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CLINICAL TRIAL

Is microductectomy still necessary to diagnose breast cancer: a 10-year study on the effectiveness of duct excision and galactography

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Abstract

Purpose Patients with spontaneous nipple discharge (SND) who have neither clinically palpable masses nor evidence of disease on imaging with mammogram and/or ultrasound are traditionally investigated with galactogram and duct excision. As breast imaging improves, it has raised the question whether galactography and microductectomy are necessary to diagnose breast cancer. The purpose of this study was to determine the incidence of malignancy in patients presenting with SND who underwent microductectomy and to evaluate the utility of duct excision and galactography in patients whose initial clinical and radiological evaluation were negative.

Methods A 10-year retrospective study was conducted in British Columbia's largest tertiary breast referral center examining the clinical, radiological and pathological results for all patients who underwent a microductectomy procedure for SND between 2008 and 2017.

Results A total of 231 microductectomies were performed and the overall incidence of malignancy was 13% ($n=32$). Following initial work up, 155 patients (67%) had only discharge on exam and no radiologically suspicious findings of malignant disease. Of these patients, 14% ($n=21$) were diagnosed with cancer by duct excision. Galactography yielded a sensitivity and specificity of 63% and 36%, respectively (PPV 15% and NPV 85%). Lastly, we found that 3% of patients ($n=8$) initially diagnosed with benign disease later developed breast cancer.

Conclusions Patients with SND should continue to be evaluated with microductectomy to prevent missing a breast cancer. Moreover, we do not recommend performing galactography for diagnosing breast cancer due to poor sensitivity and specificity though it may assist in preoperative planning.

Keywords Nipple discharge · Breast cancer · Microductectomy · Galactogram · Duct excision · Breast imaging

Introduction

Spontaneous nipple discharge (SND) is a symptom of malignancy in up to 12% of breast cancers and is the third most common complaint referred to breast clinics [1]. Differentiating between benign (physiologic, medication-induced or lactational) and malignant causes of spontaneous nipple discharge is essential to prevent missing a diagnosis of cancer. Initial evaluation of pathologic SND consists of a detailed history and thorough physical exam followed by a diagnostic mammogram (MMO) and focused ultrasound (US). If a suspicious lesion is detected a targeted biopsy is arranged to make a diagnosis and guide further management.

However, patients who have neither palpable masses nor evidence of disease on initial imaging warrant further investigation to identify the cause of the discharge. Currently, there is no consensus regarding the management of patients with clinical and imaging negative pathological discharge (CINPD). Traditionally, galactography has been utilized to localize intraductal lesions which are then surgically removed by duct excision. Galactograms have been shown

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to improve intraoperative localization of the discharging duct at the time of excision [2]. However, this procedure is invasive as it requires cannulation of the duct and administration of contrast media for the mammogram. Moreover, the test requires active discharge at the time of the evaluation and can also be technically challenging with reports of incomplete/failure rates up to 15% [3]. More recently, contrast enhanced MRI of the breast has gained popularity owing to its higher diagnostic accuracy and improved patient tolerability. Berger et al. [4] performed a systematic review comparing the diagnostic accuracy of MRI compared to galactography and found that MRI was superior with a sensitivity and specificity of 92% and 76% compared to 69% and 39% for galactograms, respectively.

Breast diagnostic imaging continues to improve but is not sensitive nor specific to definitively rule out malignancy in the setting of SND. Microductectomy remains the gold standard for patients with nipple discharge whose initial evaluations are negative. The challenge is that the majority of women presenting with SND who undergo surgical excision will have benign disease [5]. Thus, a high proportion of patients must complete an invasive procedure to rule out cancer. This is particularly concerning considering complications of microductectomy—how much ever low—include infections, nipple necrosis and duct fistulas which may require more intensive surgical interventions and may interfere with breastfeeding in women of child baring age. As imaging diagnostics have improved, it has raised the question of how frequently breast cancer is diagnosed following microductectomy and whether the procedure remains necessary.

The purpose of this study was to (1) Determine the incidence of malignancy in patients presenting with spontaneous nipple discharge who underwent microductectomy after initial clinical and radiological evaluation; (2) Determine the incidence of patients without clinical and radiological evidence of disease who were diagnosed with cancer by microductectomy; (3) Evaluate the sensitivity and specificity of galactogram for detecting any lesion and malignancy and (4) Determine the number of patients with benign disease from microductectomy who subsequently developed cancer.

