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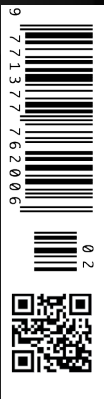
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Breast Cancer Screening After Male-to-Female Transition in Transgender Women





Breast Cancer Screening After Male-to-Female Transition in Transgender Women

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Despite the lack of general consensus about the optimal breast cancer screening approach in transgender women, it is imperative that physicians remain vigilant and aware of each transgender individual’s health risks based on their birth assigned sex and their particular mode of gender-affirming therapy.



Key Points

- Over the last decade, the number of transgender individuals seeking medical care has continued to increase.
- The transgender population has historically been more vulnerable to health disparities and structural discrimination leading to inadequate health care.
- Transgender women taking hormone therapy are at higher risk for breast cancer than natal males but lower risk compared to natal females.
- There is a lack of consensus among experts about the appropriate timing of breast cancer screening in transgender women. It is important to spread awareness among providers and transwomen about the uncommon but potential development of breast cancer following male to female transition.

Introduction

Over the last decade, the number of transgender individuals seeking medical care has continued to increase. It is estimated that currently 390 out of every 100,000 adults in the United States are transgender, which computes to almost one million Americans (Meerwijk and Sevelius 2017). Gender identity is defined as a person’s internal sense of self while gender expression is the outward display of an individual’s gender, including expression in the form of clothing, speech and mannerisms (UCSF Guidelines 2016). The definition of transgender is a person whose gender identity is different from the biological sex that was determined at birth. A transgender female is someone who was born biologically male and identifies as the female gender. A transgender male is someone who was born biologically female and identifies as the male gender (UCSF Guidelines 2016).

Compared to cisgender individuals, the transgender population has historically been more vulnerable to health disparities and structural discrimination leading to inadequate health care (Du Bois et al. 2018). In recent years, the options for gender affirming therapy have progressed and include cross-sex hormonal therapy, surgical breast augmentation and surgical

reconstruction of genitalia (Hartley et al. 2018). Research has shown that these therapies not only alter physical appearance but also improve overall quality of life for transgender individuals (Nehlsen et al. 2020). Despite the advances being made in the management of this population, there are still many questions and grey areas remaining when it comes to optimal treatment strategies. One such challenge involves the question of breast cancer screening, specifically in transwomen who transition from male to female using cross-sex hormone therapy. Best practices are still being discussed and debated, but overall it is of utmost importance for providers to remain vigilant and aware of each transgender individual’s health risks based on their birth assigned sex and their particular mode of gender-affirming therapy.

Cross-Sex Hormone Therapy

Cross-sex hormone therapy for male-to-female transition typically consists of two components: anti-androgens to reduce testosterone levels and exogenous oestrogen to develop the desired female secondary sex characteristics (Unger 2016). Spironolactone and cyproterone acetate both have anti-androgenic properties and are used to decrease testosterone levels

to the female range (<55 ng/dl). Other anti-androgens shown to be effective are GnRH agonists. Finasteride and progesterone are additional options but are less commonly used. Oestrogens can be administered orally, parenterally, or transdermally with the goal of maintaining oestradiol at the daily level of premenopausal women (100 – 200 pg/ml) (Hembree et al. 2009; Unger 2016).

Breast Development in Transgender Women

One of the main changes seen with hormone therapy in male-to-female transgender individuals is the development of breast tissue. Oestrogen therapy induces the growth and maturation of ducts, lobules and acini as seen in natal females (Sonnenblick et al. 2018). According to the Clinical Practice Guidelines of the Endocrine Society, development of breast tissue begins between 3-6 months following the onset of cross-sex hormone therapy with the maximum growth expected after 2-3 years of therapy (Hembree et al. 2009).

