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Testosterone therapy and breast histopathological features in transgender individuals

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Abstract

Testosterone therapy (TT) is administered to enhance masculinization in transgender individuals. The long term effect of exogenous testosterone on breast tissues remains unclear. Our study evaluated the modulation of breast morphology by TT in transgender individuals with special attention to duration of TT. We reviewed 447 breast surgical specimens from gender affirming chest-contouring surgery, and compared histopathological findings including degree of lobular atrophy, and atypical and non-atypical proliferations between subjects who did (n=367) and did not (n=79) receive TT. TT for one patient was unknown. TT for >12 months was associated with seven histopathological features. Longer duration of TT was significantly associated with higher degrees of lobular atrophy (p<0.001). This relationship remained significant after accounting for age at surgery, ethnicity, body mass index, and pre-surgical oophorectomy (adjusted p<0.001). Four types of lesions were more likely to be absent in breast tissues exposed to longer durations of TT: cysts (median=16.2 months; p<0.01; adjusted p=0.01), fibroadenoma (median=14.8 months; p=0.02; adjusted p=0.07), pseudoangiomatous stromal hyperplasia (median=17.0 months;

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$p<0.001$; adjusted $p<0.001$), and papillomas (median=14.7 months; $p=0.04$; adjusted $p=0.20$). Columnar cell change and mild inflammation were also less likely to occur in subjects receiving TT ($p<0.05$), but were not linked to the duration of TT. Atypia and ductal carcinoma *in situ* (DCIS) were detected in 11 subjects (2.5%) all of whom received TT ranging from 10.1 to 64.1 months. The incidental findings of high-risk lesions and carcinoma as well as the risk of cancer in residual breast tissue after chest-contouring surgery warrant the consideration of culturally sensitive routine breast cancer screening protocols for transgender men and masculine-centered gender non-conforming individuals. Long-term follow-up studies and molecular investigations are needed to understand the breast cancer risk of transgender individuals who receive TT.

Keywords

Gender dysphoria; gender affirming hormone therapy; chest-contouring surgery; transmen; gender non-conforming individuals; breast morphology

Introduction

Transgender men (TM; female-to-male) and masculine-centered gender non-conforming individuals (GNCIs; natal females) pursue testosterone therapy (TT) for gender affirmation (1,2). They may also undergo gender affirming surgeries such as chest-contouring, hysterectomy, and/or oophorectomy to treat their gender dysphoria. TT is not a prerequisite for gender affirming surgeries. Transgender individuals can start TT as early as 16 years old. TT is generally pursued continuously to maintain the desired masculinization effects (1). The amount of exogenous testosterone prescribed to transgender individuals is significantly higher than that typically prescribed to cisgender women for hypoactive sexual desire disorder (3). High doses are needed to achieve testosterone levels comparable to cisgender men whose physiological testosterone range is 10-fold higher than cisgender women (2). While TT is generally considered safe with regard to the impact on cardiovascular and cancer risk in the short- and mid-term, the long-term health effects remain unclear (4). In particular, the impact of TT on hormone sensitive tissues such as the breast is poorly understood.

Ten histopathological studies of breast tissue have been conducted in TM and GNCIs (5–14), including one from our group (6). Those studies were mainly descriptive and generally reported higher degrees of lobular atrophy and increased presence of gynecomastoid change and fibrous proliferation in TM (5–8,10,11). Some of these studies also addressed the evaluation of pathologic specimens from transgender-related surgeries (6,13,14). However, some of those previous studies did not compare their findings to a control group (8,11,14); included subjects not receiving TT in their analyses (6,13,14), or did not account for the duration of TT in their analyses (8,9,12–14). As such, the impact of exogenous testosterone in the breast may not be reflected in those reports of investigation.

The aim of this study was to evaluate if and how long it took for TT to modulate breast morphology in TM and GNCIs. To address this issue, we established a Transgender and Testosterone Therapy use (“Triple T”) research cohort at Beth Israel Deaconess Medical Center (BIDMC) (15). We reviewed 447 breast surgical specimens from gender affirming

chest-contouring surgeries performed between 2013 and 2019, and compared histopathological findings between TM and GNCIs who did and did not receive TT.

