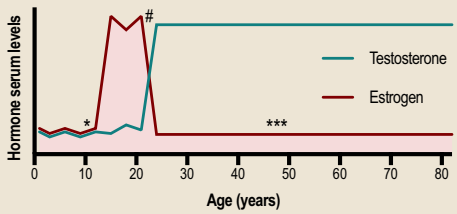
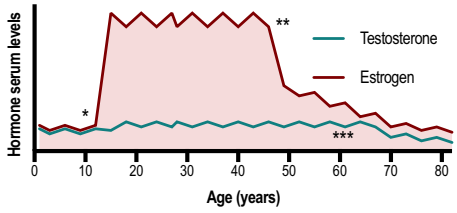
*Trans Woman Case Discussion Summary.* In the trans woman described herein, it is reasonable to assume that the germline *BRCA2* mutation puts her at a 6.8% risk for developing breast cancer, and her risk is possibly further increased by use of GAHT. She continues to receive estradiol therapy 2 mg 3 times a day. Because of the increased odds and her sister diagnosed with breast cancer, she opted for prophylactic bilateral mastectomies. She is being followed with self- and clinical breast exams. *BRCA2* mutation carriers are also at risk of developing pancreatic and prostate cancer.[40] Because the prostate is usually not removed with sex reassignment surgery, recommendations for prostate cancer screening remain valid for trans women. Prostate-specific antigen testing should be performed at the age of 40 years and repeated every 1 to 4 years in these at-risk individuals.[41] With regard to her ongoing estrogen therapy, her hormone profile is being monitored according to current guidelines to minimize the risk for thromboembolic events, hypertension, and cholestasis.[28,30]

### *Trans Men*

*Standard of Care.* The median age to initiate GAHT in female-to-male transition is 23 years.[27] Hormone regimens for trans men follow the general principle of hormone supplementation in male hypogonadism. Testosterone is administered aiming at levels within the normal reference range for men (320-1000 ng/dL; Table 2).[2] After 12 continuous months of hormone therapy genital surgery (eg, hysterectomy, ovariectomy, vaginectomy, metoidioplasty, phalloplasty, scrotoplasty) may be performed. No previous testosterone therapy is mandatory for chest-contouring surgery or aesthetic interventions.[30]

Chest-contouring surgery, unlike mastectomy for oncological or risk-reducing purposes, does not remove the entire mammary tissue because it remains a surgical procedure that is not defined by anatomic boundaries. This strategy entails the removal of most breast tissue accompanied by repositioning of the nipple-areolar complex and obliteration of the inframammary fold including

**Table 3** Synopsis of Breast Cancer Risk and Median Age at Diagnosis

| Sex | Breast Cancer Incidence Per 100,000 Years of Follow-Up (95% CI) | Median Age at GnRH Initiation (95% CI), y | Median Age at Diagnosis, y | Simplified Hormonal Profile |
|---|---|---|---|---|
| **Male (XY)** | 1.2[a] and 1.1[b] | NA | 71 |  |
| **Trans Female (XY)** | 4.1 (0.8-13.0) | 30 (23-41) | 51 |  |
| **Trans Male (XX)** | 5.9 (0.5-27.4) | 23 (19-31) | 47 |  |
| **Female (XX)** | 170[a] and 155[b] | NA | 61 |  |
| **Reference** | Gooren et al[8] | de Blok et al[27] | Fentiman et al[6] de Blok et al[27] | — |



GAHT = gender-affirming hormone treatment.
*Puberty.
***Breast cancer diagnosis.
#Initiation of GAHT.
**Menopause.
[a]Calculated expected incidence compared with trans women.
[b]Calculated expected incidence compared with trans men.

radial scoring if needed. When a mastectomy is performed, the breast tissue is removed according to anatomical borders in a subdermal plane to ensure most of the breast tissue has been removed. This might lead to a suboptimal aesthetic outcome compared with chest-contouring surgery.

*Breast Cancer Incidence.* Current knowledge on the incidence of breast cancer in trans men undergoing GAHT is limited to the 2 aforementioned population-based studies. Gooren and colleagues monitored a cohort of 795 trans men receiving GAHT over a course of 36 years (1975-2011). In this period, the authors detected 1 case of breast cancer, leading to a calculated incidence of 5.9 cases per 100,000 person-years.[8] Brown and Jones examined 1579 trans men over a course of 17 years and detected 7 cases of breast cancer. This led to a calculated incidence of 105.2 cases per 100,000 patient-years. However, only 3 of 7 individuals received GAHT before breast cancer diagnosis. It must be noted that in the study by Gooren and colleagues, trans men older than 65 years were critically under-represented (13 of 795 [0.2%]) compared with the cohort investigated by Brown and Jones (396 of 1579 [25.1%]).[9] Likewise, both studies concluded that there is no increased breast cancer incidence in trans men.

de Blok and colleagues identified 4 breast cancer cases in 1324 trans men (50% cases were ER-positive).[27] Three of the 4 cases were diagnosed several years after mastectomy. The median duration of GAHT at the time of breast cancer diagnosis was 176 months. This frequency appears to be lower than that in women (21 cases expected in the same time period) but higher than in men (0.1 cases expected in the same time period). The low number of breast cancer cases in trans men in this study could be the result of the estradiol-low state of trans men, but could also be explained by the younger median age at diagnosis of 47 years (range, 35-59 years), which was similar to that of trans women (median age of diagnosis: 51 years; range, 30-73 years) but considerably lower than in the female reference population (median age of diagnosis: 61 years; Table 3).

