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Should we routinely analyze reduction mammaplasty specimens?☆

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Summary *Background:* Reduction mammaplasty is one of the most common plastic surgery procedures. Preoperative imaging and histopathology protocols vary among countries and institutions.

We aimed to analyze the incidence of occult breast cancer and high-risk lesions in reduction mammaplasty specimens. We also analyzed whether patients with abnormal histopathology differed from the study population in terms of demographics.

Patients and methods: In total, 918 women who underwent reduction mammaplasty from January 2007 to December 2011 were retrospectively reviewed for demographics, preoperative imaging, further preoperative examinations, pathology reports, and postoperative follow-up.

Results: Abnormal histopathological findings were revealed in 88 (10%) patients with a mean age of 49.5 ± 10.2 years. The incidence of breast cancer was 1.2%, and the incidence of high-risk lesions (atypical ductal and lobular hyperplasia and lobular carcinoma in situ) was 5.5%. Age and specimen weights were significantly higher in patients with abnormal histopathology. Eighty-one percent of patients with abnormal histopathology had normal preoperative imaging revealing two high-risk and two cancer findings. Two patients developed breast cancer in the same breast in which the high-risk lesion was originally detected.

Conclusion: Women with abnormal histopathology cannot be sufficiently detected preoperatively. Therefore, histopathological analysis of reduction mammaplasty specimens seems

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mandatory. Reduction mammaplasty combined with subsequent histopathological examination offers a sufficient chance of detecting cancer and risk-increasing lesions that merits the cost of histopathology.

Introduction

Reduction mammaplasty involves many breast and plastic surgeons. Common indications for the surgery are symptomatic macromastia, breast asymmetry, and contralateral symmetrization during or after breast cancer surgery. Despite preoperative evaluation and examination of the patients, occult breast cancer and benign breast disease demonstrating increased risk of breast cancer may appear in reduction mammaplasty specimens.

The incidence of occult breast cancer in reduction mammaplasty specimens has been studied in several countries, with incidence ranging from 0.05% to 4.5%.[1–16] However, comparison between studies is made difficult because of variations in study methodologies and definition of relevant breast pathology findings. Moreover, inclusion of in situ findings or patients with previous history of breast cancer produce discrepancies.[1]

Women with benign breast disease, typically found in reduction mammaplasty specimens,[2,3,8,12,13,15,17–19] are at a higher risk of breast cancer.[20–31] Proliferative breast lesions without atypia cause slightly increased risk (1.5–2.0 times), atypical ductal hyperplasia (ADH) and atypical lobular hyperplasia (ALH) cause moderately increased risk (4.0–5.0 times), and ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS) markedly increased the risk (8.0–10.0 times) of breast cancer.[25]

The aim of our study was to analyze the incidence of occult breast cancer and findings demonstrating increased risk of breast cancer in reduction mammaplasty specimens. We also analyzed whether patients with abnormal histopathology differed from those with normal histopathology in terms of demographics.

Patients and methods

Patients who underwent reduction mammaplasty in the Department of Plastic and Reconstructive surgery, Helsinki University Hospital, between January 2007 and December 2011 were reviewed. Postoperative surveillance of the patients with abnormal histopathology until October 2015 was included. The study was approved by the University Hospital Research Board.

A total of 1255 women underwent reduction mammaplasties during the study period. Women with previous history of breast cancer were excluded, and the final study population was 918 women. The indications for the surgery were symptomatic macromastia and asymmetry of the breasts. One patient had undergone mastectomy because of burn injury, and reduction mammaplasty was performed for achieving better symmetry. Eleven patients entered the study twice and one patient entered thrice because of re-reductions. Unilateral procedures were performed in 35 cases because of congenital or postoperative asymmetry. Findings were recorded per treated patient and not per breast. Patient records were retrieved and retrospectively analyzed for demographic data, preoperative imaging, operative and histopathology reports, and postoperative follow-up.

Preoperative imaging findings were classified according to the American College of Radiology Breast Imaging Reporting and Data System,[32] as listed in Table 1.

Experienced pathologists performed the histopathological evaluation of reduction mammaplasty specimens. After fixing with formalin, the specimens were weighed and examined. The specimens were cut into 1-cm slices that were palpated for masses and areas of increased density. Samples for tissue blocks were obtained from macroscopically suspicious areas and were evaluated histopathologically. The number of tissue blocks per breast varied between four and 20, five being the most usual number.

