Incidental Pathologic Findings in Young Adult Reduction Mammaplasty

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Background: This study aims to characterize incidental microscopic findings in this population to determine whether there is a benefit to routine histopathologic examination of breast tissue in young women.
Methods: A retrospective review of young women who underwent reduction mammaplasty between June of 2010 and May of 2018 was performed at a single institution to identify demographics, age at the time of surgery, breast cancer risk factors, and pathologic data. Histologic reevaluation was performed when diagnostic clarification was needed. Descriptive, univariate, and multivariable statistical analyses were performed.
Results: A total of 798 young women were included. At the time of surgery, the mean patient age was 17.5 ± 2.0 years, the mean body mass index was 28.7 ± 5.7 kg/m^2, and the mean resection weight was 685 ± 339 g/breast. The majority of patients were reported to have pathologically normal tissue [*n* = 704 (88.2 percent)]. Of the 94 patients (11.8 percent) with abnormal findings, 21 (2.6 percent) had benign nonproliferative changes, 64 (8.0 percent) had proliferative lesions without atypia, nine (1.1 percent) had proliferative lesions with atypia, and a single patient (0.1 percent) had a borderline phyllodes tumor. Univariate and multivariate analyses revealed that age at menarche younger than 12 years was significantly associated with increased incidence of proliferative lesions.
Conclusions: Over 10 percent of young women with reduction mammaplasty have histopathologic findings. Although this study demonstrated an overall low incidence of atypical lesions, because early identification offers potential for improved surveillance, the authors continue to advocate for routine pathologic evaluation, particularly for women with early menarche. (*Plast. Reconstr. Surg.* 147: 391e, 2021.)
CLINICAL QUESTION/LEVEL OF EVIDENCE: Risk, III.

Reduction mammaplasty is a safe and effective intervention to manage symptomatic macromastia in women of all ages. According to the American Society for Aesthetic Plastic Surgery, 71,422 women underwent breast reduction in 2017.[1] Of those women, 1675 were aged 18 years or younger. Similar to older adults, adolescents and young women (defined by the World Health Organization as 10 to 19 years old and 10 to 24 years old, respectively)[2] who undergo breast reduction seek relief from physical[3] and psychosocial consequences of breast hypertrophy.[4,5] It has been well demonstrated that surgical intervention for adult macromastia offers improvement of physical symptoms, psychosocial measures, and quality of life,[4,6,7] and evaluation of adolescent and young adult patients has demonstrated similar improvements.[8,9] Furthermore, it is possible that surgical intervention in younger patients may prevent the negative effects of macromastia on psychosocial development, self-esteem, and physical health from compounding throughout development.

In adult women, gross and microscopic examination of breast reduction specimens is commonly performed because of the potential to find

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malignant lesions or atypical proliferative lesions indicative of increased future cancer risk. Many pediatric plastic surgeons opt for the same routine evaluation that is performed on adult specimens. However, the known correlation of more advanced age with cancerous and precancerous disease[10] in conjunction with the low reported incidence of malignant and premalignant disease reported in small-scale studies of young women[11] has led some to argue against histologic examination for patients younger than 25 years. At the present time, we have limited insight into the incidence, significance, or appropriate management of breast disease in this population. This study aims to characterize incidental pathologic findings of young women undergoing reduction mammaplasty and to guide management of young patients with atypical lesions through review of the best available literature.

PATIENTS AND METHODS

Patients who underwent unilateral or bilateral reduction mammaplasty at a single institution between June of 2010 and May of 2018 were reviewed retrospectively. Patients were identified by querying CPT code 19318 (reduction mammaplasty) using Epic software (Epic Systems Corp., Verona, Wis.). Inclusion criteria were as follows: female sex, unilateral or bilateral reduction mammaplasty, and age 24 years or younger at the time of surgery. Patients for whom the primary surgical indication was a concerning breast mass were excluded. Demographics, relevant history (potential risk factors for breast cancer), specimen weight, and pathologic reports were extracted from the electronic medical record. Patient demographics included age at the time of operation and race. Risk factors included environmental and medication exposures (i.e., hormonal contraceptive use in the perioperative period, cigarette smoking, alcohol consumption), body mass index, age at menarche, family or personal history of breast cancer or *BRCA* mutation, gynecologic history, endocrine history and cancer history, and established genetic diagnoses (Table 1).

Histologic findings and specimen weights were obtained from the pathology report and reviewed by a pathologist. In some cases with documented pathologic findings, either the described findings were unclear or used dated terminology. The slides for these cases were rereviewed by the pathologist (K.D.) to either confirm the report as stated or provide diagnostic clarification using currently accepted terminology (44 cases total).

