

Routine histopathological examination after female-to-male gender-confirming mastectomy

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Background: The number of transmen seeking gender-confirming surgery has risen steadily throughout the last decade. Pathologists are increasingly confronted with transmale mastectomy specimens. It is not clear whether routine histopathological examination is useful. This study explored the possible benefit of routine investigation through detailed description of lesions encountered in mastectomy specimens after female-to-male gender-confirming surgery.

Methods: Breast tissue from a cohort of transmen was reviewed. The presence of benign and malignant breast lesions was recorded. The number of terminal duct–lobule units (TDLUs) per ten low-power fields (LPFs) was quantified. Information on hormone therapy and morphometry was retrieved for selected patients.

Results: The cohort included 344 subjects with a mean age of 25.8 (range 16–61) years at the time of surgery; the age at surgery decreased significantly over time. Older individuals presented with a significantly higher number of breast lesions. The number of TDLUs per LPF was lower in heavier breasts, but did not correlate with age. Breast lesions, either benign or malignant, were present in 166 individuals (48.3 per cent). Invasive breast cancer was found in two (0.6 per cent); one tumour was an unexpected finding. The number of breast lesions encountered on histopathological examination increased significantly when more tissue blocks were taken.

Conclusion: The discovery of an unexpected breast cancer in a 31-year-old transman emphasizes the importance of thorough routine histopathological examination of mastectomy specimens. The number of tissue blocks taken should be based on age and breast weight.

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Introduction

Gender dysphoria designates the persistent distress caused by discrepancies between a person's gender identity and physical phenotype¹. Transmen are individuals who have a male gender identity but were assigned to the female sex at birth². Worldwide, about 0.4–1.3 per cent of the population experiences gender dysphoria². Although not all individuals with gender dysphoria wish to undergo (complete) gender-confirming surgery (GCS), the number of individuals seeking such surgery has grown in recent decades^{1,3}. Chest-contouring surgery can be part of the transition and consists of bilateral subcutaneous mastectomy. Mastectomy includes removal of glandular tissue and

any redundant skin, liposuction of the chest and repositioning of the nipple–areola complex^{2,3}. Mental health professionals play a crucial role in ensuring that surgery is the right treatment for a particular individual⁴. In addition to surgery, transmen are often treated with androgens to induce virilization⁵.

Transmale breast tissue is still a rare specimen in surgical pathology, and there are no well defined guidelines regarding its examination⁶. Four studies^{6–9} have mentioned histopathological analysis of transmale breast specimens. Burgess and Shousha⁷ compared 29 transmale mastectomy specimens with mammoplasty specimens from cis (non-trans) women, and did not notice any lasting adverse

effects of long-term androgen administration on breast tissue. Grynberg and colleagues⁸ examined 100 specimens, which often showed lobular atrophy and an increase in fibrous connective tissue, but no malignant or premalignant lesions were noted. Although this study⁸ provided a good qualitative description of the effects of long-term androgen therapy on breast tissue, these changes were not quantified. Quantitative analysis was performed recently in a series of 67 individuals by East and co-workers⁹, who investigated the number of terminal duct–lobule units (TDLUs). In this cohort, fibrocystic and gynaecomastoid changes were observed commonly, and these correlated with a decreased number of TDLUs. The largest cohort to date was reported by Kuroda *et al.*⁶, who investigated 186 transmale mastectomy specimens. In that cohort, one invasive breast cancer was identified, but there was no significant difference in the rate of benign and malignant breast lesions between transmen who had used androgens and those who had not.

As Ghent University Hospital has gradually become a referral centre for patients with gender dysphoria, the number of bilateral mastectomies in transmen has increased there in the last decade. Routine histopathological analysis of transmale mastectomy specimens is questioned. As detailed knowledge of transmale breast histopathology is limited, a thorough histopathological analysis of mastectomy specimens was undertaken in a large cohort of transmen. The aim of this study was to provide a description of common and uncommon breast lesions in transmale breast tissue, and to analyse whether routine histopathological analysis should be recommended.

