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FACTORS ASSOCIATED WITH SURGICAL EXCISION IN PATIENTS WITH PAPILLARY BREAST LESIONS: A 20-YEAR SINGLE-CENTER EXPERIENCE IN SOUTH KOREA

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Abstract

Background: Patients with incidental benign solitary papilloma of the breast with imaging concordance may be offered follow-up treatment. Recently, as vacuum-assisted breast biopsy (VAB) has become more common, it is increasingly being used as an alternative to core needle biopsy for initial biopsy. This study investigated the factors that necessitate surgical excision after initial needle biopsy of papillary breast lesions. **Methods:** A retrospective review was conducted of patients diagnosed with papilloma or papillary findings in pathology reports at a single institution between 2001 and 2020. Logistic regression and Cox proportional hazards models were used to analyze the factors associated with surgical excision and papilloma recurrence. **Results:** Among the 266 patients reviewed, the malignancy upgrade rate was 6.7%, with significantly higher rates in lesions with atypia ($p<0.001$). Factors associated with the need for surgical excision after initial needle biopsy included older age (odds ratio [OR] =1.064; $p=0.015$), larger tumor size (OR=3.015; $p=0.003$), and absence of intraductal lesions (OR=0.049; $p<0.001$). Additionally, a higher body mass index (BMI) was associated with the recurrence of benign papillary lesions (OR=1.156; $p=0.045$), and patients with a BMI below 25 showed a significantly lower recurrence rate. **Conclusion:** Older age, absence of intraductal lesions, and larger tumor size were associated with the likelihood of requiring surgical excision following needle biopsy. These findings suggest that VAB or vacuum-assisted excision should be considered in younger women with smaller intraductal lesions. Additionally, higher BMI was found to be significantly associated with the recurrence of benign papillomas.

Keywords: *Breast neoplasm; Papilloma, intraductal; Breast disease; Biopsy, needle; Operative Surgical Procedures.*

Introduction

Papillary lesions of the breast are a heterogeneous group of neoplasms with several morphological similarities. These lesions can present diagnostic challenges due to overlapping clinical and radiological features, potentially leading to diverse clinical outcomes [1]. Management of papillary breast lesions has evolved recently, particularly with the increasing use of vacuum-assisted breast biopsy (VAB) techniques.

Excision has been recommended when a papilloma with atypical cells is found on core biopsy [2-5]. Papillary lesions with atypia confer an increased risk of breast cancer or progression to malignancy over the long term, with pathological upgrade rates up to 67% [5,6]. However, management of solitary papillomas without atypia is not definitive. The reported rates of pure papillary lesions upgraded to malignancy have varied widely, ranging from 5% to 20% [2, 4, 7], although recent trends show a decrease to below 10% in the last decade [8].

The use of VAB has become more common due to its convenience and proven safety. VAB is increasingly being employed as an initial diagnostic tool for papillary lesions [9, 10]. This technique offers several advantages over core needle biopsy, including the ability to obtain larger tissue samples and complete removal of small lesions. The increasing use of VAB has led to a paradigm shift in the management of papillary breast lesions, with many institutions choosing VAB as the initial biopsy method. It is important to distinguish between VAB used for diagnosis and vacuum-assisted excision (VAE) used for non-surgical removal of lesions. VAE has emerged as a potential alternative to surgical excision for certain papillary lesions, particularly those classified as B3 (lesions with uncertain malignant potential).

A prospective study of 116 patients with intraductal papilloma without atypia identified in a core biopsy, the upgrade rate was found to be 1.7% according to a local review [11]. This finding suggests that routine excision may not be necessary for intraductal papilloma without atypia following a core biopsy with concordant imaging findings [11]. With the growing

use of VAB, it's becoming more common to employ VAB for initial biopsy [12]. However, if a lesion is identified as malignant in VAB, further wide excision may be required [13]. Additionally, reoperation for wide excision can be considered in cases of malignancy identified in excisional biopsy.