Materials and Methods

Study subjects

This retrospective study consists of 447 transgender individuals with available clinical information and breast surgical specimens. These subjects underwent chest-contouring surgery at Beth Israel Deaconess Medical Center (BIDMC) between 2013 and 2019. They were identified using case lists from two surgeons who perform the majority of these surgeries at BIDMC (AMT and RAB). Subject information from their pre-surgical consult questionnaires and referral letters were retrieved from electronic medical records (accessed between February 2019 and May 2020): age and year of surgery, ethnicity, self-identified gender, family history of breast and ovarian cancers, pre-surgical body mass index (BMI), how long the subject had been receiving TT at time of pre-surgical consult, route of TT administration, TT dosage, and whether the subject had pre- or post-surgical hysterectomy and/or oophorectomy (15). Duration of TT received in this study accounts for the additional time between pre-surgical consult and date of surgery, reflecting the total length of time the subject's breast tissue was exposed to testosterone. This study was approved by the Beth Israel Deaconess Medical Center (BIDMC) Committee for Clinical Investigations.

Histopathological review

Our protocol for chest-contouring specimens was to obtain one section of parenchyma from the fibrous areas per quadrant (i.e., two tissue sections/block; submitted as two blocks from each breast). Additional sections were submitted if the nipple or skin was present, and if a gross lesion or atypia was identified on the initial histologic sections. All hematoxylin and eosin (H&E) stained slides for each case were reviewed for a variety of histopathological features, as previously reported(6). Lobular atrophy was defined as an overall reduction in the number and size of the acini in each lobule. Qualitative assessment of lobular atrophy was classified as minimal (0–25%), mild (26–50%), moderate (51–75%), and marked (>75%). The stromal composition was categorized as predominantly fibrous, predominantly fatty, or mixed. Ectatic ducts were described as absent, scattered, or abundant. In addition to atypical lesions, the following features were assessed as present or absent: gynecomastoid change, cysts, apocrine metaplasia, apocrine cysts, fibroadenomatous change, fibroadenoma, usual ductal hyperplasia, pseudoangiomatous stromal hyperplasia, benign vascular lesions, secretory change, columnar cell change, papillomas, sclerosing adenosis, and calcifications. Most of the inflammation observed were mild, thus inflammation was categorized as present (mild) or absent. Atypical lesions assessed include flat epithelial atypia, atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), lobular carcinoma *in situ* (LCIS), and ductal carcinoma *in situ* (DCIS).

Statistical analysis

To evaluate whether receiving TT was associated with a histological feature, subjects were grouped into those who were receiving TT and those who did not and Fisher's or Chi-squared test was used. To determine whether the duration of TT rather than simply receiving

TT is associated with a feature, subjects not receiving TT were assigned as zero months and crude analysis was performed using Mann-Whitney or Kruskal-Wallis test. If the crude analysis was significant, multivariable logistic regression analyses were subsequently conducted adjusting for age at surgery, ethnicity, body mass index, and whether the subject had pre-surgical oophorectomy (i.e., to account for endogenous estrogen from intact ovaries). Flat epithelial atypia, ALH, DCIS, and sclerosing adenosis were present in less than four subjects and were excluded from statistical analyses. All analyses were conducted using R version 3.4.0. $p<0.05$ was considered statistically significant.

Results

Subject characteristics

Characteristics of the study population are shown in Table 1. The majority of our subjects were young, white, non-Hispanic who identified as TM. Among 447 subjects, 367 received TT and 79 did not receive TT prior to chest-contouring surgery; TT status was unknown in one patient who was subsequently excluded from subsequent analyses. Of the 367 patients who received TT, the duration of TT for 43 patients was unknown. In subjects who received TT, the most frequent route of administration was intramuscular testosterone enanthate/cypionate (314/367; 85.6%), followed by transdermal gel, patch, or cream (29/367; 7.9%), and subcutaneous pellet (5/367; 1.4%). Route of administration for 19 subjects was unknown (5.2%). Of the 29 subjects (6.5%) who had genital surgery prior to chest-contouring surgery, seven were hysterectomies, one was a bilateral oophorectomy, and the rest were total hysterectomy and bilateral salpingo-oopherectomy. One hundred and eighteen subjects (118/447; 26.4%) and 36 subjects (36/447; 8.1%) have a family history of breast or ovarian cancer, respectively.