Materials and methods

A retrospective chart review was conducted for all patients referred to the Providence Health Care Breast Centre for SND who underwent a microductectomy between January 2008 and December 2017. This study was approved by the Research Ethics Board by the University of British Columbia and Providence Health Care. Patients were excluded from our study if they met any of the following criteria: (1) microductectomy was not the sole procedure performed, (2) had a current or previous diagnosis of breast cancer in the ipsilateral breast regardless of whether it was treated and (3) referrals made for breast concerns other than nipple discharge (abnormal imaging or breast masses). Electronic medical records were analyzed and patient demographics including age and sex, clinical information, such as type of nipple discharge, laterality, palpable mass and radiological findings, were analyzed.

The standard radiological evaluation of SND consisted of a diagnostic mammography and/or diagnostic ultrasound for the majority of patients. Women under 30 initially were investigated with an ultrasound and mammogram was performed as appropriate afterwards. Mammograms consisted of two routine views cranial caudal (CC), medialateral oblique (MLO) and a lateral view and magnification at the radiologist's discretion. Ultrasonography was performed using high-frequency transducers to assess the retroareolar and central breast. The peripheral breast tissues were evaluated at the radiologist's discretion. Galactograms were performed in a subset of patients and the outcomes were categorized as positive, negative, inconclusive or technically unsuccessful. Patients were considered to have negative imaging in the absence of a mass or if image detected lesions were deemed unrelated to the discharge and/or benign.Patients who had previously documented benign lesions on mammogram or ultrasound were categorized as negative unless there was an interval change in the appearance between radiological studies that were suspicious for malignancy. Pathology reports were examined to determine the incidence of malignancy from the operative specimens. Malignancy was defined as ductal carcinoma in situ (DCIS), invasive ductal carcinoma and invasive lobular carcinoma. Student's *t* test for continuous variables and a Chi squared test for discrete variables. Significance was determined by a $p \leq 0.05$.

Results

Between 2008 and 2017, a total of 11,292 breast procedures were performed at our center. We identified 251 patients who underwent a microductectomy procedure for spontaneous nipple discharge during the study period and 227 patients met the inclusion criteria. A total of 231 procedures were performed owing to two patients undergoing bilateral microductectomies and two patients having repeat surgery on the same breast. The patient population had a mean age of 54.8 ± 13.4 (17–88 years old), 226 were female (99.6%) and one patient was male (0.04%). 155 patients (67%) undergoing microductectomy had negative clinical exam findings and no suspicious imaging findings on mammogram and ultrasound to explain the SND (see Table 1).

Overview of benign and malignant pathology diagnosed by microductectomy

The overall incidence of malignancy for patients with spontanous discharge who underwent microductectomy (Fig. 1a) was 13.8% ($n=32$): invasive cancer 3.0% ($n=7$) and ductal carcinoma in-situ 10.8% ($n=25$). The majority of patients (86.2%, $n=192$) were diagnosed with benign causes of spontanous discharge with intraductal papilloma representing the largest group 55.4% ($n=128$) followed by duct ectasia 8.7% ($n=20$), atypia 7.4% ($n=17$) and other benign (combined) 14.7% ($n=34$). Among the 231 microductectomies performed, 155 (67.1%) of patients had neither masses on clincial exam detected nor a cause of the spontanous nipple discharged identified on MMO or US. There was no statistical difference between the incidence of benign and malignant pathology between these groups (Fig. 1b). Refer to Tables 5 and 6 in "Appendix" for specific break down of pathology subcategories.

