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Breast cancer in transgender persons: a review

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ABSTRACT

Introduction: Breast cancer is one of the most common malignancies in women and is relatively rare in men (12% vs. 0.1%). The effect of sex hormones on the risk and development of cancer among transgender people is not fully understood, although it is well known that steroid hormones affect changes in breast tissue, e.g., the deposition of breast fat and the formation of lobules and ducts in transgender women and the growth of the fibrous tissue.

Matherials and methods: This paper reviews the recent literature (available on PubMed, NIH, Google Scholar, and Science Direct) from 2012 to May 2022 on the incidence of breast cancer in the transgender population. Seventeen case reports of breast cancer among transgender men were described (median age: 42; mean number of years of drug use: 7; most commonly diagnosed cancer type: invasive ductal carcinoma; most expressed receptors: estrogen and progesterone) and 15 cases in transgender women (median age: 53; average number of years of drug use: 16; most commonly diagnosed cancer type: invasive ductal carcinoma; most expressed receptors: estrogen and progesterone).

Results: The discussed cases indicate a longer hormone therapy in transgender women without a cancer diagnosis and a later age of diagnosis compared to transgender men. Both transgender men and transgender women had a lower median age of cancer diagnosis compared to cisgender women and men.

Keywords: transgender; breast cancer; cancer risk.

INTRODUCTION

Breast cancer is the most commonly diagnosed cancer worldwide. An estimated 2.26 million cases of breast cancer were reported in 2020, making it the second-leading cause of cancer deaths in women [1]. It is a genetically, etiologically, and histopathologically heterogeneous disease that can be caused by non-hereditary factors as well as hereditary predisposition [2]. It can occur as invasive carcinoma, where its cells are located outside the mammary ductal-lobular system of the breast, or as *in situ* carcinoma [3]. Diagnosed breast cancer is tested for progesterone receptor (PR) and estrogen receptor (ER) escalation, as well as for human epidermal growth factor receptor 2 (HER2) overexpression. This information has therapeutic and prognostic significance [4, 5].

It is estimated that breast cancer affects 12% of women and 0.1% of men [6]. The diagnosis in women is made at an earlier stage than in men, making breast cancer in men at the time of diagnosis characterized by lymph node involvement, larger size, and distant metastasis [7].

It is estimated that infiltrating ductal carcinoma accounts for nearly 90% of male breast cancers, while nearly 10% is carcinoma *in situ*. Male breast cancer is usually characterized by androgen receptor (AR), ER, and PR expression. Triple-negative breast cancers (TNBC) are rare [7, 8]. In women, the most common form is invasive ductal carcinoma, which accounts for nearly 80% of all cases. The remaining 20% is ductal carcinoma *in situ* [2].

Breast cancer risk factors include genetic predispositions (*BRCA1* and *BRCA2* mutations), childlessness, advanced age, smoking, overweight, alcohol consumption, and family history of cancer. It is estimated that the incidence of BRCA mutations is 1 in 400 people, with this mutation responsible for about 5–10% of all breast cancers and nearly 80% of all hereditary breast cancers. With a BRCA1 mutation, the risk of developing breast cancer in cisgender females (CF; women whose gender at birth is consistent with their gender identity) is 60–70%, and with a *BRCA2* mutation, it is 50–75%. In cisgender men (CM) with *BRCA1* or *BRCA2* mutations, the risk is lower, at 1% and 7%, respectively [9, 10, 11].

The molecular pathogenesis shows considerable gender differences; HER2 positive breast cancer occurs in 6–12% of women, compared to 1.7% of men [12].

Transgender individuals are those whose sex assigned at birth does not match their gender identity [13]. It is estimated that 0.1–2% of the general population is transgender [14]. In recent years there has been a significant increase in surgical, endocrinological, and psychological treatments related to gender dysphoria. One significant treatment is sex hormones to achieve desired physical changes [15].