Breast histopathological review

Table 2 presents the histopathological findings in 446 subjects. Supplementary Table 1 further stratifies the findings by duration of TT. Most subjects who received TT for a minimum of 12 months displayed moderate lobular atrophy ($p<0.001$). While patients who received TT for 12 to 24 months had predominantly fibrous stroma and patients who did not receive TT had mixed fibrous and fatty stroma, this did not reach statistical significance ($p=0.06$). Subjects who received TT for at least 12 months were less likely to have cysts ($p<0.001$), fibroadenoma ($p=0.03$), pseudoangiomatous stromal hyperplasia ($p<0.001$), columnar cell change ($p<0.01$), papillomas ($p=0.02$), and mild inflammation ($p=0.02$) compared to subjects who did not receive TT.

Atypical lesions (ADH, ALH, and DCIS) were detected in 11/446 patients (2.5%), all of whom received TT (Table 3; Figure 1). The seven subjects with ADH had been receiving TT between 10.1 and 34.9 months, and three of them had a known family history of breast and/or ovarian cancer. In the two subjects who had ALH, one subject had been receiving TT for 12.1 months; the duration of TT is unknown for the other ALH case. Both ALH cases had no family history of breast or ovarian cancer. One subject with both ADH and ALH received TT for 64.1 months and had a family history of breast cancer. Lastly, one case of

DCIS was identified in a subject who had been receiving TT for 61.4 months and had a strong family history of breast cancer (16). No subject had flat epithelial atypia in this study.

Associations between duration of TT and histopathological features

Longer duration of TT was significantly associated with higher degrees of lobular atrophy ($p<0.001$). The median number of months in each lobular atrophy category was 8.5 for minimal, 14.1 for mild, 16.0 for moderate, and 23.0 for marked (Figure 2E). The categories of lobular atrophy were re-classified into two groups (minimal/mild and moderate/marked) for multivariable logistic regression analyses. The relationship between duration of TT and lobular atrophy remained significant after accounting for age at surgery, ethnicity, body mass index, and pre-surgical oophorectomy (adjusted $p<0.001$; Supplementary Table 2).

Cysts were detected in the breast tissue of subjects who received TT for a median 12.2 months compared to 16.2 months in subjects whose tissue did not have cysts ($p<0.01$ and adjusted $p=0.01$; Figure 3A). The median length of TT was 2.8 months in cases with fibroadenoma compared with 14.8 months in cases without fibroadenoma ($p=0.02$ and adjusted $p=0.07$; Figure 3C). Cases with pseudoangiomatous stromal hyperplasia received TT for a median of 10.0 months compared to 17.0 months in cases without pseudoangiomatous stromal hyperplasia ($p<0.001$ and adjusted $p<0.001$; Figure 3E). Lastly, cases with papilloma received TT for a median of 3.3 months compared to 14.7 months in cases without papilloma ($p=0.04$ and adjusted $p=0.20$; Figure 3G). Results were unaltered in sensitivity analyses where 22 subjects who had pre-surgical oophorectomy were excluded (Supplementary Table 2). There was no relationship between the duration of TT with columnar cell change ($p=0.06$) or mild inflammation ($p=0.12$; Supplementary Table 2).

Discussion

We conducted a comprehensive breast histopathological review of 447 TM and masculine-centered GNCI who had chest-contouring surgeries at BIDMC between 2013 and 2019. We evaluated if and how long it took for TT to modulate breast morphology. Our study identified seven features associated with TT. Atypical lesions and DCIS were detected in 11 subjects receiving TT. Thus, the results of this study indicate that TT does not result in clinically significant alterations in breast morphology (i.e., increased frequencies of atypical lesions or carcinoma), even when TT is received for more than 12 months. The finding of incidental atypical lesions and DCIS warrants consideration of culturally sensitive routine breast cancer screening protocols for TM and GNCIs with intact breast tissues and those who had chest-contouring surgery. Chest-contouring surgery, as opposed to oncologic mastectomies, does not remove the entire mammary gland and breast cancer can still occur in residual breast tissue (17–19).

We are cautious about comparing the results of our study to previous work due to differences in study design—types of lesions evaluated, subjects of interest (i.e., including or excluding subjects who did not receive TT), controls (i.e., consisting of transgender individuals(12) or cisgender women(6,7,9,13), or no control group(5,8,14)), and accounting for the duration of TT in data analysis. We elected to use transgender individuals who did not receive TT as

controls rather than cisgender woman as they were more likely to be similar to those who received TT, especially in regards to lifestyle factors such as chest binding.

