Histopathologic Features of Breast Tissue From Transgender Men and Their Associations With Androgen Therapy

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ABSTRACT

Objectives: To assess the histopathologic features of breast tissue of transgender men (TM) undergoing gender-affirming bilateral mastectomies in relation to androgen therapy (AT).

Methods: We reviewed 374 transgender bilateral mastectomy cases from 2017 to 2020. Of these, 314 (84.4%) patients received preoperative AT. We compared these with 127 cases of cisgender females undergoing elective breast reduction.

Results: Breast specimens from TM on AT, compared with cisgender women, showed a median higher gross percentage of fibrous tissue ($P < .001$), reduced lobular density ($P = .004$), higher amount of lobular atrophy ($P < .001$), and lower incidence of cysts ($P < .001$), apocrine metaplasia ($P < .001$), calcifications ($P < .001$), columnar cell change ($P = .002$), and atypia ($P = .003$). Each additional month of AT was associated with a 2% decrease in the odds of having nonapocrine cysts ($P = .02$), a 5% decrease in the odds of having usual ductal hyperplasia ($P = .007$), and a 0.14% decrease in median lobular density (95% confidence interval, –0.18 to –0.05).

Conclusions: In this study, breast specimens from TM, particularly with a history of AT, had a higher proportion of fibrous tissue, fewer lobules, and a higher degree of lobular atrophy than cisgender females. Rare cases of atypia were not predicted by preoperative imaging or gross findings, supporting routine microscopic evaluation of these specimens.

INTRODUCTION

A growing number of individuals identify as transgender in the United States, and as a result, the number of patients seeking gender-affirming surgery has risen considerably in recent years.[1] However, despite this recent increase, many medical centers encounter only a small number of specimens from transgender individuals.[2] With the lack of current established guidelines on how to process and interpret specimens from this patient population, adequate pathologic assessment of these specimens can be challenging and prone to misinterpretation.[2,3] There is a need for more information about the histopathologic findings in this patient population to guide future practice.

KEY POINTS

- It is essential for pathologists to be able to recognize the effects of androgen therapy (AT) on breast tissue when evaluating mastectomy specimens from transgender men (TM), as these procedures are increasing in frequency.
- Specimens from TM on AT had more fibrous tissue, decreased lobular density, and more atrophic lobules than from cisgender females. These findings were related to the length of AT.
- Atypia was more prevalent in the cisgender group than in the TM on AT group. All cases of atypia in the TM group had normal imaging and gross findings. We recommend microscopic evaluation of all specimens.

KEY WORDS

Breast; Transgender men; Gender-affirming mastectomy; Androgen therapy

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Transgender men (TM) are individuals who were assigned female sex at birth but identify as male. Multidisciplinary management for TM may include psychological counseling, androgen therapy (AT), and gender-affirming surgeries, such as masculinizing mastectomy.[4] Long-term AT in these individuals aims to replace endogenous hormones with testosterone for the acquisition of masculine secondary sex characteristics.[5] Dosing can vary between patients, but the goal of AT is to achieve serum testosterone concentrations in the male reference range.[6] In addition to or instead of hormone therapy, many TM opt to undergo appearance-altering surgery. Gender-affirming mastectomy, also known as chest reconstruction or "top surgery," is a safe procedure that has been shown to improve quality of life among TM.[7] The frequency of these procedures is on the rise, and as this procedure gains popularity, pathology services will be expected to evaluate a higher volume of these specimens. Many TM who undergo gender-affirming mastectomy have a history of AT, so it is essential for pathologists to be able to recognize the effects of AT on breast tissue to avoid misinterpretation when evaluating these specimens.

The histopathologic findings in breast tissue from TM with a history of AT provide a good model to analyze the effects of testosterone on breast tissue. A handful of studies to date have described the histopathologic findings in mastectomy specimens from TM.[5,8-11] However, there is a need for more data on the findings in this population to properly educate the pathology community on appropriate processing protocols and interpretation of these specimens. This study is the largest study to date to assess the histopathologic findings of TM breast tissue with a direct comparison to a cisgender female control group undergoing elective breast reduction. In this way, this study will assess the correlation between AT and the histopathologic changes observed in breast tissue of TM.

MATERIALS AND METHODS

Study Population and Tissue Processing

This retrospective study reviewed the gross and histopathologic findings of breast specimens from 374 female-to-male TM undergoing gender-affirming mastectomy (97.1%, 363/374) or reduction mammoplasty (2.9%, 11/374). After institutional review board approval, cases were selected by searching Sunquest CoPath (Sunquest Information Systems), our network's primary laboratory information system for pathology reports from the University of Minnesota Medical Center from January 2017 through August 2020 for breast specimens from patients with "gender dysphoria" or "transgender" in the clinical history. Of these 374 TM, 314 (84%) had a history of AT. For comparison, 127 cisgender women undergoing elective breast reduction from the same time period were also evaluated. Clinical history, including age at the time of procedure, presurgical body mass index (BMI), the duration of use of AT, family history of breast or ovarian cancer, and preoperative imaging findings, was collected from the electronic medical record, Epic (Epic Systems). None of the participants had a history of breast or ovarian cancer prior to surgery.