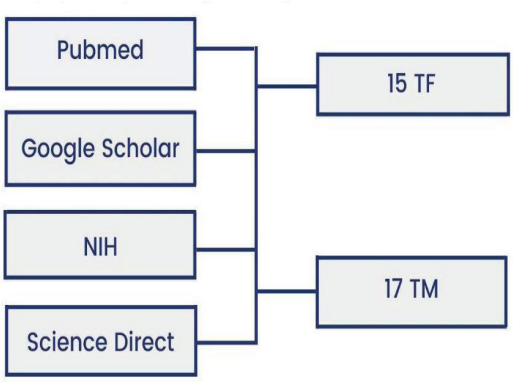
Among transgender females (TF), the use of hormonal therapy aims to induce breast development, inhibit male hair type, and stimulate female fat distribution [16] using treatments that include estrogens (E2) and anti-androgens [13] but typically not progesterone, due to the risk of complications including thromboembolic disease [17].

Among transgender males (TM), therapy aims to suppress the menstrual cycle and stimulate male hair type, as well as develop typical male physique characteristics. These features/goals are achieved through the use of testosterone [18].

Transgender individuals may also undergo surgery, such as breast augmentation, subcutaneous mastectomy, uterine or ovarian/testicular excision, phalloplasty, or vaginoplasty [13].

It is well established that steroid hormones affect changes in breast tissue, such as breast fat deposition, lobular and ductal formation, and fibrous tissue growth in transgender women [6], but the effects of sex hormones on the risk and development of cancer among transgender individuals are not fully understood.

In this study, we reviewed literature on breast cancer in transgender persons available through Pubmed, NIH, Google Scholar, and Science Direct published from 2012 to May 2022 – altogether 17 publications on transgender men and 15 on transgender women (Fig. 1).



TF – transgender females; TM – transgender males

FIGURE 1. Publications on breast cancer in transgender persons in available scientific journals

CANCER RISK VS. GENDER-AFFIRMING HORMONE THERAPY

The gender-affirming hormone therapy (GAHT) used by transgender people is a different process than the hormone replacement therapy by cisgender people (where the gender assigned at birth is consistent with gender identity). The GAHT can increase female or male hormone levels in patients before surgical removal of the gonads. In addition, the selection of an effective dose of hormones may be individually dependent/conditioned, and consequently the levels of these hormones and/or their metabolites may be elevated, which may consequently translate into an increased/decreased risk of developing sex hormone-sensitive cancers. The use of sex hormones can affect the risk of gender-specific cancers as well as other cancers or organ systems that have receptors for sex hormones (steroid hormone receptor – SHR) [19].

Among CF, mammography screening is recommended every 1–2 years after the age of 50. Earlier preventive screening is important for those with certain health conditions, including a positive family history of cancer [19].

The gender-affirming hormone therapy among transgender females and breast cancer

The use of estrogen among TF allows them to develop and maintain their breasts, but may also result in breast cancer as well as neoplasms in other estrogen-sensitive tissues [20]. Some studies have shown lower rates of breast cancer in TF compared to CF, such as de Blok in the Dutch population, showing an incidence of breast cancer in TF at 25% of the incidence in CF [13, 21]. An increased risk of cancer in TF has been shown compared to CM, and breast cancer has occurred following shorter GAHT use and at a younger age in a diagnosis of only 18 affected individuals from a study group of 2260 TF (0.8%) [13, 20, 21]. A similar underpowered study in a transgendered USA veteran population had an analogous result, where out of 5,135 individuals, just 3 breast cancers were diagnosed among TF (0.06%) and 7 among TM (0.14%) [21, 22]. Another study in the USA between 2003–2016 found that of 589 transgender individuals (without distinction of gender), 35 (5.9%) had been diagnosed with breast cancer [23].

Our knowledge on breast cancer among transgender women is based on case reports. Since 2012, only 15 cases of breast cancer among transgender women have been described; their median age was 53 years (range 38–74), the mean duration of GAHT use was nearly 16 years, and the most common type of cancer diagnosed was invasive ductal carcinoma (53.3%) – Figure 2. Cells expressing ER and PR were most abundant in the cancerous tissue (40%) – Figure 3 [24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36]. The median age of the cancer-diagnosed transgender women was lower than the cisgender women (60 years) and CM (68 years), indicating cancer diagnosis among TF at a younger age [37] – Table 1.

