



Factors associated with histologic upgrade following surgical excision of breast papillomas: a retrospective multicenter study

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Received 25 June 2026; revision requested 27 July 2026;
accepted 04 September 2026.



Epub: 23.09.2026

DOI: 10.4274/dir.2026.264219

PURPOSE

This study aimed to determine malignant, high-risk, and overall diagnostic upgrade rates after surgical excision of image-guided biopsy-proven intraductal papillomas and to identify factors associated with overall diagnostic upgrade.

METHODS

In this retrospective multicenter study, 527 surgically excised papillary lesions from 30 centers were evaluated. Malignant upgrade was defined as malignancy at excision after a biopsy diagnosis of papilloma with or without atypia; high-risk upgrade was defined as a high-risk lesion at excision after papilloma without atypia. Overall diagnostic upgrade comprised either outcome. Multivariable logistic regression assessed age, lesion size, risk status, presence of symptoms, and radiologic–pathologic concordance.

RESULTS

Papilloma without atypia accounted for 407 lesions, and papilloma with atypia for 120. The overall malignant upgrade rate was 21.4% (113/527). Among papillomas without atypia, high-risk and malignant upgrade rates were 19.7% (80/407) and 14.2% (58/407), respectively; among papillomas with atypia, malignant upgrade was 45.8% (55/120). Overall diagnostic upgrade occurred in 36.6% (193/527). Multivariable analysis identified older age [odds ratio (OR), 1.03 per year; 95% confidence interval (CI), 1.02–1.05], larger lesion size (OR, 1.02 per mm; 95% CI, 1.00–1.03), presence of symptoms (OR, 1.69; 95% CI, 1.15–2.49), and radiologic–pathologic discordance (concordance OR, 0.54; 95% CI, 0.35–0.84) as independent predictors of upgrade. Microcalcifications (OR, 2.47; 95% CI, 1.27–4.85) and asymmetry (OR, 2.18; 95% CI, 1.12–4.25) on mammography were also significantly associated with upgrade.

CONCLUSION

In this retrospective multicenter cohort of surgically excised, biopsy-proven papillary lesions, atypia and several clinical and imaging factors were associated with diagnostic upgrade. These findings may support individualized management decisions in patients with papillary breast lesions.

CLINICAL SIGNIFICANCE

Identifying clinical and imaging predictors of upgrade may facilitate risk-adapted management of papillary breast lesions and help avoid unnecessary surgical excision in carefully selected patients.

KEYWORDS

Intraductal papilloma, papillary breast lesions, atypia, core needle biopsy, diagnostic upgrade

High-risk breast lesions comprise a heterogeneous group of proliferative lesions that are considered precursors to breast carcinogenesis and are associated with an increased risk of developing breast cancer.^{1–3} These lesions include atypical ductal hyperplasia (ADH), lobular neoplasia (LN) (atypical lobular hyperplasia and lob-

ular carcinoma *in situ*), flat epithelial atypia, radial scar/complex sclerosing lesions, and papillomas with or without atypia.^{4,5} Papillary lesions, which are the focus of the present study, are identified in approximately 6% of image-guided core needle biopsies and encompass a broad histopathological spectrum. This spectrum ranges from benign intraductal papillomas to papillomas associated with atypia (including ADH, LN, and ductal carcinoma *in situ*), as well as papillary ductal carcinoma *in situ*, solid papillary carcinoma, and encapsulated papillary carcinoma, posing challenges in both diagnosis and clinical management.^{6–8}

The optimal management of papillary lesions diagnosed by image-guided biopsy remains controversial. Recent studies have identified factors associated with the risk of malignancy upgrade, suggesting that conservative management may be appropriate in selected cases.^{1,6,7} However, distinguishing benign from malignant papillary lesions relies on identifying a continuous myoepithelial cell layer, which can be difficult to assess in limited or fragmented core biopsy samples.⁹ Consequently, lesions initially diagnosed as benign papillomas on core needle biopsy may be upgraded to atypia or malignancy following surgical excision.^{9,10} Although routine surgical excision was previously recom-

mended for high-risk lesions, its necessity for benign papillary lesions is increasingly questioned, as clinical, radiological, and pathological findings do not always reliably predict malignancy risk, potentially leading to unnecessary surgical procedures.¹ Atypia is the most important determinant of the biological behavior of papillary lesions. Papillomas without atypia are associated with a 2–3-fold increased risk of breast cancer compared with the general population, whereas papillomas with atypia confer a substantially higher risk of up to 5–7-fold. Additional factors associated with increased risk include lesion size, presence of symptoms, distance from the nipple, microcalcifications on mammography, and lesion multiplicity.^{11–13}

This study aimed to determine malignant, high-risk, and overall diagnostic upgrade rates following surgical excision of papillary breast lesions diagnosed by image-guided biopsy and to identify clinical and imaging factors associated with overall diagnostic upgrade. The findings are intended to support individualized, evidence-based multidisciplinary decision-making.

