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Cytologic Evaluation of Papillary Breast Lesions: A 35-Case Series with Histopathologic Correlation and Clinical Follow-Up

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ABSTRACT

Introduction: Papillary lesions of the breast constitute a heterogeneous group ranging from intraductal papillomas to papillary carcinomas. Fine-needle aspiration cytology (FNAC) plays an important role in the initial evaluation of these lesions; however, cytologic distinction between benign and malignant papillary lesions is challenging due to overlapping morphologic features. The aim of this study was to determine the diagnostic value of cytologic findings and the associated risk of neoplasia (RON) and malignancy in papillary breast lesions.

Methods: A total of 35 cases of breast FNAC and nipple discharge cytology that demonstrated papillary architecture (2017–2024) were retrospectively evaluated. Cytomorphologic assessment focused on two diagnostic features—nuclear atypia and hypercellularity—and their correlation with histologic outcomes. The RON and the risk of malignancy (ROM) were calculated with 95% confidence intervals (CIs). Statistical analysis was performed using Fisher's exact test.

Results: All patients were female (age range: 25–71 years; mean: 47 years). Histopathologic diagnosis was available for 8 cases, and clinical follow-up for 17 cases. Nuclear atypia was identified in 5 cases (14%), while hypercellularity was observed in 17 cases (48.5%). RON and ROM were 60% and 20% in cases with nuclear atypia and 35.3% and 11.8% in cases with hypercellularity, respectively. Among all evaluable cases, overall RON was 32.0% (95% CI: 17.7–51.6) and ROM was 12.0% (95% CI: 4.2–30.0).

Conclusion: FNAC remains a valuable and minimally invasive diagnostic tool in the evaluation of papillary breast lesions. Although definitive cytologic distinction between benign and malignant lesions is not always possible, the identification of nuclear atypia and hypercellularity serves as an important indicator of neoplastic potential. The integration of immunocytochemical studies and standardized reporting systems may further improve diagnostic accuracy and reproducibility in the cytological evaluation of papillary breast lesions.

Keywords: Papillary breast lesion, fine-needle aspiration cytology, nuclear atypia, hypercellularity, risk of neoplasia, risk of malignancy

Introduction

Papillary lesions of the breast encompass a varied spectrum of neoplasms characterized by the presence of fibrovascular cores lined by epithelial cells, forming intricate papillary architectures within the ductal-lobular system. These lesions range from benign entities such as intraductal papillomas to malignant forms including encapsulated papillary carcinoma and invasive papillary carcinomas (1-3). The morphological heterogeneity inherent in this group poses significant diagnostic challenges, especially when differentiating benign from malignant lesions on cytology. Indeed, the overlapping cytomorphologic features between benign papillomas and papillary carcinomas often lead to difficulties in definitive preoperative categorization, which is critical for guiding patient management decisions (1,4).

Epidemiologically, breast papillary lesions occur predominantly in middle-aged and elderly women, although rare cases in men have been documented, further broadening the clinical presentation and diagnostic considerations. Clinically, such lesions frequently present as palpable masses or with nipple discharge; both findings prompt imaging and tissue sampling. The accurate diagnosis of papillary lesions is essential since, despite many being indolent, some can harbor areas of atypia, carcinoma in situ, or invasive carcinoma components that significantly influence prognosis and therapeutic strategy (4).

Fine needle aspiration cytology (FNAC) represents a minimally invasive, cost-effective, and rapid method for the initial evaluation of palpable and image-identified breast lesions. In resource-limited or busy clinical settings, FNAC remains a valuable diagnostic tool for breast lesions,

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including papillary neoplasms, because of its simplicity and low complication rates. However, for papillary lesions, despite FNAC's established role, the technique is subject to inherent limitations related to sampling and interpretative challenges due to the complex architecture and overlapping cytological features found in these lesions (5).

Several studies underline the pitfalls encountered with FNAC in diagnosing papillary lesions. False positives often arise from overinterpretation of reactive or atypical changes or misidentification of papillaroid fragments in non-papillary lesions such as fibroadenomas or certain invasive ductal carcinomas that present with papillary-like morphology. Conversely, false negatives may occur due to hypocellularity, scant fibrovascular cores, or sampling errors, especially when true papillary structures are absent or poorly represented in aspirates (4).

The sensitivity of FNAC in recognizing papillary breast lesions is variable; some series report figures near 54%, which reflects the cautious approach required when interpreting aspirates for such lesions. The identification and careful evaluation of true papillae, characterized by epithelial clusters surrounding fibrovascular cores, columnar cell morphology, and cellular atypia, remain cornerstones for cytologic diagnosis. Experts recommend that the presence of complex branching papillary fragments with fibrovascular cores and assessment of nuclear features such as mild to severe atypia might aid in distinguishing benign from malignant papillary lesions (4).