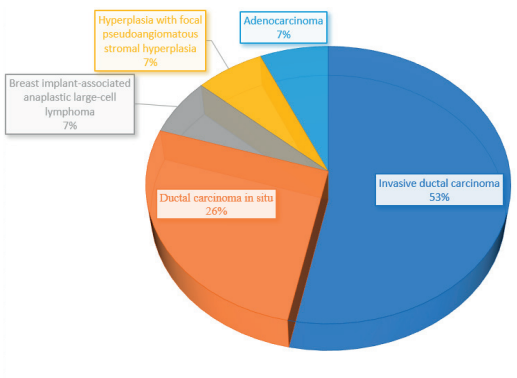
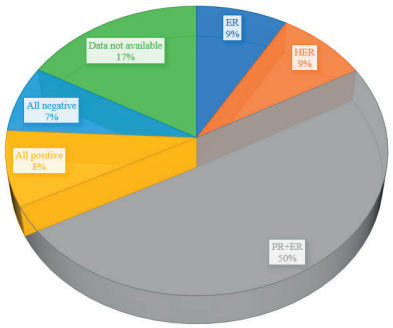


FIGURE 2. Prevalence of breast cancer types among transgender women



ER – estrogen receptor; HER – human epidermal growth factor receptor; PR – progesterone receptor

FIGURE 3. Prevalence of receptor positivity in breast cancer among transgender women

As a result of the data from the Dutch cohort study [13], the study conducted among veterans [22], and the case reports [16], various organizations (Canadian Cancer Society, Susan G. Komen Puget Sound, University Hospitals Cleveland Medical Center, University of California San Francisco) have been prompted to create guidelines for screening transgender women for breast cancer [38].

Mammography is recommended for TF with no family history of this cancer after at least 5 years of hormone intake and every 2 years starting at age 50 [38]. Having a history of breast implants (type of implant, age of implantation) is another important aid to radiographic diagnosis, as mammography is less sensitive in their presence [20].

Other experts recommend individualized and comprehensive screening programs, including, for example, gradually reducing estrogen doses with age to stimulate menopause [20]. Screening mammography should be performed every 2 years. If there is a family history of breast cancer or the presence of a genetic mutation predisposing to cancer, an individualized approach based on family history is recommended [38].

When CF are diagnosed with breast cancer, it is recommended that estrogen therapy be discontinued, regardless of hormone receptor status.

For TF, discontinuation of therapy will be associated with the return of secondary sexual characteristics. A clinical trial using low-dose estradiol administered to cisgender women with advanced breast cancer showing resistance to aromatase inhibitors resulted in disease stabilization. These results may provide a basis for continuing estrogen therapy in TF [32, 39].

The gender affirming hormone therapy among transgender males and breast cancer

The ingestion of exogenous testosterone by transgender men is intended to induce and maintain secondary male characteristics. As a result of testosterone use, TM typically have reduced breast glandular tissue and experience an increase in fibrous connective tissue [17, 38]. Testosterone itself is aromatized to estradiol, contributing to a situation where serum estradiol levels are comparable to the follicular phase of the menstrual cycle. Estradiol is not significantly reduced in serum when exogenous testosterone is used [17, 40].

TABLE 1. Breast cancer characteristics in selected case reports among transgender females