Table 1. Demographic and Clinical Characteristics

Characteristic	Value
No.	798
Mean age ± SD, yr	17.5 ± 2.0
Mean BMI ± SD, kg/m^2	28.7 ± 5.7
BMI category, %	
Underweight	0.1
Normal weight	30.6
Overweight	33.8
Obese	35.6
Race, %*	
White	51.9
Black/African descent	11.3
Asian	0.6
Native American or Pacific Islander	0.3
Other†	13.5
Unknown	22.4
Indication for surgery, %	
Macromastia	94.9
Juvenile breast hypertrophy	0.3
Congenital asymmetry	4.9
Personal history of potential risk factors, %	
BRCA mutation	0.1
Known breast mass	0.6
Alcohol use	16.0
Smoking	3.9
Hormonal contraceptive use	33.9
Progestin-only birth control	6.3
Estrogen plus progestin birth control	22.3
Unknown type of birth control pill	4.9
Previous cancer (other than breast)	0.4
Precocious puberty	0.6
Family history, %	
First-degree relative with breast cancer	2.5
Second-degree or greater relative with breast cancer	20.7
Relative with *BRCA* mutation	0.6
Procedure performed, %	
Bilateral reduction mammaplasty	95.4
Unilateral reduction mammaplasty	2.5
Unilateral reduction with contralateral mastopexy	1.4
Unilateral reduction with contralateral augmentation	0.8
Mean resection weight ± SD, g	685 ± 339

*Race was stratified by U.S. Census bureau definitions as black, white, Asian, American Indian or Pacific Islander, or other. In some cases, race was not reported and recorded as unknown.
†Of those who reported "other" race, 62.0 percent identified as Hispanic, Brazilian, or Dominican ethnicity.

The findings were categorized by their relative risk of malignancy: no increase in risk (i.e., nonproliferative changes), minor increase in risk (i.e., proliferative lesions without atypia), or moderate increase in risk (i.e., proliferative lesions with atypia)[12,13] (Table 2).

Data were tabulated in an Excel spreadsheet (Microsoft Corp., Redmond, Wash.) and descriptive statistical analysis (mean, standard deviation, and range) was performed. Statistical analyses were completed in Stata (Version 15.0; StataCorp LLC, College Station, Texas). Univariate analyses of potential risk factors were performed using the *t* test for continuous data, and the chi-square, Fisher's exact, or Wilcoxon rank sum test for categorical data. Because proliferative lesions without

Table 2. Histologic Categorization of Pathologic Findings and Reported Relative Risk for Breast Cancer*

Histologic Finding	Relative Risk
Nonproliferative lesions	1
Simple cysts	
Apocrine metaplasia	
Mastitis	
Secretory change	
Duct ectasia	
Proliferative lesions without atypia	1.3–1.9
Usual ductal hyperplasia	
Solitary intraductal papilloma	
Complex sclerosing lesion/radial scar	
Fibroadenoma	
Pseudoangiomatous stromal hyperplasia	
Proliferative lesions with atypia/ atypical hyperplasia	3.9–13.0
Atypical ductal hyperplasia	4–5†
Atypical lobular hyperplasia	
Lobular carcinoma in situ	8–10

*Relative risk adapted from Guray M, Sahin AA. Benign breast diseases: Classification, diagnosis, and management. *Oncologist* 2006;11:435–449. 10.1634/theoncologist.11-5-435, except where otherwise specified.

†Page DL, Dupont WD, Rogers LW, Rados MS. Atypical hyperplastic lesions of the female breast: A long-term follow-up study. *Cancer* 1985; 55:2698–2708. DOI: 10.1002/1097-0142(19850601)55:11<2698::aid-cncr2820551127>3.0.co;2-a.

atypia and atypical proliferative lesions may represent a spectrum of pathologic change, analyses were performed for patients having atypical proliferation only and both proliferation with and without atypia combined. Multivariable analyses were performed for patients with proliferation with and without atypia and a subsequent multivariable predictive risk algorithm table was generated by logistic regression modeling. Multivariable regression modeling results are presented with adjusted odds ratios, 95 percent confidence intervals, and p values. The predictive risk algorithm is presented with model-based probabilities with corresponding 95 percent confidence intervals. A two-tailed value of $p < 0.05$ was used to determine statistical significance. Receiver operating characteristic curve analysis was used to evaluate age at the time of surgery and age at menarche to determine whether there is an age threshold before or after which a patient is more likely to have proliferation.