Histopathologic Review

The breast specimens from each participant had previously undergone gross and histologic evaluation using our institution's standard protocols. Per our standard gross examination protocol, four tissue cassettes were obtained per case (two cassettes per side, preferentially sampling fibrous-appearing tissue). If gross abnormalities were identified, additional tissue cassettes were obtained. Gross abnormalities documented among all specimens included the presence of cysts, lymph nodes, fibrous nodules, and skin lesions. Pathology reports were reviewed for total specimen weight, gross estimate of the percentage of fibrous tissue vs fatty tissue, the presence of gross lesions, and the number of tissue cassettes submitted for each case. All H&E slides were evaluated by two reviewers (E.A.W. and K.E.R.) for the stromal composition (predominately fibrous, predominately fatty, or a near-equal mix of each), percentage of total tissue surface area composed of lobules, and the percentage of lobules within a specimen with atrophic features. The reviewers scanned the slides at low magnification to determine the percentage of surface area composed of lobules, starting with very basic distinctions (more or less than half, one-quarter, one-fifth, one-tenth), then using a ruler or 1-mm grid directly on the slide when needed to define standard percentages to the nearest 5%. The percentage of lobules with atrophic features was similarly estimated at low magnification. Atrophic features were defined as thickening of the basement membrane, intralobular collagenized stroma, diminished number of acini, and/or atrophic epithelium **FIGURE 1**. When assessing the percentage of tissue area composed of lobules, samples of skin and nipple were excluded from the total tissue area evaluation. The presence of any of the following histologic findings was assessed: inflammation, pseudoangiomatous stromal hyperplasia (PASH), apocrine metaplasia/cysts, nonapocrine cysts, usual ductal hyperplasia (UDH), duct ectasia, sclerosing adenosis, fibroadenoma, fibroadenomatous change, secretory change, columnar cell change/hyperplasia, papilloma, calcifications, benign vascular lesions, flat epithelial atypia (FEA), atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), ductal carcinoma in situ (DCIS), lobular carcinoma in situ (LCIS), and invasive carcinoma. The slide review was blinded to clinical history and gender identification.

Statistical Analysis

Categorical variables were summarized using counts and percentages and compared across groups (TM on AT vs cisgender control, TM on AT vs TM not on AT) using Fisher exact tests. The percentages of fibrous tissue, lobules, and lobular atrophy were summarized by group using the median and interquartile range and compared across groups using Kruskal-Wallis tests. Quantile regression[12] with bootstrapped 95% confidence intervals (CIs) were used to compare the median percentage of fibrous tissue, lobules, and lobular atrophy across groups when adjusting for age and BMI. Firth's method for logistic regression[13] was used to assess the association between histopathologic findings and months of AT among all TM. Quantile regression with bootstrapped 95% CIs was used to assess the association between the median percentage of fibrous tissue, lobules, and lobular atrophy adjusted for age and BMI. All tests were two-sided,

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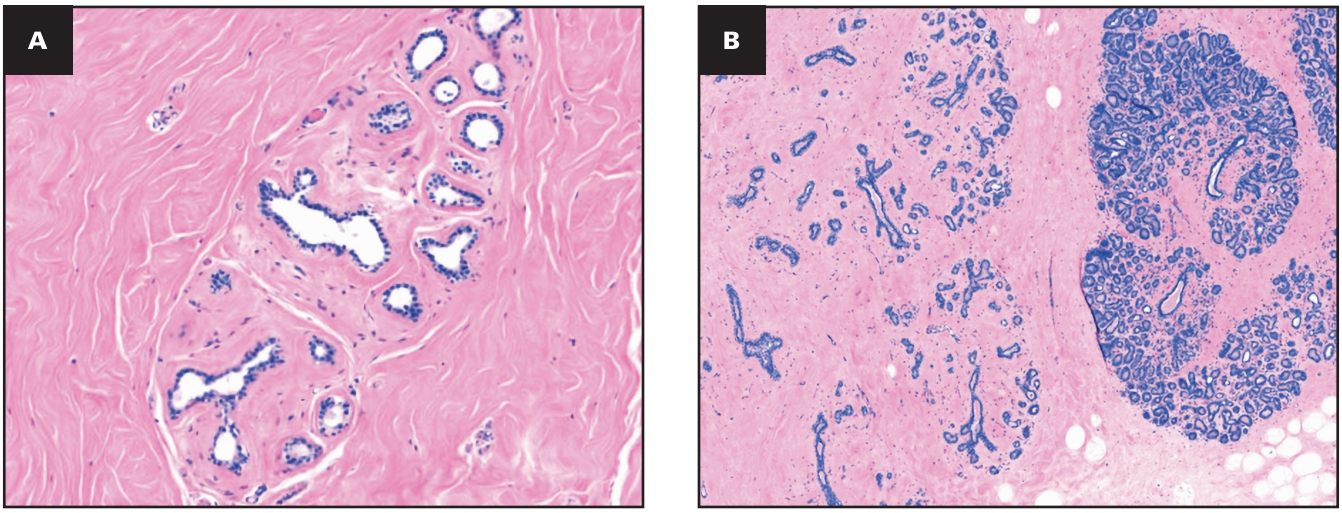

FIGURE 1 **A**, Example of lobular atrophy from a transgender man on androgen therapy showing thickening of the basement membrane, intralobular collagenized stroma, diminished number of acini, and atrophic epithelium. **B**, Example of an atrophic lobule (left) compared with a lobule without atrophic features (right) in the same specimen (H&E, ×100 [**A**] and ×40 [**B**]).