The current study focused on understanding the determinants involved in the decision-making process for performing surgical excisions with appropriate margins after an initial needle biopsy. By identifying the factors associated with the need for surgical excision, this study aimed to provide guidance for clinicians in determining the most appropriate management strategy for patients with papillary breast lesions. Furthermore, this study also investigated the recurrence patterns of benign papillary lesions by analyzing data on the factors that contribute to their recurrence. Understanding the factors associated with recurrence can help inform follow-up strategies and risk assessments of patients with benign papillary lesions.

Methods

This retrospective study was conducted at Incheon Saint Mary's Hospital, Catholic University of Korea. We reviewed the electronic medical records to identify female patients diagnosed with papilloma or papillary lesions between 2001 and 2020. This study included patients with pathologically confirmed papillary neoplasms diagnosed either through initial biopsy tissue or subsequent surgical specimens. The initial diagnostic procedures varied among patients, including needle aspiration, core biopsy, VAB, or surgical excision. Patients with a previous history of breast malignancy or those who did not have papillary lesions were excluded from the pathological reports. This study was approved by the Institutional Review Board of The Catholic University of Korea (IRB No. OC22RASI0055). And IRB was conducted in accordance with the tenets of the Declaration of Helsinki. Written Informed consent was not required from the study participants. Written Informed consent was not obtained, and a written reason for the consent process exemption was submitted.

Lesions were categorized as papillary neoplasms without atypia, with atypia, carcinoma in situ, or invasive cancer. This classification was based on pathological assessments based on epithelial atypia and the presence of the myoepithelial layer [14]. Experienced breast cancer specialists, including surgeons and radiologists, conducted clinical and radiological examinations. Symptoms such as nipple discharge and palpability were documented in the medical charts or recorded as text under the corresponding symptom section. Clinicopathological data, treatment modalities, and follow-up details were systematically recorded from the date of initial diagnosis to February 2022.

The primary objective was to identify factors associated with the need for surgical excision after initial needle biopsy. We defined the "conventional process" as cases requiring an initial needle biopsy (core or VAB) followed by surgical excision. Comparing this group with other cases, initial VAB or VAE may have been sufficient without further surgery. The secondary objective was to investigate factors contributing to the recurrence of benign papilloma, after excluding patients with malignancy from this analysis.

Categorical and continuous variables were compared using the chi-squared test and t-test, respectively. Logistic regression facilitated multivariate analysis of the primary objective. Recurrence of benign papilloma was evaluated using a Cox proportional hazards model. Significant factors were identified in multivariate analysis and further analyzed using Kaplan-Meier curves. A p-value of less than 0.05 was considered statistically significant.

Results

Among 272 patients treated for papillary breast lesions, 253 were eligible for analysis after excluding 19 patients with non-papillary lesions at initial biopsy or a history of breast malignancy. In total, 266 cases were considered for analysis (Fig. 1) including bilateral lesions. Initial pathology classified 155 papillomas without atypia, 39 with atypia, 12 cases of carcinoma in situ, and 22 invasive carcinomas. Additionally, 38 cases were excluded because of missing data or non-papillary nature. Among malignant cases of initial pathology, we observed four cases of papillary carcinoma in situ, seven cases of encapsulated papillary carcinoma, and one case of papilloma with ductal carcinoma in situ. Invasive cases included 20 cases of invasive papillary or micropapillary carcinoma and 2 cases of other combined tumor types.

