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Risk Factors for Malignancy in Benign Papillomas of the Breast on Core Needle Biopsy

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Abstract

Background This study was designed to evaluate the clinical and pathologic parameters of benign papillomas diagnosed on core needle biopsy (CNB) and predict malignancy risk after surgical excision.

Methods We retrospectively reviewed clinicopathologic findings for 160 CNB-diagnosed benign papillomas followed by surgical excision from 154 patients.

Results Ten (6.3%) of the excised lesions were diagnosed as malignant. Univariate analysis showed that those that were palpable on physical examination, detected as a mass on mammography, or >1 cm on sonography were significantly associated with malignancy. In multivariate analysis, lesions that were palpable (odds ratio (OR), 29.2; 95% confidence interval (CI), 4.06–209.58; $P = 0.001$) or detected as a mass (OR, 5.68; 95% CI 1.08–29.87; $P = 0.04$) remained significantly associated with malignancy. In a CART analysis, including all variables, lesions that were palpable and associated with a mass on mammogram were confirmed as malignant.

Conclusions Breast lesions diagnosed as benign papillomas on CNB had a 6.3% risk of being malignant. The risk was highest for lesions that were palpable and detectable as a mass on a mammogram. In addition, the low-risk patients avoid immediate surgical excision, although they should be followed carefully.

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Introduction

Papillary lesions of the breast are commonly encountered in surgical pathology and consist of a heterogeneous group from benign papilloma, atypical papilloma, to invasive papillary carcinoma [1]. In case of atypical papilloma on core needle biopsy (CNB), excisional biopsy is recommended to rule out noninvasive and invasive carcinoma. However, it is debatable whether surgical excision should be always performed in benign papilloma on CNB. The risk of underlying malignancy varies 0–36% in basis of reports of surgical excision after a diagnosis of benign papilloma on CNB [2–12].

Distinguishing between benign and malignant papillary lesions based on symptoms and radiologic imaging is problematic. Pathologic confirmations in surgical specimen are essential, because both benign and malignant papilloma can present with bloody nipple discharge [13]. Furthermore, mammographic or sonographic characteristics alone cannot sufficiently distinguish benign from malignant papilloma, because both may present as a mass or calcifications on mammography [14–17]. In this study, we evaluated the clinical and pathologic parameters of benign papilloma diagnosed on CNB and predicted which are associated with malignancy.

Materials and methods

Patients

We reviewed pathologic records of all 4,398 CNB cases performed at the Center for Breast Cancer, National Cancer Center, Korea, between January 2001 and August 2008. A total of 154 patients, who had benign papilloma diagnosed

on CNB followed by surgical excision, were included in this study; 6 had bilateral lesions, yielding 160 CNBs for the study. All patients underwent clinical and radiological examination, including bilateral two-view mammography (craniocaudal and mediolateral oblique) and sonography. Palpability was assessed by one of three experienced surgeons, and we characterized the radiological appearance of the lesion according to the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS). Lesion size was based on the greatest dimension measured by sonography. We categorized patients by the following variables: (1) age at the time of CNB diagnosis, (2) presence of nipple discharge, (3) palpability of lesion on physical examination, (4) cytology findings of nipple discharge, (5) size of the largest lesion and number of lesions revealed on sonography, (6) imaging categorization according to BI-RADS classification, (7) location of mass for nipple (central vs. peripheral; criteria, 2 cm from nipple), and (8) mammogram findings (normal, microcalcification, or mass).

Core-needle biopsy and pathology

Sonography-guided biopsies were performed using a spring-loaded device with a 14-gauge automated needle (Bard Peripheral Technologies, Tempe, Arizona). Biopsy tissues and excisional specimens were fixed in formaldehyde and embedded in paraffin. Sections were cut and stained with hematoxylin and eosin for pathological assessment and with cytokeratin-5 and high-molecular-

Table 1 Clinicopathologic characteristics and malignant risk of total benign papillary lesion on core needle biopsy

