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Original Article

Value of clinical characteristics and breast-related preoperative examinations in the differential diagnosis of breast intraductal papillary neoplasms

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Abstract: The management of breast intraductal papillary neoplasms of the breast poses a challenge for clinicians. Intraductal papillary carcinoma and papilloma resemble in their clinical features. The aim of this study was to determine whether a combination of clinical factors could be used to accurately identify intraductal papillary carcinoma. 644 patients diagnosed by breast intraductal papillary neoplasms were evolved. Descriptive statistics were employed to analyze the epidemiological and clinical data. In present study, 151 samples with nipple discharge in all patients were evaluated for the following candidate predictive tumor markers: CEA and CA15-3. Univariate and multivariate analyses were used to investigate associations among marker concentration, preoperative clinical parameters and patient histopathology outcomes. It showed the following to be significantly associated with a risk of intraductal papillary carcinoma: menopause, reproductive age, smoking and palpable mass. CEA and CA15-3 levels in nipple discharge of intraductal papillary carcinoma were significantly higher than those with intraductal papilloma ($P<0.05$). Menopause, reproductive age, smoking and palpable mass may be helpful to earlier diagnosis of intraductal papillary carcinoma. Detection of CEA and CA15-3 in nipple discharge is a simple, noninvasive technique that can be used to improve preoperative determination in patients with intraductal papillary carcinoma. Clinical analysis would enhance the accurate assessment for patients with papillary lesions.

Keywords: Clinical characteristics, diagnosis, imaging examination, intraductal papillary neoplasm, tumor marker

Introduction

The typical clinical characteristics of breast intraductal papillary neoplasms is papillary arborescent-growth pattern supported by a fibrovascular stalk with or without an intervening myoepithelial cell layer [1, 2]. Intraductal papillary carcinoma (IPC) and intraductal papilloma (IDP) are examples of papillary breast lesions [3]. Accurate diagnosis is required in differentiation IDP and IPC; however, they are somehow difficult to acquire because of the similar appearances of benign and malignant papillary lesions.

By studying the inpatient record database, we found because the number of hospitalization greatly increased due to the enlarged hospital scale. In the past four years, our reporter learnt that the number of patients of breast intraductal papillary neoplasms increased by 13-46%. However, the number of patients with papillary stays relatively stable, which is shown as the constituent ratio in **Figure 1**. So far as we know, there is no testing method could distinguish IPC from IDP in women with a complementary reliability, and the standard treatment at this time is to completely apply to all papillomas since they could be heterogeneous and associated with any potential malignancy. Although histological criteria have been established, difficulties may arise, particularly in the clinical distinction between IDP and IPC.

A large portion of patients with breast intraductal papillary neoplasms present nipple discharges contain one or several symptoms including: spontaneous unilateral, serous and bloody discharge [4]. Though IDP remains the most common etiology in these cases, the incidence of

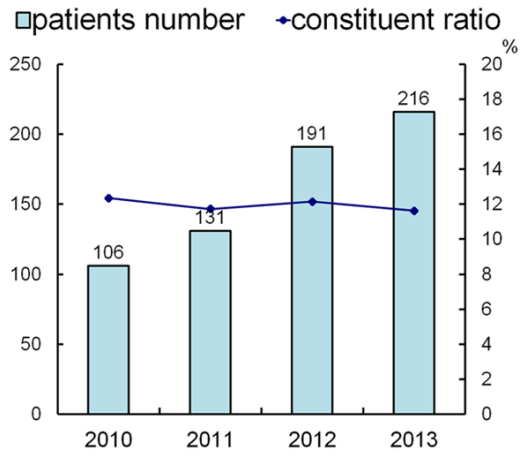

Figure 1. Numbers of patients with breast intraductal papillary neoplasms and percentage of total inpatients in department of breast surgery from 2010 to 2013. It shows the constituent ratio of patients with breast intraductal papillary neoplasms accounted for all included inpatients (858, 1117, 1572 and 1859, respectively) remain unchanged basically (11-12%). Total numbers of inpatients with breast intraductal papillary neoplasms of every year are 106, 131, 191 and 216, respectively.