A prospective multicentre study done in the Netherlands followed 229 transwomen during their first year of hormone therapy to measure breast development. The study found that the most significant growth occurred in the first 6 months of therapy followed by smaller increments of growth in the succeeding 6 months. At the end of 1 year, only 10.7% gained a bra cup size greater than an A (de Blok et al. 2018). Another study done in Florence followed participants for 2 years and found that the majority was able to reach Tanner Stage 3 breast development after 24 months of hormone therapy (Fisher et al. 2016).

Although there is a modest increase in breast size for most individuals following hormone therapy, approximately 60-70% of patients pursue surgical breast augmentation options (Wierckx et al. 2014). The standard surgical methods used in the United States utilise saline or silicone implants to augment breast size (Sonnenblick et al. 2018). However, some patients may have had injections of free substances such as free liquid silicone for the purpose of augmentation, although this practice is illegal in the United States (Sonnenblick et al. 2018).

Breast Cancer Risk with Cross-Sex Hormone Therapy

As per the American Cancer Society, the estimated lifetime risk of males developing breast cancer is 1 in 833 while the average lifetime risk in females is 1 in 8 (American Cancer Society 2019). In the US in 2020, it is estimated that there will be 276,480 new cases of invasive breast cancer diagnosed in women and 2,620 cases diagnosed in men (American Cancer Society 2020). There are many risk factors that can contribute to development of breast cancer in both men and women, including ageing, obesity, alcohol use, liver disease, radiation exposure, family history and inherited gene mutations. Another risk factor to consider is oestrogen exposure, which is of particular concern in the transgender female population as long-term exogenous oestrogen exposure is part of typical gender-affirming medical therapy. While individuals undergoing male-to-female transition may be at lower risk

than cisgender females due to less lifetime oestrogen exposure prior to therapy, there is concern that the high dose exogenous oestrogen used for sex reassignment therapy may increase the risk of breast cancer for these patients. However, the lack of longitudinal data regarding breast cancer incidence in this patient population makes it difficult to ascertain the degree to which cross-sex hormone therapy influences breast cancer risk in transgender women.

A systematic review was completed in April 2018 to identify cases of breast cancer in transgender women. A total of 18 articles were included in the review spanning the United States, Netherlands and the United Kingdom and 22 cases of breast cancer were reported. Twenty of the 22 patients were taking hormone therapy but the length of treatment varied. The median age of diagnosis in this group was 51.5 years old and the majority presented initially with a palpable breast mass. Other presentations included peri-prosthetic seroma, dislocated implants, bloody nipple discharge and asymptomatic mammography screening. The majority of the identified cases were determined to be adenocarcinomas, 10 out of 19 tested were ER positive, 5 out of 14 tested were PR positive, and 2 of 8 tested were HER2 positive (Hartley et al. 2018). One of the studies included in the review described incidence of breast cancer transwomen. A cohort study done in 2013 by Gooren et al. identified 1 confirmed case and 1 unconfirmed case of breast cancer out of 2307 transgender female patients. The calculated incidence was determined to be 4.1 per 100,000 patient years (95% CI 0.8-13.0), which is slightly higher than the expected incidence in natal males (1.2 per 100,000 patient years) and significantly lower than the expected incidence in natal females (170 per 100,000 patient years) (Gooren et al. 2013).

A large retrospective cohort study done in the Netherlands in 2019 measured the incidence and characteristics of breast cancer in transgender patients to evaluate breast cancer risk in transpatients on hormone therapy compared to the general Dutch population. The study population included 2260 transgender women who were seen at the same gender clinic in Amsterdam between 1972 and 2016. Of the 2260 transwomen, there were 15 cases of invasive breast cancer and 3 cases of noninvasive breast cancer diagnosed in 17 patients. These cases were diagnosed after a median of 18 years of hormone therapy and the median age of diagnosis was 50, which is a younger age of diagnosis compared to Dutch cisgender women. Ten of the 15 cases of invasive breast cancer were ductal in origin, 10 were ER positive, 8 were PR positive, and 1 was HER2 positive. When compared to the Dutch cisgender male population, transwomen were found to be at higher risk with a standardised incidence ratio of 46.7 (95% CI 27.2-75.4). However, transwomen were found to have a lower risk of breast cancer than the Dutch cisgender female population with a standardised incidence ratio of 0.3 (95% CI 0.2-0.4). Although the study did not include data regarding



the prescribed hormone therapy such as route, dosing and frequency, median oestradiol and testosterone levels were found to be similar between the entire cohort of patients and those diagnosed with breast cancer (de Blok et al. 2019). The data collected in this Dutch study suggests that transgender women on cross-sex hormone therapy are at an increased risk of breast cancer compared to natal males but at a decreased risk compared to natal females.

