

# Incidental Findings in Reduction Mammoplasty Specimens in Patients with No Prior History of Breast Cancer. An Analysis of 783 Specimens

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**Abstract** Breast reduction surgery is a common procedure and the rate of incidental findings in the removed specimens varies between 0% and 4.6%. There are no guidelines about pathological evaluation of breast reduction surgery. We reviewed all pathology reports of patients undergoing breast reduction surgery in a single tertiary institution in Brazil from January 2008 to August 2014. Exclusion criteria were a personal history of breast cancer, unclear reason for mastectomy and incomplete data on the pathology report. We considered “relevant findings” flat epithelial atypia, atypical hyperplasia, carcinomas in situ and invasive carcinoma. Of 1672 specimens from breast reduction surgery, 783 met inclusion criteria. Median patient age was 40 (8–77), 91% underwent bilateral mastectomy and 57% of the specimens weighed less than 200 g. In 55% of cases, 4 or more paraffin blocks were sampled. There were 40 (5.1%) relevant findings and the most common was atypical lobular hyperplasia (16–2%). There were 3 invasive carcinomas (0.38%). In multivariate analysis, the only variables associated with a higher odds of relevant pathological findings were patient age  $\geq 40$  (OR 4.73 CI95% 1.98–11.3  $p < 0.001$ ) and sampling of  $\geq 4$  paraffin blocks from each specimen (OR 6.69 95% CI 2.25–19.9  $p < 0.001$ ). The

incidence of pre-malignant and malignant lesions in specimens from breast reduction surgery is around 5%, but this risk is significantly higher for patients older than 40 years-old. Sampling at least 4 paraffin blocks from each specimen significantly increases detection rates.

**Keywords** Breast cancer · Mammoplasty · Breast reduction surgery · Incidental findings

## Introduction

Breast reduction is a common cosmetic surgery in the United States, with an estimated 114,470 procedures in the year 2014 [1]. Common indications are relief of symptoms from macromastia and breast symmetrization after contralateral mastectomy for carcinoma [2].

Breast cancer is currently the most frequent cancer in women in the United States, second only to skin cancer, with an estimated 231,840 new cases in 2015 [3]. Due to its high incidence, there is a fairly significant possibility of incidental findings with prognostic significance in women undergoing breast reduction surgery [4, 5].

The rate of clinically relevant findings after breast reduction surgery ranges from 0% to 4.6% [6–16]. What findings should be considered relevant [17] as well as the optimal number of tissue sections analyzed [18] remain a matter of debate. In this study, we will evaluate the incidence of pre-malignant and malignant lesions in a population undergoing breast reduction surgery at a tertiary center in Sao Paulo, Brazil and study the correlation between patient characteristics, number of tissue sections analyzed and pathologic diagnosis.

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## Methods

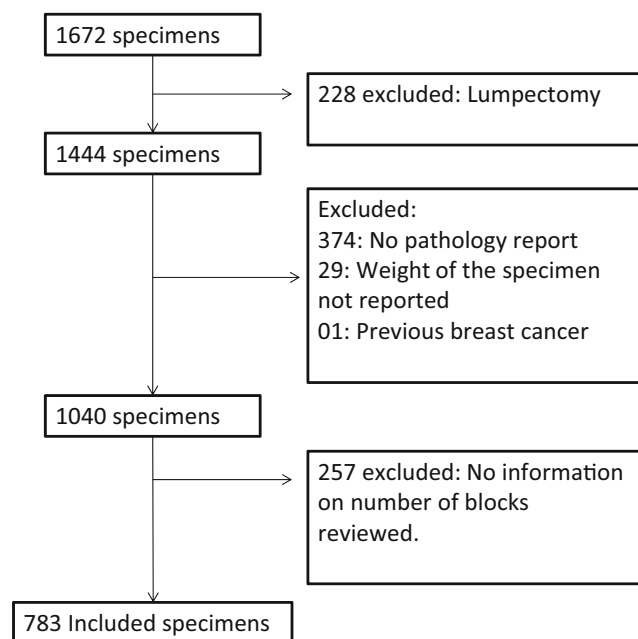
### Patient and Specimen Selection

We reviewed the pathology reports from all patients undergoing breast reduction surgery at Hospital Israelita Albert Einstein between January 2008 and August 2014 and identified 1672 specimens. After excluding patients with a prior history of breast cancer, insufficient or inadequate material, unclear reason for mastectomy and unclear number of paraffin blocks analyzed, the final sample size included 783 breast tissue specimens (Fig. 1). For this type of study formal consent is not required.