Methods

This retrospective multicenter study included 527 patients from 30 centers diag-

Main points

- The malignant upgrade rate was 14.2% in papillomas without atypia and 45.8% in those with atypia.
- Radiologic–pathologic concordance was associated with 46% lower odds of diagnostic upgrade.
- Each 1-mm increase in lesion size was associated with a 2% increase in the odds of diagnostic upgrade, and each additional year of patient age was associated with an approximately 3% increase in the odds of diagnostic upgrade.
- The presence of symptoms was associated with 69% higher odds of diagnostic upgrade.
- Atypia, older age, larger lesion size, symptoms, mammographic microcalcifications and asymmetry, and radiologic–pathologic discordance should be considered when planning the management of papillary breast lesions.

nosed with papillary lesions on image-guided biopsy who subsequently underwent surgical excision. The study was approved by the Acibadem University and Acibadem Healthcare Group's Medical Research Ethics Committee (ATADEK; decision no. 2024-6/227, date: 18 April 2024). Informed consent was waived due to the study's retrospective design.

Study population

The source cohort initially comprised 1,000 patients with papillary lesions diagnosed on image-guided biopsy. Of these, 473 patients who did not undergo subsequent surgical excision were excluded, leaving 527 surgically excised lesions for analysis (Figure 1). Accordingly, the analytic cohort represents the surgically excised subset rather than the full population of biopsy-diagnosed papillomas.

Data collection and imaging evaluation

Data extracted from medical records included demographic characteristics (age, risk factors, and presenting symptoms); imaging modalities [mammography, ultrasonography, and magnetic resonance imaging (MRI) and corresponding findings; lesion size (mm); Breast Imaging Reporting and Data System (BI-RADS) category (3, 4A, 4B, 4C, or 5); biopsy technique (core needle or vacuum assisted); needle gauge (7–12 or 14–16 G); and the number of tissue samples (< 4 or ≥ 4) obtained during biopsy. The imaging guidance modality [ultrasound (US), mammography, or MRI] was recorded for each case.

All imaging data were retrieved from the Picture Archiving and Communication System. Mammography, US, and MRI findings were reviewed at the participating centers by breast radiologists with at least 5 years of experience using BI-RADS terminology. The final BI-RADS category for each lesion reflected the integrated assessment of all available imaging modalities by the interpreting breast radiologist at the participating center. When MRI was available, MRI findings were considered along with mammographic and/or ultrasonographic findings in assigning the final BI-RADS category. Mammographic findings were recorded as present or absent; when present, they were classified as asymmetry, mass, microcalcifications, or architectural distortion. In cases with microcalcifications, morphology was categorized as amorphous, coarse heterogeneous, fine pleomorphic, or fine linear branching, and distribution as grouped, segmental, regional,

linear, or diffuse, in accordance with BI-RADS descriptors. Newly developed or increasing calcifications on follow-up imaging were classified as suspicious. US findings were recorded as present or absent and, when present, categorized as “mass” or “non-mass.” For patients who underwent MRI, lesions were classified according to the BI-RADS MRI lexicon as mass or non-mass enhancement based on contrast enhancement patterns. For statistical analysis, MRI findings were also analyzed separately within the subgroup of patients who underwent MRI. Imaging assessments were performed at the participating centers, and no central imaging re-review or formal interobserver agreement analysis was performed.

Histopathological evaluation and definitions

Image-guided biopsy results were categorized as papilloma without atypia or papilloma with atypia. Final surgical pathology was classified as benign, high-risk, or malignant. Malignant upgrade was defined as malignancy at surgical excision after a biopsy diagnosis of papilloma with or without atypia.

High-risk upgrade was defined only for papillomas without atypia that were classified as high-risk at excision. Papillomas with atypia that remained high-risk at excision were not considered upgraded. Overall diagnostic upgrade comprised either malignant upgrade or high-risk upgrade. Rates were calculated using the relevant denominator for each outcome.

Radiologic–pathologic concordance was recorded at the participating centers after image-guided biopsy and was defined as whether the biopsy histology adequately explained the imaging findings of the targeted lesion. Surgical excision pathology was not used to define biopsy concordance. The multicenter dataset did not include a central blinded re-review, formal consensus adjudication, or interobserver agreement analysis.

Statistical analysis

All analyses were performed using the R programming language (R Foundation for Statistical Computing, Vienna, Austria) in the RStudio environment (Posit Software, PBC, Boston, MA, USA). Statistical significance was