RESULTS

Demographic Characteristics and Risk Factors

A total of 801 young women were identified according to the criteria described; three patients were excluded because of lack of an available pathology report. Of the 798 patients included, mean age at surgery was 17.5 ± 2.0 years (range, 11 to 24 years). Mean body mass index was 28.7 ± 5.7 kg/m^2 (range, 18.0 to 66.3 kg/m^2), with 0.1 percent patients underweight, 30.6 percent normal weight, 33.8 percent overweight, and 35.6 percent obese based on Centers for Disease Control and Prevention pediatric standards. Race according to U.S. Census Bureau definitions was documented for 64.2 percent of patients; 51.9 percent were white, 11.3 percent were black, 0.6 percent were Asian, and 0.3 percent were Native American or Pacific Islander. Of the 35.9 percent for whom race was documented as either "other" or "unknown," over half (62.0 percent) identified as Hispanic/Latino, Brazilian, or Dominican in ethnicity (Table 1).

None of the patients included in the study had a personal history of breast cancer, although three (0.4 percent) carried a previous nonbreast cancer diagnoses (i.e., acute lymphoblastic leukemia, cellular mesoblastic nephroma treated with chemotherapy, and ganglioneuroblastoma). Family history was notable for breast cancer in 181 patients (22.6 percent); 20 (2.5 percent) included a first-degree relative and 165 (20.7 percent) included a second-degree or greater relative. Five patients (0.6 percent) had a family history of a *BRCA* mutation, and one patient had a known *BRCA1* mutation herself. Mean age at menarche was 11.9 ± 1.5 years (range, 7 to 16 years). Hormonal contraceptive use was reported by 267 patients (33.5 percent), alcohol use was reported by 128 patients (16.0 percent), and tobacco use was reported by 31 patients (3.9 percent). Five patients (0.6 percent) had a history of precocious puberty (Table 1).

Surgical Characteristics

The most common indication for surgery was bilateral macromastia [n = 757 (94.9 percent)] followed by congenital breast asymmetry [n = 39 (4.9 percent)]. Only two patients (0.3 percent) had true juvenile breast hypertrophy, defined as several months of rapid, extreme breast growth followed by a longer period of slower but continued breast growth in a peripubertal female that results in extreme breast enlargement.[14] Bilateral reduction mammaplasty was the most common procedure performed [n = 761 (95.4 percent)], followed by unilateral reduction mammaplasty [n = 20 (2.5 percent)], unilateral reduction mammaplasty with contralateral mastopexy [n = 11 (1.4 percent)], and unilateral reduction mammaplasty with contralateral augmentation [n = 6 (0.8 percent)]. All reduction mammaplasty and mastopexy specimens were sent for pathologic analysis, for

a total of 1570 specimens. The mean amount of tissue removed per breast was 685 ± 339 g (range, 19 to 3000 g) (Table 1).

Pathologic Characteristics

Histologic examination revealed normal breast tissue in the majority [n = 704 (88.2 percent)] (Fig. 1). Of the 94 patients (11.8 percent) with pathologic findings, 21 (2.6 percent) had nonproliferative changes (e.g., ductal ectasia, simple cysts, apocrine metaplasia), 64 (8.0 percent) had proliferative lesions without atypia (Figs. 2 and 3), nine (1.1 percent) had atypical proliferative lesions (Fig. 4), and a single patient (0.1 percent) had a borderline phyllodes tumor (Table 3).[15] Similar to what is commonly seen in adults, some patients had overlap in findings of both nonproliferative and proliferative changes. Eight patients (1.0 percent) were reported to have masses palpable on physical examination before surgery; six (0.8 percent) were pathologically determined to be fibroadenomas, one (0.1 percent) was the borderline phyllodes tumor, and one (0.1 percent) had no clinical intraoperative or pathologic findings. The patient found to have a phyllodes tumor

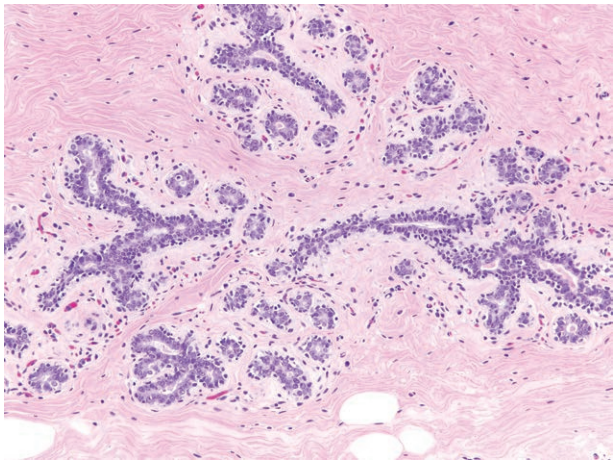

Fig. 1. Normal breast tissue: an example of a terminal ductal lobular unit without proliferation or atypia (hematoxylin and eosin, original magnification, ×20).