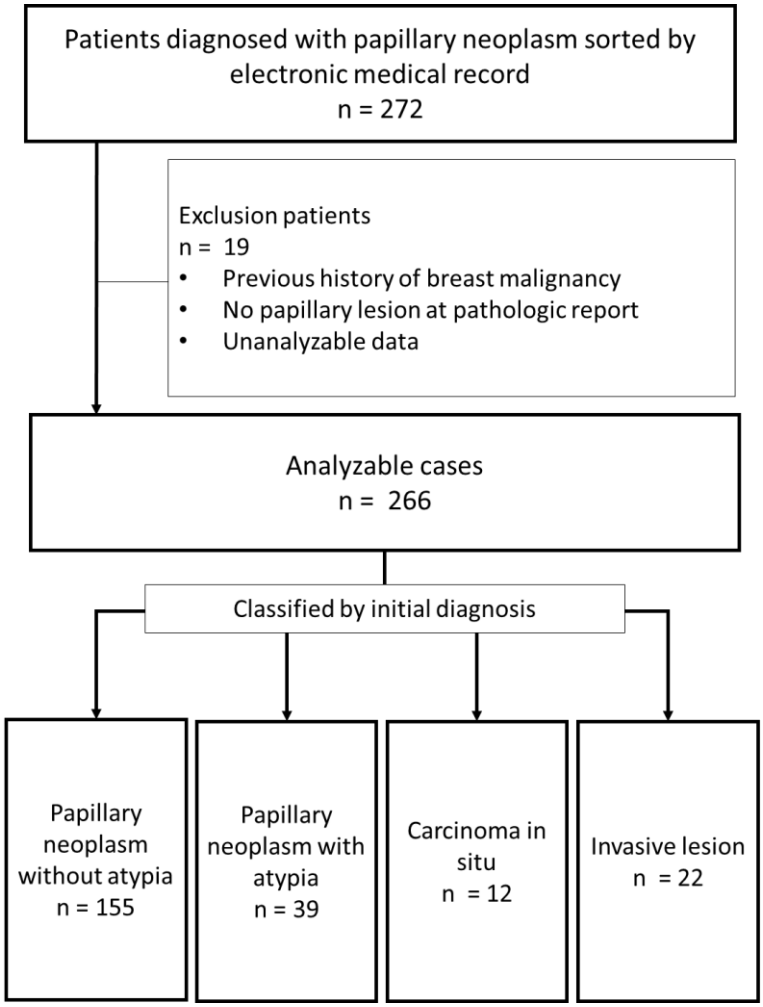

Figure 1. Schematic of the process used to select eligible cases for analysis.

Analysis of benign papillary lesions (194 cases) revealed a significant rate of malignancy upgrade in the atypia group (23.1%, 9 out of 39 cases; $p<0.001$, **Table 1**).

The mean age in the conventional process group was 56 years, compared to 47 years in the vacuum-assisted procedure group ($p<0.001$). The body mass index (BMI) was also significantly higher in the conventional group (25.2 vs. 23.1; $p=0.007$). Differences were notable in palpability, nipple discharge, radiologic size, Breast Imaging Reporting and Data System (BI-RADS) category, presence of intraductal lesions, biopsy method, WHO classification, and tumor size in permanent pathology (**Figure 2**, **Table 2**).

Table 1. Comparison of malignancy upgrades of papillary lesions according to the presence or absence of atypia

	Papillary lesion without atypia (n=155) No. (%)	Papillary lesion with atypia (n=39) No. (%)	p-value
Not upgrade	84 (54.2%)	25 (64.1%)	<0.001
Upgrade	4 (2.6%)	9 (23.1%)	
NA	67 (43.2%)	5 (12.8%)	

* NA: not applicable

Table 2. Patient characteristics and factors associated with the conventional process (initial needle biopsy followed by surgery) (n=266)

		N (%) of possible cases by vacuum-assisted procedure	N (%) of requiring cases for conventional process	*p*-value
Total cases		218	48	
Baseline characteristics				
Age (yr)				<0.001
	Number	218	48	
	Mean	46.7	56.2	
	Range	13-78	33-80	
BMI				0.007
	Number	135	40	
	Mean	23.1	25.2	
	Range	15.0-33.7	19.5-42.4	
Family history of breast cancer				0.875
	No	209 (96.3%)	46 (18.0%)	
	Yes	8 (3.7%)	2 (4.2%)	
	Missing	1	0	
Symptoms				
Palpable				0.001
	No	171 (78.4%)	27 (56.3%)	
	Yes	47 (21.6%)	21 (43.8%)	
Nipple discharge				
	No	143 (65.6%)	41 (85.4%)	0.007
	Yes	75 (34.4%)	7 (14.6%)	
Radiologic features				
Image size (cm)				<0.001
	No	207	47	
	Mean	1.1	1.9	
	Range	0.2-4.7	0.5-5.3	
BI-RADS				<0.001
	2	1 (0.5%)	0 (0.0%)	
	3	19 (8.7%)	1 (2.1%)	
	4	55 (25.2%)	13 (27.1%)	
	4A	93 (42.7%)	6 (12.5%)	
	4B	40 (18.3%)	12 (25.0%)	
	4C	6 (2.8%)	4 (8.3%)	
	5	2 (0.9%)	10 (20.8%)	
	6	0 (0.0%)	2 (4.2%)	
	Missing	2 (0.9%)	0 (0.0%)	
Lesions				0.491
	Single	189 (87.1%)	40 (83.3%)	
	Multiple	28 (12.9%)	8 (16.7%)	
	Missing	1	0	
Intraductal lesions				<0.001
	No	45 (20.6%)	42 (87.5%)	
	Yes	173 (79.4%)	6 (12.5%)	
	Missing	0	0	
Initial biopsy methods				0.002
Fine needle aspiration		32 (16.1%)	2 (4.2%)	