### Pathology Review

No central review of pathology specimens was performed and we extracted the findings from the original reports, done by different pathologists. Between 2008 and 2011, each pathologist decided how many paraffin blocks should be reviewed from each sample. From 2011 on, this procedure was standardized and a minimum of four blocks was analyzed.

In the current study, we defined the following pathologic findings as relevant: Flat epithelial atypia (FEA), atypical lobular hyperplasia (ALH), atypical ductal hyperplasia (ADH), lobular carcinoma in situ (LCIS), ductal carcinoma in situ (DCIS) and invasive ductal or lobular carcinoma (IDC or ILC).



**Fig. 1** Sample selection

### Statistical Analysis

Because there could be a variable number of paraffin blocks for each breast in any given patient, we decided to evaluate each breast separately. The analysis took into consideration abnormal findings (FEA, ALH, ADH, LCIS, DCIS, IDC or ILC), the presence of carcinoma in situ (DCIS and LCIS) or the presence of invasive carcinoma (IDC or ILC).

The number of paraffin blocks was categorized as less than 4 or 4 or more blocks. Categorical variables were described as absolute and relative frequencies plotted in bar charts and compared using a Chi-squared or Fisher's exact test. Continuous variables were presented as medians and inter-quartile ranges, plotted as boxplots and compared using the Mann-Whitney test.

We studied the association between the number of blocks and probability of abnormal findings using a model for generalized estimating equations (GEE) [19] and a matrix of exchangeable working correlation structure to account for the correlation between specimens from the same patient. The model results are presented as odds ratios (OR), their 95% confidence intervals (95% CI) and *p*-values. We initially performed a univariate model and all independent variables with a *p*-value lower than 20% were fitted in the multivariate analysis.

We used the statistical package R, version 3.0.3 (R Core Team). For the GEE models, we used the package "geepack". Unless otherwise specified, significance was set at 5%.

## Results

Of the 1672 breast specimens identified in our database from January 2008 to August 2014, 783 met the inclusion criteria for this study (Fig. 1). Median age was 40 (8–77), 91% underwent bilateral breast reduction and in 76% of cases, 4 or more paraffin blocks were evaluated. Table 1 has other general patient and specimen characteristics.

Out of the 783 specimens, 40 (5.1%) had relevant pathologic findings and 85% of these alterations were found in the 357 specimens evaluated after the standardization of at least 4 paraffin blocks per sample. Most specimens with relevant findings (58%) had more than one alteration. The most common finding was atypical lobular hyperplasia (16/40; 40%). There were 5 carcinomas in situ (12.5%) and 3 invasive carcinomas (7.5%). Over 80% of abnormal findings happened in breast specimens from women over 40 years-old.

Breast specimens with relevant findings were more common in women older than 40 years-old ( $p < 0.001$ ) and when 4 or more blocks were sampled ( $p = 0.003$ ) (Table 2). In the univariate and multivariate analysis, patient age and number of blocks sampled were associated with a higher probability of relevant findings (Table 3).

**Table 1** Patient and specimen characteristics

Breast cancer specimens		Findings	
Total	N(783)	Total breast specimens/relevant findings	(783/40)
Patient age - years		Before padronization	426/6
Median	40	After padronization	357/34
IQR	8–77	Number of findings/ specimen (%)	
Age – number of patients (%)		1 finding	17(42%)
≥ 40	402(51.4%)	>1 finding	23(58%)
< 40	381(48.6%)	Laterality of findings no(%)	
Laterality of surgery – n. (%)		Unilateral	22(55%)
Unilateral	68(8.7%)	Bilateral	18(45%)
Bilateral	715(91.3%)	Findings - Total: no(%)	40(100%)
Mean weight of the specimen (%)		Flat epithelial atypia (FEA)	04(10%)
< 200 g	446(57%)	Atypical lobular hyperplasia	16(40%)
≥ 200 g	337(43%)	Atypical lobular hyperplasia +Others	07(17.5%)
Number of paraffin blocks(%)		Atypical ductal hyperplasia	02(5%)
Non-specified	257(excluded)	Atypical ductal hyperplasia + FEA	03(7.5%)
<4	214(27.4%)	DCIS/LCIS + Others	05(12.5%)
≥ 4	569(72.6%)	Invasive carcinoma	03(7.5%)

## Discussion

We have reviewed 783 breast specimens from healthy women undergoing reduction mammoplasty and found 40 pre-malignant and malignant lesions. These alterations were more likely to be found when 4 or more paraffin blocks were sampled and when patients were older than 40 years-old.

