



# Benign breast papillary lesions diagnosed on core biopsy: upgrade rate and risk factors associated with malignancy on surgical excision

Christine MacColl<sup>1,2</sup> · Amir Salehi<sup>2</sup> · Sameer Parpia<sup>3</sup> · Nicole Hodgson<sup>4</sup> · Milita Ramonas<sup>5</sup> · Phillip Williams<sup>2</sup>

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## Abstract

Evaluation of radiologically detected breast lesions is a common task in surgical pathology. Some benign lesions on biopsy are associated with an upgrade to in situ or invasive carcinoma on excision. The non-atypical breast papilloma has published upgrade rates of 0 to 29%. Traditionally, papillomas have been managed surgically, but the wide range of upgrade rates has raised uncertainty about the need for routine surgical excision. This study aims to identify risk factors associated with upgrade and determine the upgrade rate of non-atypical papillomas at our institution. In a retrospective review of pathology reports, we identified 266 patients with a diagnosis of benign papilloma on breast core biopsy. One hundred eighty-two patients underwent surgical resection. The final surgical pathology reports of all patients were reviewed and divided into one of two groups—benign or malignant. Twenty-one patients had a final diagnosis of in situ or invasive carcinoma, resulting in an upgrade rate of 12%. Radiologically detected lesions with calcifications were at higher risk for upgrade (OR = 4.45, 95% CI 1.08–18.27) than lesions without calcifications. Additionally, advanced patient age (OR = 1.07, 95% CI 1.03–1.13) and lesion size greater than 0.5 cm (OR = 2.59, 95% CI 0.38–17.48) was associated with upgrade to malignancy. Routine surgical excision of all papillomas is not recommended. Younger patients without high-risk features may benefit from clinical and radiologic follow-up alone. Accurate risk stratification will spare low-risk women unnecessary surgery.

**Keywords** Breast neoplasms · Core biopsy · Intraductal papilloma · Upgrade

## Introduction

Evaluation of radiologically detected breast lesions is a common task in surgical pathology. The number of patients undergoing breast core biopsies has increased throughout the

world with the use of breast cancer screening programs [1]. Some lesions, which are benign on biopsy, are associated with an upgrade to high-risk lesions, in situ carcinoma, or invasive carcinoma on excision. A common lesion with potential for upgrade is the intraductal papilloma. Papillomas are composed of well-developed fibrovascular cores covered by two cell types—a basal or myoepithelial layer and a luminal epithelial layer [1]. Some authors believe that papillomas have potential for gradual transformation to intraductal papillary carcinoma or papillary ductal carcinoma in situ (DCIS), which occurs over decades. Transformation may result from replacement of the luminal epithelial layer with a neoplastic cell population, leading to in situ and eventually invasive carcinoma [2]. This hypothetical progression remains poorly understood, and other authors propose that intraductal papillary carcinoma is truly a de novo proliferation [2]. In our review of the recent literature (2015–2018), the intraductal papilloma has an incidence of upgrade ranging from 0 to 16% [3–10]; findings and author recommendations are summarized in Table 1. Bianchi et al. [5] published an extensive review of the literature dating back to 1999 and identified 54 studies evaluating the upgrade

✉ Christine MacColl  
christine.maccoll@medportal.ca

<sup>1</sup> Department of Pathology and Molecular Medicine, McMaster University Medical Center, 1200 Main Street West, Hamilton, ON L8N 3Z5, Canada  
<sup>2</sup> Department of Pathology and Molecular Medicine, Juravinski Hospital – Hamilton Health Sciences, 711 Concession St, Hamilton, ON L8V 1C3, Canada  
<sup>3</sup> Department of Oncology, McMaster University, 711 Concession St, Hamilton, ON L8V 1C3, Canada  
<sup>4</sup> Department of Surgery, Juravinski Hospital – Hamilton Health Sciences, 711 Concession St, Hamilton, ON L8V 1C3, Canada  
<sup>5</sup> Department of Radiology, Juravinski Hospital – Hamilton Health Sciences, 711 Concession St, Hamilton, ON L8V 1C3, Canada

of papillary lesions without atypia on biopsy to malignant lesions on excision. Within those 54 studies, the upgrade rate ranges widely from 0 to 29%.