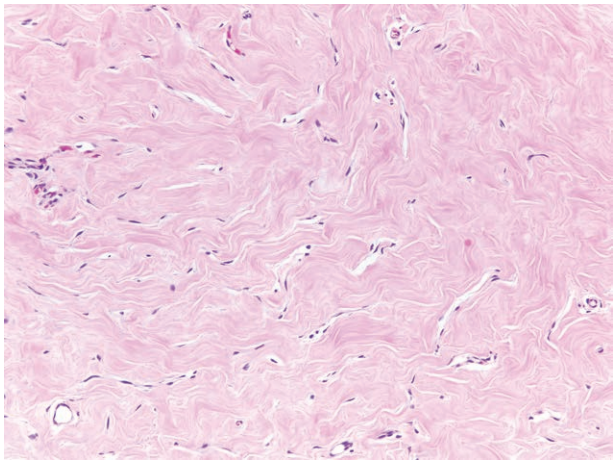

Fig. 3. Pseudoangiomatous stromal hyperplasia: a benign stromal (myofibroblastic) proliferation, which can present clinically as a mass on physical examination or imaging, characterized by dense, collagenous stroma with slit-like spaces lined by fibroblasts, mimicking a vascular lesion with endothelial lining (hematoxylin and eosin, original magnification, ×20).

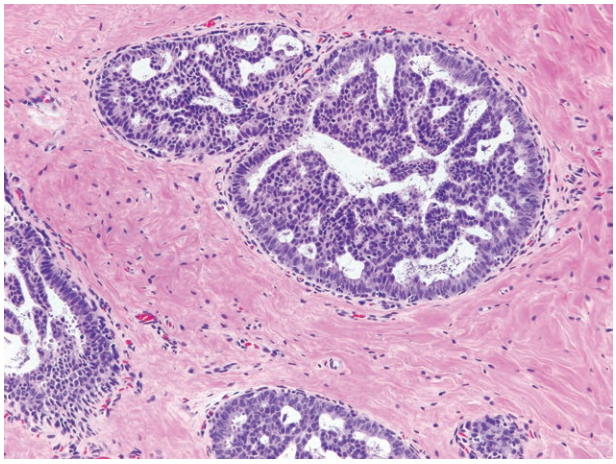

Fig. 2. Usual ductal hyperplasia: a common proliferative lesion without atypia, characterized by overlapping benign epithelial cells of variable size, shape, and orientation, bridging across and sometimes filling ductal lumina, creating irregular and slit-like fenestrations (hematoxylin and eosin, original magnification, ×20).

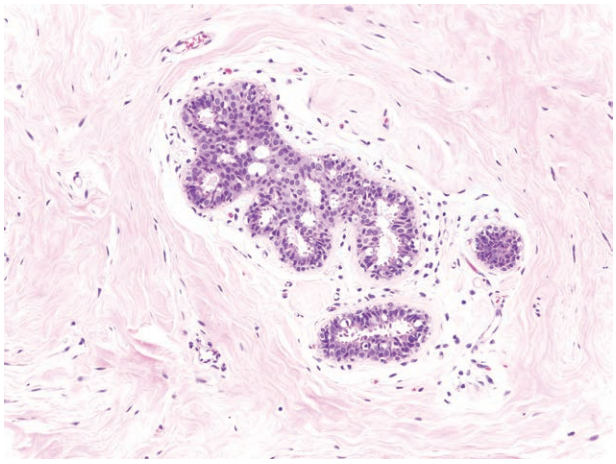

Fig. 4. Atypical ductal hyperplasia: the most common atypical proliferation in our cohort. In this photograph, it is seen involving the duct on the upper left, characterized by monomorphic cells, proliferating and expanding the duct, creating round, regular spaces, around which the cells polarize and appear to respect each other's borders.

Table 3. Summary of Pathologic Findings

Pathologic Finding	No. (%)
Breast tissue within normal limits	704 (88.2)
Any pathologic finding	94 (11.8)
Lesions without atypia	
Nonproliferative changes	
Ductal ectasia	6 (0.8)
Chronic inflammation	3 (0.4)
Apocrine metaplasia/apocrine cysts	20 (2.5)
Simple cysts	9 (1.1)
Multinucleated stromal giant cells	2 (0.3)
Lactational/secretory change	2 (0.3)
Stromal hyperplasia/proliferation	
Pseudoangiomatous stromal hyperplasia	14 (1.8)
Juvenile hypertrophy with prominent vascular stromal proliferation	1 (0.1)
Epithelial hyperplasia	
Usual ductal hyperplasia	19 (2.4)
Fibroepithelial proliferations	
Fibroadenomatous change	19 (2.4)
Fibroadenoma	36 (4.5)
Complex sclerosing lesion/radial scar	2 (0.3)
Other findings	
Angiolipoma	2 (0.3)
Perilobular hemangioma	1 (0.1)
Accessory nipple	1 (0.1)
Atypical lesions	
Epithelial	
Columnar cell change	1 (0.1)
Flat epithelial atypia*	3 (0.4)
Atypical ductal hyperplasia	5 (0.6)
Atypical lobular hyperplasia	4 (0.5)
Stromal	
Borderline phyllodes tumor	1 (0.1)