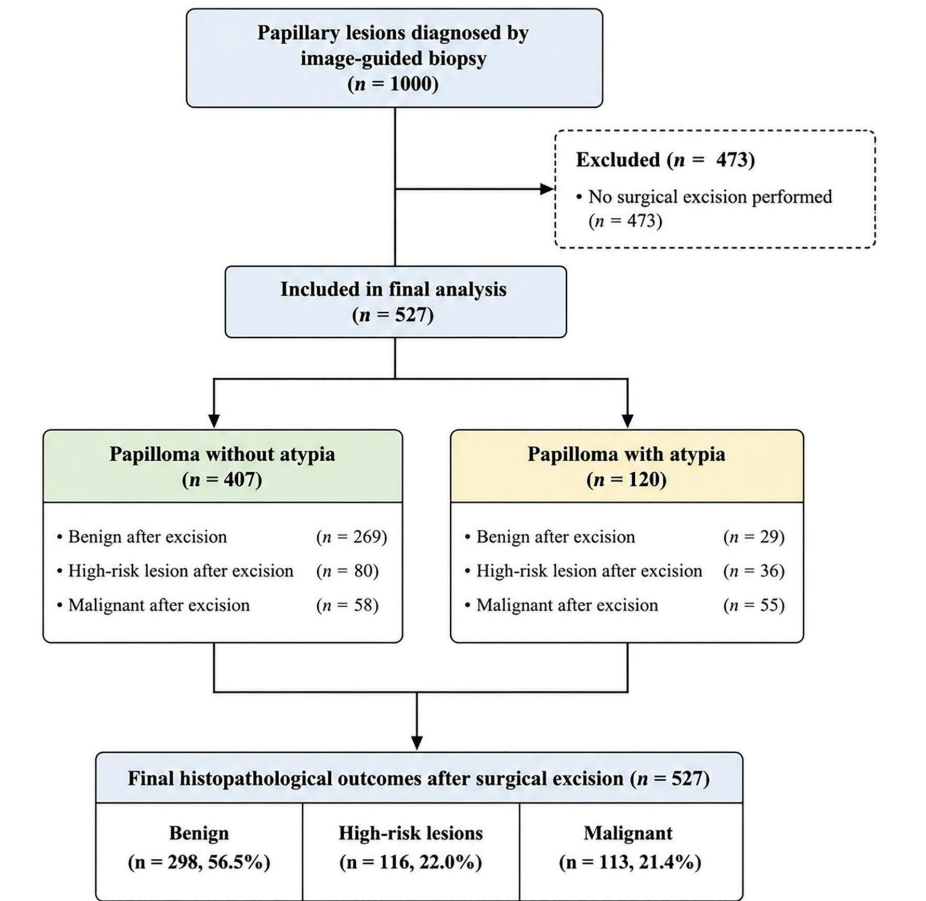


Figure 1. Study flowchart showing patient selection from the initial 1,000 biopsy-diagnosed papillary lesions to the 527 surgically excised lesions and the post-excision pathological outcomes.

set at $P < 0.05$ with 95% confidence intervals (CIs). Distribution of continuous variables was assessed using Q-Q plots, the Kolmogorov–Smirnov test, and measures of skewness and kurtosis. Continuous variables were summarized as mean $\pm$ standard deviation or median (interquartile range), as appropriate; categorical variables were expressed as frequencies and percentages. The Mann–Whitney U test was used for continuous variables, and the chi-square or Fisher’s exact test was used for categorical variables.

A multivariable logistic regression model was used to evaluate the associations of age, lesion size, risk status, symptoms, and radiologic–pathologic concordance with overall diagnostic upgrade. In addition, BI-RADS category was analyzed separately and was not entered simultaneously with radiologic–pathologic concordance in this model because the final BI-RADS category represented an integrated imaging assessment and showed a strong association with radiologic–pathologic concordance (Cramér’s $V=0.69$), indicating substantial overlap in the imaging-related information captured by these variables. The association between BI-RADS category and radiologic–pathologic concordance was quantified using Cramér’s V . Separate logistic regression models evaluated mammographic, ultrasonographic, and MRI findings; the absence of the corresponding finding served as the reference category. The Wald test was used to assess variables with more than two categories. Receiver operating characteristic (ROC) curve analysis and the Youden index were used to evaluate lesion size for discrimination of papillomas with and without atypia; the area under the curve (AUC), sensitivity, specificity, and corresponding 95% CIs were calculated for the optimal threshold. Because only 10 patients underwent vacuum-assisted biopsy, no adjusted subgroup model was run; a descriptive sensitivity check excluding these cases was reported.

Reporting guideline

This study was designed and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology statement.

Results

Among the 527 papillary lesions, 407 (77.2%) were papillomas without atypia, and 120 (22.8%) were papillomas with atypia at biopsy. After surgical excision, 298 lesions (56.5%) were benign, 116 (22.0%) were high-

risk, and 113 (21.4%) were malignant. The overall malignant upgrade rate was 21.4% (113/527), and the overall diagnostic upgrade rate was 36.6% (193/527).

Among papillomas without atypia, 80 of 407 lesions (19.7%) showed high-risk upgrade and 58 of 407 (14.2%) showed malignant upgrade, yielding an overall diagnostic upgrade rate of 33.9% (138/407). Among papillomas with atypia, 55 of 120 lesions (45.8%) showed malignant upgrade. The 36 lesions with atypia that remained high-risk after excision were not classified as high-risk upgrades (Table 1).