The present study aimed to evaluate the predictive value of nuclear atypia and hypercellularity in cytologically diagnosed papillary breast lesions and to determine the corresponding risks of neoplasia (RON) and risk of malignancy (ROM).

Methods

This retrospective single-center study included cases of breast FNAC and nipple discharge cytology that were evaluated in our pathology department between August 2017 and September 2024. Among these cases, those demonstrating papillary structures on cytologic examination were selected (n=35). Demographic data on the patients were retrieved from the hospital information system. Cases in which the cytologic material lacked papillary architecture or was deemed inadequate were excluded from the study. All cases were reviewed by a single experienced cytopathologist to ensure diagnostic consistency.

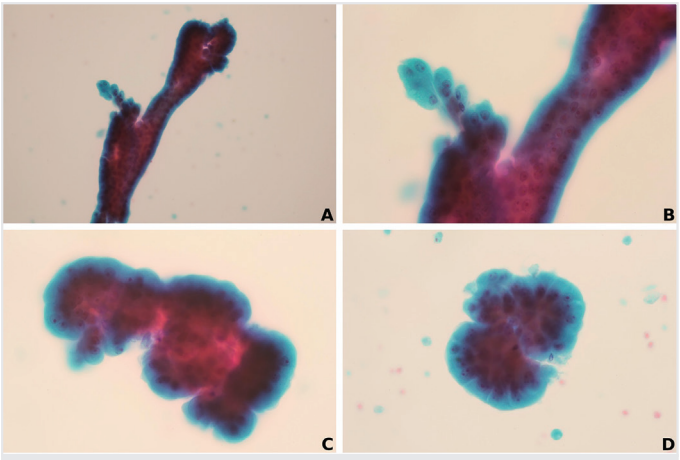

Figure 1. A) A well-formed papillary structure with ductal epithelial cells arranged in a single row around a fibrovascular core (PAP, × 400). B) High-magnification view of the cells forming the papillary structure. No nuclear atypia is identified (smooth nuclear contours and fine chromatin). (PAP ×1000). C) Complex three-dimensional crowded cell clusters detached from the tips of papillary structures (PAP, × 1000). D) A rounded cell cluster with contours resembling a papillary cap (PAP, × 1000)
PAP: Papanicolaou

All specimens were submitted as fluid aspirates and processed using a liquid-based cytology (LBC) technique. The primary LBC slides were prepared using the SurePath Pap Test kit (BD Diagnostics). Specimens were fixed in an ethanol-based solution (CytoRich™ Red, BD Diagnostics) and subjected to two centrifugation steps. The cellular material was subsequently vortexed to ensure homogenization, and then was evenly distributed as a thin layer on microscope slides. A single smear was prepared from each case and stained with the Papanicolaou method. Cell block material was available for all cases.

All cases demonstrated papillary structures on cytologic evaluation (Figure 1). All cases were further assessed for two key diagnostic features: (1) nuclear atypia, defined by the presence of nuclear enlargement, irregular nuclear contours, and coarse chromatin, either individually or in combination; and (2) hypercellularity, reflecting the proliferative nature of the lesion.

The impact of these cytologic features on the RON and ROM. was analyzed. For each case, the availability of histopathologic diagnosis was recorded, and cytologic–histologic concordance was assessed. Immunohistochemical evaluation was performed only on available histologic sections from selected cases and was not applied to cytologic material.

Ethical approval for the study was granted by the University of Health Sciences Türkiye, İstanbul Training and Research Hospital Ethics Committee (decision number: 303, date: 05.12.2025). Due to the retrospective nature of the study, the requirement for informed consent was waived by the ethics committee.

Statistical Analysis

RON and ROM values were calculated with 95% Wilson confidence intervals (CIs). The association between nuclear atypia and malignancy was analyzed using Fisher's exact test due to the small sample size. Statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). A p value <0.05 was considered statistically significant.

Results

The patients ranged in age from 25 to 71 years (median: 45 years; mean: 47 years), and all were female. The lesions were located in the right breast in 12 cases (34%) and in the left breast in 23 cases (66%). Periareolar localization was observed in 14 cases. Lesion size varied between 5 and 60 mm (mean: 22 mm). Thirty-one cases were obtained by fine-needle aspiration, while four were smear preparations of nipple discharge. All cases were cytologically diagnosed as intraductal papillary lesions, and the presence or absence of atypical features was documented in the reports.