Core needle biopsy		94 (43.3%)	36 (75.0%)	
Vacuum-assisted biopsy		12 (5.5%)	2 (4.2%)	
Surgical excision		71 (32.7%)	8 (16.7%)	
Others		5 (2.3%)	0 (0.0%)	
Missing data				
Permanent pathology				
WHO classification				<0.001
Benign papilloma		121 (55.5%)	0 (0.0%)	
Papilloma with atypia, DCIS		20 (9.2%)	2 (4.2%)	
Papillary DCIS		0 (0.0%)	5 (10.4%)	
Papillary carcinoma		0 (0.0%)	34 (70.8%)	
Others		2 (0.9%)	3 (6.3%)	
Missing data		75 (34.4%)	4 (8.3%)	
tumor size (cm)				<0.001
	No	143	43	
	Mean	1.2	2.4	
	Range	0.3-4.0	0.4-8.4	
	Missing	75	5	
Follow-up data				
Follow-up duration (month)				0.366
	No	218	48	
	Mean	51.7	58.1	
	Range	0-229	0-197	
Recurrence (benign)				0.178
	No	202 (92.7%)	47 (97.9%)	
	Yes	16 (7.3%)	1 (2.1%)	
Recurrence (total)				0.574
	No	199 (91.3%)	45 (93.8%)	
	Yes	19 (8.7%)	3 (6.3%)	

*yr; year, BMI; body mass index, BI-RADS; Breast Imaging Reporting and Data System, WHO; World Health Organization, DCIS; ductal carcinoma in situ