The BI-RADS categories were BI-RADS 3 in 38 lesions (7.2%), 4A in 288 (54.6%), 4B in 137 (26.0%), 4C in 59 (11.2%), and 5 in 5 (0.9%). Overall diagnostic upgrade rates in-

creased across categories from 18.4% in BI-RADS 3 to 60.0% in BI-RADS 5 (Table 2). The final BI-RADS category represented the integrated assessment of all available imaging modalities. The BI-RADS category showed a strong association with radiologic–pathologic concordance (Cramér’s $V=0.69$), indicating considerable overlap in the imaging-related information captured by these variables; therefore, BI-RADS was evaluated separately rather than entered simultaneously with concordance into the multivariable model. The analytic database retained final pathology in broad benign, high-risk, and malignant categories; exact diagnoses of the two non-malignant BI-RADS 5 lesions and a complete malignant subtype distribution were not consistently available across centers.

Table 1. Biopsy diagnosis, surgical excision outcomes, and separate upgrade rates						
Biopsy diagnosis	Total, n (%)	Benign at excision, n (%)	High-risk at excision, n (%)	High-risk upgrade, n/N (%)	Malignant upgrade, n/N (%)	Overall diagnostic upgrade, n/N (%)
Papilloma without atypia	407 (77.2)	269 (66.1)	80 (19.7)	80/407 (19.7)	58/407 (14.2)	138/407 (33.9)
Papilloma with atypia	120 (22.8)	29 (24.2)	36 (30.0)	Not applicable	55/120 (45.8)	55/120 (45.8)
Total	527 (100)	298 (56.5)	116 (22.0)	80/407 eligible (19.7)	113/527 (21.4)	193/527 (36.6)

High-risk upgrade was defined only for papillomas without atypia. Papillomas with atypia that remained high-risk at excision were not considered upgraded. Overall diagnostic upgrade comprised high-risk or malignant upgrade.

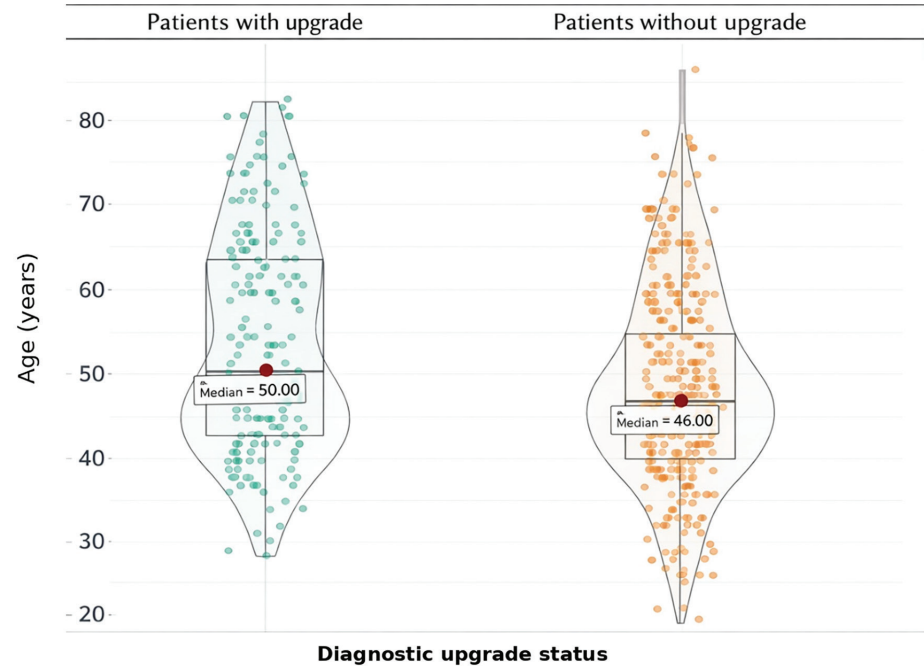


Figure 2. Age according to overall diagnostic upgrade status. Violin outlines show the distribution, box plots show the interquartile range with the central median line, individual dots represent patients, and the red dot and label indicate the median (50 years with upgrade and 46 years without upgrade).

The clinical and lesion characteristics of patients according to overall diagnostic upgrade status are summarized in Table 3.

The median age was 47 years. Patients with overall diagnostic upgrade were older than those without upgrade (median, 50 vs. 46 years; $P < 0.001$) (Figure 2). A total of 301 patients (57.1%) were symptomatic. Presenting symptoms included nipple discharge, nipple retraction, palpable mass, pain, and tenderness; pain and tenderness were non-specific symptoms. Upgrade occurred in 42.2% of patients who were symptomatic and 29.2% of patients who were asymptomatic ($P = 0.002$).

Median lesion size was greater in patients with upgrade than in those without upgrade (14 vs. 12 mm; $P < 0.001$) (Figure 3). In the adjusted model, each 1-mm increase in lesion size was associated with 2% higher odds of upgrade [odds ratio (OR), 1.02; 95% CI, 1.00–1.03; $P = 0.011$], and each additional year of age was associated with 3% higher odds (OR, 1.03; 95% CI, 1.02–1.05; $P < 0.001$). Presence of symptoms was associated with higher odds (OR, 1.69; 95% CI, 1.15–2.49; $P = 0.008$), whereas radiologic–pathologic concordance was associated with lower odds (OR, 0.54; 95% CI, 0.35–0.84; $P = 0.005$) (Table 4).