Risk factors associated with malignant spontaneous discharge and sensitivity and specificity of clinical and radiological variables

Evaluation of clinical and radiological factors associated with malignant spontaneous nipple discharge was determined between all patients and clinical and imaging negative patients (Table 2). There was no difference in the mean age between benign and malignant pathology (54 vs. 58 years, $p=0.292$). However, we found that malignancy was associated with women over the age of 50 in the clinical and radiologically negative cohort (65% vs. 37%, $p=<0.001$). Furthermore, bloody nipple discharge and an abnormality detected on mammogram was associated with malignancy (50.8% vs. 81.3%, $p=0.001$) and (8.1% vs. 14.3%, $p=0.001$), respectively. We next examined clinical variables (bloody vs. non-bloody discharge and mass on clinical exam) as well as galactography and calculated their sensitivity and specificity in patients presenting with spontaneous discharge who underwent a microductectomy. The sensitivity, specificity, PPV and NPV are displayed in Table 3. Galactogram had a sensitivity and specificity of 0.63 and 0.36 and a PPV and NPV of 15.0% and 84.8%, respectively. A total of 123 galactograms were performed: 76.4% ($n=94$) produced interpretable results (positive or negative) whereas 19.5% ($n=24$) were unsuccessful due to technical issues or patient intolerance to the procedure and 4.1% ($n=5$) were inconclusive.

Re-operation in patients with benign pathology from microductectomy

We found that 3% ($n=8$) of patients who underwent a microductectomy who were initially diagnosed with a non-cancerous lesion were later diagnosed with a malignancy: 2 DCIS and 6 invasive ductal carcinomas (see Table 4). The mean duration between initial microductectomy and re-operation of the ipsilateral breast was 33 months. Two patients under went a second procedure within 1 year from their microductectomy.

Discussion

Spontaneous nipple discharge is a common breast symptom that warrants thorough investigation to differentiate between benign and malignant etiologies. Patients are evaluated with a history and physical examination followed by mammography and ultrasonography as first-line imaging modalities—and if warranted—image guided biopsy of suspicious lesions. The majority of patients presenting with nipple discharge are diagnosed with benign

Table 1 Overview of patient demographics

Total number of patients	251	
Exclusions	24	
	Procedure other than microductectomy	11
	Previous ipsilateral breast cancer	4
	Incomplete information	9
Number of eligible patients for the study	227	
Total number of procedures	231	
Patient mean age and range	54.8 ± 13.4 (17–88)	
Male	1 (0.04%)	
Female	226 (99.6%)	
Presentation of patients with spontaneous nipple discharge		
Positive clinical, MMO and/or US	76	32.9%
Negative/non-diagnostic clinical, MMO or US	155	67.1%