Kuroda *et al.* (12) did not observe any significant difference in the occurrence of cysts or fibroadenomas among their case and control groups, but their trend for fibroadenomas was similar to our study—i.e., the number of subjects with fibroadenoma was lower in those on androgen therapy (1/56; 1.8%) compared with those not on androgen therapy (9/130; 6.9%; p=0.173). Although some studies did not distinguish between subjects who were or were not receiving TT, they had a similar proportion of subjects with cysts (21.5% to 45.0%) (5,8,9) when compared to our study; and also had very low occurrences of papillomas (0% to 4.3%) (5,7,8), ADH/ALH (0% to 2.4%) (8,13,14), and flat epithelial atypia (0% to 1.5%) (5,14). Pseudoangiomatous stromal hyperplasia in transgender breast tissues was only evaluated by our group (6). The lack of association between TT and columnar cell change or mild inflammation in our study may be due to loss of statistical power after excluding 43 subjects with missing information about the duration of their TT. We observed a null relationship between TT and gynecomastoid changes. Reports of gynecomastoid change in TM and GNCIs are highly variable and conflicting—detected (5), significantly present (6), not significantly present (8), or not evaluated (7,9,12–14). Nevertheless, the main finding of TT associated with lobular atrophy in our study agreed with the majority of previous work (5–11).

The morphological alterations in transgender breast tissue observed in our study are likely the result of the complex interaction between endogenous estrogen and progesterone (from breast, ovarian, and adipose tissues(20)) and high levels of exogenous testosterone exposure for at least 12 months in young, pre-menopausal adults. We hypothesize that genetic makeup influences how TT modulates breast morphology. Some individuals may be conferred protective effects whereby TT leads to lobular atrophy and reduced formation of low risk lesions (i.e., lowering breast cancer risk) (15). Long-term TT in others may lead to the formation of atypical lesions or breast tumorigenesis. There are 26 known breast cancer cases in TM (12,16,26–28,17–19,21–25). TM and GNCIs are thought to be at low risk of breast cancer (18) due to breast tissue removal as part of gender reassignment and/or gender affirming surgeries, and perhaps due to the protective histological changes observed in our study. No study has investigated how TT influences breast cancer risk in at-risk individuals (e.g. germline *BRCA1/2* mutation). Establishing screening protocols for TM and GNCIs will be important because it remains unclear to what extent the breast cancer risk is modified after they receive TT, undergo chest-contouring surgery and have hormonally responsive residual breast tissue, undergo oophorectomy, or any combination of these factors. Studying the molecular underpinnings of how TT modulates pre- and post-menopausal breast biology and cancer risk may ultimately enable us to identify biomarkers for later breast cancer risk of importance to the transgender population that may also be applicable for breast cancer prevention in cisgender women.

The standards for grossing breast specimens from chest-contouring surgeries have not been established and sampling protocols vary by institution. The presence of atypical lesions in our transgender individuals raises the question of whether additional lesions can be identified by evaluating more tissue blocks. Incidental findings of carcinoma and atypical

lesions from cisgender reduction mammoplasty specimens are about 7.0% to 8.7% (13,29) and are higher than transgender chest-contouring surgeries (2.7% reported in this current study and 2.8% by Hernandez *et al.* (13)), even when more tissue blocks were evaluated for the latter (13). As such, Hernandez *et al.*, recommend submitting four tissue blocks per breast for both types of surgery (13). Ambaye *et al.*, reported a correlation between the number of tissue blocks evaluated and the number of incidental findings of carcinoma and atypical lesions only in women older than 40 years old. They also proposed a tiered sampling strategy of reduction mammoplasty specimens based on subject age, medical and family history. In our practice, we follow the same protocol for specimens from reduction mammoplasty as for chest-contouring surgery. For grossly unremarkable specimens, we submit four tissue sections per breast. Based on the ages of our subjects (<40 years old) and the small number of carcinoma and atypical lesions in the current study, our sampling protocol for TM and GNCIs undergoing chest-contouring surgeries is adequate.