malignancy in the setting of nipple discharge is reported as a range from 5% to 21% [5]. Evaluation options for suspicious nipple discharge include ultrasonography, exfoliative cytologic analysis, galactography and ductoscopy. Galactography has been has been shown as a method of choice for determining the location and extent of abnormalities in the duct [6-8]. We have learnt from prior studies, malignant exfoliative cytology was commonly observed in women with breast cancers [9, 10]. Malignant cytology was a very specific, but not very sensitive, method to detect breast cancer. Physical examination and mammography are widely accepted screening tools in determining IPC and IDP both in screening and in clinical practice. Unfortunately, physical examination is not sensitive enough to determine IPC, on the other hand, 10 to 40 percent of early breast cancer could not be examined by mammography neither [11-13]. Here, we list the individual sensitivity of capillary lesion: 4% for exfoliative cytology, 74% for galactography and 78% for ductoscopy [14].

Nipple discharge contains highly concentrated proteins secreted from the ductal and lobular epithelium [15, 16] which contains no contaminants from other breast organs, so it is an ideal fluid for biomarkers testing. Tumor markers, such as carcinoembryonic antigen (CEA), cancer antigen 15-3 (CA15-3) are all glycoproteins with altered glycan profiles in cancer progression. CEA is overexpressed in the majority of colon cancers, half of all breast cancers and nonsmall cell lung cancers [17-19]. CA15-3 is a transmembrane glycoprotein expressed in normal epithelial cells and up-regulated in carcinomas of epithelial origin, including breast cancer, ovarian cancer, pancreatic cancer, and multiple myeloma [20]. CA15-3 has been shown to be an independent predictor of cancer recurrence as well as a powerful prognostic indicator for patients at advanced-stage breast cancer [21]. In our previous study, it showed that statistically higher levels of CEA and CA15-3 were found in patients with breast cancer as compared to those in the benign group. The cutoff values of CEA and Ca15-3 were 224.3 ng/ml and 1368.2 U/ml, respectively. To the best of our knowledge, there are no available published studies regarding to the expression of CEA and CA15-3 in nipple discharge about breast intraductal papillary neoplasms. Moreover, the use of tumor markers in nipple discharge alone to make a differential diagnosis between IPC and IDP remains a controversial topic.

In this study we sought to examine preoperative examinations as well as epidemiologic features and their effects the diagnostic significance before surgery. We also examined the diagnostic utility of CEA and CA15-3 in nipple discharge in the distinction of IPC from IDP. Their presenting signs as well as auxiliary examinations and pathology findings were evaluated.

Materials and methods

Study method and subjects

644 patients include in this study were recruited from newly diagnosed breast intraductal papillary neoplasms patients ascertained by histopathological examination and treated at the Department of Breast Surgery, in Qilu Hospital of Shandong University, during the period of January 1st, 2010 to January 1st, 2014. All patients enrolled in the study were informed and agreed that their medical records will be used for research purposes, and both the study design and method were approved by the Ethics Committee of Qilu Hospital of

