Papillomas and Atypical Papillomas in Breast Core Needle Biopsy Specimens

Risk of Carcinoma in Subsequent Excision

Andrew A. Renshaw, MD,[1] Robert P. Derhagopian, MD,[2] Dolores M. Tizol-Blanco, MD,[3] and Edwin W. Gould, MD[1]

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Abstract

We sought to define the risk associated with papillomas and atypical papillomas in breast core needle biopsy specimens from a series of approximately 8,500 biopsies performed during 8 years. From a total of 62 papillary lesions (including papillomas and atypical papillomas), 40 (65%) had histologic follow-up. Overall, 15 (38%) of 40 patients had ductal carcinoma in situ (12 cases) or invasive carcinoma at excision (3 cases). Eight cases diagnosed as papilloma had benign follow-up. Slides were available for review in 38 cases and reclassified into benign papilloma with florid hyperplasia and no or minimal atypia (18 cases), papilloma with separate foci of atypical ductal hyperplasia (7 cases), and severely atypical papillomas "suspicious" for papillary carcinoma (13 cases). Carcinoma was identified in 0 (0%), 2 (29%), and 12 (92%) cases, respectively. We conclude that while atypical papillary lesions and papillomas with associated atypical ductal hyperplasia in breast core needle biopsy specimens are associated with a risk of carcinoma, lesions diagnosed as papilloma or papilloma with no or minimal atypia are benign and do not need to be excised.

Core needle biopsy of the breast is being used increasingly to define radiologically and clinically identified lesions. There is abundant evidence that atypical papillary lesions, consisting of papillomas with atypia or atypical ductal hyperplasia, are associated with a significant risk of carcinoma and need to be excised.[1-7] However, the significance of a diagnosis of papilloma in these specimens is controversial. Only a few small series exist,[1-6] but taken together these series suggest a small risk of carcinoma. As a result of this uncertainty, a recent influential review[8] suggested that "there is a small but definite chance of atypia or malignancy on excision," and "until more data become available it may be most prudent to recommend excision for all papillary lesions, even those with completely benign features on core needle biopsy."

As a result of this, we began recommending excision for all papillary lesions. Since then it has been our impression that papillomas are not associated with an increased risk of carcinoma. To further investigate this, we reviewed our experience with papillary lesions in breast core needle biopsy specimens.

Materials and Methods

The results of breast core needle biopsy specimens interpreted from August 20, 1996, to November 1, 2003, at Baptist Hospital of Miami, Miami, FL, were reviewed. All biopsy specimens with a diagnosis of a papillary lesion were identified. Cases originally were classified as papilloma or atypical papillomas. Atypical papillomas included papillomas with atypical features or papillomas with coexistent atypical

ductal hyperplasia, as previously defined.[9] On review, cases were reclassified into 1 of 3 categories: benign papillomas with no or minimal atypia **Image 1**, benign papillomas with adjacent atypical ductal hyperplasia **Image 2**, and severely atypical papillomas **Image 3**.

Severely atypical papillomas had features suggestive of papillary carcinoma. Criteria for this diagnosis are based on the previously outlined criteria[10] and include the presence of hyperchromatic nuclei, marked nuclear atypia, cribriform pattern, absent supporting stroma, and a monotonous cell population. In general, however, the cells resembled those of intermediate-grade ductal carcinoma in situ, solid or cribriform type, and included a solid or cribriform architecture without streaming or else resembled those of papillary carcinoma and consisted of sheets of somewhat elongated, hyperchromatic, and atypical cells or multiple layers of elongated cells covering papillary fronds. Benign papillomas with adjacent atypical ductal hyperplasia had areas that qualified as atypical ductal hyperplasia as previously defined.[9] All other papillary lesions were placed in the category of benign papilloma with no or minimal atypia.

All breast core needle biopsy specimens were obtained by clinicians; more than 95% were performed by radiologists and consisted almost exclusively of 11- and 14-gauge core needle biopsy specimens performed under ultrasound or stereotactic guidance.

All specimens were received fixed and were processed routinely. Up to 5 cores were processed in a single block; if more than 5 cores were present, an additional block was prepared. Each block was sectioned entirely to produce 8 slides and between 2 and 5 levels per slide. All diagnoses