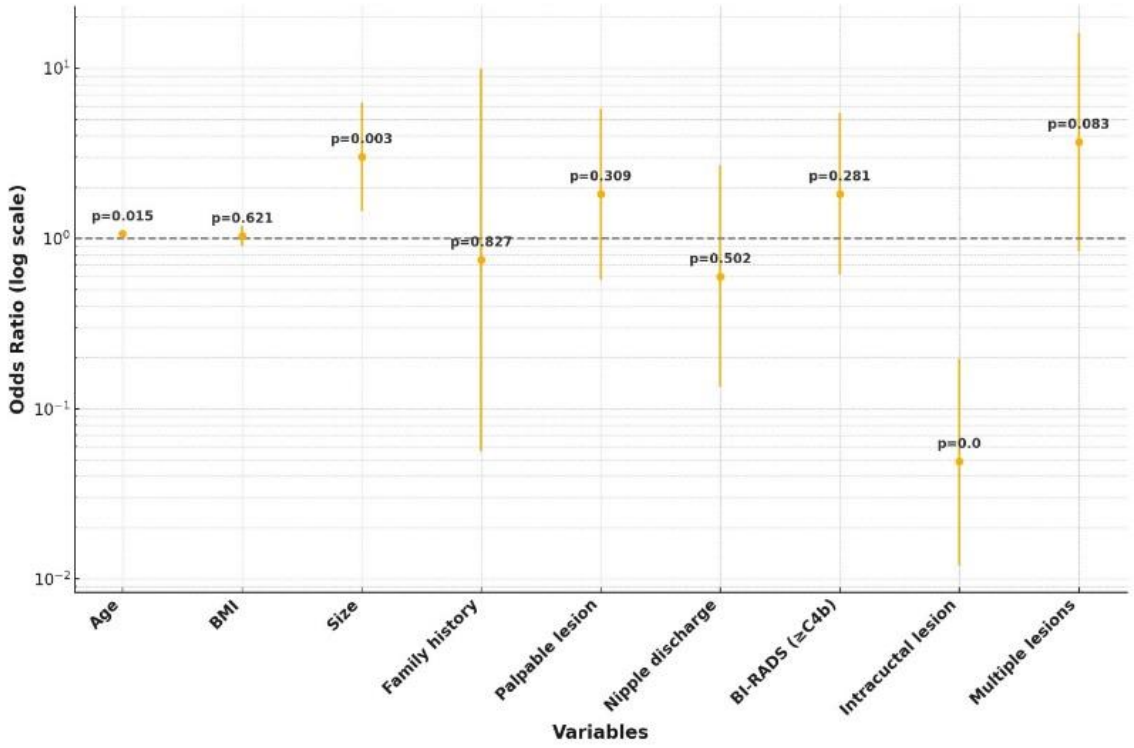

Figure 2. Graph for odds ratios associated with the conventional process (initial needle biopsy followed by surgery)

Factors significantly associated with the conventional treatment process included older age (OR=1.064; 95% CI, 1.012–1.119; ***p*=0.015**), larger tumor size (OR=3.015; 95% CI, 1.450–6.265; ***p*=0.003**), and absence of intraductal lesions (OR=0.049; 95% CI, 0.012-0.197; ***p*<0.001**) (**Table 3**). The presence of multiple lesions showed a trend towards significance (OR=3.685; 95% CI, 0.843–16.108; *p*=0.083). Recurrence of papillary lesions was correlated with a higher BMI (OR=1.156; 95% CI, 1.003–1.333; ***p*=0.045**; **Figure 3, Table 4**).

Table 3. Clinical factors associated with requirements for the conventional process (initial needle biopsy followed by surgery)

		OR (95% CI)	*p*-value
Age	Per unit (years)	1.064 (1.012–1.119)	0.015
BMI	Per unit (kg/m²)	1.034 (0.905–1.182)	0.380
Size	Per unit (cm)	3.015 (1.450–6.265)	0.003
Family hx of breast cancer	Present	0.749 (0.056–9.954)	0.827
Palpable	Yes	1.822 (0.574–5.782)	0.309

Nipple discharge	Present	0.598 (0.134–2.680)	0.502
BI-RADS	≥ C4b	1.825 (0.611–5.454)	0.281
Lesions	Multiple	3.685 (0.843–16.108)	0.083
Intraductal lesion	Present	0.049 (0.012-0.197)	<0.001

* Hx: history; OR: odds ratio; CI: confidence interval, BMI: body mass index, BI-RADS: breast imaging-reporting and data system

Table 4. Multivariate Cox regression analysis of factors associated with event-free papilloma without malignancy

		OR (95% CI)	*p*-value
Age	Per unit (years)	0.972 (0.915–1.032)	0.356
BMI	Per unit (kg/㎡)	1.156 (1.003–1.333)	0.045
Size	Per unit (cm)	1.159 (0.566–2.373)	0.687
BI-RADS	≥ C4b	1.131 (0.251–5.088)	0.872
Intraductal lesion	Present	1.689 (0.395–7.211)	0.479