The association between atypical proliferative lesions and breast cancer has been extensively studied, and it is known that these conditions share similar molecular and genetic characteristics [20–23]. For example, the risk of breast cancer is 4–5 times higher in patients with atypical hyperplasia [24–26] and up to 3 times higher in those with atypical lobular hyperplasia [27].

The incidence of invasive carcinoma in reduction mammoplasties is variable and, in small studies, it has been reported to be as high as 5% [6–16]. However, in larger cohorts, the average incidence is 0.06–0.38% [4, 8, 28], which is consistent with our finding of 0.38% breast specimens with invasive carcinoma.

Other groups have reported a higher probability of relevant findings in women older than 40 years-old [29–32]. In our study, 80% of the pre-malignant or malignant lesions were found in specimens from women older than 40, with an odds ratio of 4.7 for this age group. Based on similar observations, some authors have recommended a more intense evaluation of patients at this age group, including diagnostic breast imaging before surgery and adequate evaluation of surgical margins in the breast specimen [33, 34].

**Table 2** Main characteristics of specimens from normal breast tissue and those with relevant findings ( $N = 783$ )

Variable	Categories	Normal breast ( $n = 743$ )	Relevant findings ( $n = 40$ )	Total ( $N = 783$ )	$p$ -value
Age	<40 y/o	374 (50.3)	7 (17.5)	381 (48.6)	<0.001
	≥40 y/o	369 (49.7)	33 (82.5)	402 (51.4)	
Number of paraffin blocks	<4	211 (28.4)	3 (7.5)	214 (27.4)	0.003
	≥4	532 (71.6)	37 (92.5)	569 (72.6)	
Laterality	Unilateral	67 (9.0)	1 (2.5)	68 (8.7)	0.244
	Bilateral	676 (91.0)	39 (97.5)	715 (91.3)	
Median specimen weight [IQR](g)		149.00	198.25	150.00	0.085
		[73.62; 252.38]	[99.38; 310.25]	[74.75; 257.25]	

Numeric variables reported as absolute frequencies (%) and specimen weight reported as median [interquartile range – IQR]

All  $p$ -values for Fisher's exact test, except for "age" in which Chi-squared was used

**Table 3** Univariate and multivariate GEE model for probability of relevant pathologic findings

Independent variables	Univariate analysis			Multivariate analysis		
	OR	CI 95%	<i>p</i> -value	OR	CI 95%	<i>p</i> -value
Left breast	1.02	(0.73–1.43)	0.906			
Bilateral surgery	2.79	(0.38–20.66)	0.316			
Age $\geq$ 40 y/o	4.80	(2.01–11.46)	<0.001	4.73	(1.98–11.30)	<0.001
Weight of the breast specimen (g)	1.00	(1.00–1.002)	0.096			
Block number $\geq$ 4	6.85	(2.27–20.60)	<0.001	6.69	(2.25–19.9)	<0.001

OR odds ratio, CI confidence interval

We found no association between amount of tissue removed (in grams) and the odds of relevant findings ( $p = 0.096$ ), which is different from what is reported in the literature [35]. Multiple factors could have influenced this analysis, including difference in breast sizes, differences in pathological analysis and differences in the definition of relevant findings.

In more than 50% of breast samples with relevant findings, there were other alterations, what suggests an effect of field carcinogenesis and a true risk of developing breast cancer. In a large study in Sweden, with over 3000 women undergoing reduction mastectomies, the procedure was associated with a reduction in the incidence of breast cancer, probably because of the removal of pre-malignant lesions [36].

In our database, 92% of the relevant findings were identified when 4 or more paraffin blocks were sampled, with an odds ratio of 6.7 when compared to less than 4 blocks. In a recent retrospective study done at 2 centers, Mohamed et al. [32] showed a significant higher number of relevant findings when 7 or more blocks were sampled and recommended that at least 10 blocks should be sampled for women older than 40 years old. For those younger than 40, with no visible lesions and no risk factors, 2 could be enough. The optimal number of blocks remains a matter of debate, but it is clear that this procedure should be standardized and 4 samples could be a reasonable cut-off.

Finally, there is no consensus on the management of patients with incidental findings in reduction breast mammoplasty [37, 38], but these women could benefit from more intense breast cancer screening and even from the consideration of chemoprophylaxis.

## Conclusions

Even though most patients undergoing reduction mammoplasty will have normal breasts, there is a significant chance of identifying pre-malignant and malignant lesions, especially

for women older than 40. Adequate sampling has a significant impact on the sensitivity of the pathological evaluation and we recommend that at least 4 paraffin blocks should be sampled from each specimen.

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