In conclusion, TT received for at least 12 months was associated with seven breast histopathological features. The vast majority of our study cohort is young, thus their long-term breast cancer risk remains uncertain. The findings of a small number of incidental high-risk lesions and DCIS coupled with risk of breast cancer in residual tissue after chest-contouring surgery warrant the consideration of routine breast cancer screening for TM and GNCIs. Long-term follow-up studies as well as molecular studies are needed to understand the breast cancer risk of these transgender individuals.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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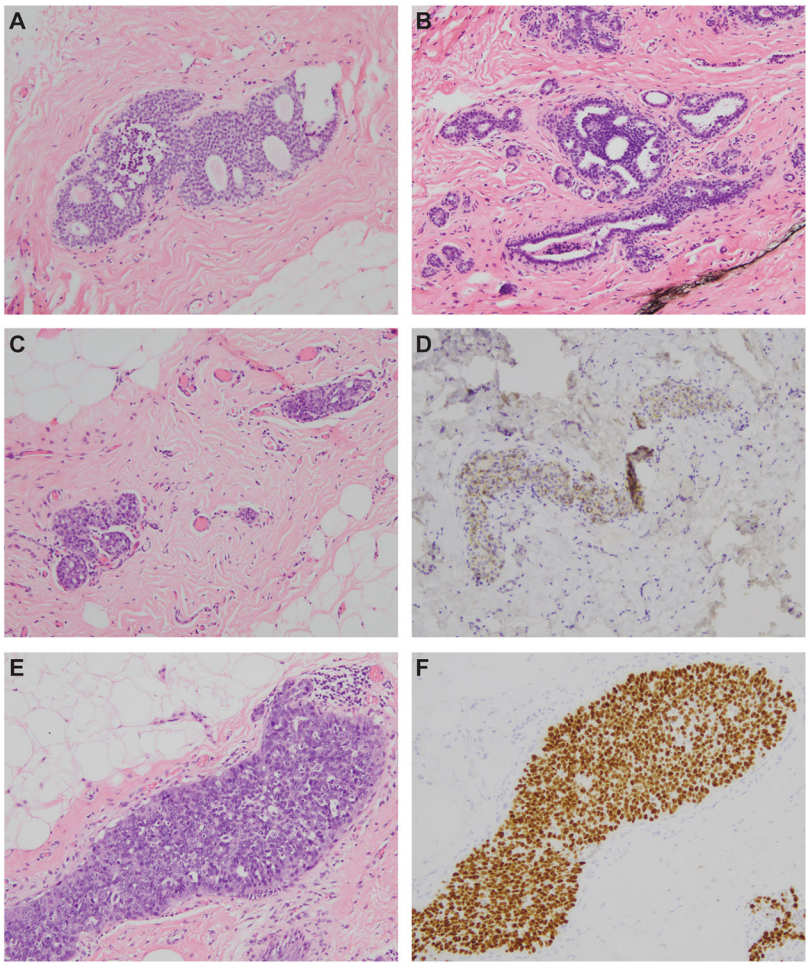

Figure 1.

Example images of atypical lesions in breast tissues of transgender patients who underwent chest-contouring surgeries. **(A, B)** Atypical ductal hyperplasia. **(C)** Atypical lobular hyperplasia with loss of E-cadherin expression **(D)**. **(E)** Ductal carcinoma *in situ* (DCIS) showing positivity for estrogen receptor expression **(F)**. This DCIS case had been previously described in Torous & Schnitt, 2019 and discussed in Eismann *et al.* 2019.