Author	Age	Type of cancer	ER status	HER2 status	PR status	BRCA2 status	Family status	Duration of estrogen use	Country
Cole et al., 2022 [24]	70	invasive ductal carcinoma	+	–	+	+	+	4	Lebanon
Sieberg et al., 2021 [25]	70	invasive ductal carcinoma	+	–	+	+	+	2	USA
Lienhoop et al., 2020 [26]	74	invasive ductal carcinoma	+	–	+	N/D	N/D	40	na/o
Nehlsen et al., 2020 [27]	53	ductal carcinoma *in situ*	–	–	–	–	–	33	USA
Patzelt et al., 2018 [28]	40	breast implant-associated anaplastic large-cell lymphoma	N/D	N/D	N/D	N/D	N/D	13	Czech Republic
Tongson et al., 2017 [29]	38	hyperplasia with focal pseudoangiomatous stromal hyperplasia	N/D	N/D	N/D	N/D	+	1	USA
Corman et al., 2016 [30]	53	ductal carcinoma *in situ*	+	–	+	+	+	7	Belgium
Gooren et al., 2015 [31]	52	adenocarcinoma	+	N/D	–	–	–	30	Thailand
Gooren et al., 2015 [31]	46	invasive ductal carcinoma	+	+	+	N/D	+	9	USA
Teoh et al., 2015 [32]	41	invasive ductal carcinoma	–	–	–	N/D	N/D	14	UK
Sattari, 2015 [33]	59	invasive ductal carcinoma	+	–	+	–	–	7	USA
Gondusky et al., 2015 [34]	51	ductal carcinoma *in situ*	–	–	–	–	+	37	USA
Maglione et al., 2014 [35]	65	ductal carcinoma *in situ*	+	N/D	+	–	+	13	USA
Maglione et al., 2014 [35]	55	invasive ductal carcinoma	–	+	–	N/D	N/D	N/D	USA
Pattison and McLaren, 2013 [36]	41	invasive ductal carcinoma	–	–	–	N/D	–	15	Australia

ER – estrogen receptor; HER2 – human epidermal growth factor receptor 2; PR – progesterone receptor; BRCA2 – mutations 2 breast cancer risk factors include genetic predispositions; N/D – no data

Breast cancer risk in transgender men is associated with a history of mastectomy, older age, and longer duration of testosterone therapy. These factors result in a lower risk of breast cancer in TM compared to cisgender women. However, breast cancer risk may increase when receptor activity is stimulated by exogenous testosterone in residual breast tissue [17]. To date, 2 possible pathways have been described. In the 1st, testosterone is converted to dihydrotestosterone (DHT) by 5α-reductase, which has a direct impact in AR-positive breast cancer, as the dissociation time of DHT from AR is 5 times slower compared to testosterone. In the 2nd case, testosterone is converted to estradiol by cytochrome P450 aromatase. Activation of ER in breast tissue occurs through E2 stimulation of breast cell proliferation [17, 41]. These pathways are only theoretical, as no higher incidence of breast cancer has been documented among transgender men compared to the general population [17].

Since 2012, only 17 cases of breast cancer among TM have been described. Analysis of the data showed that the median age of cancer diagnosis was 42 years (range 20–53), the average use of GAHT was nearly 7 years. The most common type of cancer diagnosed was invasive ductal carcinoma (58.8%) – Figure 4. Most expressed receptors in the tumor tissue were ER and PR – 29.3% (Fig. 5). The percentage of mastectomies performed before breast cancer diagnosis was estimated at 58.8% [31, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54] – Table 2.

Compared to cisgender women, where the median age of diagnosis was 62 years, TM were diagnosed earlier. Cancer diagnosis occurred after an average of 7 years of GAHT use, which is a short period of therapy and may also suggest a genetic predisposition to cancer [45].

Transgender males may undergo thoracic masculinization surgery, which involves removing some or all of the breast tissue and repositioning of the areolae to ultimately achieve a male chest shape [38]. However, after a subcutaneous mastectomy, a small amount of residual breast tissue is usually left under the nipple-areola complex to prevent the formation of an indentation in the chest. That remaining tissue may develop neoplastic lesions [17].

TABLE 2. Breast cancer characteristics in selected case reports among transgender men