In a separate ROC analysis evaluating lesion size for discrimination of papillomas with and without atypia, the Youden index identified an optimal threshold of 23.5 mm. The AUC was 0.608 (95% CI, 0.560–0.657), with a sensitivity of 26.6% (95% CI, 21.0–32.9) and a specificity of 92.3% (95% CI, 88.6–95.0) at this threshold.

Biopsy was performed under US guidance in 97.5% of cases, mammographic guidance in 1.9%, and MRI guidance in 0.6%. Core needle biopsy was used in 517 patients (98.1%) and vacuum-assisted biopsy in 10 (1.9%). Needle gauge was 14–16 G in 96.6% and 7–12 G in 3.4%. Three of 10 vacuum-assisted biopsy cases (30.0%) showed overall diagnostic upgrade. After excluding these 10 cases, the upgrade rate was 36.8% (190/517), similar to the full-cohort rate of 36.6%; no adjusted sensitivity model was run because of the extremely small subgroup.

Mammography was available in 383 patients (72.6%). Findings included microcalcifications in 46 (12.0%), asymmetry in 49 (12.8%), mass in 162 (42.3%), and architectural distortion in 10 (2.6%); 116 patients (30.2%) had no mammographic abnormality. In separate mammographic models, asymmetry (OR, 2.18; 95% CI, 1.12–4.25; $P = 0.02$)

and microcalcifications (OR, 2.47; 95% CI, 1.27–4.85; $P = 0.008$) were associated with upgrade. Mass and architectural distortion were not statistically significant (Table 5).

US was available in 523 patients (99.2%); among 515 patients with a US-detected lesion, 457 had a mass, and 58 had a non-mass finding. In addition, MRI was performed in 239 patients (45.3%); among 226 patients with an MRI-detected lesion, 175 had mass enhancement, and 51 had non-mass enhancement. US and MRI morphology were evaluated in separate modality-specific models and were not significantly associated with upgrade (Table 5).

Radiologic–pathologic concordance was present in 402 patients (76.3%), specifically, in 131 of 193 patients with upgrade (67.9%)

and 271 of 334 without upgrade (81.1%). Representative non-upgraded and malignantly upgraded cases are shown in Figures 4 and 5.

Discussion

This large multicenter study demonstrated an overall malignant upgrade rate of 21.4% and an overall diagnostic upgrade rate of 36.6% among surgically excised, biopsy-proven papillary lesions. The marked difference in malignant upgrade between papillomas with and without atypia, along with the contribution of clinical, imaging, and radiologic–pathologic factors, supports a risk-adapted rather than uniform management approach. Because the analysis was restricted to lesions that proceeded to surgical

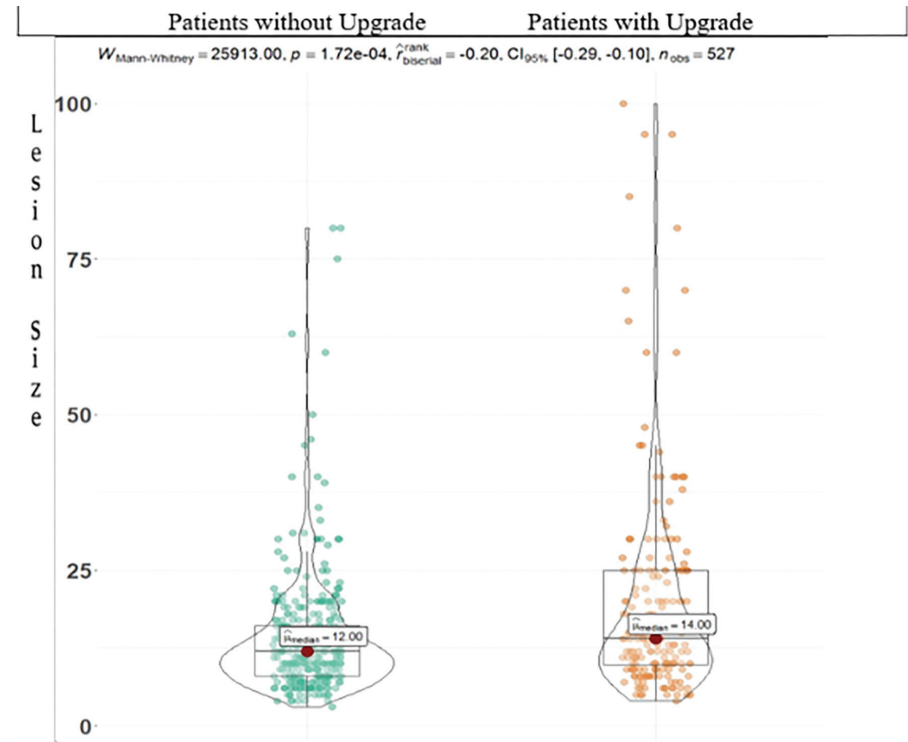


Figure 3. Lesion size according to overall diagnostic upgrade status. Violin outlines show the distribution, box plots show the interquartile range (IQR) with the central median line, individual dots represent patients, and the red dot and label indicate the median. Median lesion size was 14 mm (IQR, 15 mm) in patients with upgrade and 12 mm (IQR, 8.75 mm) in patients without upgrade. CI, confidence interval.