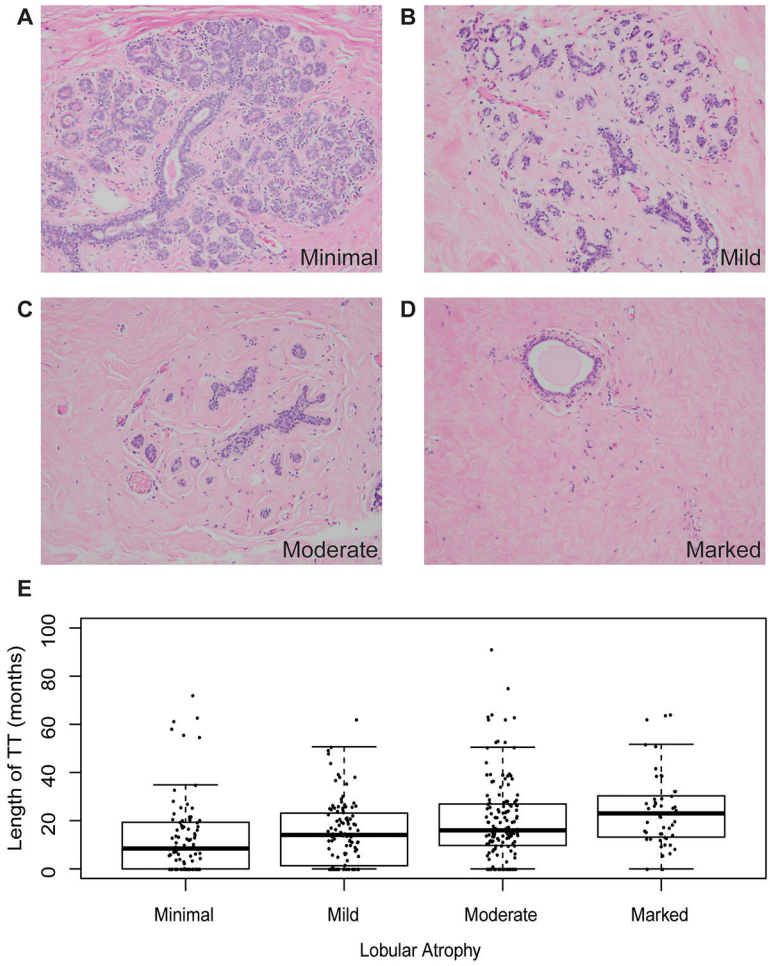

Figure 2.

Panels **A**, **B**, **C** and **D** are representative images of increasing degrees of lobular atrophy from minimal to marked—starting from involution of the epithelium and increase of the fibrous tissue to total disappearance of the terminal duct lobular unit and replacement by fibrous tissue. (**E**) The length of testosterone therapy (TT) is significantly associated with increasing degree of lobular atrophy in transgender individuals (p<0.001, Kruskal-Wallis test).

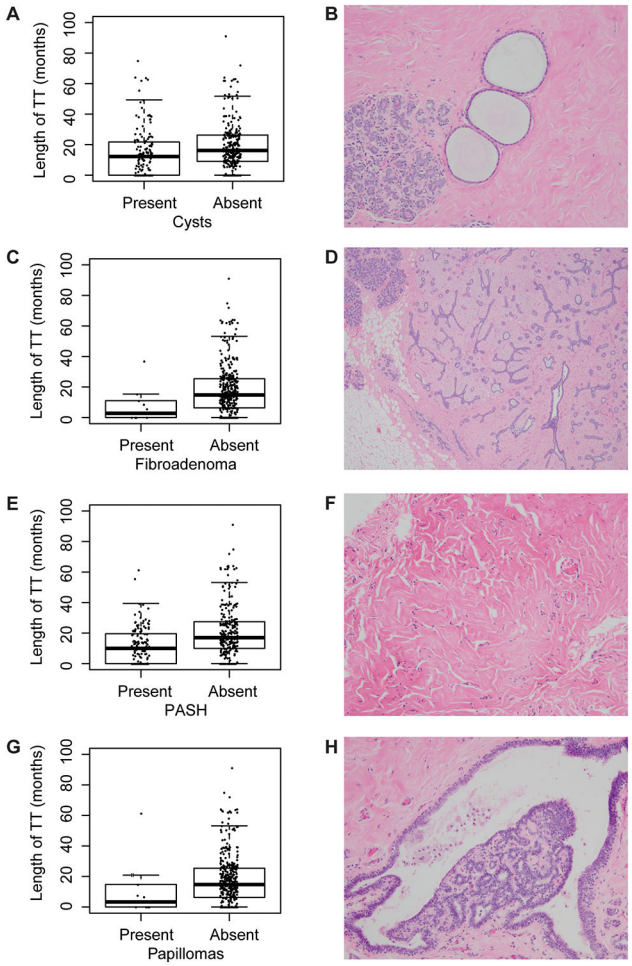

Figure 3.