Methods

Transmen were selected by searching the electronic histopathological reports of the Department of Pathology at Ghent University Hospital between 1 January 2005 and 12 July 2017. The following data were retrieved from histopathological reports: date of birth, age at time of bilateral mastectomy, bilateral breast weight, presence of skin in the specimen, and number of sampled tissue blocks. For a subgroup of patients treated at the hospital's Department of Endocrinology, patient information (height, weight, use of hormone therapy) was retrieved from electronic patient files. All data were coded in an anonymous fashion. The study was approved by the local ethics committee.

Macroscopic examination and processing

All mastectomy specimens were examined carefully. Standard measurement included weighing of freshly received

specimens (*Table S1*, supporting information), after which the resection margins were inked. The breasts were cut into 5-mm slices (*Fig. 1*), and all slices were investigated for abnormalities. All encountered anomalies were biopsied for microscopic analysis. When no macroscopic anomalies were noted, at least two random tissue fragments from each breast were sampled. Random samples included the nipple defect and some fibrous breast tissue. If the breast was entirely fatty, the fat was sampled. Tissue fragments were put into neutral-buffered formalin for fixation over 8–72 h, after which they were processed and embedded in paraffin blocks¹⁰. Finally, 4- μ m tissue sections were cut and stained with haematoxylin and eosin.

Histopathological review

All haematoxylin and eosin-stained slides were retrieved from the archives of the Department of Pathology at Ghent University Hospital and were reviewed systematically by two pathologists using a multihead light microscope. In case of disagreement, a third pathologist was consulted to obtain a consensus diagnosis.

The stroma/fat ratio was assessed macroscopically based on the haematoxylin and eosin-stained slides, and subdivided into four categories: less than 25 per cent fat, 25–49 per cent fat, 50–75 per cent fat, more than 75 per cent fat. The presence of the following breast lesions was noted: apocrine metaplasia, lactational changes, columnar cell changes, sclerosing adenosis, fibroadenomas, usual duct hyperplasia, flat epithelial atypia, atypical duct hyperplasia, ductal carcinoma *in situ* (DCIS), lobular carcinoma *in situ* (LCIS) and invasive carcinoma. Columnar cell changes and columnar cell hyperplasia were classified together as columnar cell lesions because they represent a spectrum and it is hard to define a quantitative threshold between the two¹¹. Apocrine metaplasia was not assessed in the subareolar area as it might easily be confused with apocrine sweat glands.

The number of TDLUs was counted in the left and right breast in ten low-power fields (LPFs) (at 40 \times magnification with a field number of 20). TDLUs were not counted in the proximity of lactiferous ducts, as the subareolar region generally contains only very few TDLUs.

Immunohistochemistry

When an invasive cancer was encountered, one representative formalin-fixed paraffin-embedded tissue block was selected for immunohistochemical analysis of oestrogen receptor (ER), progesterone receptor (PR), HER2/neu and Ki-67 expression. *HER2* amplification status of invasive