Table 2. Overall diagnostic upgrade rates according to BI-RADS category			
BI-RADS category	Total lesions, n (%)	Lesions with upgrade, n	Upgrade rate within category, %
3	38 (7.2)	7	18.4
4A	288 (54.6)	92	31.9
4B	137 (26.0)	58	42.3
4C	59 (11.2)	33	55.9
5	5 (0.9)	3	60.0
Total	527 (100)	193	36.6

$P < 0.001$ by chi-square test for the overall distribution across BI-RADS categories. BI-RADS, Breast Imaging Reporting and Data System.

excision, the reported upgrade rates reflect a surgically selected population and should be interpreted within this clinical context. Separating the outcomes improved interpretation. Papillomas without atypia showed a 19.7% high-risk upgrade rate and a 14.2% malignant upgrade rate, whereas papillomas with atypia showed a 45.8% malignant upgrade rate. These findings fall within the broad ranges previously reported for papillomas with and without atypia,^{6,11,12,16,17} and the relatively high estimates in the present study are consistent with its surgically selected population. High-risk outcomes in lesions already diagnosed with atypia at biopsy were not counted as upgrades.

Older age, larger lesion size, presence of symptoms, and radiologic–pathologic discordance emerged as independent predictors of overall diagnostic upgrade in the multivariable model. Each additional year of age and each 1-mm increase in lesion size were associated with 3% and 2% higher odds of upgrade, respectively, and the presence of symptoms was associated with 69% higher odds. In contrast, radiologic–pathologic concordance was associated with 46% lower odds of upgrade. Taken together, these findings suggest that upgrade risk is influenced by a combination of patient-related, lesion-related, and radiologic–pathologic factors rather than by any single parameter. The association between lesion size and upgrade is consistent with the findings obtained by Oktay et al.¹ and Salisbury et al.,¹⁵ although other studies have not identified a reliable size threshold.¹⁴

The ROC analysis identified a 23.5-mm lesion-size threshold for distinguishing papillomas with and without atypia. However, although specificity was high (92.3%), sensitivity was low (26.6%) and overall discrimination was modest (AUC, 0.608; 95% CI, 0.560–0.657).

Therefore, lesion size alone is insufficient for reliable discrimination, and the 23.5-mm threshold should be interpreted alongside other clinical, imaging, and pathological factors rather than as a standalone clinical decision cut-off. The protective association of radiologic–pathologic concordance further emphasizes the importance of post-biopsy imaging–pathology correlation. In this retrospective dataset, concordance reflected whether biopsy histology adequately explained the imaging findings of the targeted lesion. However, the absence of central blinded re-review, formal consensus adjudication, and interobserver agreement testing limits assessment of reproducibility across

Table 3. Comparison of clinical and lesion characteristics according to overall diagnostic upgrade

Variable	Patients with upgrade (n=193)	Patients without upgrade (n=334)	P value
Age*			< 0.001
Mean ± SD	52.9 ± 13.2	47.3 ± 12.3	
Median (IQR)	50 (21)	46 (16)	
Risk factors present, n (%)	43 (22.3)	84 (25.1)	0.52
Symptoms present, n (%)	127 (65.8)	174 (52.1)	0.002
Lesion size (mm)*			< 0.001
Mean ± SD	20.2 ± 19.4	14.4 ± 11.9	
Median (IQR)	14 (15)	12 (8.75)	
BI-RADS category, n (%)			< 0.001
3	7 (3.6)	31 (9.3)	
4A	92 (47.7)	196 (58.7)	
4B	58 (30.1)	79 (23.7)	
4C	33 (17.1)	26 (7.8)	
5	3 (1.6)	2 (0.6)	
Radiologic–pathologic concordance present, n (%)	131 (67.9)	271 (81.1)	< 0.001

*Variables are presented as both mean ± standard deviation and median (interquartile range). Continuous variables were compared using the Mann–Whitney U test; categorical variables were compared using the chi-square or Fisher's exact test, as appropriate. The P value for BI-RADS represents the overall comparison across categories. SD, standard deviation; IQR, interquartile range; BI-RADS, Breast Imaging Reporting and Data System.

Table 4. Multivariable logistic regression model for overall diagnostic upgrade

Variable	Adjusted OR	95% CI	P value
Radiologic–pathologic concordance	0.54	0.35–0.84	0.005
Lesion size	1.02	1.00–1.03	0.011
Age	1.03	1.02–1.05	< 0.001
Risk factors present	0.92	0.59–1.43	0.70
Symptoms present	1.69	1.15–2.49	0.008

The dependent variable was overall diagnostic upgrade. Reference categories were radiologic–pathologic discordance for concordance, absence of risk factors for risk status, and absence of symptoms for symptom status; ORs for age and lesion size represent the change associated with each 1-year and 1-mm increase, respectively. BI-RADS category was evaluated separately and was not included in the primary multivariable model because of its strong association with radiologic–pathologic concordance (Cramér's V=0.69), indicating considerable overlap in the imaging-related information captured by these variables. OR, odds ratio; CI, confidence interval; BI-RADS, Breast Imaging Reporting and Data System.