TABLE 1 Characteristics of Study Participants

Characteristic	All TM (n = 374)	TM on AT (n = 314)	TM Not on AT (n = 60)	Cisgender Female Controls (n = 127)
Age at surgery, median (IQR), y	23 (20.0-28.0)	23.0 (20.0-27.0)	25.0 (20.0-30.0)	35.0 (22.5-47.5)
BMI at surgery, median (IQR), kg/m^2	27.6 (23.0-34.7)	27.7 (23.1-35.0)	27.2 (22.7-31.7)	31.6 (27.9-36.0)
Length of androgen therapy, median (IQR), mo	15.5 (8.0-25.0)	18.0 (12.0-28.0)	0	0
Family history of breast or ovarian cancer, %	35	33.4	43.3	30.7
First-degree relative, %	6.4	6	8.3	11
Second-degree relative, %	31.8	30.25	40	22
Preoperative imaging, %	83.2	81.5	91.7	62.2

AT, androgen therapy; BMI, body mass index; IQR, interquartile range; TM, transgender men.

and a *P* value less than .05 was considered statistically significant. Due to the exploratory nature of the study, the results were not adjusted for multiple comparisons. All analyses were conducted using R version 3.6.3 or higher.[14]

RESULTS

Characteristics of Study Participants

Of the 374 TM identified on record review, 67 (17.9%) underwent gender-affirming mastectomy in 2017, 132 (35.3%) in 2018, 153 (40.9%) in 2019, and 22 (5.9%) in the first 8 months of 2020. Excluding the partial and pandemic year of 2020, this shows a substantial increase in the volume of TM seeking gender-affirming mastectomy in recent years. Characteristics of the study participants are shown in TABLE 1. Median age and BMI were significantly higher in the cisgender control group than the TM on AT group (both $P < .001$); the median age and BMI did not differ significantly between the TM on and not on AT groups ($P = .124$ and $P = .230$, respectively). Of the 374 TM undergoing gender-affirming mastectomy, 314 (84.0%) had a history of AT and 60 (16.0%) had never taken AT prior to surgery. Of the TM on AT, most (262/314, 83.4%) were on intramuscular injection therapy (testosterone cypionate/enanthate). Transdermal gel, cream, or patch was the second most common type of administration (32/314, 10.2%), and 20 participants (6.4%) had received a combination of both intramuscular and transdermal therapy over the course of their hormone treatment. Among all the TM in this study, 35.0% (131/374) had a family history of a first- or second-degree relative with breast or ovarian cancer, 57.3% (214/374) had no known family history of breast or ovarian cancer, and 7.7% (29/374) had an unknown family history. Among the cisgender control group, 30.7% (39/127) had a family history of breast or ovarian cancer, 64.5% (82/127) had no family history of breast or ovarian cancer, and 4.8% (6/127) had an unknown family history.

Preoperative imaging with mammography or breast ultrasound was performed on 83.2% (311/374) of the total TM with a median Breast Imaging-Reporting and Data System (BI-RADS) score of 1. Five (age range, 20-47 years) of the TM participants who underwent preoperative imaging had a BI-RADS score of 3 or higher, and subsequent image-guided breast core biopsy specimen showed a fibroadenoma with no atypia or malignancy in all five cases. Of the cisgender control cases, 62.2% (79/127) underwent breast imaging prior to surgery, with a median BI-RADS score of 1. Two cisgender

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TABLE 2 Gross Characteristics of the Breast Specimens

Characteristic	All TM (n = 374)	TM on AT (n = 314)	TM Not on AT (n = 60)	Cisgender Female Controls (n = 127)
Total weight, median (IQR), g	1,062.3 (571.0-1,784.6)	1,001.1 (534.7-1,729.0)	1,403.4 (901.7-1,867.9)	1,501.0 (1,108.5-1,902.85)
% fibrous tissue, median (IQR)	40.0 (20.0-60.0)	40.0 (20.0, 60.0)	38.8 (23.8-70.0)	20.0 (15.0-30.0)
% with gross abnormalities	3.5	3.5	3.3	7.1
No. of tissue cassettes submitted per case, median (range)	4 (4-11)	4 (4-11)	4 (4-11)	4 (4-8)

AT, androgen therapy; IQR, interquartile range; TM, transgender men.

participants (aged 39 and 49 years, respectively) received a BI-RADS score of 3 or higher, and subsequent image-guided breast core biopsy specimen showed a benign lymph node and benign breast tissue, respectively, with no atypia or malignancy.

Gross Findings

Gross characteristics of the breast specimens among groups are shown in TABLE 2, including total weight of the breast specimens, the percentage of total tissue on gross examination that appears to be fibrous (vs fatty), the prevalence of gross abnormalities, and number of tissue cassettes submitted for each case. None of the abnormalities observed and documented during gross examination corresponded to findings of atypia or malignancy on microscopy. The median percentage of fibrous breast tissue was significantly higher in the TM on AT group compared with the cisgender control group ($P < .001$); there was not a significant difference in the median percentage of fibrous tissue between the TM on AT and TM not on AT groups ($P = .308$). In addition, when controlling for age and BMI, the TM on AT group had a median percentage of fibrous breast tissue 6.81 percentage points higher than the control group (95% CI, 0.84-10.63).

Histopathologic Findings

Among the TM specimens, 322 (86.1% of all TM: 86.0% of TM on AT; 86.2% of TM not on AT) were predominantly fibrous on microscopy, 36 (9.6% of all TM: 3.4% of TM on AT; 10.8% of TM not on AT) were predominantly fatty, and 16 (4.3% of all TM: 3.2% of TM on AT; 9.4% of TM not on AT) were an equal mix of fibrous and fatty. Among the cisgender control group, 76.4% were predominantly fibrous on microscopy, 14.2% were predominantly fatty, and 9.4% were an equal mix of fibrous and fatty. Comparisons of the histopathologic findings among the TM on AT and cisgender controls with associated *P* values are summarized in TABLE 3. Among the 374 bilateral TM breast specimens, 79 (21.1%) had inflammation, 58 (15.5%) had nonapocrine cysts, 53 (14.2%) had duct ectasia, 52 (13.9%) had apocrine cysts/metaplasia, 37 (9.9%) had fibroadenomatous change, 22 (5.9%) had UDH, 19 (5.1%) had calcifications, 11 (2.9%) had a fibroadenoma, 11 (2.9%) had columnar cell change/hyperplasia, 7 (1.9%) had sclerosing adenosis, 4 (1.1%) had PASH, 4 (1.1%) had a benign vascular lesion, 1 (0.3%) had secretory change, and none had a papilloma. There was a significantly lower prevalence of apocrine cysts/metaplasia, nonapocrine cysts, columnar cell change/hyperplasia, papilloma, calcifications, UDH, sclerosing adenosis, and atypia (particularly LCIS) among the TM on AT group compared with the cisgender control group.