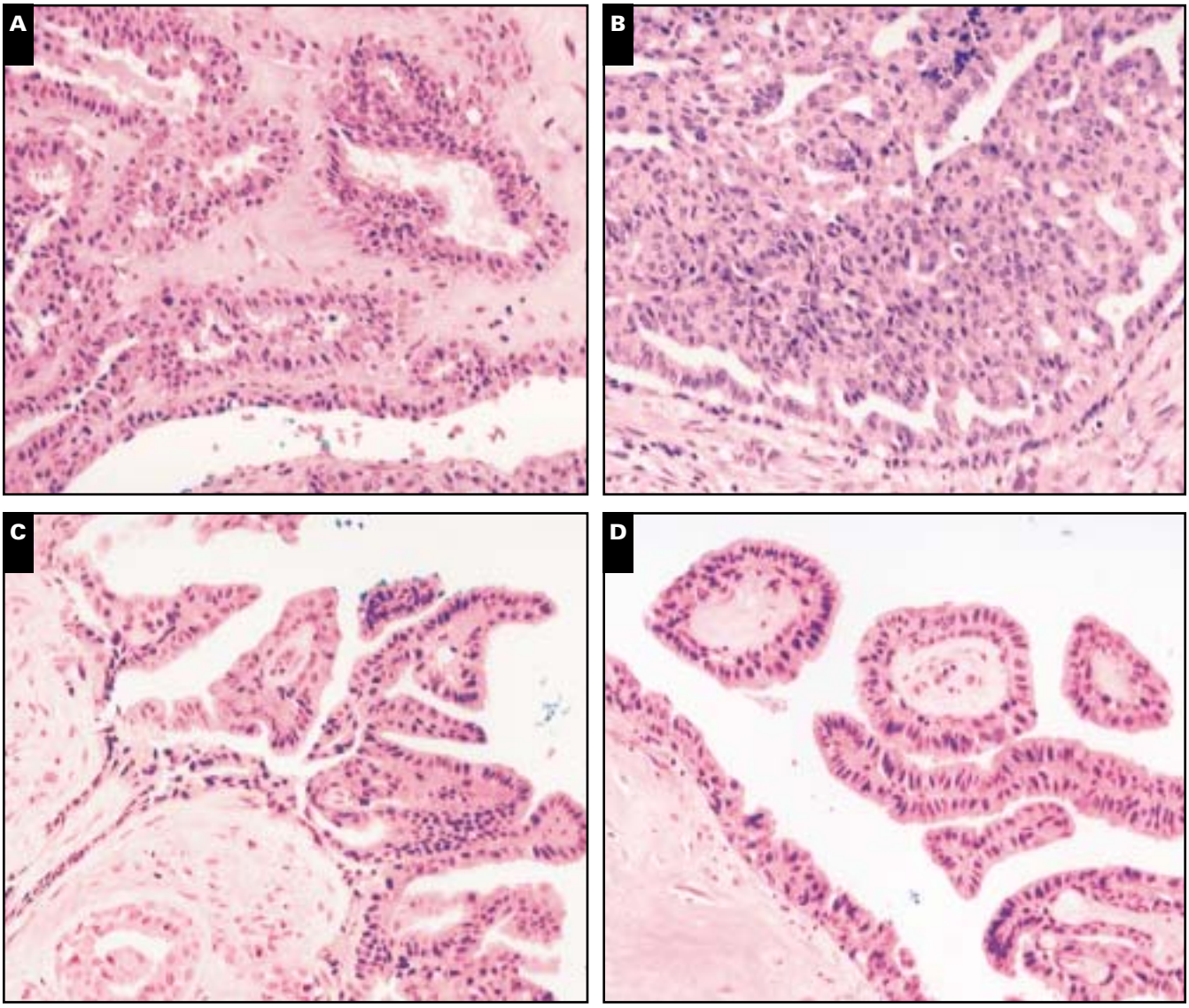

Image 1 Benign papilloma (**A**) with florid hyperplasia (**B**) and no or minimal (**C** and **D**) atypia (**A-D**, H&E, ×200).

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were based on examination of H&E-stained slides; immunohistochemical studies were not a part of this study.

Statistical comparison was performed using a 2-tailed Fisher exact test.

Results

During the period August 1996 to November 2003, approximately 8,500 biopsies were performed. A total of 62 papillary lesions (0.73%) were identified. Of these 62 papillary lesions, 40 (65%) had histologic follow-up. These 40 women were 30 to 81 years old (mean, 58.2 years), and biopsy was performed for a mass alone in 35 cases and a mass plus calcifications in 5 cases.

Overall, 15 (38%) of 40 patients had ductal carcinoma in situ (12 cases) or invasive carcinoma at excision (3 cases). Atypical ductal hyperplasia was identified in 8 cases. Eight cases originally diagnosed as papilloma had benign follow-up.

Slides were available for review in 38 cases and reclassified by one of us (A.A.R.) into benign papilloma with florid hyperplasia and no or minimal atypia (18 cases) (Image 1), benign papilloma with separate foci of atypical ductal hyperplasia (7 cases) (Image 2), and severely atypical papillomas "suspicious" for papillary carcinoma (13 cases) (Image 3). Carcinoma subsequently was identified in the excision in 0 cases (0%), 2 cases (29%), and 12 cases (92%), respectively. The rate of carcinoma in severely atypical papillomas was significantly greater than in benign papillomas ($P < .0001$) or benign papillomas with adjacent atypical ductal hyperplasia ($P = .007$).