Table 5. Association of imaging findings with overall diagnostic upgrade in separate modality-specific logistic regression models

Modality	Finding	Upgrade, n/N (%)	OR	95% CI	P value
Mammography	Asymmetry	24/49 (49.0)	2.18	1.12–4.25	0.02
Mammography	Mass	58/162 (35.8)	1.27	0.79–2.05	0.33
Mammography	Architectural distortion	6/10 (60.0)	3.41	0.93–13.9	0.07
Mammography	Microcalcifications	23/46 (50.0)	2.47	1.27–4.85	0.008
Ultrasonography	Mass	157/457 (34.4)	0.52	0.06–4.40	0.52
Ultrasonography	Non-mass finding	32/58 (55.2)	1.23	0.14–10.83	0.84
MRI	Mass enhancement	66/175 (37.7)	1.08	0.73–1.60	0.70
MRI	Non-mass enhancement	20/51 (39.2)	1.16	0.62–2.12	0.64

Each imaging modality was analyzed in a separate logistic regression model. For mammographic variables, the reference category was absence of the corresponding mammographic finding. For ultrasonographic and MRI findings, the reference categories were no ultrasound-detected lesion and no MRI-detected lesion, respectively. OR, odds ratio; CI, confidence interval; MRI, magnetic resonance imaging; BI-RADS, Breast Imaging Reporting and Data System.

centers. Upgrade rates increased with higher BI-RADS categories, but the 18.4% rate in BI-RADS 3 lesions should not be generalized to routine BI-RADS 3 practice. These lesions were a small, selected subgroup that underwent biopsy and surgical excision. The final BI-RADS category represented an integrated assessment of all available imaging modalities and showed a strong association with radiologic–pathologic concordance (Cramér’s $V=0.69$), suggesting considerable overlap in the imaging-related information captured by these variables. To reduce redundancy, BI-RADS was evaluated separately rather than entered simultaneously with concordance into the multivariable model. In our study, mammography findings of asymmetry and microcalcifications were significantly associated with diagnostic upgrade, whereas the presence of a mass or architectural distortion was not. In contrast, no significant association was observed between ultrasonography or MRI findings and upgrade. These findings are consistent with previous studies suggesting that individual imaging features may have limited predictive value when considered in isolation.^{11,12,14-17} However, ultrasonography and MRI findings in the present study were categorized primarily as mass vs. non-mass lesions, and detailed morphological features were not analyzed separately. In addition, MRI was available in only 45.3% of patients, and diffusion-weighted imaging, apparent diffusion coefficient values, and other detailed MRI characteristics were not consistently available because of the retrospective multicenter design. These limitations may have reduced our ability to fully assess the predictive contribution of ultrasonography and MRI features. Furthermore, technical factors such as biopsy method, needle gauge, and number of samples were not analyzed in detail because of their highly unbalanced distribution across centers. The small number of vacuum-assisted biopsies also limited meaningful comparison. However, excluding the 10 vacuum-assisted biopsy cases yielded an overall diagnostic upgrade rate of 36.8%, very similar to the 36.6% rate observed in the full cohort. Previous studies have reported lower upgrade rates with vacuum-assisted biopsy and have proposed vacuum-assisted excision as a potential alternative to surgical excision for selected papillomas without atypia.^{6,11,18-20} Given the limited number of vacuum-assisted biopsy cases in the present study, these observations should be interpreted in the context of the existing literature rather than as direct evidence from our cohort.

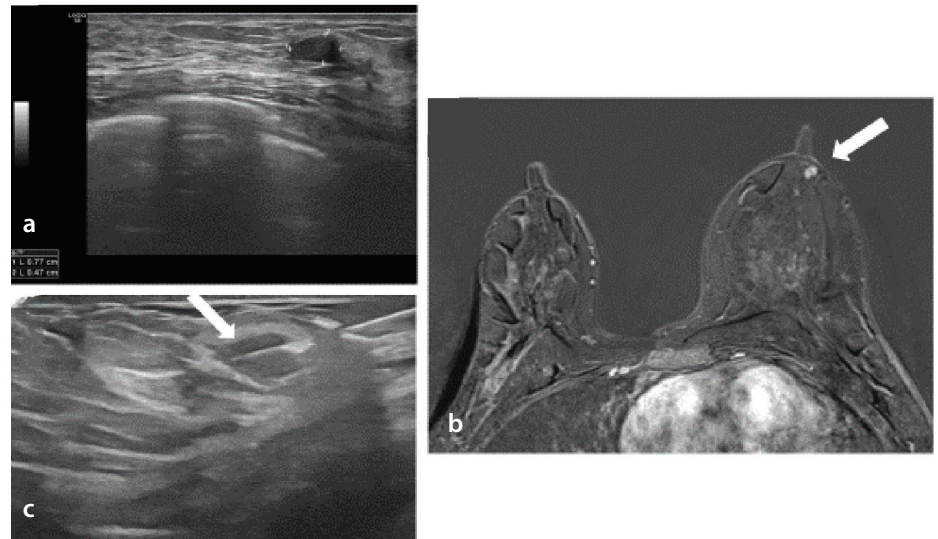


Figure 4. Representative non-upgraded papilloma. (a) A 34-year-old patient presenting with breast pain had an oval, circumscribed, hypoechoic intraductal nodule in the left retroareolar region on ultrasound (US), (b) homogeneous enhancement of the circumscribed retroareolar nodule on subtraction magnetic resonance imaging, and (c) US-guided core needle biopsy of the lesion. Core biopsy showed intraductal papilloma without atypia; surgical excision showed intraductal papilloma with stromal fibrosis, dilated benign ducts, and columnar cell hyperplasia, without diagnostic upgrade.