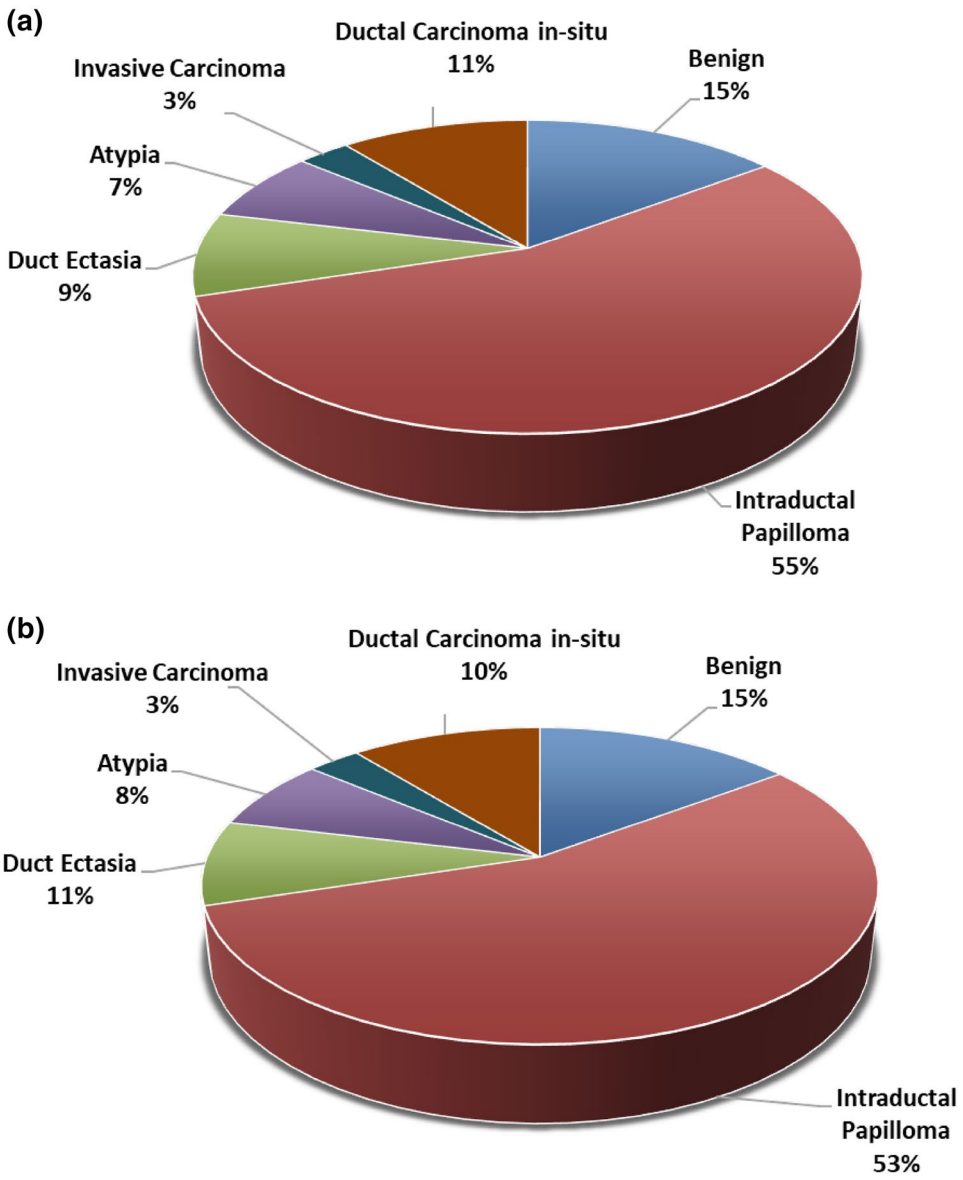

Fig. 1 Incidence of benign and malignant pathology diagnosed by microductectomy in **a** all patients and **b** clinically and radiographically negative patients. Created with Power Point

causes including intraductal papilloma or duct ectasia. An even smaller percentage of patients will be diagnosed with cancer as the cause of the discharge. The algorithm for diagnosis and treatment is less defined in the subset of patients who have neither clinically detectable lesions or masses which can be biopsied based on the initial mammogram and/or ultrasound. Thus, clinicians and surgeons are precariously faced with the challenge of how to best manage these patients by either offering additional imaging with galactography and/or MRI prior to microductectomy.

The majority of our patients had benign pathology diagnosed by microductectomy. Intraductal papilloma was the most common cause of nipple discharge which is consistent with previous literature [5–7]. The overall incidence of malignancy was 14% (3% invasive cancer and 11% DCIS). Of particular interest are the 67% ($n=155$) of patients whose clinical exam and initial radiological work up with MMO and US was completely negative thus prompting further evaluation with microductectomy ± galactography and/or MRI. Within this subset of clinical and imaging negative patients—3% had invasive carcinoma and 10% had DCIS which is concordant with the results of others [6, 7]. In contrast, Gray and colleagues [8] have deemed patients with unilateral (bloody or serous) discharge, single duct and negative MMO and US as low risk of cancer. In their study, they cite a 0% risk of malignancy and recommend close follow up opposed to duct excision. Sable et al. [9] reported 5% of patients with nipple discharge who underwent duct excision were diagnosed with cancer. Our results do not support this

Table 2 Clinical and radiological risk factors associated with malignancy

Risk factor	All patients			Clinical and image negative patients		
	Benign (*n*, %)	Malignant (*n*, %)	*p* value	Benign (*n*, %)	Malignant (*n*, %)	*p* value
Age (mean, range)	54 (17–88)	58 (26–86)	0.216	54 (17–79)	59 (28–86)	0.292
Under 30	5 (2.5%)	2 (6.3%)	–	4 (3.0%)	1 (5.0%)	–
30–49	69 (34.7%)	9 (28.1%)	–	46 (34.1%)	6 (30.0%)	–
50–69	99 (49.7%)	12 (37.5%)	–	63 (46.7%)	8 (40.0%)	–
Over 70	26 (13.1%)	9 (28.1%)	–	22 (16.3%)	5 (25.0%)	–
Total patients	199 (100%)	32 (100%)	–	135 (100%)	20 (100%)	–
Age below 50	74 (37.2%)	11 (34.4%)		85 (63%)	7 (35%)	–
Age above 50	125 (62.8%)	21 (65.6%)	0.760	50 (37%)	13 (65%)	<0.001
Bloody discharge	101 (50.8%)	26 (81.3%)	0.001	72 (53.3%)	16 (80.0%)	0.025
Mass on examination	14 (7.1%)	5 (15.6%)	0.107	–	–	–
Abnormal mammogram	16 (8.1%)	4 (14.3%)	0.001	–	–	–
Abnormal ultrasound	48 (26%)	5 (20%)	0.569	–	–	–
Abnormal galactogram	68 (64%)	14 (74%)	0.393	49 (63.6%)	10 (73.7%)	0.255