*Flat epithelial atypia is not an independent risk factor for cancer but can be a feature of either atypical hyperplasia or proliferation without atypia, such as usual ductal hyperplasia (and occurred in one patient with usual ductal hyperplasia in our study) (Said SM, Visscher DW, Nassar A, et al. Flat epithelial atypia and risk of breast cancer: A Mayo cohort study. *Cancer* 2015;121:1548–1555. DOI: 10.1002/cncr.29243.).

underwent an initial ultrasound-guided biopsy before breast reduction because of the size and growth pattern of this mass. The biopsy indicated fibroadenoma; thus, the final diagnosis was unanticipated. A borderline phyllodes tumor is defined as a rare fibroepithelial tumor arising from the stromal tissue of the breast. They can have varied behavior ranging from benign, to borderline, to malignant. In this case, the tumor was classified as borderline based on prominent infiltration into the surrounding adipose tissue. She went on to have interval sonography postoperatively, with no evidence of recurrence.

Further information is listed in Table 4 for the nine patients (1.1 percent) with atypical proliferative lesions. Four of these patients pursued longer term clinical follow-up in an adult high-risk breast oncology clinic. Seven patients with atypical proliferations also had proliferative lesions without atypia on the contralateral side.

Univariate analysis of risk factors in the nine patients with atypia demonstrated statistically fewer young women with atypia reported use of hormonal birth control compared to those without atypia ($p = 0.032$). There was no difference between progestin-only and estrogen plus progestin birth control. No other significant differences were noted (Table 5). Univariate analysis of risk factors for patients with proliferative lesions with or without atypia revealed that age at menarche of 12 years or younger (determined with receiver operating characteristic curve analysis) was significantly more common than for those without proliferative changes ($p = 0.012$) (Table 6). No significant age at surgery threshold was found for proliferative changes using receiver operating characteristic curve analysis.

Multivariable analysis looking at all patients with proliferative lesions found that age at menarche of 12 years or younger was the only independent risk factor ($p = 0.009$) for proliferation. Breast cancer in first-degree relatives was the next strongest predictor, but it was not significant ($p = 0.307$) (Table 7). However, when used together in a predictive risk algorithm, age at menarche of 12 years or younger and a first-degree relative with breast cancer had an additive impact on risk of having proliferative lesions with or without atypia (Table 8).

Table 4. Detailed Findings for Young Women with Atypical Proliferative Lesions

Patient	Age at Surgery (yr)	Atypical Pathologic Lesions	Pathologic Changes without Atypia	Age at Menarche (yr)	Significant History
1	15	ADH, FEA	UDH, PASH	13	
2	16	ADH	PASH	12	Maternal aunt with breast cancer at age 40 yr
3	17	ADH	UDH	13	Maternal great aunt with breast cancer at age 37 yr
4	18	ADH	—	11	—
5	19	ADH, CCC	UDH	11	—
6	15	ALH	UDH	10	Great grandmother at ≥80 yr
7	17	ALH	UDH, PASH, simple cyst	12	—
8	17	ALH, FEA	UDH	14	—
9	17	ALH	UDH, fibroadenomatous change	15	—

ADH, atypical ductal hyperplasia; ALH, atypical lobular hyperplasia; CCC, columnar cell change; FEA, flat epithelial atypia; PASH, pseudoangiomatous stromal hyperplasia; UDH, usual ductal hyperplasia.

Table 5. Univariate Analysis of Risk Factors in Patients with Atypical Proliferative Lesions

Variable	Atypia	Others	*p**
No.	9	789	
Age at surgery, yr			0.288
Mean	17	17	
IQR	16–17	16–19	
Race			0.999
White	5 (56)	409 (52)	
Black	1 (11)	89 (11)	
Others	3 (33)	291 (37)	
Mean age at menarche ± SD, yr	12.4 ± 1.7	11.9 ± 1.5	0.335
Mean BMI ± SD, kg/m^2	27.1 ± 3.9	28.7 ± 5.7	0.403
BMI category			0.648
Underweight (BMI < 18)	0 (0)	1 (0.1)	
Normal weight (BMI 18-25)	4 (44)	240 (30)	
Overweight (BMI > 25)	2 (22)	268 (34)	
Obese (BMI > 30)	3 (33)	281 (36)	
History of ETOH use	2 (22)	126 (16)	0.642
History of smoking	0 (0)	31 (4)	0.999
History of hormonal contraception	0 (0)	270 (34)	0.032†
Family history of *BRCA* mutation	0 (0)	5 (0.6)	0.999
Family history of breast cancer	3 (33)	178 (23)	0.441
First-degree relative with breast cancer	0 (0)	20 (3)	0.999
Second-degree relative with breast cancer	3 (33)	162 (21)	0.410
Grams removed (largest breast)	693.6 ± 208.9	727.3 ± 349.5	0.773
History of any hormonal BC	0 (0)	267 (34)	0.033
Progestin only BC	0 (0)	50/749 (7)	0.999
Estrogen plus progestin BC	0 (0%)	178/749 (24)	0.126