There were inverse associations between the length of testosterone therapy and the presence of cysts (**A**,**B;** $p<0.01$), fibroadenomas (**C**,**D;** $p=0.02$), pseudoangiomatous stromal hyperplasia (PASH; **E,F;** $p<0.001$), and papillomas (**G**,**H;** $p=0.04$, Mann-Whitney test). The first column displays the boxplots showing the median, 25th and 75th quartile, with whiskers indicating the 5th and 95th percentile. The second column contains representative images of the histopathological feature corresponding to the boxplots in the first column.

Table 1.

Characteristics of study subjects.

	All subjects	Testosterone use	No testosterone use
N (%)	447 (100.0)	367 (82.1)	79 (17.7)
Age at surgery, median [IQR]	25.0 [22.0, 30.0]	25.0 [21.0, 29.0]	27.0 [23.0, 32.0]
Year of surgery, *n* (%)			
2013	1 (0.2)	1 (0.3)	0 (0.0)
2014	7 (1.6)	5 (1.4)	2 (2.5)
2015	40 (8.9)	33 (9.0)	7 (8.9)
2016	75 (16.8)	68 (18.5)	7 (8.9)
2017	105 (23.5)	83 (22.6)	22 (27.8)
2018	112 (25.1)	94 (25.6)	17 (21.5)
2019	107 (23.9)	83 (22.6)	24 (30.4)
Ethnicity, *n* (%)			
White	337 (75.4)	278 (75.7)	58 (73.4)
Black or African American	37 (8.3)	31 (8.4)	6 (7.6)
Asian	18 (4.0)	17 (4.6)	1 (1.3)
Native American/Pacific Islander	3 (0.7)	2 (0.5)	1 (1.3)
Mixed race	8 (1.8)	7 (1.9)	1 (1.3)
Unspecified race or ethnicity	44 (9.8)	32 (8.7)	12 (15.2)
Gender, *n* (%)			
Transgender male	336 (75.2)	313 (85.3)	23 (29.1)
Non-conforming	59 (13.2)	20 (5.4)	39 (49.4)
Not specified	52 (11.6)	34 (9.3)	17 (21.5)
Length of testosterone therapy at time of chest-contouring surgery, *n* (%)			
<1 year	77 (17.2)	77 (21.0)	-
>=1 to <2 years	134 (30.0)	134 (36.5)	-
>=2 to <5 years	95 (21.3)	95 (25.9)	-
>=5 years	18 (4.0)	18 (4.9)	-
Current user, unknown duration	43 (9.6)	43 (11.7)	-
Never used	79 (17.7)	-	79 (100.0)
Unknown	1 (0.2)	-	-
BMI at surgery, median [IQR]	25.8 [23.2, 29.9]	26.0 [23.3, 30.1]	25.1 [22.6, 29.5]
Hysterectomy and/or oophorectomy, *n* (%)			
Yes, before	29 (6.5)	25 (6.8)	4 (5.1)
Yes, after	50 (11.2)	45 (12.3)	5 (6.3)
No	368 (82.3)	297 (80.9)	70 (88.6)
Family history of breast cancer, *n* (%)			
Yes, first degree	9 (2.0)	7 (1.9)	2 (2.5)
Yes, second degree	70 (15.7)	57 (15.5)	13 (16.5)
Yes, unknown degree	39 (8.7)	34 (9.3)	5 (6.3)
No	252 (56.4)	214 (58.3)	38 (48.1)

	All subjects	Testosterone use	No testosterone use
Unknown	77 (17.2)	55 (15.0)	21 (26.6)
Family history of ovarian cancer, *n* (%)			
Yes	36 (8.1)	32 (8.7)	4 (5.1)
No	306 (68.5)	257 (70.0)	49 (62.0)
Unknown	105 (23.5)	78 (21.3)	26 (32.9)

Table 2:

Histopathological features reviewed in this study, stratified by testosterone therapy duration. Statistical analyses were not conducted for features that occurred in less than four subjects (i.e., flat epithelial atypia, atypical lobular hyperplasia, carcinoma *in situ*, and sclerosing adenosis).