Breast Cancer Screening Considerations in Transgender Women

Based on the studies that have been published thus far, it appears that transgender women taking hormone therapy are at higher risk for breast cancer than natal males but lower risk compared to natal females. The overall incidence appears to be low, but breast cancer does occur in this patient population and commonly presents at a younger age than in cisgender individuals. While universal breast cancer screening guidelines have not yet been published due to lack of transgender population data and longitudinal studies, several groups have proposed possible suggestions for screening.

Maglione et al. (2014) recommended screening for transwomen with additional risk factors such as BRCA2 mutation, family history, Klinefelter syndrome. For patients age 50–69 who have utilised hormone therapy, current Canadian Society Guidelines recommend mammography every two years. However, they do not recommend screening in patients who have not taken hormone therapy (Hartley et al. 2018). Clinical practice guidelines published in 2009 from The Endocrine Society in the United States suggest screening transgender women as biological women (Hembree et al. 2009). The Center of Excellence for Transgender Health at the University of California San Francisco published “Guidelines for the Primary and Gender-Affirming Care of Transgender and Gender Nonbinary People” in 2016. This group recommended screening mammography every 2 years after age 50 and after the patient has been on hormone therapy for at least 5 years. Similar to cisgender women, breast exams are not recommended in the transgender population (UCSF Guidelines 2016).

Breast cancer screening in transgender women can be done via mammography, ultrasound and MRI just as in cisgender women (Sonnenblick et al. 2018). Selecting a method of imaging should be based on the form of breast development and augmentation. In patients with implants or hormonally developed breasts, mammography or ultrasound is suggested. However, in patients

who chose free silicone for augmentation, breast MRI may be a more beneficial modality (Maglione et al. 2014). The challenges associated with surgically augmented breasts are the same between transgender and cisgender women. Breast tissue may be obscured and the radiodensity of the breast may be reduced if there is compression by the implant. The Eklund, or Pushback technique that is used for cisgender females with implants is also recommended in transgender patients with breast augmentation for more accurate viewing (Tang and Gui 2011).

Overall there is a lack of consensus among experts about the appropriate timing of breast cancer screening in transgender women. Therefore, it is more important to spread awareness among providers and transwomen about the uncommon but potential development of breast cancer following male to female transition. If patients change their legal sex, they may no longer be flagged and invited for population-based screenings, including screening mammography, so it is imperative that doctors and patients alike remain vigilant about preventative care (de Blok et al. 2019). A retrospective review done in 2015 at a urban health centre in Massachusetts found that transgender patients were less likely than cisgender patients to follow breast cancer screening guidelines with an odds ratio of 0.53 (95% CI 0.31–0.91), which further emphasises the need for better outreach and communication with sexual minorities (Bazzi et al. 2015). As with all areas of medicine, the decision about when to begin screening and how often to screen for breast cancer should be made after an in-depth discussion about the benefits and risk of radiologic imaging as well as the patient’s individual risk factors.

Conclusion

Although there is not a large body of research about the risk of breast cancer in transgender women, the studies discussed here suggest that this patient population is at a lower risk of breast cancer than cisgender women but at higher risk than cisgender men. The suggested recommendations from various experts are not uniform, emphasising the need for further longitudinal research to determine the optimal screening guidelines. Because the breast cancer screening recommendations are still unclear, it is imperative that physicians facilitate individualised discussions with each transgender woman about breast cancer risk and screening as part of preventative health appointments.

Conflict of Interest

None. ■

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