Characteristic	No. of benign subset ($n = 150$)	No. of malignancy subset ($n = 10$)	P value
Age (years)			
≤45	64 (42.7)	4 (40)	0.87
>45	86 (57.3)	6 (60)	
Nipple discharge			
No	92 (61.3)	3 (30)	0.05
Yes	58 (38.9)	7 (70)	
Palpability			
No	140 (93.3)	5 (50)	0.001
Yes	10 (6.7)	5 (50)	
Atypical cell in nipple discharge			
No	42 (28)	5 (50)	0.32
Yes	2 (1.3)	1 (10)	
Cytology not done	106 (70.7)	4 (40)	
Size on sonography (cm)			
≤1.0	95 (63.3)	2 (20)	0.01
>1.0	55 (36.7)	8 (80)	
Centrality			
Central	97 (64.7)	6 (60)	0.68
Peripheral	27 (18)	1 (10)	
Unknown	26 (17.3)	3 (30)	
Multiplicity			
No	114 (76)	7 (70)	0.71
Yes	36 (24)	3 (30)	
BI-RADS			
C3, C4a	126 (84)	6 (60)	0.14
C4b, C5	22 (14.7)	3 (30)	
Unknown	2 (1.3)	1 (10)	
Microcalcification on mammography			
No	140 (93.3)	8 (80)	0.17
Yes	10 (6.7)	2 (20)	
Mass on mammography			
No	124 (82.7)	4 (40)	0.005
Yes	26 (17.3)	6 (60)	

BI-RADS Breast Imaging Reporting and Data System; *C* category

Data are numbers with percentages in parentheses unless otherwise indicated

weight cytokeratin stain for immunohistochemical analysis. An experienced pathologist (YK) reviewed the slides and categorized them as benign or malignant.

Statistical analysis

To identify factors associated with malignancy, we performed univariate analysis (chi-square test or Student's *t* test) and multivariate analysis (logistic regression) using Stata 10.0 for Windows (Texas, USA). A significance level of 0.1 was necessary for a covariate to be entered into multivariate analysis. To investigate which variables were associated with the likelihood of malignancy, we performed classification and regression tree (CART) analysis using Waikato Environment for Knowledge Analysis (version 3.4.10, University of Waikato, New Zealand). We also used the J48 classifier algorithm, which is an implementation of the C4.5 decision tree learner.

Ethics

This study protocol was reviewed and approved by the Institutional Review Board of the National Cancer Center at Goyang and complied with the recommendations of the Declaration of Helsinki for biomedical research involving human subjects.

Results

The median patient age was 47 (range, 27–81) years. Table 1 shows the clinicopathologic characteristics of the CNB-diagnosed benign papillary lesions. After surgical excision, ten (6.3%) of the lesions were diagnosed as malignant—four of them in the 45 years or younger age group. Age was not associated with malignancy ($P = 0.87$).

Ten (6.3%) of the 160 excised lesions were diagnosed as malignant. The diagnoses of the excisional specimens were as follows: 10, showed fibrocystic change; 131, benign papilloma; 9, atypical ductal hyperplasia; 1, ductal carcinoma in situ; 2, intraductal papillary carcinoma; 3, invasive ductal carcinoma; and 4, invasive papillary carcinoma. Table 1 summarizes the diagnosis upgrade rates for all lesions according to clinical, radiological, and pathological variables. Only lesions that were palpable (50% malignant vs. 6.7% benign; $P = 0.001$), detectable as a mass on mammography (60% malignant vs. 17.3% benign; $P = 0.005$), or >1 cm on sonography (80% malignant vs. 36.7% benign; $P = 0.01$) were significantly associated with malignancy. However, location or number of the lesions and BI-RADS in sonography was not related with malignant risk (C4b or C5; 30% malignant vs. 14.7% benign; $P = 0.14$).

Table 2 Multivariate analysis for malignancy of benign papillary lesions diagnosed by core needle biopsy according to clinical characteristics

Characteristic	Odd ratio	95% CI	*P* value
Nipple discharge	6.63	0.99–44.41	0.05
Palpability	29.26	4.06–209.58	0.001
Size on sonography (>1 cm)	2.77	0.45–16.88	0.27
Mass on mammography	5.68	1.08–29.87	0.04

CI confidence interval

In multivariate analysis, lesions that were palpable (odds ratio (OR), 29.2; 95% confidence interval (CI), 4.06–209.58; $P = 0.001$) or detectable as a mass (OR, 5.68; 95% CI 1.08–29.87; $P = 0.04$) were significantly associated with malignancy (Table 2).

Figure 1 presents the results of CART analysis. Palpability together with the presence of a mass on a mammogram was associated with the highest risk of malignancy (4/4, 100%), whereas nonpalpable lesions had the lowest risk (5/145, 3.4%).