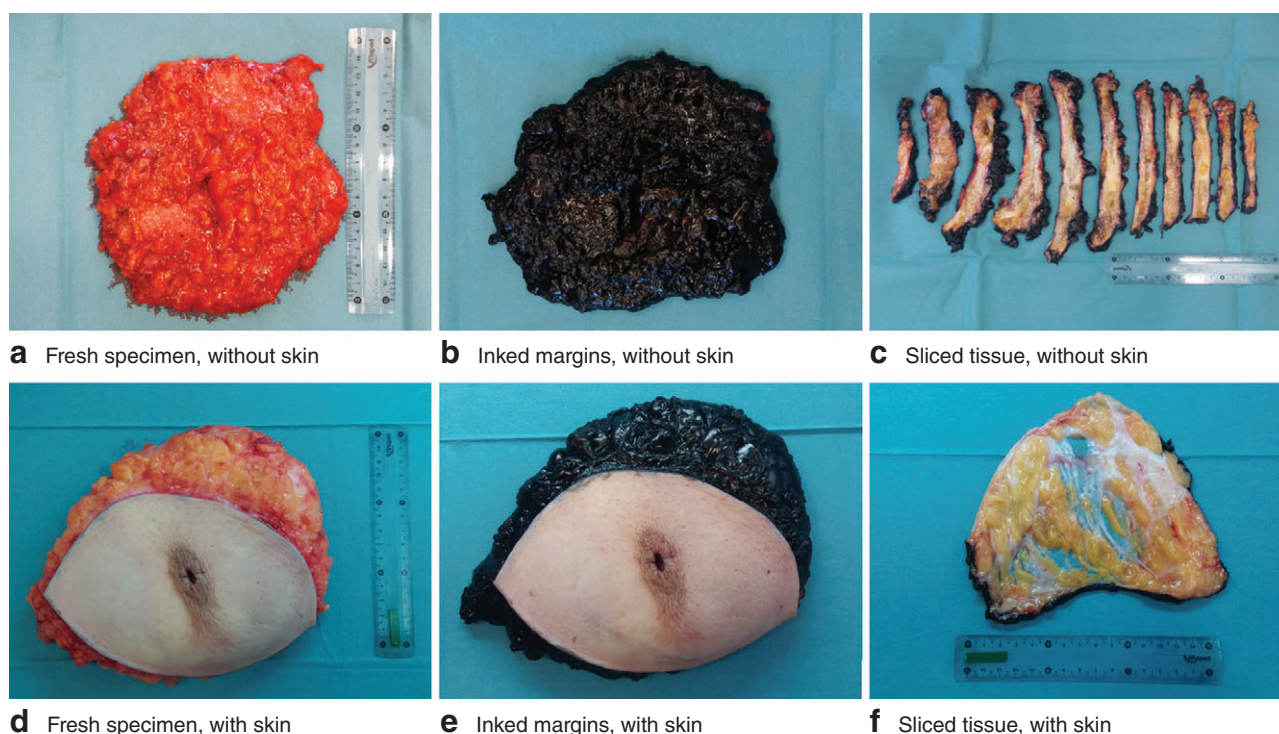


Fig. 1 Macroscopic examination of transmale mastectomy specimens **a–c** without and **d–f** with skin. Fresh specimens are weighed and measured (**a,d**), and resection margins are then inked (**b,e**). After thinly slicing the tissue (**c,f**), all slices are examined. The ruler measures 15 cm

breast tumours was assessed by dual-probe fluorescence *in situ* hybridization (FISH). All analyses were done as described previously^{10,12}.

Statistical analysis

Data were analysed using SPSS® version 24.0 (IBM, Armonk, New York, USA). Correlations between age, bodyweight, mean breast weight, number of tissue blocks, number of breast lesions and number of TDLUs were analysed by determination of the Pearson or Spearman correlation coefficient, as appropriate. Associations between these continuous variables and categorical variables such as composition of the stroma and year of surgery were analysed by Mann–Whitney *U* or Kruskal–Wallis tests. Multiple linear regression was used to assess the effect of multiple variables on the number of breast lesions. All statistical tests were two-sided, and $P < 0.050$ was considered to be statistically significant.

Results

In total, 344 transmen were included who underwent bilateral mastectomy in the Department of Plastic Surgery at

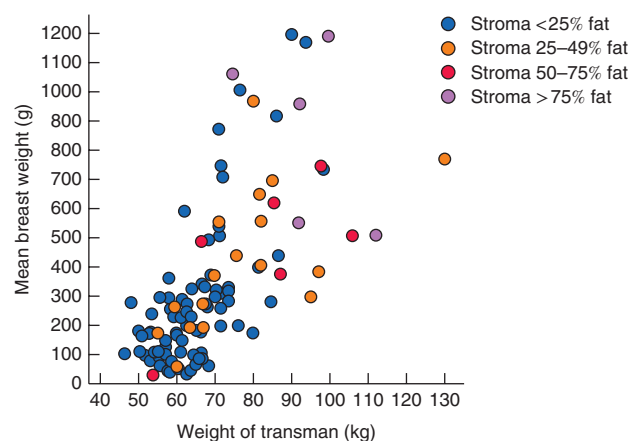


Fig. 2 Scatterplot showing the correlation between the weight of the transman and both mean breast weight and composition of the stroma (both $P < 0.001$, Spearman correlation). The higher the body weight, the heavier the breasts and the greater the amount of fatty tissue