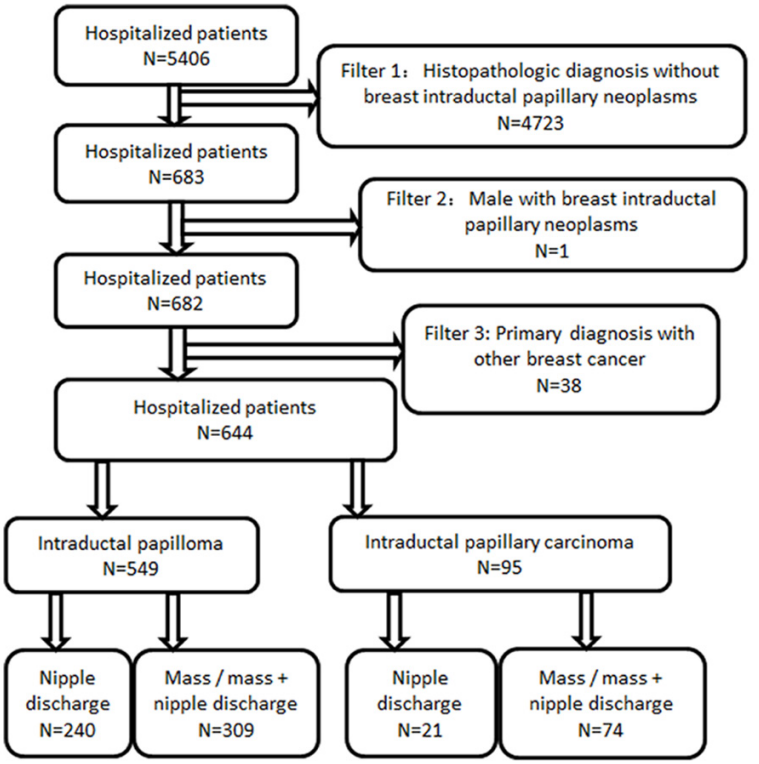

Figure 2. Screening process summary of included patients in study design. We separated patients into two sets: Intraductal papilloma and Intraductal papillary carcinoma.

Table 1. Detection of mammography, ultrasonography, exfoliative cytology, ductoscopy and galactography in comparison to histopathological results

	Intraductal papilloma	Intraductal papillary carcinoma	*P* value
Mammograpgy	437	75	<0.001
Positive	78	37	
Negative	359	38	
Ultrasonography	591	92	0.22
Positive	483	80	
Negative	108	12	
Exfoliative Cytology	215	25	<0.001
Positive	5	5	
Negative	210	20	
Ductoscopy	125	3	Nonsense
Positive	109	1	
Negative	16	2	
Galactography	205	27	0.21
Positive	159	18	
Negative	46	9	

Shandong University. **Figure 2** provides an overview of our study screening process and the performance of analysis. A total number of 5406 patients' medical records and dataset were available during this period. 644 subjects were eligible for the final analysis, among which, there were 346 patients with nipple discharge. Study cohort included women with unilateral or bilateral nipple discharge. There were 27 patients with bilateral nipple discharge. The epidemiological characteristics, such as occupation, complaint, age, menarche, menopause, average menstrual cycle, age at first child, number of child, lactation, tubal ligation, interval between menarche and primiparity, smoking, diabetes, hypertension, family history, mammary gland disease history, body mass index and palpable mass, all these were approved to be related with breast disease were administrated in one questionnaire. Each of the participants was genetically unrelated.

Nipple discharge collection and laboratory methods

Nipple discharge was successfully obtained from one or both breasts of 145 (42%) of the 346 female. 151 subjects produced sufficient nipple discharge for CEA and CA15-3 analyses. All samples were collected prior to excisional biopsy or mastectomy. Nipple discharge samples were collected by a trained surgeon using eppendorf tubes. Nipple was cleansed first with alcohol swabs to remove cellular debris, and nipple discharge was then expressed by manual compression of the breast. No serious complications occurred during the process. Droplet of nipple discharge was collected in an eppendorf tube. The

Table 2. Univariate (multivariate) logistic regression results for the relationship between intraductal papillary carcinoma and clinical epidemiological factors

Variable	Subgroup	Intraductal papillary carcinoma	Intraductal papilloma	Univariate analysis		Multivariate analysis	
		Total no.	Total no.	OR (95% CI.)	*P*	OR (95% CI.)	*P*
Occupation					0.18		
	Worker	10	60	1.69 (0.92-3.09)	0.09		
	Farmer	61	289	1.88 (0.89-3.94)	0.1		
	Teacher	15	120	1.27 (0.61-2.61)	0.52		
	Others	9	80				
Complaint				2.74 (1.64-4.57)	<0.001	1.91 (0.95-3.82)	0.07
	Nipple discharge	21	240				
	Mass with/without nipple discharge	74	309				
Age				4.98 (3.16-7.85)	<0.001	1.64 (0.73-3.66)	0.23
	<50	42	438				
	≥50	53	111				
Menarche				1.78 (1.15-2.77)	0.01	1.37 (0.82-2.3)	0.23
	≤14	39	304				
	>14	56	245				
Menopause				5.5 (3.47-8.7)	<0.001	2.89 (1.34-6.23)	0.007
	Premenopausal	43	450				
	Postmenopausal	52	99				
Average menstrual cycle				1.65 (1.05-2.59)	0.03	1.37 (0.81-2.31)	0.24
	≤28	34	263				
	>28	61	286				
Age at first child*					0.001		0.006
	≤26	8	8	5.87 (2.13-16.22)	0.001	5.51 (1.79-16.99)	0.003
	≤30	63	370	7.15 (2.41-21.18)	<0.001	7.01 (2.1-23.39)	0.002
	>30	20	143				
Number of child				1.41 (0.49-4.08)	0.53		
	Nullipara	4	32				
	Multipara	91	517				
Lactation				1.24 (0.57-2.68)	0.59		
	No	8	56				
	Yes	87	493				
Tubal ligation				4.12 (1.64-10.36)	0.003	3.18 (1.01-10.03)	0.49
No	No	87	537				
Yes	Yes	8	12				
Interval between menarche and primiparity*				0.8 (0.51-1.27)	0.35		
	<10	56	347				
	≥10	35	174				
Smoking				24.09 (2.66-217.94)	0.005	21.25 (1.9-237.74)	0.013
	No	91	548				
	Yes	4	1				
Diabetes				2.1 (0.86-5.12)	0.101		
	No	88	529				
	Yes	7	20				
Hypertension				3.17 (1.95-5.14)	<0.001	1.29 (0.68-2.43)	0.43
	No	62	470				
	Yes	33	79				
Family history				1.21 (0.64-2.33)	0.56		
	Yes	12	82				
	No	83	467				
Mammary gland disease history				0.69 (0.3-1.55)	0.37		