There were four (1.1%) cases of incidentally found atypia among the TM specimens that included one case of FEA, one case of ADH, and two cases of ALH. The two cases of ALH were in TM on AT FIGURE 2A, and the cases of FEA and ADH were in TM not on AT. Neither carcinoma in situ nor invasive cancer were found among any of the TM specimens. Of these four cases, two had a family history of breast cancer, and all four had benign preoperative imaging. This is compared with seven (5.5%) cases of incidental atypia (including LCIS) found among the cisgender control group, including one case of FEA, one case of ADH, one case of ALH, two cases of LCIS, one case with both FEA and ALH, and one case of both ALH and LCIS FIGURE 2B. Three of these seven cases had a family history of breast cancer, and all seven had benign preoperative imaging. There was a significantly higher prevalence of atypia in the cisgender group than the TM on AT group ($P = .003$). These results were not adjusted for age and BMI differences between the groups given the low number of atypia cases in this study.

The median percentage of lobules exhibiting features of atrophy in each specimen was significantly higher among the TM on AT group compared with the cisgender control group ($P < .001$) TABLE 3. When controlling for age and BMI, the TM on AT group had a median percentage of atrophic lobules approximately 34.56 percentage points higher than the control group (95% CI, 13.43-53.01). The percentage of tissue area on microscopy composed of lobules was significantly lower among the TM on AT compared with the control group ($P = .004$) FIGURE 3. When controlling for age and BMI, the TM on AT had a median lobular density by area that was 4.95 percentage points lower than the cisgender control group (95% CI, –8.12 to –3.30).

When comparing the TM on AT group with the TM not on AT group TABLE 4, TM on AT had a significantly lower median percentage of tissue area composed of lobules ($P < .001$). However, there was no significant difference in the median percentage of atrophic lobules between the two groups ($P = .882$). When adjusting for age and BMI, the TM on AT group had a median lobular density by area that was 10.00 percentage points lower than the TM not on AT group (95% CI, –15.00 to –5.00). Among all TM, prevalence of histopathologic findings was analyzed in relation to duration of AT rounded to the nearest month FIGURE 4. Each additional month of AT was associated with a 2% decrease in the odds of having nonapocrine cysts ($P = .02$) and a 5% decrease in the odds of having UDH ($P = .007$). The median percentage of tissue composed of lobules on microscopy decreased by 0.14% with each additional month of AT when controlling for age and BMI (95% CI, –0.18 to –0.05) FIGURE 5.

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TABLE 3 Microscopic Findings of the Breast Specimens With Comparison Between the Transgender Men on Androgen Therapy and Control Group[a]

Histopathologic Findings	TM on AT (n = 314)	Cisgender Control (n = 127)	*P* Value[b]
Inflammation	64 (20.4)	36 (28.3)	.079
Nonapocrine cysts	37 (11.8)	48 (37.8)	**<.001**
Duct ectasia	41 (13.1)	18 (14.2)	.759
Apocrine metaplasia/cysts	37 (11.8)	45 (35.4)	**<.001**
Fibroadenomatoid change	32 (10.2)	19 (15.0)	.188
Usual ductal hyperplasia	13 (4.1)	14 (11.0)	**.014**
Calcifications	14 (4.5)	22 (17.3)	**<.001**
Fibroadenoma	9 (2.9)	6 (4.7)	.385
Columnar cell change/hyperplasia	8 (2.5)	13 (10.2)	**.002**
Sclerosing adenosis	4 (1.3)	7 (5.5)	**.016**
PASH	2 (0.6)	2 (1.6)	.327
Benign vascular lesion	3 (1.0)	1 (0.8)	>.999
Secretory change	1 (0.3)	3 (2.4)	.074
Papilloma	0 (0.0)	3 (2.4)	**.023**
Atypia	4 (1.1)	7 (5.5)	**.003**
Flat epithelial atypia	1 (0.3)	2 (1.6)	.082
Atypical ductal hyperplasia	1 (0.3)	1 (0.8)	.288
Atypical lobular hyperplasia	2 (0.6)	3 (2.4)	.146
Lobular carcinoma in situ	0 (0.0)	3 (2.4)	**.023**
Ductal carcinoma in situ	0 (0.0)	0 (0.0)	—
Invasive carcinoma	0 (0.0)	0 (0.0)	—
Area composed of lobules, median (IQR), %	5.00 (1.00-10.00)	10.00 (1.00-20.00)	**.004**
Lobules with atrophic features, median (IQR), %	70.00 (20.00-95.00)	10.00 (0.00-40.00)	**<.001**

AT, androgen therapy; IQR, interquartile range; PASH, pseudoangiomatous stromal hyperplasia; TM, transgender men; —, *P* value could not be calculated due to zero events.
[a]Date are given as No. (%) except where otherwise indicated.
[b]Bold values represent statistical significance ($P < .05$).