Histopathological findings in reduction mammaplasty specimens were categorized according to a consensus statement outlined by the Cancer Committee of the College of American Pathologists.[25] In short, abnormal histopathological findings in our study included proliferative breast lesions without atypia, ADH, ALH, LCIS, DCIS, and invasive cancer. High-risk lesions included ADH, ALH, and LCIS. Invasive cancer and DCIS were categorized as cancer findings because of their similar clinical management. All other histopathological findings were defined as normal breast tissue. In 69 patients, no sample was obtained for histopathology. The percentages of abnormal findings were calculated from the number of samples available (n = 849).

Table 1 BI-RADS classification.

Category	Definition	Likelihood of cancer
BI-RADS 0	Incomplete	N/A
BI-RADS 1	Negative	Essentially 0%
BI-RADS 2	Benign	Essentially 0%
BI-RADS 3	Probably benign	>0%, but ≤2%
BI-RADS 4	Suspicious	>2%, but <95%
BI-RADS 5	Highly suggestive of malignancy	≥95%
BI-RADS 6	Known biopsy-proven malignancy	N/A

Adopted from ACR BI-RADS Atlas, Breast Imaging Reporting and Data System.

Descriptive statistics were reported as the mean value (±SD). Pearson's chi-square test was applied in bivariate analyses with categorical variables. Mann–Whitney *U* test was applied for difference in medians. P-values of <0.05 were considered statistically significant.

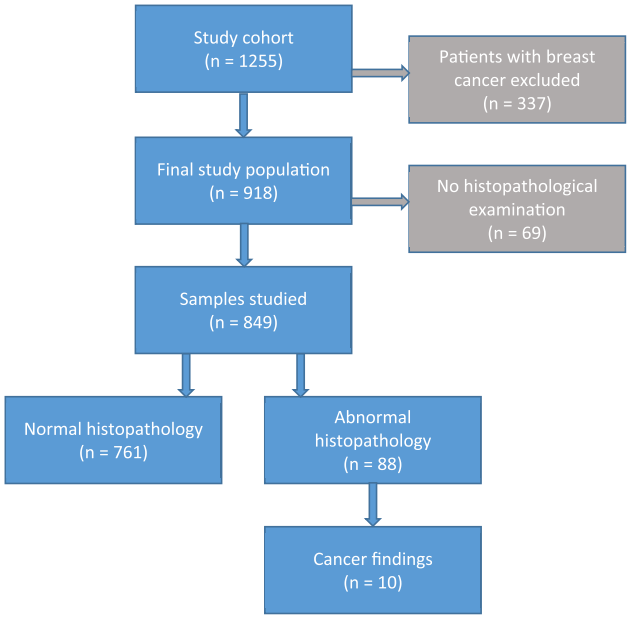
Results

A total of 918 women underwent reduction mammaplasty. Flowchart 1 illustrates the samples that were available and studied. In 69 (7.5%) patients, with a mean age of 40.6 ± 12.7 years, no sample was obtained for histopathological analysis. Histopathological evaluation of reduction mammaplasty specimens revealed abnormal findings in 88 (10%) patients and normal breast tissue in 761 (90%) patients. The mean age (±SD), body mass index, reduction mammaplasty specimen weight, past medical history, previous breast surgery, and smoking habits of the patients with normal and abnormal histopathology are listed in Table 2. There was a statistically significant difference in age ($p < 0.001$) and specimen weights ($p < 0.001$) between patients with abnormal and normal histopathologies such that abnormal histopathology correlated with a higher age and heavier specimen.

Preoperative imaging

Preoperative imaging had been conducted in 89% of the patients. There were 12 patients in whom preoperative imaging was not conducted and the histopathological analysis of reduction mammaplasty specimen was not performed.

In patients with abnormal histopathology, preoperative imaging was normal in 81% and suspicious of malignancy in 19% of the patients. Preoperatively two of 10 patients with cancer findings and two of 47 patients with high-risk lesions were detected.



Flowchart Illustration of samples available and studied.

Table 2 Demographic characteristics of the patients.