Traditionally, the management of benign breast papillary lesions has been surgical excision to exclude malignancy with complete histologic examination. In our region and institution, the guidelines, as per Cancer Care Ontario, still recommend surgical referral and the majority of patients undergo surgical excision. The wide range of published upgrade rates has raised uncertainty about the need for routine surgical excision of all papillomas.

The current study aims to determine the incidence of upgrade to malignancy in benign breast papillary lesions diagnosed on core biopsy. Additionally, we aim to evaluate histopathological, radiological, and clinical features associated with higher risk of malignancy on excision.

## Materials and methods

This multi-institution, retrospective study was conducted primarily in the Department of Pathology and Molecular Medicine at the Juravinski Hospital and Cancer Center. Patients were also included from the Hamilton General Hospital, McMaster University Medical Centre, and St. Joseph's Healthcare Hamilton. The project was approved by the Hamilton Integrated Research Ethics Board (project number 2227-C).

The pathology reports of all breast core biopsies performed between January 2006 and May 2017 were searched electronically for a diagnosis of “papilloma” or “papillary” lesion. Galactography and breast cytology are extremely rare at our institution and were not included in the search. The pathology

reports of interest were screened to exclude cases with an associated malignancy or atypia, such as atypical ductal hyperplasia (ADH). All non-atypical papillary lesions, regardless of size, were included. For cases meeting inclusion criteria, a dataset was populated with clinical, radiological, and histologic details. Pathology reports from surgical excisions, performed within 6 months of biopsy diagnosis, were retrieved and divided into one of two groups—benign or malignant. As defined by previous authors, an “upgrade” was defined as in situ or invasive carcinoma identified in the resection specimen [4, 8]. Core biopsy and resection slides from upgraded cases were reviewed by a blinded breast pathologist (AS or PW), including all H&E and immunohistochemistry ordered by the original pathologists. There were no additional stains ordered by the authors.

## Statistics

The proportion of patients upgraded to malignancy and corresponding 95% confidence interval (CI) was calculated using the Wilson Score approach. Logistic regression with Firth's penalization was used to investigate the relationship between upgrade to malignancy and baseline characteristics. Variables to be included in the model were pre-specified: patient age, BIRADS, type of radiologic abnormality, and lesion size.

## Results

From January 2006 to May 2017, there were over 14,000 breast biopsies performed at our institutions. During that period, 266 patients were diagnosed with a papillary lesion without atypia on breast core biopsy. The median age of the cohort

**Table 1** Review of the recent literature—upgrade rate and management recommendations for patients diagnosed with intraductal papilloma on breast core biopsy

Paper	Year	Patients, <i>n</i>	Upgrade to malignancy, <i>n</i> (%)	Management recommendation
Leithner et al. [3]	2018	62	10 (16)	Observation alone might not be appropriate; particularly for patients with peripheral papillomas
Foley et al. [4]	2015	188	27 (14)	Excision is recommended due to potential for upgrade; there is a role for prospective observational trials in women younger than 35
Bianchi et al. [5]	2015	68	9 (13)	Further assessment by surgical or vacuum-assisted excision
Seely et al. [6]	2017	47	4 (9)	N/A
Ko et al. [7]	2017	135	9 (7)	Close follow-up with ultrasound for patients with lesions 1.0 cm or less
Armes et al. [8]	2017	67	4 (6)	Refer for multidisciplinary review before surveillance is recommended; particularly low-risk patients include those with incidental papillary lesions adjacent to another benign lesion
Hong et al. [9]	2016	234	14 (6)	Close observation in women less than 55 years of age and with mass size 1.0 cm or less
Moon et al. [10]	2016	44	0 (0)	Uniform surgical excision is not a reasonable management strategy

was 56 years, a median of four cores were obtained per patient, and additional baseline characteristics are shown in Table 2.