	Yes	7	57				
	No	88	492				
BMI*					0.2		
	<25	10	37	1.79 (0.84-3.8)	0.13		
	<30	31	149	1.3 (0.59-2.89)	0.52		
	≥30	54	357				
Palpable mass				2.81 (1.73-4.57)	<0.001	2.19 (1.13-4.24)	0.02
	No	25	275				
	Yes	70	274				

Abbreviation: 95% CI, 95% confidence interval; ND, Nipple discharge; BMI, Body mass index. *Missing data: 32 for Age at first child, 32 for Interval between menarche and primiparity, 6 for BMI.

tube was then stored in dedicated refrigerator at 4°C. The quantity of collected nipple discharge varied from 20 μL to 200 μL. Samples were transfered to the laboratory department within 8 hours after collection. Viscous samples were diluted up to 20-fold with normal saline before centrifugation and storage at 4°C. Concentrations of CEA and CA15-3 in nipple discharge were measured via an automated test system utilizing sandwich electro chemiluminescence immunoassay (ECLIA) assay kits (Roche Cobas e601 analyzer, Roche Diagnostics). All tumor markers assays were performed at Qilu Hospital of Shandong University according to manufacturer's protocol. The laboratory personnel were blinded to the clinical information. Commercial reference control sera were used for quality control and calibration.

Auxiliary examination

Mammography was performed in craniocaudal and mediolateral views. The lesions were characterized retrospectively using the relevant Breast Imaging Reporting and Data System (BIRADS) criteria of the American College of Radiology, based on the combination of mammographic and ultrasonography results [22]. Exfoliative cytology review was performed on two slides stained using the Papanicolaou method. The slides were examined without the knowledge of clinical or pathologic findings. All slides were evaluated by a single cytopathologist. Each specimen was classified as benign, mildly atypical, severely atypical, and malignant. A positive cytologic test was defined as severely atypical or malignant. Galactography was performed with 0.1 to 0.4 ml of Iopromide injected in one single duct. Craniocaudal and 90° lateral views were obtained, as were compression views when appropriate. For the purpose of the study, the galactographic findings were classified into 2 groups: (1) normal and (2) tumor(s). Group 2 includes intraductal filling defects with or without duct dilatation or obstruction. The sonographic findings were also classified as (1) normal, (2) tumor(s). Groups 1 was classified as having negative and group 2 as having positive sonographic findings. If ductoscopy revealed significant findings (1 or more papillomatous growths), it would be included in positive group. If the ductoscopy findings were normal, or if insignificant "abnormalities" were present (wispy fronds or flat red patches), it would then be classified in negative group. The results of preoperative investigations: clinical examination, breast mammography, galactography, breast ultrasonography and exfoliative cytological analysis of nipple discharge were compared with the end histological diagnosis obtained from surgery to determine their sensitivity and specificity at predicting malignancy. In our study, 49 patients were admitted to hospital with bilateral breast papillary lesions, and they were given the extra auxiliary examinations recorded. **Table 1** shows the specific information of galactography, ductoscopy and exfoliative cytology compared to histological results.