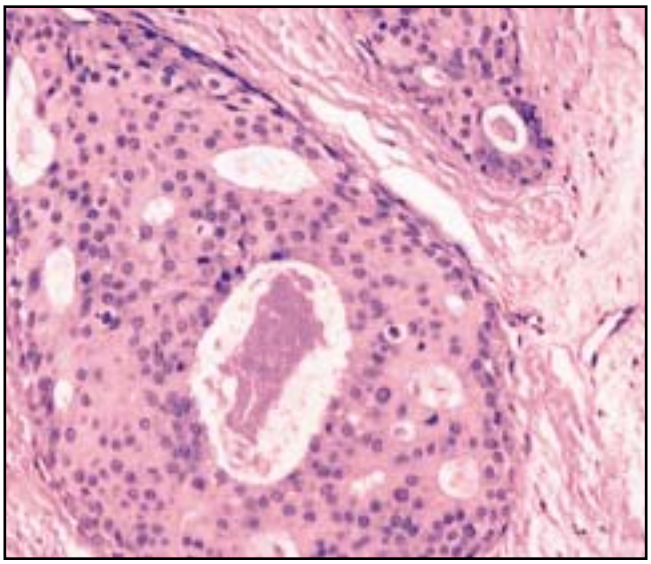

Image 2 Papilloma with separate foci of atypical ductal hyperplasia (H&E, ×200).

Discussion

There is abundant evidence that atypical papillary lesions, consisting of papillomas with atypia suspicious for papillary carcinoma or atypical ductal hyperplasia, are associated with a significant risk of carcinoma and need to be excised.[1-7] The data in this report would strongly support the idea that atypical papillomas are high-risk lesions and warrant excision. However, the significance of a diagnosis of papilloma in these specimens in the literature is controversial. Only a few small series exist.[1-6] In a total of 47 previously reported cases with histologic follow-up, 5 (11%) cases of malignancy were identified at excision. Based on this finding, excision often is recommended.[8] However, in 2 series with carcinoma at excision,[2,4] the cases with carcinoma did not correlate with the radiographic findings, and in the remaining 2 series in which carcinoma was found (both reported in abstract form only),[3,5] insufficient information was available to assess the adequacy of the biopsy. Nevertheless, in part as a result of this recommendation, we have been aggressive in identifying minimal atypia in papillomas and recommending excision for all such cases. This likely accounts for the large number of atypical papillary lesions that were reclassified as papillomas with no or minimal atypia in this series.

If there is a risk of carcinoma associated with papillomas, the combined evidence from previous studies and the present study suggest it is relatively low. Other benign lesions that otherwise are not associated with an increased immediate risk of carcinoma at the site where they occur, including radial scars and lobular carcinoma in situ, also have been shown to be associated with a low risk of carcinoma when found in breast core needle biopsy specimens. However, while preliminary reports suggested that lobular neoplasia, including atypical lobular hyperplasia and lobular carcinoma in situ, was associated with an increased risk of ductal carcinoma in situ and invasive carcinoma,[2,11-18] subsequent[19] and larger series[20] were unable to confirm this, and subsequent studies strongly suggested that in cases in which significant lesions were identified, the lesion of interest was not sampled at the time of biopsy.[21] Nevertheless, reports of a relatively low incidence (10%) of carcinoma after a diagnosis of lobular neoplasia persist.[22]

However, recent studies also suggest that false-negative results owing to the radiologist failing to sample the lesion are relatively common, accounting for an error rate of approximately 10%.[23-26] Certainly the rate of carcinoma found at excision after a diagnosis of lobular neoplasia fits