Histopathologic diagnosis was available for eight cases (seven excisional specimens and one tru-cut biopsy). Cytomorphologic evaluation revealed nuclear atypia in 5 of 35 cases (14%). Among these, three had histologic follow-up: two were diagnosed as intraductal papilloma, and one as ductal carcinoma in situ with a papillary pattern. A closer examination of the cytologic features of these three cases revealed that nuclear atypia was focal and mild in the two cases with histologic diagnoses of intraductal papilloma. In contrast, the case diagnosed as ductal carcinoma in situ exhibited mild-to-moderate nuclear atypia. Two additional cases were followed clinically for 9 months and 22 months, respectively, without recurrence.

RON among cases with nuclear atypia was 60%, and the ROM was 20%. The distribution of cases by cytologic features and associated risk rates is summarized in Table 1. There was no statistically significant difference in malignancy frequency between cases with atypia and those lacking atypia (Fisher's exact test, p=0.544).

Hypercellularity, reflecting proliferative activity, was identified in 17/35 cases (48.5%). Six of these cases underwent histologic evaluation, revealing four intraductal papillomas, one invasive ductal carcinoma, and one ductal carcinoma in situ. The remaining 10 cases were followed clinically for 2–56 months (mean, 32 months), and no recurrence or suspicious radiologic findings were detected. The calculated RON and ROM for proliferative cases were 35.3% and 11.8%, respectively. Detailed correlations between cytologic findings and histologic or clinical follow-up are presented in Table 2. The association between proliferation and malignancy was not statistically significant (Fisher's exact test, p=1.000).

Both cytologic features—nuclear atypia and hypercellularity—were concurrently observed in three cases (8.5%). Two of these were diagnosed as intraductal papillomas on excision, and one case showed no recurrence during a 9-month follow-up. All cases showing both features were histologically neoplastic (RON 100%), as summarized in Table 1.

Ten cases were lost to follow-up or had follow-up periods shorter than six months. Seventeen cases were clinically monitored for 9–73 months (mean, 32 months), and none developed suspicious lesions or malignancy during the follow-up period.

Overall, cytologic evaluation identified 35 cases consistent with intraductal papillary lesions. Of these, 25 had either histopathologic correlation (n=8) or sufficient clinical follow-up (n=17). All tissue samples demonstrated neoplastic lesions, including three malignant cases. Based on evaluable cases, the RON was 32.0% (95% CI: 17.7–51.6) and the ROM was 12.0% (95% CI: 4.2–30.0) (Table 3). When all cytologically diagnosed cases were considered, the overall RON and ROM were 22.9% and 8.6%, respectively.

Immunohistochemical studies were not performed on cytologic material; however, in five cases of intraductal papilloma, myoepithelial markers (p63, calponin, and CK5/6) were applied to the corresponding tissue sections, confirming an intact myoepithelial cell layer.

Discussion

The cytologic diagnosis of papillary breast lesions remains one of the most challenging aspects of breast cytopathology because of the substantial morphologic overlap between benign and malignant entities. All histologically correlated cases in our series were found to be neoplastic. The calculated RON was 32%, and the ROM was 12%, values consistent with previously reported malignancy rates ranging between 8% and 20% in similar series (4,6).

The clinical management of papillary breast lesions depends heavily on accurate diagnostic classification. While benign papillomas can be managed conservatively or with limited excision, papillary carcinomas generally require more extensive surgical intervention, occasionally including sentinel lymph-node biopsy, owing to the potential—though low—risk of nodal metastasis, as described in encapsulated papillary carcinoma (7).

In our cohort, the presence of nuclear atypia and proliferative activity on cytologic examination correlated positively with histologically confirmed neoplasia. Cases with nuclear atypia revealed RON and ROM values of 60% and 20%, respectively, whereas proliferative smears revealed values of 35% and 12%, respectively. These findings parallel previous observations that papillary carcinomas tend to exhibit greater cellularity and more prominent nuclear atypia compared with papillomas (8,9). The

Table 1. Distribution of evaluated cases according to cytologic features and corresponding risk rates

Group	Evaluated cases (n)	Neoplasia (n)	Malignancy (n)	RON (%)	ROM (%)
Nuclear atypia (+)	5	3	1	60.0	20.0
Proliferation (+)	17	6	2	35.3	11.8
Both features (+)	3	2	0	66.7	0
All evaluable cases	25	8	3	32.0	12.0

RON: Risk of neoplasia, ROM: Risk of malignancy

Table 2. Cytologic findings and histologic follow-up of cases with proliferative or atypical features