*Effect of GAHT and Genetics on Breast Cancer Risk.* On the basis of previous preclinical and clinical studies, it might be hypothesized that testosterone is protective with regard to breast cancer risk.[42-44] However, breast tissue removal as part of the routine gender reassignment in trans men might be the central driver for breast cancer risk reduction. Whether there is a risk-reducing effect of testosterone supplementation in the absence of surgery is not yet clear.

It has been discussed that at high levels, testosterone can be partially aromatized to estradiol and could conceivably drive endometrial or breast cancer development.[24] If this was the case, aromatase inhibitors (such as anastrozole) might be useful to prevent breast cancer.[45] However, Chan et al observed that when exogenous testosterone is used to achieve testosterone levels that fall within the normal range for men, serum estradiol levels in transgender men do not increase and actually decrease, possibly because of a decrease in body fat and/or suppression of the hypothalamic pituitary axis.[46]

In the trans man case presented herein, low endogenous estradiol levels support these observations and suggest that exogenously administered testosterone did not reach a critically high level to be aromatized to estradiol.

Testosterone acts via the androgen receptor (AR), which is widely expressed in all molecular subtypes of breast cancer and has been reported in 86% of DCIS.[47] AR signaling has been described as antiestrogenic in ER-positive breast cancer. In the absence of ER signaling, however, it might become a proproliferative stimulus.[48] No clinical study has yet systematically compared the benefit and risks of androgen supplementation when a transgender patient is being treated for ER-negative or ER-positive breast cancer. The trans man described herein had ER-positive DCIS and the tissue was not tested for AR expression. In this case estradiol and dihydrotestosterone levels were closely monitored to enable adjustment of testosterone dosing and to minimize the potential risk attributable to exogenous GAHT.

Because of this individual's strong family background for male breast cancer and despite him testing negative for 23 breast cancer-related genes, he might still harbor an undetected genetic alteration. Thus, a hereditary component, which increases his risk for breast cancer is likely present but yet remains to be accurately diagnosed.

*General Screening Recommendations.* Screening recommendations in trans men are dependent on the surgical intervention performed. For genetically predisposed trans men, bilateral risk-reducing mastectomy can be recommended; if a mastectomy is performed, there would be no need for further imaging for screening purposes. Because most trans men undergo chest reconstruction for their gender confirmation surgery, annual examinations of the sub- and periareolar breast, along with chest wall and axillary examinations remain the main screening tool.[38] For trans men who undergo breast reduction or retain their original anatomy, routine annual screening should be performed using mammography starting at the age of 40 years.[38,49] If there is minimal residual breast tissue and mammography is not feasible, ultrasound and MRI can be performed. This is because breast cancer may occur in residual breast tissue after chest-contouring surgery and testosterone supplementation.[23,25,27]

*Trans Man Case Discussion Summary.* In the trans man case, DCIS was diagnosed in the course of chest reconstruction surgery. No additional surgical excision of the residual breast tissue was performed. He currently receives intensive screening including biannual alternating imaging of the residual breast tissue using MRI and ultrasound because mammography is not feasible. Clinical experience on the use of testosterone supplementation when an early stage of ER-positive breast cancer has been diagnosed remains limited. To maintain masculinization, low-dose transdermal application of testosterone may be applied because these doses might minimize the amount of circulating testosterone and thus avoid unnecessary aromatization to estradiol.[23]

### *Trans Women and Trans Men*

*Psychosocial Implications.* The physical changes induced by sexual transition are usually accompanied by great psychosocial relief of the individual.[2] Recommendations that might terminate the pursuit of further feminization in trans women and masculinization in trans men are usually unacceptable. Consequently, future research into the therapeutic strategies for breast cancer in transgender people will have to be done with the goal to harmonize the intended and hazardous effects of hormonal treatment.

## Conclusion

The risk of breast cancer in transgender individuals receiving GAHT remains largely unexplored. Screening for genetic risk and early diagnosis are crucial because pausing GAHT upon breast cancer diagnosis is often not desired by the transgender individual. Dedicated long-term studies in transgender populations with comprehensive data on the effect of GAHT are urgently needed to better estimate breast cancer risk and to tailor clinical guidelines particularly for individuals at genetic risk. Further, systematic observational studies of transgender individuals might allow us to better understand the differential contributions of exogenous hormones, genetics, and their interaction to breast cancer risk. Prospective planning of these studies is urgently needed to gather data that can guide the care for transgender individuals as they age.

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## Disclosure

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

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