Table 3 Sensitivity and specificity of clinical and radiological variables

	Bloody discharge	Mass on examination	Galactogram
Sensitivity	0.81	0.16	0.63
Specificity	0.49	0.93	0.36
PPV	20.5%	26.3%	15.0%
NPV	94.2%	87.1%	84.8%

approach of watchful waiting as 13% of malignancies would have been left in-situ thus delaying definitive management.

Several risk factors have been identified that increase the risk of malignancy in women with nipple discharge. These include unilateral, single duct and bloody nipple discharge, age over 50 and discharge associated with skin changes and/or a detectable mass [10]. Our results support these previously reported risk factors with the exception of mass on clinical exam which was not significant ($p=0.107$). We identified abnormalities on mammography as a potential risk factor for malignancy. Among the 20 patients with suspicious mammograms, 4 were diagnosed with a malignancy (3 DCIS and 1 invasive cancer) by microductectomy. Three of these patients had biopsies which

Table 4 Overview of patients with benign pathology who developed cancer in the ipsilateral breast

Age at cancer diagnosis	Initial pathology	Months between microductectomy and cancer diagnosis	Pathology	Treatment	Lymph nodes status
69	Intraductal papilloma	9	Invasive ductal carcinoma	Partial mastectomy with SLNB	Positive
79	Intraductal papilloma	67	Invasive ductal carcinoma	Total mastectomy with SLNB	Positive
44	Intraductal papilloma	54	Ductal carcinoma in situ	Nipple sparing mastectomy with SLNB	Negative
51	Intraductal papilloma	13	Invasive ductal carcinoma	Partial mastectomy with SNLB	Positive
53	Intraductal papilloma	28	Invasive ductal carcinoma	Fine wire localization and excision	X
63	Atypical ductal hyperplasia DINb	54	Ductal carcinoma in situ	Fine wire localization and excision	X
47	Fibroadenoma/epithelial hyperplasia	32	Invasive ductal carcinoma	Total mastectomy	Negative
43	Benign fibroglandular tissue	7	Invasive ductal carcinoma	Skin sparing mastectomy with SLNB	Negative

were negative for cancer warranting surgery. In our study, patients with SND who had a mass detected by mammography whom had a biopsy proven cancer would not have been captured as they would have been offered a breast conserving surgery or mastectomy opposed to microductectomy. Biopsy sampling error may have potentially missed the causative lesion in these patients. Nevertheless, nipple discharge with suspicious abnormalities on mammogram have been shown to increase the risk of cancer [11]. Thus, if mammography shows a suspicious lesion and the image-guided biopsy is discordant with the radiology, further investigation of the suspicious lesion with a repeat core needle biopsy, microductectomy and/or additional imaging with MRI should be offered.

One of the most challenging clinical scenarios is how to best approach a patient with nipple discharge when there is no clinical mass nor evidence of disease on initial diagnostic evaluation with mammography and ultrasound. Galactography has been used as a second line modality to assess this subset of patients prior to surgery and its utility has been highly debated in the literature. Pre-operative galactograms have been shown to increase the likeliness to identify an intraductal lesion at the time of major duct excision [2]. However, the drawback with galactography is that it does not differentiate between benign and malignant lesions and has a high failure rate between 15 and 23% even in the hands of experienced radiologists [3, 12]. In our study, galactography identified intraductal masses in 64.3% ($n=83$) of the 129 patients who underwent this procedure. The sensitivity and specificity were low with values of 63% and 36%, respectively. Moreover, the failure rate of the galactogram was 19.5% and was inconclusive in 4.1% of patients. Recently, a large meta-analysis was performed comparing MRI vs. galactography in 921 patients which are concordant with the results from our centre. Berger and colleagues [4] recently reported the pooled sensitivity and specificity for any abnormality was 92% and 76% for MRI compared to 69% and 39% for galactography. Breast MRI has been shown to be a superior modality to galactography in several studies and particularly useful in patients whose initial mammogram and ultrasound failure to reveal a cause of nipple discharge [12]. Our center utilizes breast MRI, however, only 20 were performed within our patient cohort and were not included in our analysis. Nevertheless, further studies focusing on cost-analysis between galactography, MRI vs. proceeding directly to surgical removal of the duct will prove beneficial in weighing the diagnostic value vs. healthcare cost when deciding on how to proceed with clinical and radiologically negative patients with nipple discharge.