Demographic data	Normal histopathology	Abnormal histopathology
	n = 761	n = 88
Mean age[a]	44.0 ± 12.9	49.5 ± 10.2
Mean BMI	27.7 ± 3.9	28.5 ± 3.8
Previous medical condition[b]	399 (52%)	51 (58%)
Smoking	Yes: 88 (12%) No: 673 (88%)	Yes: 7 (8.0%) No: 81 (92%)
Previous breast surgery	66 (8.7%)	5 (5.7%)
Mean weight (g) of the specimens[a]	1136.6 ± 627.7	1331.2 ± 581.7

Plus–minus values are means ± SD.
[a] There is a statistical difference in age ($p < 0.001$) and specimen weights ($p < 0.001$) between patients with abnormal and normal histopathology.
[b] Five most common medical conditions: hypertension, asthma, depression or depressed mood, hypercholesterolemia, and hypothyroidism.

Abnormal histopathology

Abnormal histopathological findings were revealed in 88 (10%) patients with a mean age of 49.5 ± 10.2 years. Incidences of abnormal findings are presented in Table 3. Two simultaneous abnormal findings were revealed in nine patients, three simultaneous abnormal findings were revealed in one patient, and four simultaneous abnormal findings were revealed in two patients.

High-risk lesions (ADH, ALH, and LCIS) were identified in 47 (5.5%) patients and also in two patients along with cancer. In the subgroup of invasive cancer and DCIS, we could identify 10 (1.2%) patients. The mean age of these patients was 55.5 ± 6.6 years. Two patients were simultaneously identified with DCIS and lobular cancer.

The incidence of abnormal histopathological findings by age is presented in Table 4. A closer look at young women, <30 years of age, revealed one patient (27 years) with ADH finding. Similarly, among patients with age 30–40 years,

Table 3 Abnormal histopathological diagnosis.

Diagnosis	Number of patients	%
Sclerosing adenosis	20	2.4%
Intraductal papilloma	19	2.2%
Phylloid tumor	2	0.2%
ADH	40	4.7%
ALH	4	0.5%
LCIS	8	0.9%
DCIS	6	0.7%
Carcinoma ductale	4	0.5%
Carcinoma lobulare	2	0.2%

Two simultaneous abnormal findings were revealed in nine patients, three simultaneous abnormal findings were revealed in one patient, and four simultaneous abnormal findings were revealed in two patients.

Table 4 Abnormal histopathological findings by age.

	Findings by age				
	<40 n = 288	40–49 n = 240	50–59 n = 209	≥60 n = 112	Total n = 849
Abnormal histopathology[a]	14 (4.9%)	29 (12.1%)	28 (13.4%)	17 (15.2%)	88 (10.4%)
Low-risk lesion[b]	11 (3.8%)	15 (6.3%)	7 (3.3%)	4 (3.6%)	37 (4.4%)
High-risk lesion[c]	5 (1.7%)	12 (5.0%)	19 (9.1%)	11 (9.8%)	47 (5.5%)
Cancer[d]	0 (0.0%)	2 (0.8%)	5 (2.4%)	3 (2.7%)	10 (1.2%)

Abnormal histopathological findings in total ($p < 0.001$) and high-risk lesions ($p < 0.001$) and cancer findings ($p = 0.003$) were more frequent with increasing age.

[a] Two simultaneous abnormal findings were revealed in nine patients, three simultaneous abnormal findings were revealed in one patient, and four simultaneous abnormal findings were revealed in two patients.

[b] Sclerosing adenosis, intraductal papilloma, phylloid tumor.

[c] ADH, ALH, and LCIS.

[d] Invasive cancer and DCIS.

four patients were diagnosed with ADH. Abnormal histopathological findings in total ($p < 0.001$) and high-risk lesions ($p < 0.001$) and cancer findings ($p = 0.003$) were more frequent with increasing age as shown in Table 4. However, in the subgroup of patients with high-risk lesions, 36% were <50 years of age.

In cases with abnormal postoperative histopathology, family history of breast cancer was positive in 12 patients and negative in 17 patients. The family history was not available for 59 (67%) patients.

Postoperative surveillance

The mean follow-up period for patients with abnormal histopathology and patients with no histopathological analysis was 6.2 ± 1.4 years. In our study, two patients developed breast cancer on the same breast in which the high-risk lesion was revealed in the reduction mammaplasty specimen (Table 5). Active surveillance with both mammogram and ultrasound every 2 years was recommended for the majority of the patients with high-risk lesions (ADH, ALH, and LCIS). For 12 patients, information about surveillance could not be found.