Author	Age	Type of cancer	ER status	HER2 status	PR status	BRCA2 status	Family history	Mastectomy	Duration of testosterone use	Country
Oberc et al., 2022 [42]	20	granular cell tumor	–	N/D	N/D	N/D	N/D	no	1	Canada
Fledderus et al., 2020 [43]	50	ductal carcinoma *in situ*	N/D	N/D	N/D	N/D	+	yes	3	Netherlands
Kopetti et al., 2020 [44]	28	invasive carcinoma	+	+	–	–	–	yes	2.5	Switzerland
Light et al., 2020 [45]	44	invasive ductal carcinoma	+	–	+	N/D	N/D	yes	2	Australia
Chotai et al., 2019 [46]	58	invasive ductal carcinoma	+	–	+	N/D	+	yes	10	Singapore
Fundytus et al., 2020 [47]	48	invasive ductal carcinoma	+	–	+	N/D	+	yes	19	Canada
Tanini et al., 2019 [48]	36	invasive carcinoma of no special type	+	+	+	–	+	no	3	Italy
Tanini et al., 2019 [48]	33	ductal carcinoma *in situ*	+	N/D	+	N/D	+	no	2.5	Italy
Eisman et al., 2019 [49]	29	ductal carcinoma *in situ*	+	N/D	N/D	–	+	no	4	USA
Barghouthi et al., 2018 [50]	28	invasive ductal carcinoma	–	+	–	–	+	no	1	USA
Treskova et al., 2018 [51]	58	invasive ductal carcinoma	+	–	–	N/D	N/D	no	25	Czech Republic
Katayama et al., 2016 [52]	41	invasive ductal carcinoma	+	+	+	N/D	–	yes	15	Japan
Gooren et al., 2015 [31]	48	invasive ductal carcinoma	–	–	–	N/D	N/D	yes	9	Netherlands
Gooren et al., 2015 [31]	41	tubular adenocarcinoma	+	–	+	N/D	N/D	yes	7	Netherlands
Nikolic et al., 2012 [53]	42	invasive ductal carcinoma	–	+	–	N/D	–	no	2.5	Serbia
Shao et al., 2011 [54]	53	invasive ductal carcinoma	+	+	–	–	+	yes	5	USA
Shao et al., 2011 [54]	27	invasive ductal carcinoma	+	+	–	–	+	yes	6	USA

ER – estrogen receptor; HER2 – human epidermal growth factor receptor 2; PR – progesterone receptor; BRCA2 – mutations 2 breast cancer risk factors include genetic predispositions; N/D – no data

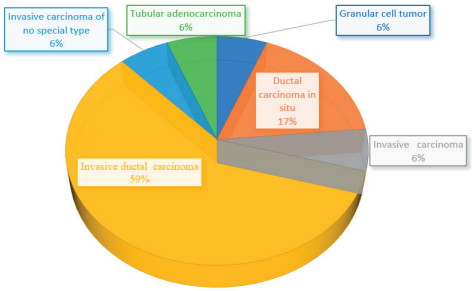
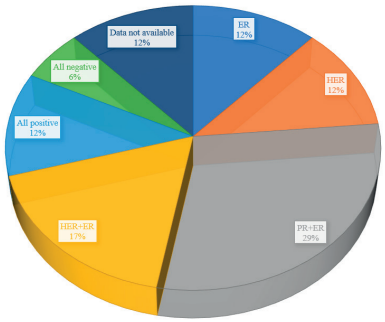


FIGURE 4. Prevalence of cancer types among transgender men



ER – estrogen receptor; HER – human epidermal growth factor receptor; PR – progesterone receptor

FIGURE 5. Prevalence of receptor positivity in breast cancer among transgender men

Transgender men should undergo screenings according to the guidelines for cisgender women [17]. Narayan et al. showed that as many as 64.3% of the TM study group had mammography [55]; this test is especially important for those transgender men who have not undergone bilateral mastectomy or have opted for breast reduction surgery [17]. In addition, abnormalities detected by screening mammography or changes in breast mass should be verified using imaging. A completed mastectomy can make mammography difficult, so alternative modalities including magnetic resonance imaging and ultrasound can be used for targeted treatment. A recent study found that transgender people are less likely to get cancer screenings compared to cisgender people. This may have to do with the fact that these screenings conflict with the transgender person's gender identity. Therefore, there is a need to create educational programs for both patients and physicians to detect cancers early and provide comprehensive care for these patients [38].

No consistent guidelines have been published on the use of GAHT in transgender men after breast cancer treatment. In some patients, re-treatment with low-dose testosterone is initiated. Testosterone without or with an aromatase inhibitor is used to prevent the conversion of testosterone to estrogen, but the efficacy of this prophylactic treatment is unknown and the subject of research. In several cases, during a follow-up of up to 5 years, no recurrence of cancer was found with repeated testosterone intake [31, 50, 52, 53, 54, 55].

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