		Receiving testosterone *n* (%)	Not receiving testosterone *n* (%)	*p*-value*
n		367	79	
Lobular atrophy				**<0.001**
	Minimal	69 (18.8)	26 (32.9)	
	Mild	97 (26.4)	27 (34.2)	
	Moderate	139 (37.9)	23 (29.1)	
	Marked	62 (16.9)	3 (3.8)	
Stroma				0.06
	Fatty	20 (5.4)	3 (3.8)	
	Fibrous	187 (51.0)	30 (38.0)	
	Mixed	160 (43.6)	46 (58.2)	
Ectatic ducts				0.70
	Absent	37 (10.1)	7 (8.9)	
	Scattered	245 (66.8)	57 (72.2)	
	Abundant	85 (23.2)	15 (19.0)	
Atypical lesions				
Flat epithelial atypia		0 (0.0)	0 (0.0)	-
Atypical ductal hyperplasia		8 (2.2)	0 (0.0)	0.36
Atypical lobular hyperplasia		3 (0.8)	0 (0.0)	-
Ductal carcinoma *in situ*		1 (0.3)	0 (0.0)	-
Benign lesions				
Gynecomastoid change				0.31
	Present	144 (39.2)	26 (32.9)	
	Absent	223 (60.8)	53 (67.1)	
Cysts				**<0.001**
	Present	110 (30.0)	43 (54.4)	
	Absent	257 (70.0)	36 (45.6)	
Apocrine metaplasia				0.71
	Present	46 (12.5)	11 (13.9)	
	Absent	321 (87.5)	68 (86.1)	
Apocrine cysts				0.07
	Present	34 (9.3)	13 (16.5)	
	Absent	333 (90.7)	66 (83.5)	
Fibroadenomatous change				0.66
	Present	86 (23.4)	16 (20.3)	
	Absent	281 (76.6)	63 (79.7)	
Fibroadenoma				**0.03**
	Present	6 (1.6)	5 (6.3)	

	Receiving testosterone *n* (%)	Not receiving testosterone *n* (%)	*p*-value*
Absent	361 (98.4)	74 (93.7)	
Usual ductal hyperplasia			0.25
Present	88 (24.0)	24 (30.4)	
Absent	279 (76.0)	55 (69.6)	
Pseudoangiomatous stromal hyperplasia			**<0.001**
Present	109 (29.7)	47 (59.5)	
Absent	258 (70.3)	32 (40.5)	
Benign vascular lesion			1.00
Present	31 (8.4)	6 (7.6)	
Absent	336 (91.6)	73 (92.4)	
Secretory change			0.55
Present	17 (4.6)	2 (2.5)	
Absent	350 (95.4)	77 (97.5)	
Columnar cell change			**<0.01**
Present	22 (6.0)	13 (16.5)	
Absent	345 (94.0)	66 (83.5)	
Papillomas			**0.02**
Present	5 (1.4)	5 (6.3)	
Absent	362 (98.6)	74 (93.7)	
Sclerosing adenosis			-
Present	1 (0.3)	2 (2.5)	
Absent	366 (99.7)	77 (97.5)	
Calcifications			0.33
Present	40 (10.9)	12 (15.2)	
Absent	327 (89.1)	67 (84.8)	
Mild inflammation			**0.02**
Present	66 (18.0)	24 (30.4)	
Absent	301 (82.0)	55 (69.6)	

* P values for lobular atrophy, stroma, and ectatic ducts were calculated using Chi-squared. P values for atypical or benign lesions were calculated using Fisher's test.

Table 3.

Eleven cases of atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), and ductal carcinoma *in situ* (DCIS) that occurred in subjects who received testosterone therapy (TT).

Lesion type	Length of TT (months)	Route of administration	Age at surgery	Ethnicity	Family history of breast cancer	Family history of ovarian cancer
ADH	16.9	Intramuscular	18	White	Unknown	Unknown
ADH	Unknown but receives TT	Intramuscular	20	White	No	No
ADH	Unknown but receives TT	Intramuscular	25	Unknown	Yes, unknown degree	Unknown
ADH	25.6	Transdermal	26	White	Yes, unknown degree	Yes
ADH	34.9	Transdermal	28	White	No	No
ADH	10.1	Transdermal	29	White	Yes, second degree	Yes
ADH	25.2	Intramuscular	39	White	No	No
ALH	Unknown but receives TT	Intramuscular	29	White	No	No
ALH	12.1	Intramuscular	21	Mixed race	No	No
ADH and ALH	64.1	Intramuscular	25	White	Yes, second degree	No
DCIS	61.4	Intramuscular	29	White	Yes, second degree	No