Findings	Number of cases	Histologic follow-up available	Neoplasia (n)	Malignancy (n)
Nuclear atypia (+)	5	3 (histology) + 2 (clinical follow-up)	3	1 (*in situ* DCIS)
Proliferation (+)	17	6 (histology) + 11 (clinical follow-up)	6	2 (1 IDC, 1 DCIS)
Both features (+)	3	2 (histology) + 1 (clinical follow-up)	2	0
Total	35	8 (histology) + 17 (clinical follow-up)	8	3

IDC: Invasive ductal carcinoma, DCIS: Ductal carcinoma *in situ*

Table 3. Calculated risk metrics for the evaluated cases

Metric	Count	Rate (%)	95% confidence interval
RON	8/25	32.0	17.7–51.6
ROM	3/25	12.0	4.2–30.0

RON: Risk of neoplasia, ROM: Risk of malignancy

combined evaluation of atypia and hypercellularity therefore appears to improve the prediction of neoplastic potential in papillary lesions.

The diagnostic accuracy of FNAC for papillary lesions has been variably reported, ranging from 54% to 88% (4,7). Simsir et al. (6) found that 66% of cytologically "papillary" lesions were benign on excision, but that hypercellularity and nuclear atypia were significant discriminators between papillomas and papillary carcinomas. Similarly, Sauer (7) emphasized that the substantial morphologic overlap between benign and low-grade malignant papillary lesions often necessitates histologic confirmation for definitive classification. Our findings align with these observations and highlight the importance of cautious interpretation of atypical cytologic features.

Immunocytochemistry on cell-block preparations can provide additional diagnostic confidence. Markers such as p63, smooth muscle actin (SMA), and calponin can help identify the presence or absence of a myoepithelial layer and thus aid in distinguishing papillomas from papillary carcinomas. In this setting, p63 demonstrates nuclear staining, whereas SMA and calponin show cytoplasmic staining in myoepithelial cells. Although Reis-Filho et al. (10) demonstrated the diagnostic value of p63 staining in cytologic preparations, no immunohistochemical analyses were applied to the cytologic materials in our study. Nonetheless, in five cases of intraductal papilloma, immunostaining for myoepithelial markers (p63, calponin, and CK5/6) was performed on histologic sections, confirming the presence of a myoepithelial cell layer.

The International Academy of Cytology, Yokohama System for Reporting Breast Cytology, established in 2017, provides a standardized framework for classifying breast FNA samples into five categories: C1 (insufficient), C2 (benign), C3 (atypical), C4 (suspicious), and C5 (malignant) (11). The observed 12% malignancy rate corresponds well with the ROM reported for the indeterminate (C3/C4) categories of the Yokohama System, ranging between 5% and 75% (11). This suggests that the threshold for recommending excision in our series was appropriately conservative. The finding that all histologically sampled cases were neoplastic further reinforces the value of FNAC as a reliable triage tool, especially when interpreted alongside clinical and radiologic findings.

Study Limitations

Several limitations should be acknowledged. The retrospective, single-center design and the limited number of histologically correlated cases reduce the statistical power to assess cytologic-histologic concordance. Moreover, the absence of a standardized scoring system for cytologic atypia introduces potential interobserver variability, a limitation noted in earlier studies (6,9). Despite these constraints, our findings emphasize that combined assessment of nuclear atypia and proliferative activity provides meaningful insight into the neoplastic potential of papillary breast lesions.

Conclusion

FNAC remains a valuable first-line diagnostic modality in the evaluation of papillary breast lesions. Although a definitive cytologic distinction between benign and malignant lesions may not always be achievable, recognizing proliferative and atypical features aids in risk stratification and guides appropriate surgical management. The integration of immunocytochemical studies and standardized reporting frameworks such as the Yokohama System may further enhance diagnostic accuracy and reproducibility in papillary breast cytology.

Ethics

Ethics Committee Approval: Ethical approval for the study was granted by the University of Health Sciences Türkiye, İstanbul Training and Research Hospital Ethics Committee (decision number: 303, date: 05.12.2025).

Informed Consent: Due to the retrospective nature of the study, the requirement for informed consent was waived by the ethics committee.

Footnotes

Authorship Contributions: Surgical and Medical Practices - B.Ö.; Concept - A.B.; Design - B.Ö.; Data Collection or Processing - A.B.; Analysis or Interpretation - B.Ö.; Literature Search - A.B.; Writing - B.Ö.

Conflict of Interest: No conflict of interest was declared by the authors.

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