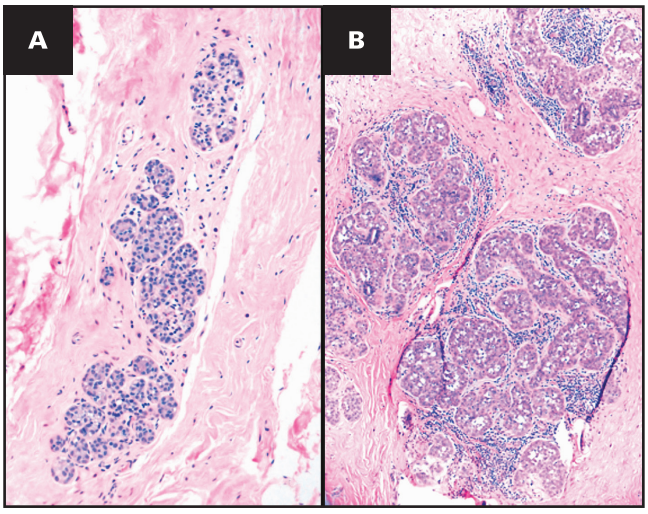

FIGURE 2 Lobular neoplasia in a transgender man on androgen therapy (atypical lobular hyperplasia) (**A**) and a cisgender control case (lobular carcinoma in situ) (**B**) (H&E, ×200 [**A**] and ×100 [**B**]).

DISCUSSION

With an estimated 0.6% of the US population identifying as transgender, an increasing number of patients seek gender-affirming surgeries every year.[1] As a result, surgical pathologists are encountering breast specimens from these patients with increasing frequency. In this study, the number of TM undergoing gender-affirming mastectomy more than doubled within 2 years, with 67 patients in 2017 increasing to 153 patients in 2019. Despite the increase in the number of TM mastectomy specimens within pathologists' caseloads, there are no established guidelines for best sampling and review practices for these cases.[15] It is important for surgical pathologists to be familiar with the histopathologic differences in breast tissue from TM and be aware of the utility of pathologic examination in these cases.

This review of breast specimens from 314 TM on AT undergoing gender-affirming chest reconstruction revealed several histopathologic differences compared with a female cisgender control group, including a lower prevalence of cysts and calcifications TABLE 3. The younger age and lower BMI of TM on AT may have contributed in part to these observed differences, in addition to the effects of AT. Specimens from all TM (including those on AT and those not on AT) had a higher proportion of fibrous tissue vs fatty tissue on gross examination than the cisgender control group, even after controlling for higher average median age and BMI of the cisgender control group. Interestingly, there was not a significant difference in the median percentage of fibrous tissue identified grossly between the TM on AT and TM not on AT groups.

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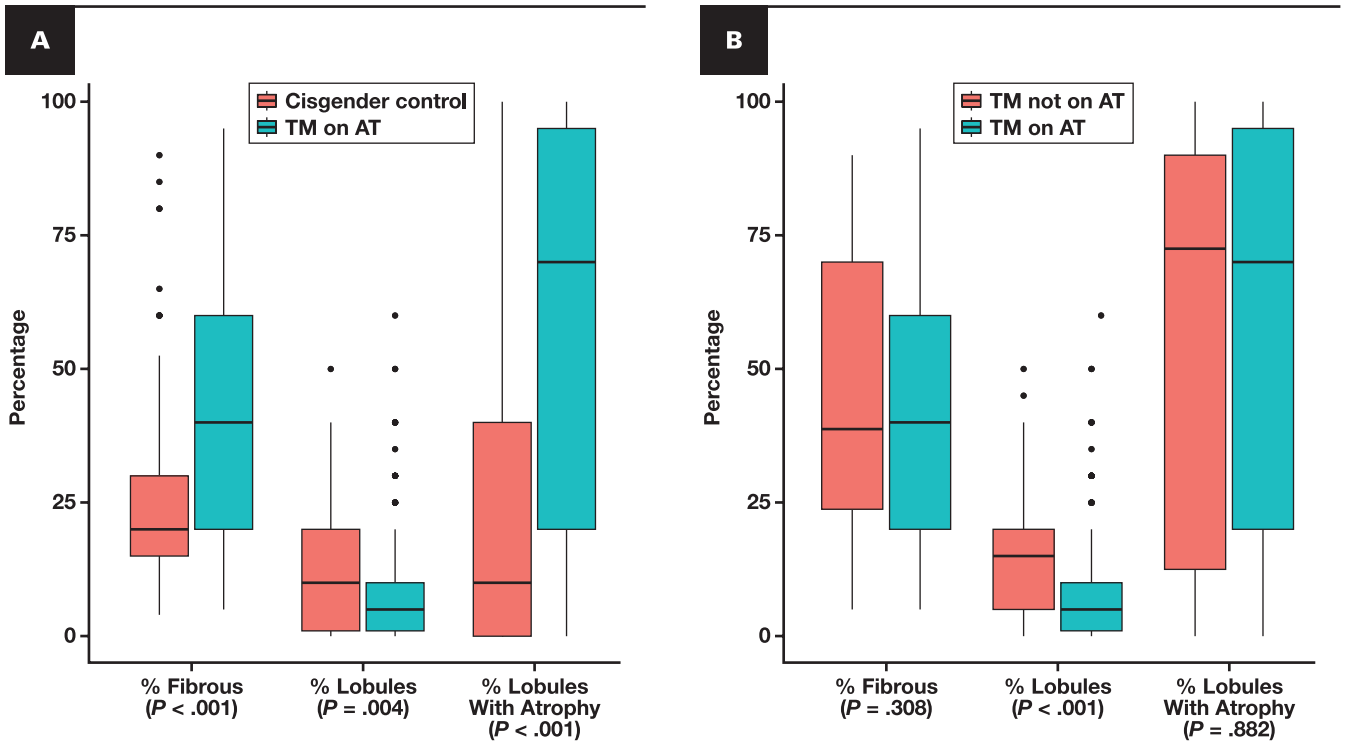

FIGURE 3 Comparison of percentage of fibrous tissue on gross examination, percent area composed of lobules on microscopy, and percentage of lobules exhibiting atrophic features in the transgender men (TM) on androgen therapy (AT) group vs the cisgender control group (**A**) and TM on AT vs TM not on AT (**B**) (Kruskal-Wallis test).