IQR, interquartile range; BMI, body mass index; ETOH, ethanol; BC, birth control.
*The *p* values were obtained using the *t* test, the χ^2 test, Fisher's exact test, or the Wilcoxon rank sum test.
†Statistically significant.

Table 6. Univariate Analysis of Risk Factors in Patients with Proliferative Lesions with and without Atypia

Variable	Any Proliferation (%)	Others (%)	*p**
No.	73	725	
Age at surgery, yr			0.653
Mean	17	17	
IQR	16–19	16–19	
Race			0.075
White	36 (49)	378 (52)	
Black	14 (19)	76 (10)	
Others	23 (32)	271 (37)	
Mean age at menarche ± SD, yr	11.6 ± 1.5	11.9 ± 1.5	0.055
Age at menarche <12 yr†	54 (74)	424 (58)	0.012‡
Mean BMI ± SD, kg/m^2	29.1 ± 7.3	28.6 ± 5.6	0.518
BMI category			0.874
Underweight (BMI <18 kg/m^2)	0 (0)	1 (0.1)	
Normal weight (BMI 18–25 kg/m^2)	23 (32)	221 (31)	
Overweight (BMI >25 kg/m^2)	26 (36)	244 (34)	
Obese (BMI >30 kg/m^2)	24 (33)	260 (36)	
History of ETOH use	11 (15)	117 (16)	0.812
History of smoking	3 (4)	28 (4)	0.757
History of hormonal contraception	26 (36)	244 (34)	0.736
Family history of *BRCA* mutation	0 (0)	5 (0.7)	0.999
Family history of breast cancer	15 (21)	166 (23)	0.655
First-degree relative with breast cancer	3 (4)	17 (2)	0.417
Second-degree relative with breast cancer	14 (20)	151 (21)	0.734
Grams largest breast	788.9 ± 439.6	720.7 ± 337.3	0.110
History of any hormonal BC	25 (34)	242 (33)	0.881
Progestin-only BC	7/71 (10)	43/687 (6)	0.309
Estrogen plus progestin BC	16/71 (23)	162/687 (24)	0.999

IQR, interquartile range; BMI, body mass index; ETOH, ethanol; BC, birth control.
*The *p* values were obtained using *t* test, the χ^2 test, Fisher's exact test, or the Wilcoxon rank sum test.
†Age at menarche cutoff determined using receiver operating characteristic curve analysis.
‡Statistically significant.

Table 7. Multivariable Logistic Regression Analysis of Proliferative Lesions with and without Atypia*

Covariate	OR	95% CI	*p*
Age at menarche <12 yr	2.11	1.21–3.68	0.009†
First-degree relative family history of breast cancer	1.93	0.55–6.84	0.307

*Multivariable logistic regression modeling was used to obtain odds ratios, 95% confidence intervals. and *p* values. All variables were included in backward elimination multivariable model building, with the final model including the two covariates with the strongest associations with any proliferation.
†Statistically significant.

Table 8. Multivariable Predictive Risk Algorithm for Proliferative Lesions with or without Atypia

Age at Menarche <12 Yr	First-Degree Relative with Breast Cancer	Probability of Proliferation (%)	95% CI (%)
Yes	Yes	19.6	6.5–46.1
Yes	No	11.2	8.6–14.4
No	Yes	10.4	3.1–29.5
No	No	5.7	3.6–8.8

DISCUSSION

Reduction mammaplasty is increasingly popular among adolescent and young women because of the growing body of data demonstrating its benefits.[16] Management of young women undergoing reduction mammaplasty poses unique challenges not previously examined in adult reduction mammaplasty patients. With this rising popularity, it is important to continually evaluate the value of costly histopathologic tissue analysis within this population and optimize our ability to interpret abnormal findings and direct patients toward the best plan of care. The importance of pathologic assessment of older adult breast tissue is established, but it remains unknown whether similar analysis is warranted in younger women, or if not, at what age breast specimens should be sent for pathologic evaluation. Conflict lies in the fact that the majority of breast reduction specimens in young women have no pathologic findings, versus the equally important fact that malignant or high-risk findings in young women may portend a worse prognosis and there may be potentially significant clinical advantages of early detection of lesions conferring an increased risk of malignancy. Documenting the incidence of these findings can help surgeons and patients in this age range make an informed decision about whether or not to send tissue for pathologic analysis.