In 69 patients without histopathological analysis, preoperative imaging had been conducted for 57 (82.6%) patients, all with normal result. Retrospective survey of patient records showed no indication of future oncological treatment.

Discussion

Reduction mammaplasty continues to be a common procedure in plastic and breast surgery. Despite thorough preoperative evaluation and imaging, occult breast cancer and findings demonstrating increased risk of breast cancer are revealed in the specimens. We detected a considerable number (10%) of abnormal findings in patients who

Table 5 Patients with subsequent cancer.

	Patient 1	Patient 2
Age at reduction mammaplasty	55	58
Preoperative imaging	MMG[a] + US[b] BI-RADS 2	MMG + US BI-RADS 2
Histopathology of the specimen	ADH	LCIS
Postoperative surveillance	MMG + US every 2 years	Recommended: screening MMG Realized: symptomatic liponecrosis → annual imaging and several biopsies
Cancer diagnosis method	Screening MMG	Skin biopsy
Time of cancer diagnosis	4 years, 10 months	6 years, 8 months
Treatment	Mastectomy + SNB[c] + axillary clearance, hormone therapy	Mastectomy, axillary clearance, preoperative neoadjuvant chemotherapy, postoperative radiotherapy, and hormone therapy
Type of cancer	Carcinoma ductale bifocale, gr I, pT1 (20 + 2 mm), pN0 (i+)	Carcinoma lobulare bifocale, gr I, pT2 (30 + 15 mm), pN3a (14/21)

TNM classification of malignant tumors, 7th edition. Wiley Blackwell, Oxford UK 2009.

[a] MMG: Mammogram.

[b] US: Ultrasound.

[c] SNB: Sentinel node biopsy.

underwent reduction mammaplasty. According to previous studies, the incidence of invasive carcinoma and DCIS varies between 0.05% and 2.5%.[1–16] In our study, the incidence of breast cancer was 1.2%, which corresponds to that in previous studies.

Benign breast disease is an important predictor of future breast cancer risk.[20–31] Hartmann et al.[31] showed that the cumulative incidence of breast cancer at 25 years was 29% in women with ADH or ALH. Similarly, King et al.[28] showed a 2% annual incidence of breast cancer among women with LCIS and an overall cumulative cancer incidence of 26% at 15 years. Coopey et al.[30] showed an estimated 10 year cancer risk with ADH, ALH, and LCIS at 17%, 21%, and 24%, respectively. In our study, we detected high-risk lesions in 5.5% of the patients distributed across all age groups. Therefore, reduction mammaplasty reveals a group of women with marked and persistent elevation in breast cancer risk.

In our study population, 11% of the patients with high-risk lesions were <40 years of age, the youngest being 27 years old. Hassan et al.[1] reported that there is no need for histopathological analysis in patients <30 years of age as significant pathology is uncommon in younger patients. However, McEvoy[29] et al. evaluated breast cancer risk in women aged <35 years with ADH, ALH, and LCIS and discovered that 12% developed breast cancer after a mean of 7.5 years. They recommended close clinical follow-up. Similarly, Hartmann et al.[31] showed in the Mayo Clinic cohort study that breast cancer risk is increased in young women with atypia. Given the markedly increased risk of breast cancer in women with ADH, ALH, and LCIS, sending reduction mammaplasty specimens for histopathological analysis also for women <40 years of age captures this population for future surveillance.

In our study, there was a statistically significant difference in age and specimen weights between patients with normal and abnormal histopathologies. Patients with abnormal histopathology were older, and the specimens were heavier. Other variables did not differ between these groups. From these findings, it is difficult to set a certain "cutoff" threshold for when to send specimens for histopathological analysis. Recent studies[28,31] have shown that family history of breast cancer does not increase the risk of breast cancer in patients with atypia beyond that of atypia itself. This indicates that on the basis of demographics and family history, histopathological analysis should not be preoperatively ruled out.

Standard use of preoperative imaging before reduction mammaplasty remains controversial as no consensus for such criteria exists. In our study, the majority of the patients (81%) with abnormal findings in reduction mammaplasty specimens had normal preoperative imaging. Similarly, others[3,9–11,33] have noticed that incidental discovery of atypical hyperplasias, in situ findings, or cancers in reduction mammaplasty specimens are not associated with abnormal preoperative mammograms. In our study, preoperative diagnostics revealed only two high-risk lesions (ADH and LCIS) and two cancers. Small invasive cancers, DCIS, and high-risk lesions may remain undetected with imaging, including MRI. Considering the low number of preoperatively detected abnormal findings, our results indicate that preoperative imaging does not sufficiently detect high-risk or malignant findings. Therefore, histopathological analysis of reduction mammaplasty specimens seems difficult to bypass.