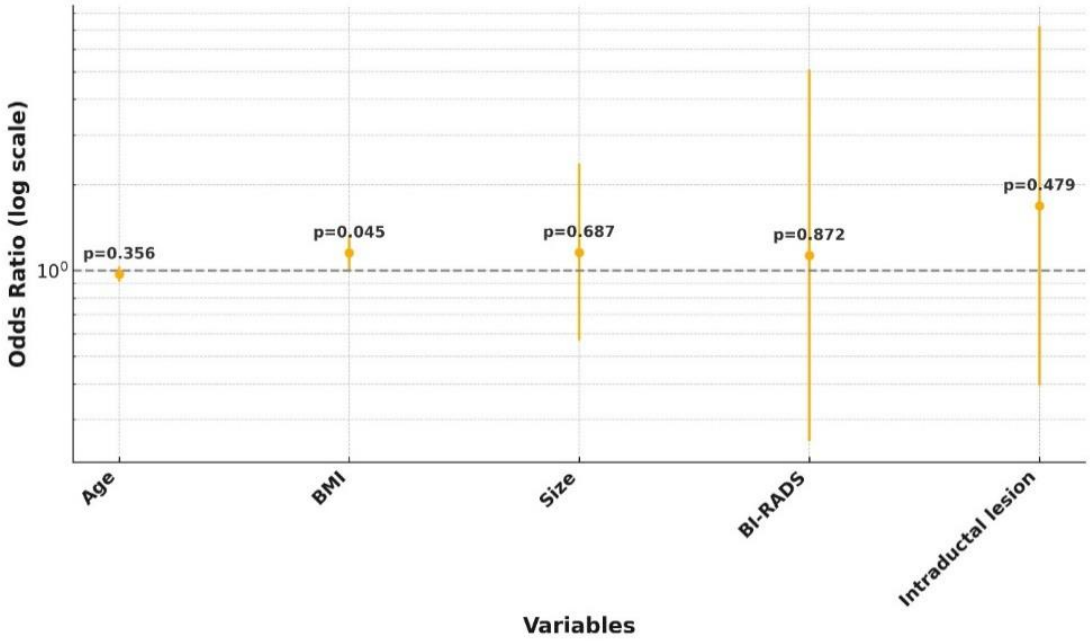

Figure 3. Graph for odds ratios associated with the recurrence of benign papillary neoplasm

No other factors were found to be associated with recurrence. Further analysis of benign papillary lesion recurrence based on BMI revealed that patients with a BMI < 25 had a significantly lower recurrence rate than those with a BMI ≥ 25 (**Figure. 4**).

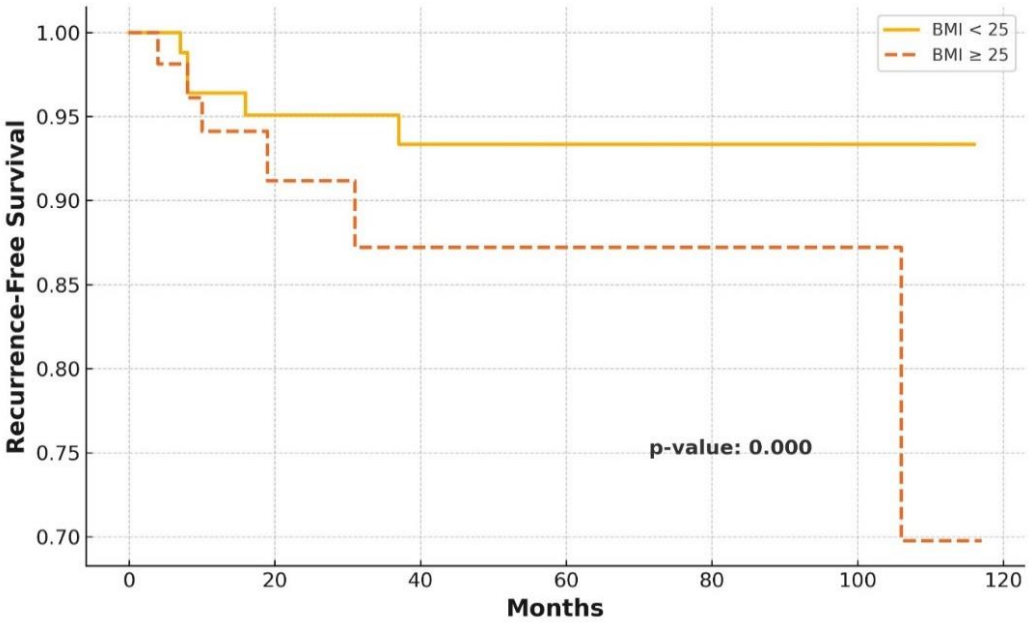

Figure 4. Kaplan-Meier recurrence-free survival curve for patients with BMI < 25 and BMI ≥ 25

Discussion

This study aimed to elucidate the factors that necessitate surgical excision after the initial biopsy in patients with papillary breast lesions. We identified older age, larger tumor size, and absence of an intraductal component as significant predictors of the need for surgical excision. These findings suggest that a more refined treatment strategy may be appropriate for younger women with smaller intraductal masses. In such cases, an initial excisional biopsy or vacuum-assisted procedure could be a viable option.