Gross examination cannot distinguish between fibrous tissue that is predominantly stromal and fibrous tissue that retains glandular elements. The TM not on AT group is small, with only 4 (6.7%) participants older than 50 years at the time of surgery, compared with 2 (0.6%) TM not on AT and 29 (22.8%) cisgender controls. Therefore, both of the TM groups are expected to have very little menopause-related transformation of glandular tissue to fatty tissue, and the overwhelming number of premenopausal participants in these groups may have resulted in little difference between the gross proportions of fibrous vs fatty tissue. Because tissue identified as fibrous on gross examination was preferentially sampled, it is not surprising that most of the tissue examined microscopically was fibrous (rather than fatty) in all groups. The tissue sampled showed more lobules exhibiting features of atrophy and decreased lobular density by area on microscopy in TM (including those on AT and those not on AT) than the cisgender control group when controlling for differences in age and BMI between the groups. The decrease in lobular density was more striking in TM on AT than TM not on AT. In addition, increased duration of AT was associated with reduced lobular density among the TM. These findings show a strong correlation between increased stromal fibrosis and lobular atrophy in breast tissue and AT use.[8,9] The reduction in the odds of nonapocrine cysts in TM related to increased duration of AT in our study is similar to the findings of Baker et al.[11]

Previous studies classifying the histopathologic features of TM breast tissue have often used the term gynecomastoid change to describe these features of stromal fibrosis and lobular atrophy.[8,9,11] However, while the changes seen in TM after androgen therapy can resemble gynecomastia in cisgender men, the histologic findings in these very different patient populations occur as the result of distinct pathways. While gynecomastia has a long list of potential causative factors, several of these causative factors result in increased exposure of male breast tissue to estrogen.[16] In contrast, breast tissue from TM on AT shows the effects of testosterone on female tissue. In order to avoid potential confusion to some medical professionals and patients, we have decided to not use the term gynecomastoid change in relation to histologic changes such as lobular atrophy and stromal fibrosis observed in specimens from TM on AT.

The presence of atypia was very low among the total TM population in this study, with only 4 (1.1%) of 374 patients having premalignant breast lesions and no cases of incidentally found invasive carcinoma. Previous studies have shown a similarly low incidence of atypia in TM breast specimens, ranging from 1.5% to 3%.[8,9,11,15] In this study, the incidence of atypia in TM is significantly lower than the incidence of atypia in the cisgender control group. Because there are so few cases of atypia in our study, we are not able to control for possible confounding factors such as differences in age and BMI between the groups. Other studies comparing TM and cisgender females have found the incidence of breast cancer to be lower in TM vs cisgender females.[17-19] In this study, the use of AT was highly associated with a change in breast composition

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TABLE 4 Microscopic Findings of the Breast Specimens With Comparison Between the TM on AT Group and TM Not on AT Group[a]

Histopathologic Findings	TM on AT (n = 314)	TM Not on AT (n = 60)	*P* Value[b]
Inflammation	64 (20.4)	15 (25.0)	.490
Nonapocrine cysts	37 (11.8)	21 (35.0)	**<.001**
Duct ectasia	41 (13.1)	12 (20.0)	.161
Apocrine metaplasia/cysts	37 (11.8)	15 (25.0)	**.013**
Fibroadenomatoid change	32 (10.2)	5 (8.3)	.815
Usual ductal hyperplasia	13 (4.1)	9 (15.0)	**.004**
Calcifications	14 (4.5)	5 (8.3)	.205
Fibroadenoma	9 (2.9)	2 (3.3)	.692
Columnar cell change/hyperplasia	8 (2.5)	3 (5.0)	.394
Sclerosing adenosis	4 (1.3)	3 (5.0)	.085
PASH	2 (0.6)	2 (3.3)	.122
Benign vascular lesion	3 (1.0)	1 (1.7)	.505
Secretory change	1 (0.3)	0 (0.0)	>.999
Papilloma	0 (0.0)	0 (0.0)	—
Atypia	2 (0.6)	2 (3.3)	.122
Flat epithelial atypia	0 (0.0)	1 (1.7)	.160
Atypical ductal hyperplasia	0 (0.0)	1 (1.7)	.160
Atypical lobular hyperplasia	2 (0.6)	0 (0.0)	>.999
Lobular carcinoma in situ	0 (0.0)	0 (0.0)	—
Ductal carcinoma in situ	0 (0.0)	0 (0.0)	—
Invasive carcinoma	0 (0.0)	0 (0.0)	—
Area composed of lobules, median (IQR), %	5.00 (1.00-10.00)	15.00 (5.00-20.00)	**<.001**
Lobules with atrophic features, median (IQR), %	70.00 (20.00-95.00)	72.50 (12.50-90.00)	.882

AT, androgen therapy; IQR, interquartile range; PASH, pseudoangiomatous stromal hyperplasia; TM, transgender men; —, *P* value could not be calculated due to zero events.
[a]Date are given as No. (%) except where otherwise indicated.
[b]Bold values represent statistical significance ($P < .05$).

to include increased fibrous stoma and a reduction in lobular density. This correlation suggests that AT use may decrease the risk of breast cancer due to the reduction in functional breast tissue for atypia to arise in. However, the exact relationship between AT and the risk for the development of breast cancer remains unclear, with conflicting results showing both increased and decreased risk in previous studies of cisgender females.[20-22] Given the low frequency of reported breast cancer among TM, it is not possible to conclude a correlation between AT and the development of breast cancer at this time.[23] While further studies are needed to accurately assess this correlation, our results support the hypothesis that AT reduces the incidence of atypia.