Ghent University Hospital. The number of bilateral mastectomies increased steadily over time, ranging from two surgical interventions in 2005 to 91 in 2016. The mean age of the transmen was 25.8 (range 16–61) years at the time

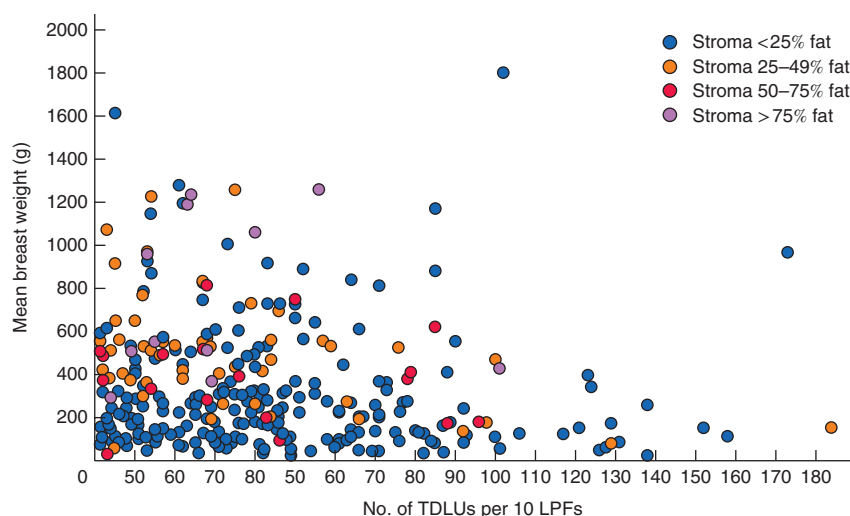


Fig. 3 Scatterplot showing the association between mean breast weight and number of terminal duct-lobule units (TDLUs) per ten low-power fields (LPFs) ($P=0.006$, Spearman correlation). Heavier breasts have fewer TDLUs per ten LPFs. Although most breasts with predominantly fatty composition showed fewer than 50 TDLUs per ten LPFs, there was no significant correlation between the composition of the mammary stroma and the number of TDLUs ($P=0.153$, Kruskal–Wallis test)

of surgery. Age at time of surgery decreased significantly over time, from 39 years in 2007 to 23 years in 2017 ($P<0.001$).

Specimen weight and presence of skin in the specimen were recorded for 336 and 319 patients respectively. Specimens had a mean weight of 345.5 (range 22–1800) g. Higher mean breast weight was significantly associated with older age ($P<0.001$). As the presence of skin in the mastectomy specimen was significantly associated with mean breast weight ($P<0.001$), older patients tended to have redundant skin ($P<0.001$). Specimens without skin had a mean weight of 143 (22–959) g, whereas specimens with skin had a mean weight of 470 (38–1800) g.

When mastectomy specimens were classified according to the composition of the mammary stroma, 11 transmen (3.2 per cent) presented with less than 25 per cent fibrous tissue, 19 (5.5 per cent) had 25–49 per cent, 55 (16.0 per cent) had 50–75 per cent and 259 (75.3 per cent) had more than 75 per cent. The composition of the mammary stroma correlated significantly with mean breast weight ($P<0.001$), as more fibrous tissue was observed in smaller breasts.

Bodyweight and height were noted for 110 patients. Mean BMI at the time of surgery was 25 (range 20–38) kg/m². There was a strong correlation between the weight of the individual and mean breast weight ($P<0.001$), and consequently also with the composition of the mammary stroma ($P<0.001$). As bodyweight increases, the breasts tend to be heavier and to contain more fat (Fig. 2).

Administration of androgens was recorded for 113 patients (32.8 per cent). Ninety-six of these patients (85.0 per cent) were treated with testosterone undecanoate (Nebido®; Bayer Pharma, Berlin, Germany) before surgery, with a mean duration of 10 (range 1–29) months. None of the above variables differed significantly between this subgroup and the remainder of the cohort, nor were there significant differences between the treated and untreated group.