One hundred eighty-two patients underwent surgical resection, 62 were followed clinically, and 22 were lost to follow-up. Among the patients who underwent surgical resection, 23 had a diagnosis of malignancy on their resection pathology report and 159 patients had only benign findings. Upon expert review (PW and AS) of the 23 upgraded cases, 2 were

excluded—one for lack of convincing papillary lesion on biopsy and one for presence of atypia on biopsy. Within the included upgraded group (21 patients), 15 had an in situ carcinoma (either DCIS or lobular carcinoma in situ (LCIS)), 1 was diagnosed with an encapsulated papillary carcinoma, and 5 patients had an invasive carcinoma. Within the in situ carcinoma group, there were 12 patients upgraded to DCIS—including two cases of papillary DCIS, one micropapillary DCIS, and one mixed papillary-micropapillary DCIS. All five

**Table 2** Clinical, radiologic, and histologic baseline characteristics

Feature	Non-surgical or lost to follow-up ( <i>n</i> = 84)	Final diagnosis on surgical excision		<i>p</i> value*
		Benign ( <i>n</i> = 159)	Malignant ( <i>n</i> = 21)	
Age (years), median	58	55	64	< 0.01
BIRADS, <i>n</i> (%)				
3	13 (15)	43 (27)	0	
4	69 (82)	105 (66)	16 (76)	< 0.01
5	1 (1)	3 (2)	4 (19)	
Missing	1 (1)	8 (5)	1 (5)	
Radiographic abnormality, <i>n</i> (%)				
Mass with calcifications	2 (2)	7 (4)	4 (20)	
Mass without calcifications	60 (71)	126 (79)	13(62)	0.03
Other**	22 (26)	26 (17)	4 (19)	
Lesion size (cm), <i>n</i> (%)				
≤ 0.5 cm	14 (17)	20 (13)	1 (5)	
> 0.5 cm	48 (57)	113 (71)	16 (76)	
No mass	22 (26)	26 (16)	4 (19)	
Lesion size (cm), median	0.9	0.9	1.1	
Radiologic-pathologic correlation, <i>n</i> (%)				
Concordant	33 (39)	100 (63)	13 (62)	
Discordant	0	0	0	
Unknown	51 (61)	59 (37)	8 (38)	
Myoepithelial IHC on biopsy, <i>n</i> (%)				
Yes	33 (39)	82 (52)	7 (33)	
No	51 (61)	77 (48)	14 (67)	
Days from biopsy to surgery, median	n/a	67	60	
Gauge of biopsy needle, <i>n</i> (%)				
9	2 (2)	1 (1)	0	
11	0	1 (1)	0	
14	49 (58)	107 (67)	11 (52)	
18	7 (8)	8 (5)	2 (10)	
Missing	26 (31)	42 (26)	8 (38)	
Number of cores, median	4	4	4	
Biopsy histologic presence of, <i>n</i> (%)				
Calcifications	18 (21)	24 (15)	5 (24)	
Sclerosis	21 (25)	37 (23)	5 (24)	

*SD* standard deviation

\**p* value for comparison between benign and malignant group

\*\*other includes patients with calcifications only or a non-mass radiologic abnormality

invasive cases were ductal carcinoma NOS, although one patient had an additional mucinous component. The biomarker status was variable among these five patients (Fig. 1). Overall, upgrade in our population occurred in 21 of 180 patients, resulting in a 12% incidence of upgrade (95% confidence interval (CI) 8–17).

### Patients with benign and upgraded diagnoses on surgical excision

A comparison of the two groups revealed four important differences. Firstly, as expected, higher BIRADS was associated with increased risk of malignant disease ( $p < 0.01$ ). Secondly, the upgraded group had a median age that was 9 years older than patients with benign diagnoses. With each increased year, the patient's relative risk for upgrade to malignancy increased by 7% (OR = 1.07, 95% CI 1.03–1.13). Thirdly, patients with biopsies targeting lesions with calcifications were at greater risk for upgrade (OR = 4.45, 95% CI 1.08–18.27) than patients without radiologically identified calcifications. Finally, lesion size greater than or equal to 0.5 cm (OR = 2.59, 95% CI

0.38–17.48) was associated with increased risk of malignancy on surgical excision (Table 3).

### Patients managed non-surgically or lost to follow-up

Sixty-two patients were managed non-surgically, which involved clinical and/or imaging follow-up alone. Sixty of 62 patients are alive and malignancy free in the ipsilateral breast after a median length of follow-up of 1.1 years. One patient was diagnosed with ipsilateral papillary DCIS 10 months after the original biopsy. One patient died from an unrelated malignancy. Twenty-two patients had no electronic records after the date of breast core biopsy (Fig. 1).