The four TM who were found to have atypia in this study were not referred for high-risk screening. The cisgender women with atypia were referred to oncology for high-risk screening per National Comprehensive Cancer Network guidelines including alternating mammogram and breast magnetic resonance imaging every 6 months.[24] There is a lack of current established guidelines for cancer screening in transgender patients.[23] In TM who have undergone gender-affirming mastectomy, there is no reliable evidence to suggest screening mammography.[25] Breast reduction usually leaves behind sufficient viable breast tissue to allow for screening mammogram, while risk-reducing mastectomy for cisgender women does not. The procedure for gender-affirming mastectomy (chest reconstruction) for TM has a different overall goal than risk-reducing mastectomy for cisgender women. There are several methods to perform gender-affirming subcutaneous mastectomies; they all involve removal of breast tissue and excess skin, reduction in size and change in position of the nipple-areola complex, and elimination of the inframammary fold.[26] Some remnant upper pole breast tissue remains.[27] The breast tissue that remains after risk-reducing mastectomy for cisgender women and gender-affirming mastectomy for TM is usually not sufficient for mammogram to be a reasonable screening option. Both of these patient groups are typically followed with physical examination. There are several cases in the literature of breast cancer arising in a TM, after gender-affirming mastectomy, even in the absence of atypia or carcinoma in the mastectomy specimens, confirming that mastectomy does not eliminate the risk of breast cancer for these patients.[28-30] With the increased number of TM undergoing gender-affirming mastectomy and receiving AT, continued study is required to establish appropriate clinical guidelines for breast cancer screening and to optimize care of this group.

The low incidence of atypia among the TM in this study brings into question the utility and cost-effectiveness of routine histologic slide review for TM breast specimens. One recent study revealed that in the review of TM mastectomy cases, pathologists reviewed 2.8 times more slides on average than for cisgender reduction

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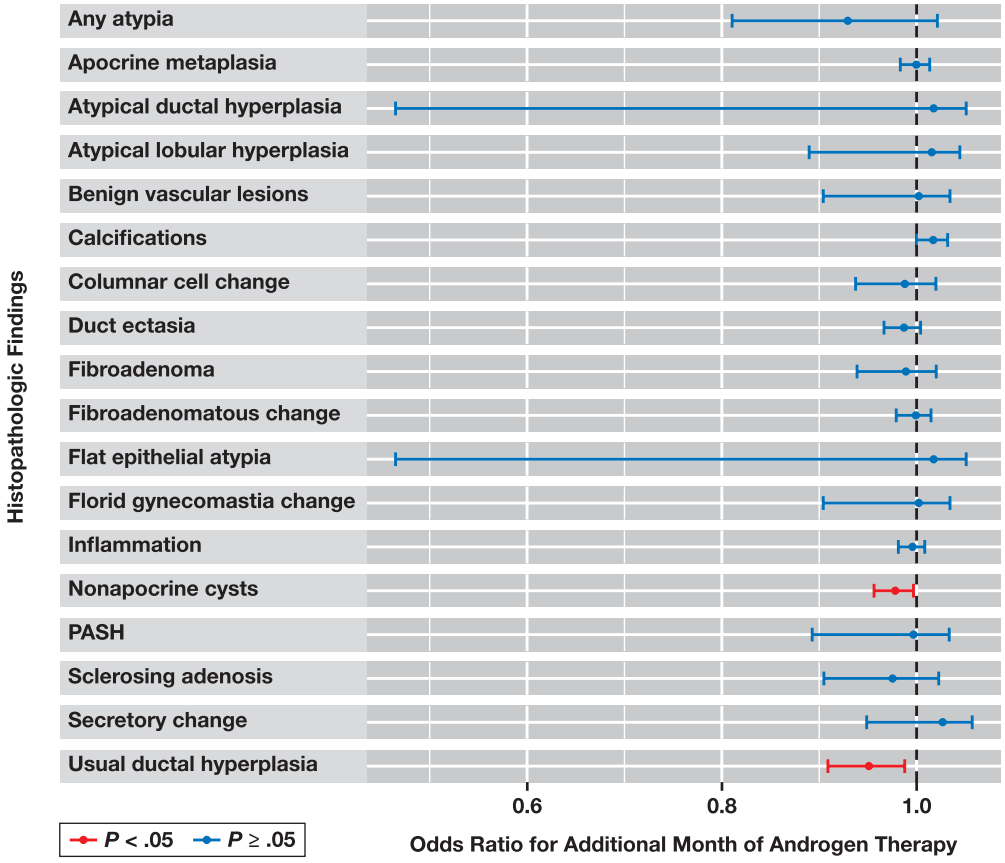

FIGURE 4 Odds ratios and 95% confidence intervals for the prevalence of histopathologic findings with each additional month of androgen therapy among the transgender men (using Firth's method for logistic regression). PASH, pseudoangiomatous stromal hyperplasia.