In our study, there were 69 (7.5%) patients with no sample for histopathological analysis. Some surgeons based their decision on the young age of the patients. However, older patients were also present in this group (range 19–66 years). The reason for not sending older, e.g., >40 years, patients' samples for histopathological analysis remains unclear. In addition, there were 12 patients with no preoperative imaging or histopathological analysis of reduction mammaplasty specimen eliminating all pre- and postoperative diagnostics.

Current risk management options for women with ADH, ALH, or LCIS include active surveillance, chemoprevention, and, more rarely, bilateral prophylactic mastectomy.[26,28–30,34] During the study period, mammogram and ultrasound were recommended every 2 years for the majority of these high-risk patients. The current surveillance protocol in our unit for women <50 years includes both mammogram and ultrasound annually. For women between 50 and 69 years, mammogram is recommended annually, and for women of >69 years, mammogram is recommended every 2 years. Houssami et al.[35] found no difference in the sensitivity of screening mammogram for breast cancer detection between women with ADH, ALH, or LCIS and a control group lacking a history of these findings. However, they stated that these patients may benefit from adjunct (ultrasound or MRI) screening because of lower mammogram specificity and higher interval cancer rates. Berg et al.[36] also stated that in women with increased risk of breast cancer, supplementation of ultrasound resulted in not only a higher rate of cancer detection but also an increase in false-positive findings. For women <35 years of age with ADH, ALH, and LCIS, McEvoy et al.[29] recommended MRI starting at 25–29 years of age and screening mammograms for those >30 years. Thus, this supports that active surveillance with tailored imaging is justified.

The use of chemoprevention for risk management has been shown to reduce breast cancer incidence among women with atypical hyperplasia and LCIS at 10 years from 21% to 8%.[30] Similarly, King et al.[28] showed a reduction in breast cancer incidence at 10 years from 21% to 12% in women with LCIS on chemoprevention compared to women with no chemoprevention. Current guidelines by the American Society of Clinical Oncology[34] recommend the discussion of tamoxifen as an option to reduce the risk of breast cancer in pre- and postmenopausal women at increased risk of breast cancer or with LCIS and the discussion of raloxifene and exemestane with postmenopausal women. Morrow et al.[26] concluded that substantial and persistent elevation in breast cancer risk in these women is sufficient to justify a discussion of chemoprevention with those in good health, particularly premenopausal women. To our knowledge, in our health care system, chemoprevention is barely ever offered to patients with increased risk of breast cancer.

In our study, only two patients developed breast cancer during the rather short follow-up period. Both cancers were ipsilateral to the high-risk lesion. Hartmann et al.[31] showed that cancers developing within 5 years of diagnosis of atypia were more likely to be ipsilateral than cancers arising later.

It has been reported that routine histopathological analysis of reduction mammaplasty specimens is not cost-effective because the incidence of occult cancers in the specimens is low.[1,37] However, as Kececi et al.[18] suggested, these figures are usually calculated for individual cancers detected and do not consider risk-increasing findings. High-risk lesions should be considered in determining whether histopathological analysis of specimens is cost-effective or not. The importance of high-risk lesions for the patients is clear over time.[18]

There are some limitations to our study. Because of its retrospective nature, we could not standardize preoperative routines and histopathological sampling. Nevertheless, this study cohort represents common plastic surgery practice. In this study, the follow-up time is short (mean 6.2 $\pm$ 1.4 years), which probably affected the number of subsequent cancers. With longer follow-up, more cancers may be detected in these high-risk patients.

To conclude, preoperative diagnostics and demographics do not sufficiently detect malignant or cancer risk-increasing findings. Therefore, histopathological analysis of reduction mammaplasty specimens seems mandatory. Reduction mammaplasty combined with subsequent histopathological examination offers a sufficient chance of detecting cancer and risk-increasing lesions that merits the cost of histopathology.

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None.

Conflict of interest statement

None.

STROBE guidelines

Authors have adhered to the STROBE guidelines.

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