### Discussion

Non-atypical intraductal papillomas of the breast have a relatively indolent clinical course [1]. When diagnosed on core biopsy, the management remains controversial, due to the poorly defined risk of unsampled or subsequent development

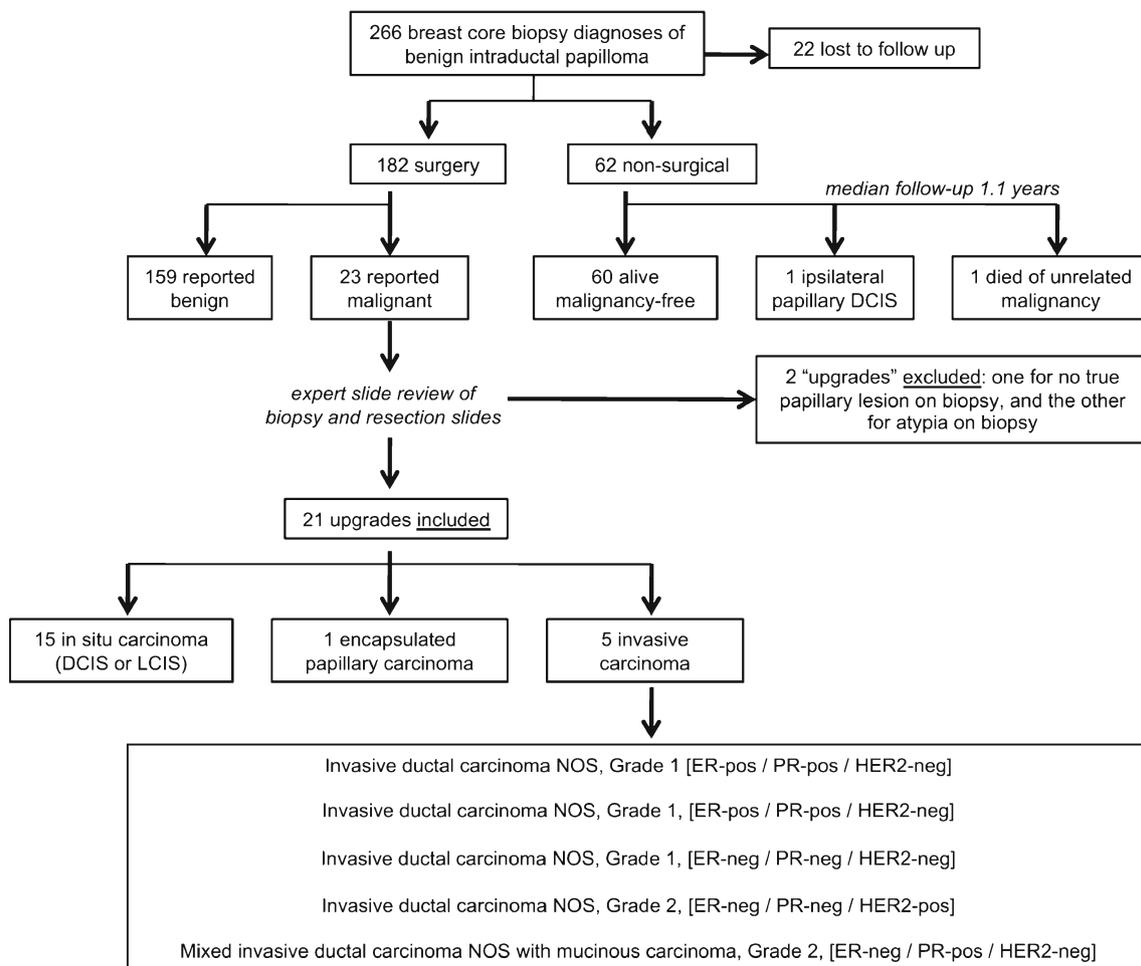


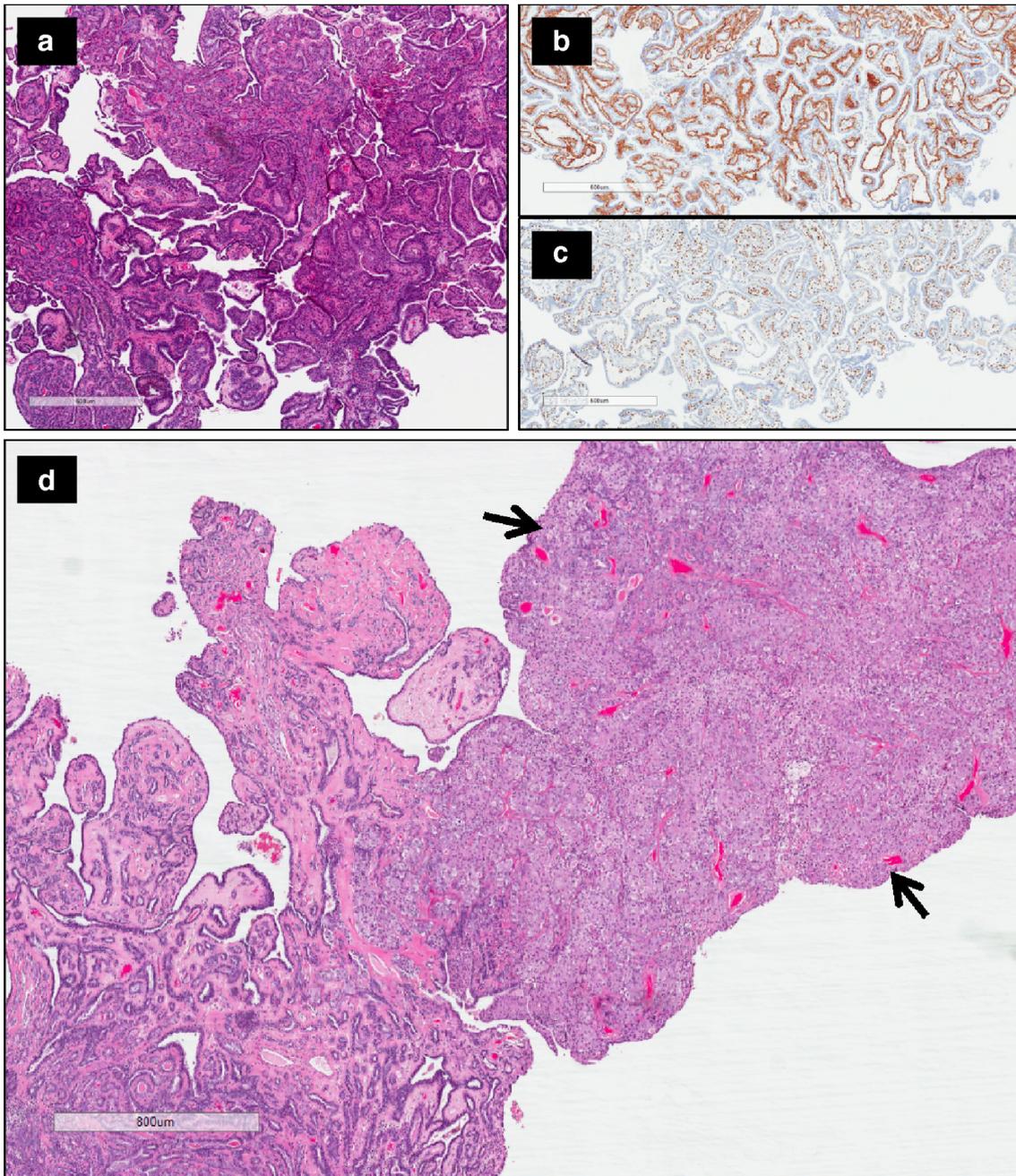
Fig. 1 Experimental design and patient outcome

**Table 3** Results of logistic regression assessing the association between risk factors and upgrade to malignancy in 150 patients with radiologically detected mass

Variable	Odds ratio (95% confidence interval)
Age	1.07 (1.03, 1.13)
Biopsy target: mass with calcifications vs. mass without calcifications	4.45 (1.08, 18.27)
Lesion size: $\leq 0.5$ cm vs $> 0.5$ cm	2.59 (0.38, 17.48)

of malignancy. Traditionally, the default management recommendations have been surgical excision. Bianchi et al. [5] identified older studies with published upgrade rates as high as 27 and 29% [11, 12]; as expected, these authors support routine surgical excision. In contrast, many authors, including Moon et al. [10], found a 0% rate of upgrade.