How Pathologic Findings Differ in Young Women versus Older Women

Several studies have examined the prevalence of incidental risk-increasing lesions and carcinoma in adult reduction mammaplasty specimens. Among adults, the prevalence of invasive cancer or ductal carcinoma in situ is low (0.2 to 2.3 percent).[17,18] The prevalence of atypical proliferation, a marker for moderately increased risk of future cancer risk, is somewhat higher (0.71 to 13.8 percent).[17,19–22] Fewer studies have examined findings in young patients specifically, but the incidence of carcinoma and atypia is felt to be lower at younger age. In one study of 2498 women of all ages with reduction mammaplasty, 0.6 percent of women aged 40 years or younger had atypical proliferation (which included atypical ductal hyperplasia, atypical lobular hyperplasia, ductal carcinoma in situ, lobular carcinoma in situ, and focal epithelial atypia) and none had invasive carcinoma, compared to 7.5 percent and 0.2 percent of women older than 40 years.[17] Moreover, in that study, no cases of atypical proliferation were found in women younger than 24 years, although the number of patients in this age range was not specified and presumed to be low based on the reported mean age of 41 ± 14 years. In another study by Koltz et al.,[11] no proliferative lesions or carcinoma was identified in 76 women younger than 18 years who underwent reduction mammaplasty.[11] Ours represents the largest study to date of pathologic findings in breast reductions in young women. As anticipated, the incidence of malignancy was nonexistent; however, there was a small but appreciable incidence of atypical proliferations that confer a moderately increased risk of malignancy and a substantial prevalence of typical proliferations without atypia that confer minor increased risk. The prevalence of atypia differed from previous smaller studies, likely because of the small sample size of young women in those studies.[11,17] As the low incidence of atypia in our cohort precluded statistical power, we analyzed both atypical proliferations and all proliferations combined (with and without atypia), given that they may represent steps along a pathologic spectrum (thus, looking at the entire cohort may help decipher who most benefits from pathologic evaluation).

How Relative Risk Associated with Atypia Differs in Young Women versus Older Women

Although we found the incidence of atypical proliferation in young women to be low (1.1 percent), this may represent a higher risk lesion than it does in older women. Evidence suggests that

younger women with atypia have a greater risk of developing breast cancer than do older women with the same cellular change.[23,24] In a sample of 807 young women, McEvoy et al. evaluated the outcome of 58 women aged 19 to 35 years with atypical hyperplasia or lobular carcinoma in situ and found a 9.05 relative risk of breast cancer at 7 years,[25] nearly twice as high as that reported for older adults with similar lesions. In their study, the mean age of 31 years was notably older than our population, but their findings beg the question of whether risk in women younger than 24 years may be even higher.

Breast cancer is rare in young women, and less than 2 percent of women diagnosed with breast cancer annually in the United States are younger than 35 years.[26] However, women who develop breast cancer before age 35 tend to have more aggressive disease.[27] A recent population-based study of 150,588 women with breast cancer found younger age to be an independent predictor of decreased survival when controlling for other factors.[28] Thus, finding atypical proliferative lesions at a very young age may be indicative of those young women having both an increased risk of developing invasive disease and of that disease being particularly biologically aggressive.

A peculiar finding in our population was that atypical proliferative lesions were significantly less likely in young women with hormonal birth control use. This is counterintuitive, as a history of hormonal contraception is weakly associated with an increased risk of breast cancer in adult women.[29] It is far too early to suggest hormonal birth control confers a protective benefit against atypical proliferations, particularly given the small numbers of patients with atypia in our cohort and the fact that this finding was not further borne out in patients with proliferative changes overall. This is an area that would benefit from larger multi-institutional studies.

Is Routine Pathologic Analysis of Mammaplasty Specimens Worthwhile?

Risk-increasing pathology is infrequently found in young women and adolescents, which begs the question: Is routine analysis worthwhile? On average, pathology claims add $307 to the total cost of reduction mammaplasty.[30] Considering this average cost paired with the incidence of atypia found in our study, an expenditure of $27,221 would be needed to detect one at-risk patient. However, supporting routine pathologic examination is the argument that detection of a higher risk lesion may change future breast cancer screening and overall management of that patient moving forward.