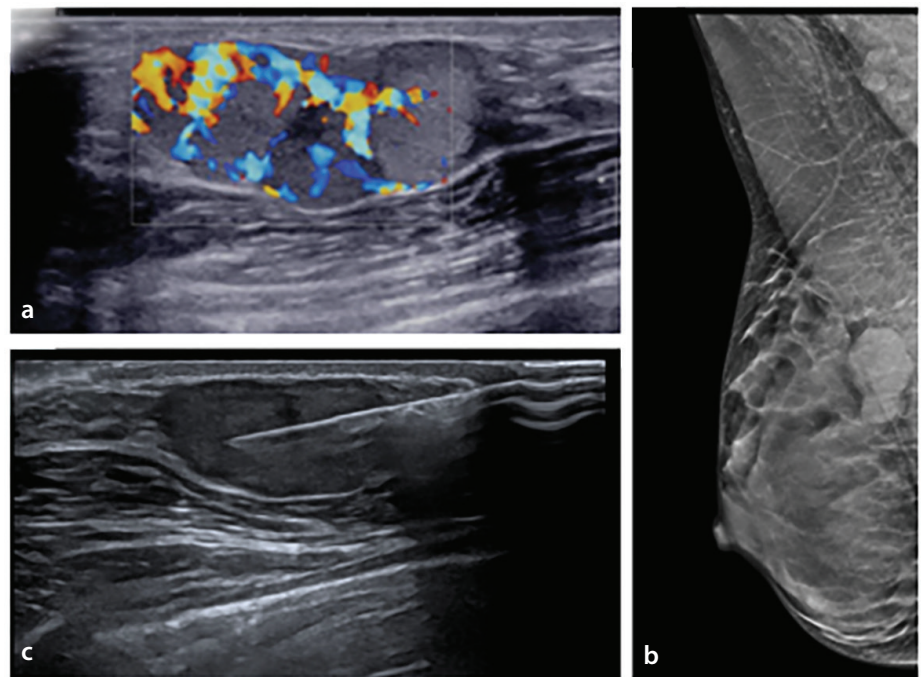


Figure 5. Representative malignantly upgraded papilloma. (a) A 41-year-old patient presenting with a palpable mass had a peripherally located, oval, microlobulated, hypoechoic 28×18-mm mass with vascularity on Doppler ultrasound (US), (b) a corresponding microlobulated oval mass on the right mediolateral oblique mammogram, and (c) US-guided core needle biopsy. Core biopsy showed intraductal papilloma with atypia; surgical excision showed invasive solid papillary carcinoma.

Several additional limitations should be acknowledged. First, the retrospective multicenter design inevitably introduced heterogeneity in imaging protocols, biopsy techniques, needle gauges, sample numbers, and pathological assessment across participating centers. In addition, imaging and pathology were not subjected to standardized central

review, and intercenter agreement was not formally assessed. Moreover, detailed ultrasonographic and MRI descriptors were not uniformly available, and potentially relevant variables such as lesion multiplicity and distance from the nipple were not consistently recorded. Likewise, detailed histopathologic subtype information was not uniformly

available for all malignant lesions or for the two non-malignant BI-RADS 5 cases. These limitations may have reduced the precision of modality-specific analyses and should be considered when interpreting the findings. Despite these limitations, the large multicenter cohort and comprehensive assessment of clinical, imaging, biopsy, and radiologic-pathologic factors strengthen the clinical relevance of our findings and provide a broad perspective on diagnostic upgrade in papillary breast lesions.

In this multicenter cohort, papillomas with atypia had a substantially higher malignant upgrade rate than those without atypia. Older age, larger lesion size, presence of symptoms, asymmetry and microcalcifications on mammography, and radiologic-pathologic discordance were associated with overall diagnostic upgrade. These factors may support individualized multidisciplinary decisions regarding surgical excision. Because the study population consisted of surgically excised lesions, the observed upgrade rates should be interpreted within this clinical context. Further prospective multicenter studies with standardized protocols are warranted to validate these findings and refine risk-adapted management strategies for papillary breast lesions.

Footnotes

Conflict of interest disclosure

Serap Gültekin, Işıl Başara Akın and Gamze Durhan serve as Section Editors for Diagnostic and Interventional Radiology.

They had no involvement in the peer review of this article and had no access to information regarding its peer review. The other authors declared no conflicts of interest.

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