Recent trends have moved towards risk stratification rather than a uniform surgical approach. In previous studies, clinical and radiologic follow-up has been shown to be appropriate in particularly low-risk situations, including lesion size  $\leq 1.0$  cm



**Fig. 2** Example of upgrade. **a** Breast core biopsy showing papilloma without cytologic atypia, H&E. **b, c** Myoepithelial cell layer highlighted by SMMHC and p63, respectively. **d** Surgical resection from the same patient showing DCIS (→) arising in a papilloma, H&E

[7, 9], women < 55 years old [9], and papillary lesions discovered incidentally due to a separate, adjacent benign lesion [8] (Table 1).

The current study identifies an upgrade rate of 12% (21/180) and is consistent with the recent literature range of 0–16%. Our 12% upgrade rate is likely influenced by the considerable number of women with a benign biopsy who opted for non-surgical management (32%) with only one of the non-surgical patients later diagnosed with an ipsilateral in situ carcinoma.

We chose to include LCIS as an upgraded diagnosis since the relative risk for subsequent invasive carcinoma is 4 to 12 times higher than the baseline population [2]. Classic LCIS is usually an incidental finding associated with a separate mammographically detected lesion. Florid and pleomorphic LCIS often produce mammographically detectable calcifications, necrosis, or masses [13]. Since the three cases of LCIS in our patient population had classic morphology, they were likely incidental findings.

In our patient population, upgrade to malignancy was significantly associated with older age at time of biopsy and higher BIRADS. Among patients presenting for biopsy of a lesion, we found that a lesion size greater than 0.5 cm and presence of calcifications increased the risk for a malignant diagnosis on surgical resection. Patients without a radiologically identifiable lesion were at lower risk for upgrade. This non-mass group included women with micropapillomas, which have been demonstrated previously to have a 0% rate of upgrade [14]. The wide confidence intervals, however, indicate that more information is needed from larger patient samples to standardized management guidelines. Our study was limited by the infrequent occurrence of upgrade to malignancy; only 21 upgrades among the entire group and 17 upgrades among the patients with radiologically targeted mass lesions.

Pathologists evaluating papillomas on breast core biopsies are encouraged to use a simple panel of immunohistochemistry to identify a myoepithelial layer in the fibrovascular cores and in the lining of the glandular components within broader papillae. Although IHC is routinely utilized to rule out invasion, it can also aid in the detection of ductal carcinoma in situ arising in a papilloma. Myoepithelial cells are typically absent within the foci of DCIS, however, will be retained at the periphery of the lesion [2]. A panel-based approach of two markers may ease interpretation [15]. SMMHC and p63 stain nearly 100% of myoepithelial cells [16] and are used routinely at our institution (Fig. 2). While p63 is highly specific for myoepithelium, SMMHC expression is also seen in vascular smooth muscle cells (100%) and occasionally in stromal myofibroblasts (8%) [16].

Management and risk stratification of benign breast papillomas have been an evolving topic of interest for decades. The current study identified 180 patients undergoing surgical

resection for a non-atypical papilloma identified on breast core biopsy, which is one of the largest sample sizes to date. Our data contributes to a body of literature with a wide range of findings and recommendations. Clarity in treatment guidelines and risk stratification would have multidisciplinary implications, including practice changes in pathology, surgery, radiology, and family medicine.

In conclusion, within our patient population, the upgrade rate from benign papilloma on core biopsy to malignancy on excision is 12%; however, routine surgical excision is not recommended. Risk factors associated with malignancy are advanced patient age and high BIRADS score. Among patients with radiologically identified lesions, higher risk was associated with size greater than 0.5 cm and radiologically identified calcifications. Younger women with biopsies targeting non-mass abnormalities and low BIRADS may benefit from clinical and imaging follow-up alone. Accurate risk stratification will spare low-risk women unnecessary surgery and increase operating room availability for women with more aggressive disease.

**Authors' contribution** The authors contributed to this study as follows: C. MacColl and P. Williams: study design and execution, identification of cases, review of histological slides, and manuscript preparation. A. Salehi: review of select histologic slides, support of study, and breast pathology consultant. S. Parpia: study design and statistical analysis. N. Hodgson: support of study and surgical consultant. M. Ramonas: support of study and radiological consultant. Participating investigator, Cathy Chang, retrieved and filed all histopathological slides for review.

## Compliance with ethical standards

The project was approved by the Hamilton Integrated Research Ethics Board (project number 2227-C).

**Conflict of interest** The authors declare that they have no conflicts of interest.

**Abbreviations** BIRADS, breast imaging-reporting and data system; SMMHC, smooth muscle myosin heavy chain

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