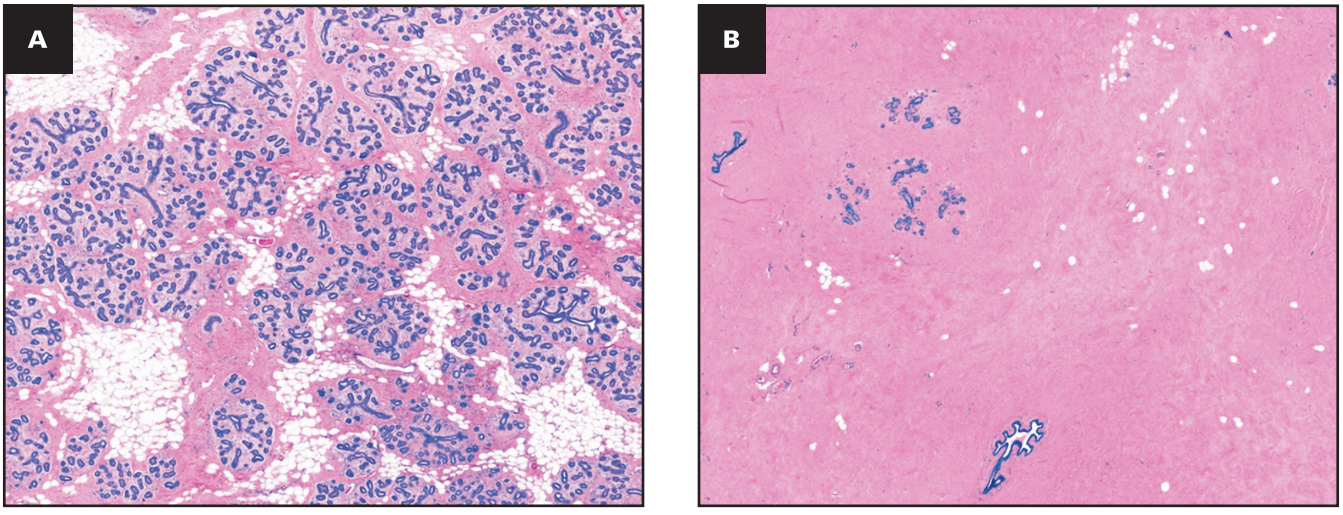

FIGURE 5 Comparison of density of lobules among specimens from transgender men in relation to androgen therapy length. **A**, Mastectomy specimen from a transgender man after 11 months of androgen therapy (age, 18 years; body mass index [BMI], 25.84 kg/m^2). **B**, Mastectomy specimen from a transgender man after 31 months of androgen therapy (age, 18 years; BMI, 24.09 kg/m^2) showing markedly reduced density of lobules compared with Figure 2A (H&E, ×20 [**A**, **B**]).

mastectomy specimens, with a 2.5 times lower rate of significant pathologic findings.[15] Given this low incidence of atypia and increased burden on anatomic pathologists, one might make the argument for limiting evaluation to gross examination, with tissue sampling and microscopic examination if there are gross abnormalities, a known family history of breast cancer, or abnormal preoperative imaging. However, none of the participants in this study with premalignant lesions identified on histologic review had

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gross abnormalities documented during gross evaluation. These lesions would have been missed if the specimens underwent gross examination only. In addition, significant preoperative imaging findings and breast cancer family history did not predict the atypical lesions in this study population of TM. One other large series of gender-affirming mastectomies identified an unexpected invasive carcinoma in a 31-year-old TM (1 of 344 patients in that study),[3] and several other studies have identified DCIS in gender-affirming mastectomy specimens.[9,11,15] While we did not identify any cases of DCIS or invasive carcinoma in our study, other studies and case series show that both gross and microscopic examination of gender-affirming mastectomy specimens is required to identify these infrequent cases of breast carcinoma.[23,31] Given the 1.1% incidence of atypia among the TM in this study without correlation to a clinical history that would suggest increased risk of malignancy, routine histologic slide review in this patient population should be continued on all cases, with conservative sampling.

While routine histologic review in these cases should be continued, the utility of preoperative imaging was not appreciated in this study. There are currently no official recommendations for preoperative screening breast imaging in TM.[2,23,25,32,33] Most of the TM in this study underwent breast imaging prior to surgery despite the younger age of the cohort, and most had benign imaging findings. Of the five cases of abnormal imaging that instigated biopsy evaluation, all five biopsy specimens revealed fibroadenomas. Routine breast imaging for the purposes of cancer screening is not recommended in young participants, as their dense breast tissue decreases the sensitivity and specificity of this screening method, potentially resulting in false-positive imaging results.[34] In addition, abnormal breast imaging findings in younger patients are more likely to be the result of benign lesions such as fibroadenomas than in postmenopausal women.[35] Had the participants in this study not undergone preoperative imaging, these five cases of fibroadenoma would likely have gone unrecognized, eliminating the need for preoperative breast core biopsy and saving the patient psychological and physical stress, radiation exposure, and money. Moreover, mammography alone can be stressful for TM, as the test is not consistent with their gender identity. Given the low incidence of atypia among TM and the additional stress and less predictive breast imaging in these younger patients, routine preoperative imaging for all TM may not be necessary. It is currently done at the discretion of the clinical team and was done in 83% of TM in our study, despite their mean age being 23 years. Assessment of the utility of preoperative imaging among TM should be determined on an individual basis with patient-specific risk factors in mind, such as age and family history. Current guidelines for screening mammography of TM are to follow the same guidelines as for cisgender women, regardless of whether or not the TM is taking AT.[25]

In conclusion, this study was the largest study to date to describe the histopathologic findings in breast specimens from TM with a direct comparison to a cisgender control group. TM, particularly those on AT, were found to have increased fibrous tissue on gross examination, increased lobular atrophy, and decreased density of lobules compared with cisgender breast reduction controls. In addition, the decrease in the density of lobules was correlated to the length of AT among the TM. Although consistent with previous assessments of the effects of AT in TM breast tissue, there are still limited data in relation to this patient population, and more studies are needed to confidently characterize the changes in breast tissue from the effects of AT. It is important for pathologists to recognize changes associated with AT use to ensure accurate diagnosis. In addition, pathologists need to acknowledge the possibility of incidental atypia and even carcinoma in these cases. For evaluation of gender-affirming mastectomy specimens, we recommend a careful gross examination, with limited tissue sampling in the absence of gross abnormalities, known image-detected lesions or breast cancer risk factors, and expanded tissue sampling as indicated on a case-by-case basis. Recent trends suggest that cases of gender-affirming mastectomy will continue to increase, and further study is required to establish guidelines for preoperative evaluation (including imaging) of TM and for postoperative physical examination and/or imaging for TM with atypia or carcinoma identified in their mastectomy specimens.

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