Lastly, we found that 3% of patients who were initially diagnosed with a non-cancerous lesion by microductectomy were later diagnosed with a cancer in the ipsilateral breast. On average, cancer was detected within 3 years from their initial duct excision. Two of these patients required re-operation within the first year from their microductectomy. It is possible that there may have been a failure of the duct excision to successfully remove the causative lesion, however, since imaging abnormalities were later identified it is also possible that another process was evolving. Overall, the number of patients diagnosed with cancer after a negative duct excision is low.

Conclusions

Nipple discharge is a common problem referred to breast surgeons and is particularly challenging when initial efforts to identify the causative lesions proves futile with mammography and ultrasonography. We recommend proceeding with microductectomy in patients who have no palpable masses and non-suspicious imaging from initial work up with mammogram and ultrasound given the 13% detection rate of malignancy. Moreover, duct excision offers definitive management for symptomatic nipple discharge regardless of the etiology. Pre-operative galactogram is neither sensitivity nor specific and given its high failure rate we have begun to limit our use of this imaging modality. The role of MRI in the evaluation of nipple discharge is promising but still warrants further investigation. Its use is beyond the scope of this study; however, patients with negative initial evaluation with MMO and US may benefit from MRI—particularly in women of childbearing age or those who wish to avoid surgery for other reasons. However, these women should be counselled on the risk of a false negative resulting in a delay in definitive management in the setting of persistent nipple discharge.

Compliance with ethical standards

Conflict of interest The authors of this manuscript have no conflicts of interest to declare for this publication.

Ethical approval This study was approved by the Research Ethics Board by the University of British Columbia and Providence Health Care. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Appendix

See Tables 5 and 6.

Table 5 Incidence of benign and cancerous pathology from microductectomy in all patients

Pathology	Patients (*n*)	Percentage (%)	
Total benign (other)	34		14.7
Benign tissue	9	3.9	
Fibroadenoma	6	2.6	
Inflammatory	6	2.6	
Fibrocystic changes	12	5.2	
Complex sclerosing lesion	1	0.4	
Duct ectasia	20		8.7
Total atypia	17		7.4
Flat epithelial atypia (DIN 1a)	3	1.3	
Atypical ductal hyperplasia (DIN 1b)	9	3.9	
Mixture of DIN 1a and DIN 1b	3	1.3	
Atypical lobular hyperplasia (LIN 1)	2	0.9	
Lobular carcinoma in situ (LIN 2)	0	0.0	
Intraductal papilloma	128		55.4
Total cancerous	32		13.8
Invasive carcinoma	7	3.0	
Ductal carcinoma in-situ	25	10.8	
Total	231	100	100

Table 6 Incidence of benign and cancerous pathology from microductectomy in clinically and radiologically negative patients

Pathology	Patients (*n*)	Percentage (%)	
Total benign (other)	23		14.8
Benign tissue	7	4.5	
Fibroadenoma	2	1.3	
Inflammatory	4	2.6	
Fibrocystic changes	9	5.8	
Complex sclerosing lesion	1	0.6	
Duct ectasia	17		11
Total atypia	17		7.4
Flat epithelial atypia (DIN 1a)	3	1.9	
Atypical ductal hyperplasia (DIN 1b)	7	4,5	
Mixture of DIN 1a and DIN 1b	2	1.3	
Atypical lobular hyperplasia (LIN 1)	1	0.6	
Lobular carcinoma in situ (LIN 2)	0	0.0	
Intraductal papilloma	82		52.9
Total cancerous	20		12.9
Invasive carcinoma	4	2.6	
Ductal carcinoma in-situ	16	10.3	
Total	155	100	100

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