Discussion

Many controversies surround the appropriate management of papillary lesions on CNB. In Table 3, current studies for benign papilloma on core needle biopsy are summarized. This study is the largest study for benign papilloma with surgical excision. Additionally, all lesions of this study were preoperatively evaluated by sonography and mammogram. This study demonstrated that 6.3% of benign papillary lesions on CNB revealed malignancy after surgical excision and the risk of malignant risk were higher in the lesions with palpation and mass formation on mammogram. When we reanalyzed these data only for the

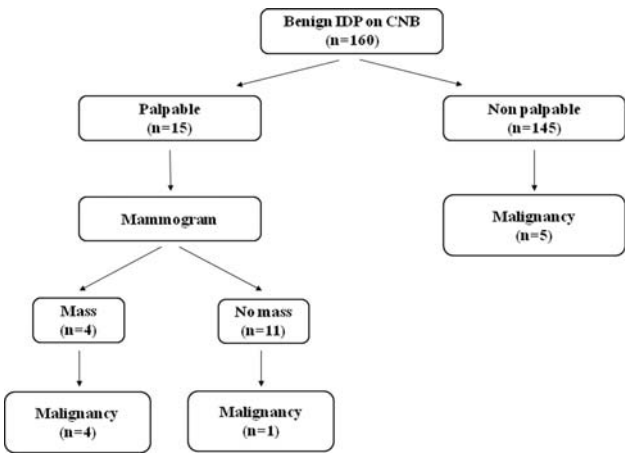

Fig. 1 Classification and regression tree (CART) analysis of core needle biopsy (CNB)-diagnosed benign papillomas

Table 3 Treatment recommendations in current literature for benign papillomas diagnosed on core needle biopsy

Study	Year	No. of benign papilloma on CNB	No. of surgical excision	No. (%) upgraded to malignancy	Routine excision recommended
This study	2009	160	160	10 (6.3)	Yes
Ahmadiyeh et al. [28]	2009	86	29	1 (3.4)	No
Sakr et al. [29]	2008	53	48	4 (7.5)	Yes
Rizzo et al. [12]	2008	345	142	18 (5.2)	Yes
Ashkenazi et al. [9]	2007	39	20	7 (17.9)	Yes
Sydnor et al. [30]	2007	38	38	1 (2.6)	No
Liberman et al. [10]	2006	50	25	5 (10)	Yes
Mercado et al. [11]	2006	43	36	2 (4.7)	Yes
Plantade et al. [31]	2006	86	37	5 (5.8)	No
Agoff et al. [8]	2004	25	11	0 (0)	No
Ivan et al. [4]	2003	30	6	0 (0)	No
Puglisi et al. [32]	2003	31	31	2 (6.5)	Yes
Rosen et al. [27]	2002	44	14	1 (2.3)	No
Mercado et al. [6]	2001	12	6	1 (8.3)	Yes

invasive lesions, the palpable lesions were associated with invasive lesions in multivariate analysis (OR, 28.1; 95% CI 3.64–215.86; $P = 0.001$, data not shown).

Whether CNB-diagnosed benign papillary lesions should be excised is currently under debate. Some studies conclude that they should be excised because they can become malignant [7, 18] or increase the risk of invasive breast cancers [19, 20], whereas others suggest that excision is not necessary, especially when imaging results agree with the diagnosis [21]. In a recent review of the Mayo Clinic experience with breast papilloma, benign papillary lesions were found to impart a cancer risk similar to that of conventional proliferative fibrocystic change [22].

Some investigators assert that all papillary lesions, with or without associated atypia or malignancy, should be surgically excised [23, 24]. Others, however, assert that a properly performed CNB is adequate for accurate diagnosis, and further surgery is unnecessary [25, 26]. Several studies of large CNBs suggest that lesions without atypia and with concordant imaging classified as BIRADS 4 or a more benign classification do not require excision [4, 25, 27]. Although such studies, with improved lesion categorization, could in theory avoid a substantial number of unnecessary invasive procedures, we found in the present study that benign papillomas classified as BIRADS 3 had a risk of being malignant.

Although we found a greater frequency of malignancy among cases presenting with nipple discharge than in cases presenting without discharge, the difference was not statistically significant. Sakr et al. [17], on the other hand, reported that nipple discharge was significantly associated with malignancy in CNB-diagnosed benign papilloma, and Rizzo et al. [12] reported that asymptomatic papillomas were associated with a higher rate of upgrade than symptomatic ones. Thus, the predictive value of nipple discharge remains unclear.

Conclusions

Breast lesions diagnosed as benign papillomas on CNB had a 6.3% risk of being malignant. The risk was highest for lesions that were palpable and detectable as a mass on a mammogram. In addition, low-risk patients avoid immediate surgical excision, although they should be followed carefully.

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