In our study, only nine young women (1.1 percent) with atypia were found, limiting our ability to identify statistically significant risk factors because of the small sample. For that reason, we analyzed all proliferation as an aggregate, including both proliferations without atypia conferring minor increased risk, and atypical proliferations associated with moderately increased risk. This is intended to imply not that proliferations without atypia will necessarily degenerate into atypical proliferations, but that by looking at this larger pathologic spectrum, it may be possible to identify the subset of patients that would most benefit most from pathologic analysis.

Mean age at menarche in young women with symptomatic macromastia was 11.9 years, younger than the median of 12.4 years in the general U.S. population.[31] This is an important observation, as earlier onset of menarche is associated with progressively increased lifetime risk for breast cancer.[32] Not surprisingly, in this study, menarche at a young age (<12 years) was associated with proliferative pathologic lesions with or without atypia. There was no relationship between age at surgery and proliferation, indicating that within the young adult population, there is no age before which pathologic analysis is less likely to reveal proliferative changes. In addition, over two-thirds of our population was overweight or obese at the time of surgery, which is also a risk factor for breast cancer development.[32] We did not, however, find weight to be significantly associated with proliferative changes. Finally, although family history of breast cancer is known to be a risk factor for breast cancer, we did not find it to be a statistically significant independent risk factor for proliferative disease. However, when combined with menarche before age 12 years in a predictive risk algorithm, history of a first-degree relative with breast cancer did confer greater risk of proliferative changes. As such, young women with earlier onset of menarche appear most likely to benefit from pathologic evaluation, especially if there is a family history of breast cancer. Larger, multi-institutional studies are warranted to more clearly delineate risk factors in the 1 percent of young women with atypical proliferation.

Management of Adolescents and Young Women with Atypia

The current gaps in understanding of this disease process in young women limit the ability of clinicians to guide adolescent patients with

abnormal breast disease toward appropriate long-term care and to educate patients about their risk for malignancy. National Comprehensive Cancer Network screening guidelines for young patients with elevated risk of breast cancer caused by *BRCA* mutations include annual magnetic resonance imaging starting at age 25 years,[33] but a clear management approach for adolescents with risk-increasing atypical lesions has not yet been established. McEvoy et al. found that only 62 percent of patients aged 19 to 35 years who had atypical ductal hyperplasia, atypical lobular hyperplasia, or ductal carcinoma in situ received follow-up care.[25] Similar to the National Comprehensive Cancer Network recommendations for *BRCA* mutations, McEvoy et al recommended magnetic resonance imaging screening beginning at age 25 and mammograms beginning at age 30 for young women with atypical lesions. In the early years of this study, no formal surveillance program existed. However, in more recent years, we have begun to refer patients with atypia for early screening through a high-risk clinic at a collaborating adult institution where personalized screening protocols are designed based on pathologic findings, family history, and other risk factors. Because of the potential value this proactive approach offers for early detection of future malignancy, we will continue to opt for routine pathologic analysis, recognizing that limited knowledge about the natural history of proliferative lesions in young patients makes it difficult to quantify that potential benefit. Further investigation is needed to evaluate the benefit of early surveillance in this population.

Limitations

Although this is the largest study to date of pathologic findings in young women undergoing breast reduction, it is still a single-center study and the population size of 798 is too small to parse out the nuances of risk factors given the infrequency of atypia. In particular, the small number with atypia limited the analyses that were performed for the broader group of proliferative lesions with and without atypia. Thus, it is possible that the findings of increased risk of proliferative disease with age at menarche of 12 years or younger, compounded by family history, may not apply to women with atypical proliferation. Moreover, as mentioned previously, even when risk-increasing lesions are identified, there is not yet enough knowledge about the natural history of atypia in young women to make definitive recommendations about how it should be managed. However, we have identified that the risk of atypia is higher than what has previously been reported in smaller studies and present the best available literature to guide the clinician's management when atypical proliferation is inadvertently identified. A further limitation because of the retrospective nature of this study relates to *BRCA* mutation status. We cannot accurately characterize who has been tested but was negative, because that is not always reliably recorded in the medical record. In addition, many at-risk young adults have simply not yet undergone genetic testing at the ages included. Thus, we have potentially underestimated the incidence of *BRCA* mutations in our cohort.

CONCLUSIONS

Carcinoma was not detected in 798 adolescent and young women undergoing breast reduction. The incidence of moderate risk-increasing atypical lesions was low, but minor risk-increasing typical proliferations were more common. Multivariable analysis suggests that menarche at age younger than 12 years is a risk factor for proliferative lesions in general; however, this did not bear out statistically in the small population with atypia. Given that proliferative disease, especially with atypia, could be associated with future development of carcinoma, we favor routine evaluation of mammaplasty specimens to help inform clinical decision-making and guide future breast cancer screening in this small subset of patients.

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