Histopathological findings

A mean of 5 (range 2–17) tissue blocks were submitted per patient. The number of breast lesions found on histopathological analysis correlated significantly with the amount of tissue sampled ($P<0.001$). Multiple regression analysis demonstrated that this association was independent of age and mean breast weight. The mean number of TDLUs per ten LPFs was 40 (range 0–184). The number of TDLUs per ten LPFs correlated significantly with mean breast weight ($P=0.006$), as heavier breasts tended to have fewer TDLUs per ten LPFs (Fig. 3). The number of TDLUs per ten LPFs did not vary by age ($P=0.064$). Thirty-five patients (10.2 per cent) were younger than 18 years, but this subgroup did not have a significantly different number of TDLUs per ten LPFs compared with the remainder of the cohort ($P=0.330$). Androgen therapy did not have a significant effect on the number of TDLUs per ten LPFs ($P=0.601$).

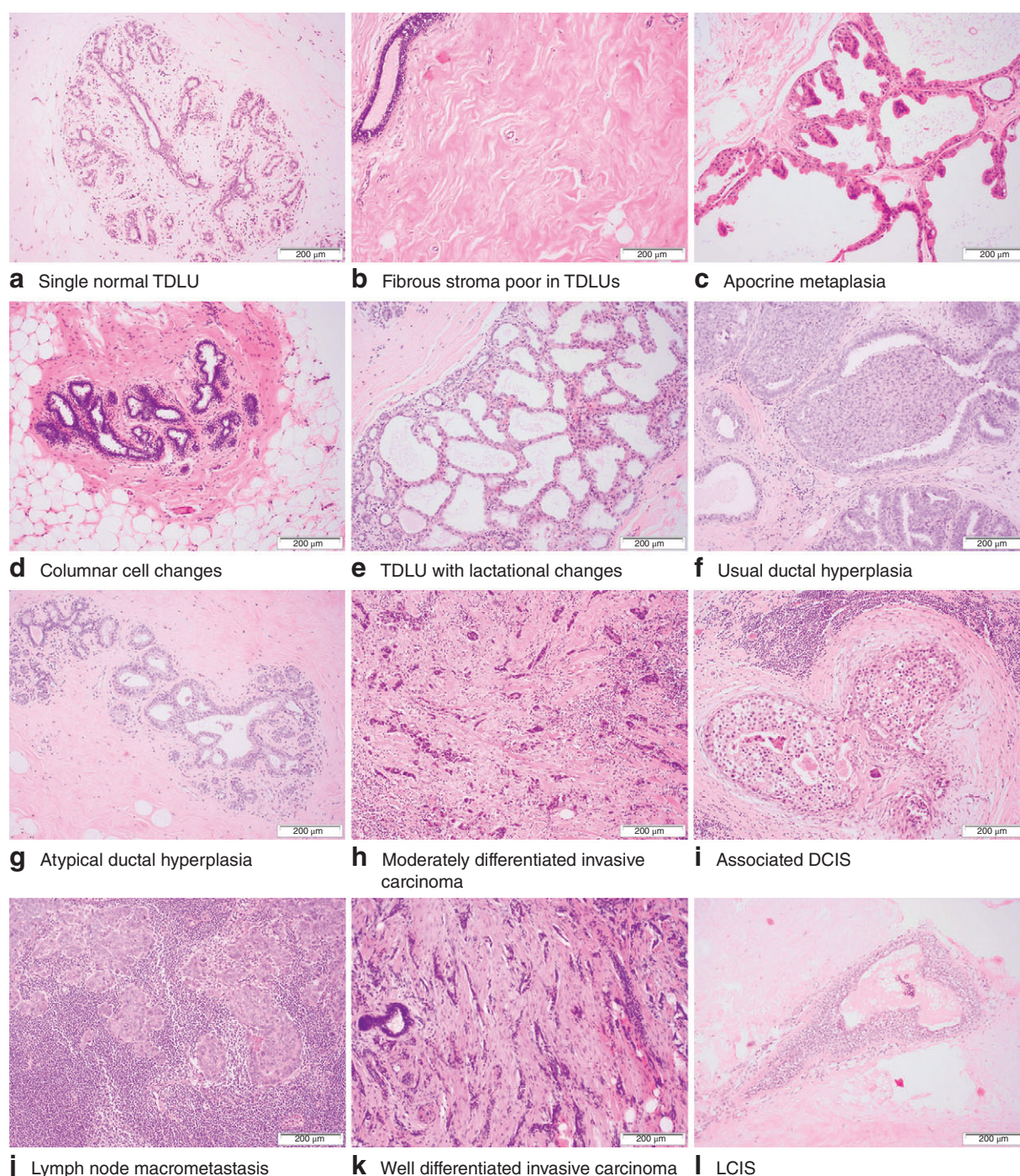


Fig. 4 Photomicrographs illustrating the spectrum of common and less common benign and malignant lesions in transmale breast tissue (haematoxylin and eosin stain, original magnification 100×): **a** a single normal terminal duct–lobule unit (TDLU); **b** extensive fibrous mammary stroma poor in TDLUs; **c** apocrine metaplasia; **d** columnar cell changes; **e** a TDLU with lactational changes; **f** usual ductal hyperplasia; **g** atypical ductal hyperplasia. A 31-year-old transman presented with **h** a moderately differentiated invasive carcinoma of no special type with **i** associated ductal carcinoma *in situ* (DCIS) and **j** one lymph node macrometastasis. A 52-year-old transman presented with **k** a well differentiated invasive carcinoma of no special type and **l** lobular carcinoma *in situ* (LCIS) in the ipsilateral and contralateral breast

Histopathological findings were present in 166 transmen (48.3 per cent). Columnar cell lesions and apocrine metaplasia were noted in 102 (29.7 per cent) and 83 (24.1 per cent) respectively. Fifty-seven transmen (16.6 per cent) had usual duct hyperplasia (*Fig. 4*); 13 (3.8 per cent) had lactational changes, and fibroadenoma and sclerosing adenosis were observed in 13 (3.8 per cent) and 11 (3.2 per cent) transmen respectively. One transman (0.3 per cent) had a cavernous haemangioma. Five (1.5 per cent) had atypical ductal hyperplasia. LCIS, DCIS and invasive breast cancer were detected in two transmen (0.6 per cent). Flat epithelial atypia was not observed.