The malignancy upgrade rate in this study was 6.7%, which is consistent with recent trends showing rates < 10% 8. Notably, lesions with atypia had a significantly higher upgrade rate of 23.1%, consistent with previous studies on the need for surgical excision 4, 5.

In this study, the absence of an intraductal lesion was associated with a higher likelihood of surgical excision, which warrants further discussion. Some studies have shown that intraductal papilloma does not significantly increase the risk of malignancy 15. However, in most studies, intraductal papilloma was associated with the risk of breast cancer, regardless of atypia 16. Additionally, patients needing conventional procedures had lesions with a mean size of 1.9 cm. This is notably larger than the mean size of intraductal lesions, which measured 1.2 cm, and is also similar in size to that in the vacuum-assisted procedure group (1.1 cm). This size discrepancy supports the consideration of vacuum-assisted procedure for smaller lesions, particularly for younger patients. However, the optimal size threshold for VAE versus surgical excision requires further studies.

Symptoms, such as palpability and nipple discharge, did not significantly affect the decision to undergo surgical excision in this study. This may be due to the undescribed or missing data on these symptoms in many cases. Although the presence of multiple papillary lesions is generally considered to increase cancer risk [17], this study did not find this to be a significant factor. However, a trend was observed with a *p*-value of 0.083 (OR=3.685), suggesting a possible correlation. Current guidelines from the American Society of Breast Surgeons do not recommend surgical excision of papillomas for multiple lesions [18].

Our analysis of benign papilloma recurrence showed a significant association with higher BMI (≥25). Few studies have reported the recurrence of benign breast papilloma, and this study analyzed the factors associated with the recurrence of benign breast papilloma at a long-term follow-up (mean follow-up:53 months). This finding contrasts with those of previous studies, suggesting that obesity may reduce the risk of benign disease. Johansson et al. found that obesity (BMI >30) was associated with a reduced risk of all benign breast diseases, except epithelial proliferation (hazard ratio=0.74; 95% CI, 0.55–1.00) [19]. The present study concluded that being overweight was associated with a higher recurrence rate (BMI ≥25), although we analyzed recurrence, not incidence

This study has several limitations that should be acknowledged. As this was a single-center retrospective study, it was subject to the inherent limitations of this design. However, conducting a prospective study on this topic would be challenging due to the complexities of obtaining consensus on treatment decisions for benign diseases in real-world clinical practice and the lack of clarity in symptoms and specific diagnoses in medical charts compared to malignancy data. Second, the sample size was small. Although the sample size is comparable to other studies on papillary breast lesions, future research would benefit from a multicenter approach, a larger sample size, or a meta-analysis to validate our results. Lastly, this analysis did not consider family history of breast cancer as a potential factor influencing recurrence, despite its known association with an increased risk in premenopausal women [19]. This omission was due to the incomplete nature of the family history data in the medical records of the patients with benign breast papilloma. Despite these limitations, this study provides valuable insights into the factors associated with the need for initial needle biopsy followed by surgical excision in the recent trend toward preferring the minimal-access technique.

In conclusion, this study provides valuable insights into the factors associated with the need for surgical excision after initial needle biopsy in the recent trend toward preferring minimal-access technique. These results suggest that vacuum-assisted procedures may be useful in younger women with smaller intraductal lesions. Furthermore, patients with a higher BMI are at an increased risk of recurrence for benign papillary lesions. Consequently, we recommend that these patients undergo regular follow-up examinations to monitor for potential recurrences.

Conflict of Interest Statement:

The authors declare that they have no affiliations with or involvement in any organization or entity with any financial interests in the subject matter or materials discussed in this manuscript.

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Data Availability

Statement: Data used to support the findings of this study are available from the corresponding author upon request.

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