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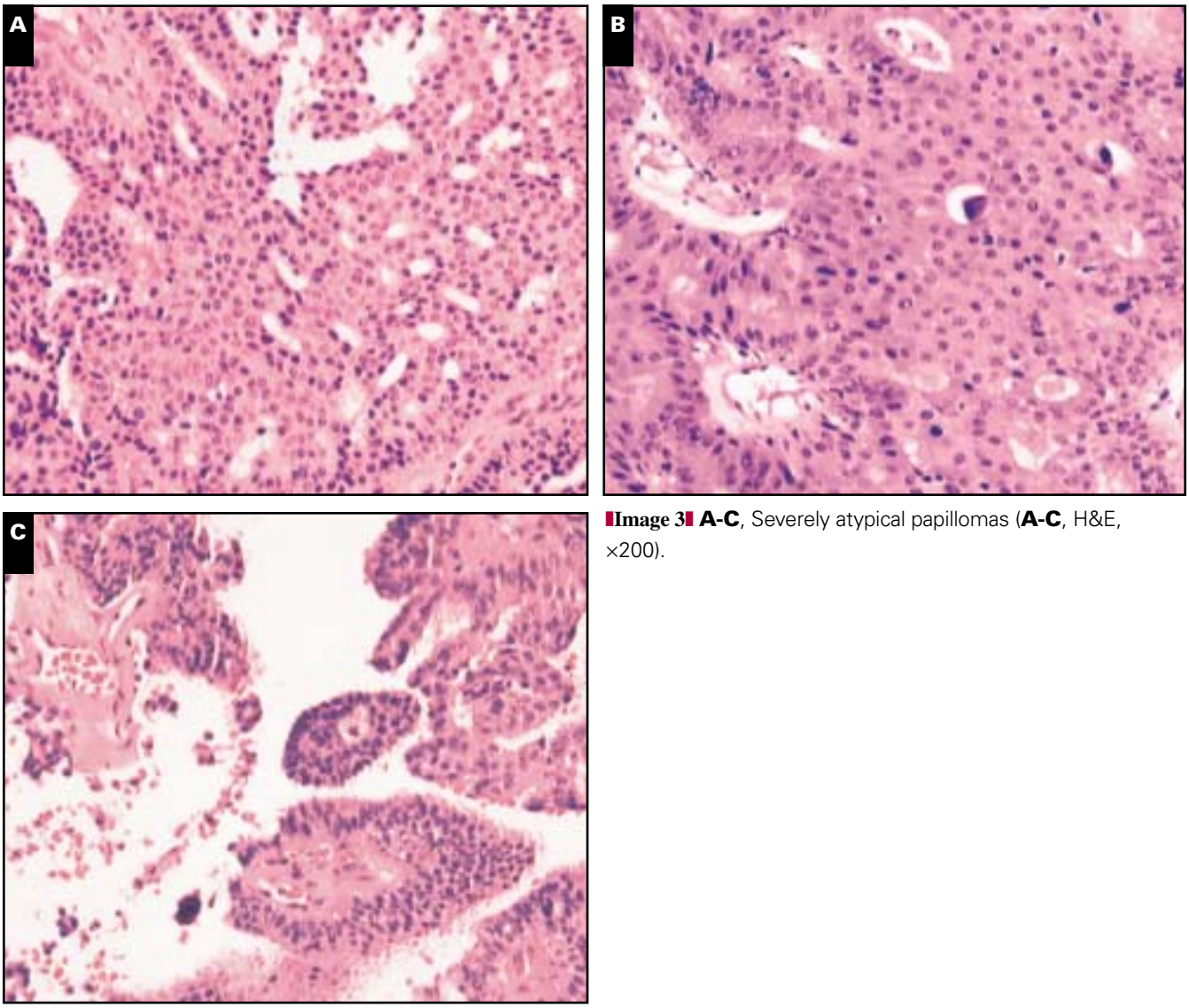

Image 3 **A-C**, Severely atypical papillomas (**A-C**, H&E, ×200).

well within this range, as does the risk for radial scars.[8,27] This is in contrast with the 16% to 19% risk of invasive carcinoma at excision after a diagnosis of ductal carcinoma in situ alone[25,28-31] (although some studies suggest the risk is closer to 13%[32]) and the rate of carcinoma found for atypical ductal hyperplasia of approximately 30%[8,25,33] (although some studies found lower rates[32]). This suggests that both of these lesions are markers associated with increased risk above that related to inadequate sampling.

Taken together, these results strongly suggest that the incidence of carcinoma associated with a diagnosis of benign papilloma at excision is related to sampling rather than any increased risk related to the diagnosis itself. Indeed, *every* reported case of carcinoma arising in association with a papilloma on core needle biopsy in which adequate documentation is provided shows histologic and imaging noncorrelation, and the overall rate of malignancy for papillomas is well within the sampling error rate. As a result, in contrast with recent recommendations,[8] we believe that there currently is little if any evidence that papillomas are associated with any increased risk of carcinoma as long as there is radiologic concordance. As others have suggested,[1,6,7] as long as the radiographic findings correlate with the histologic findings, a diagnosis of papilloma on core needle biopsy is not an indication for excision.

We have shown in a relatively large series of cases that the diagnosis of papilloma in breast core needle biopsy specimens is benign. In cases with radiologic concordance, excision is not necessary.

From the Departments of [1]Pathology, [2]Surgery, and [3]Radiology, Baptist Hospital of Miami, Miami, FL.

Address reprint requests to Dr Renshaw: Dept of Pathology, Baptist Hospital of Miami, 8900 N Kendall Dr, Miami, FL 33176.

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