The number of breast lesions correlated with patient age at surgery ($P < 0.001$). One hundred and seventy-eight patients with no significant histopathological findings had a mean age of 23 (range 16–46) years, whereas 166 patients with one or more breast lesions, either benign or malignant, had a mean age of 29 (16–61) years. As patients become older, the number of breast lesions increases. As recently treated patients tended to be younger and the number of breast lesions significantly correlated with age at surgery, the number of breast lesions declined gradually throughout the last decade ($P = 0.002$).

Transmen with invasive breast cancer

Two transmen had invasive cancer (*Fig. 4*). A 31-year-old individual had an unexpected moderately differentiated invasive carcinoma of no special type, which was found on macroscopic examination of the specimen. The tumour was located centrally in the right breast and measured 4 mm. This tumour was hormone receptor-positive, HER2-negative and surrounded by DCIS. The left breast had apocrine metaplasia, without *in situ* or invasive carcinoma. Subsequent axillary dissection showed one lymph node macrometastasis. This nulliparous transman had no significant medical history and no family history of breast and/or ovarian cancer. Genetic counselling was performed in another medical centre. Adjuvant therapy included chemotherapy, radiotherapy and an aromatase inhibitor. This individual had been treated with androgens for 16 months before surgery.

Screening mammography revealed a lesion in the left breast of a 52-year-old transman in the transitioning phase. Histopathological examination showed a well differentiated invasive carcinoma of no special type. The tumour was located in the superior external quadrant of the left breast and measured 12 mm. This tumour was hormone receptor-positive and HER2-negative, and was surrounded by DCIS and LCIS. The right breast had only a small focus

of LCIS. As this tumour was discovered before mastectomy, a sentinel node procedure was performed, which showed no lymph node metastasis. This individual had a family history of breast and endometrial cancer. Genetic counselling showed no germline mutations in *BRCA1*, *BRCA2*, *PALB2* or *TP53* genes. This transman had not been treated with androgens before surgery; he was treated with adjuvant tamoxifen.

Discussion

With the increasing number of transmen seeking GCS, bilateral mastectomy specimens will be encountered more often by surgical pathologists. Despite this, information about histopathological anomalies in transmale breast tissue is limited.

The number of transmen asking for bilateral mastectomy rose steadily throughout the last decade, and their age decreased. This had a significant impact on the number of breast lesions found on histopathological analysis; the number of breast lesions diagnosed per patient diminished gradually. However, the mean breast weight and the number of TDLUs per ten LPFs did not vary by the year in which surgery was performed.

The number of breast lesions detected increased significantly when more breast tissue was sampled, and this association remained statistically significant when both transmen with invasive breast cancer were excluded from the analysis. Knowing about the presence of benign breast lesions neither harms nor benefits an individual. However, premalignant lesions such as DCIS or LCIS often do not present with any macroscopically discernible abnormalities and will be found only by sampling the breast tissue thoroughly. The identification of DCIS or LCIS, especially at a younger age, might not only indicate a higher individual risk for subsequent breast cancer, but may also identify an increased (perhaps unknown) familial risk of breast cancer. As for the individual, it is important to note that not all mammary glandular tissue is removed after bilateral mastectomy¹³. Microscopic foci of glandular tissue can extend deep into the axilla and may spread through the pectoral fascia. Consequently, the subsequent risk of breast cancer is never zero¹⁴. Several transmen have developed breast cancer several years after surgery^{15–17}. Knowledge about (pre)malignant breast lesions could encourage both individuals and their doctors to have more careful follow-up. As the number of breast lesions (either benign or malignant) increases with age and breast weight, the number of tissue blocks taken should depend on individual age and breast weight (*Table S1*, supporting information).

In this cohort, breast imaging was not performed routinely before surgery. In Belgium, biannual mammography is standard breast cancer screening for women aged 50–69 years¹⁸, and transmen in this age group often participate in the screening programme. Screening mammography identified one invasive cancer in a 52-year-old transman. Mammography is less sensitive for screening in people younger than 40 years, as they tend to have denser breasts¹⁹. As any significant breast lesion will be noted during histopathological investigation, preoperative breast imaging is probably unnecessary, but evidence on this topic is limited. A study of reduction mammoplasty specimens showed that sensitivity of preoperative imaging for cancer detection was only 20 per cent when compared with histopathology²⁰.

The value of routine histopathological examination has been illustrated in this cohort, by the finding of an unexpected breast cancer in a 31-year-old transman. The incidence was 0.3 per cent in this cohort, similar to the rate of 0.5 per cent reported in Japan⁶. The unexpected cancer here had a maximum diameter of only 4 mm, which highlights the importance of careful macroscopic examination by thinly slicing the breast tissue.

The effect of androgens on breast tissue was studied in a subgroup of 113 transmen, of whom only 17 were not treated before surgery. Androgen therapy did not have a significant effect on the number of TDLUs, breast weight or the number of breast lesions.

Determining the risk of breast cancer in transmen is challenging because of its multifactorial character. The risk depends upon their age, family history, personal lifestyle, environmental factors, length of exposure to androgens, and whether they have undergone mastectomy¹³. Irwig^{13,21} has stated that transmen have lower age-specific breast cancer rates compared with cis women. This reduction can be attributed partly to the removal of breast tissue. However, androgens may also be responsible, because they are suspected to alter breast composition^{13,21}. Androgens reduce the amount of glandular tissue and increase the amount of fibrous connective tissue⁸. Evidence for these assumptions is sparse, as reports on thorough histopathological analyses of transmale mastectomy specimens are limited. There is no evidence on long-term testosterone treatment in transmen with a genetic predisposition for breast cancer. Colebunders and colleagues²² reported the first transwoman with a known *BRCA1* mutation and discussed the accompanying therapeutic dilemma. This case stresses the importance of routine enquiry about oncological family history. Screening for *BRCA* mutations in transmen should follow the guidelines as for cis individuals²².

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S.M.J.V.R. and J.V.D. contributed equally to this publication.

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Supporting information

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