Statistical analysis

Descriptive statistics were employed to describe the epidemiological, clinical, and diagnostic data. Comparisons between different samples sources were performed using one-way analysis of variance (ANOVA). Pearson's chi-square test and Fisher's exact probability test were applied to categorical data (such as exfoliative cytology, menopause status, palpable masses). All of the statistically significant variables observed in univariate analysis were investigated by means of multivariate analysis using the Cox proportional hazards model. The unpaired t-test was applied when comparing two independent groups. Levels of tumor mark-

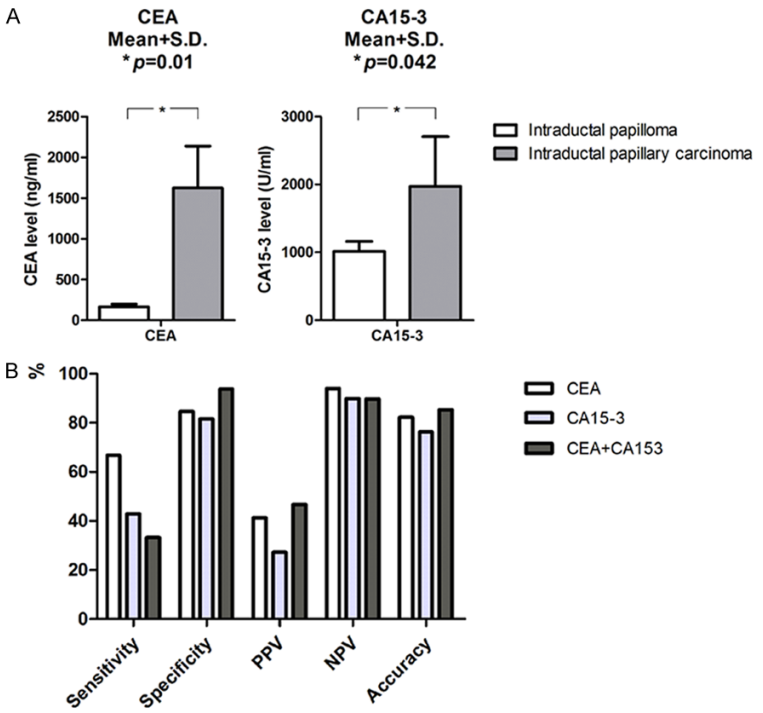

Figure 3. Diagnostic parameters of CEA and CA15-3 in nipple discharge. A shows the CEA and CA15-3 levels in nipple discharge shows that statistically higher concentrations in intraductal papillary carcinoma group (P=0.01, P=0.042, respectively). Probabilities of intraductal papillary carcinoma according to preoperative CEA status (white column), CA15-3 status (gray column) and CEA+CA15-3 status (black column) in B. The highest probability was 66.7% (CEA) in Sensitivity column, 93.8% (CEA+CA15-3) in Specificity column, 46.7% (CEA+CA15-3) in PPV column, 94% (CEA) in NPV column and 85.4% (CEA+CA15-3) in Accuracy column. Abbreviations: PPV=positive predictive value, NPV=negative predictive value.

ers are expressed in the form of the mean ± standard deviation. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy were calculated between two groups. Accuracy was defined as (true-positive + true-negative)/(true-positive +false-positive + true-negative + false-negative). *P* values below 0.05 were considered significant. The combination of tumor markers was carried out in a parallel manner with an "and" rule, wherein the test result was calculated as positive if the cutoff point for CEA and CA15-3 were both exceeded. Statistical analysis was performed using SPSS software (version 17.0; SPSS, Inc.) and data analysis software (Microsoft Excel).

Results

A total of 644 participants (549 papillomas and 95 papillary carcinomas) were evolved in this study. All patients were female, whose age range was 16-79 years (mean age 46 years). 383 patients (59.5% of 549) had the main complaints of a palpable mass with or without nipple discharge. 164 patients (25.5%) were over the age of 40. 151 patients (23.4%) were in menopause. A history of breast diseases was reported in 64 patients (9.9%). A palpable mass as one sign of physical examination was reported in 344 patients (53.4%). Based on their body mass index (BMI), the subjects were categorized into three groups, below 25 kg/m^2, 25 kg/m^2 to 30 kg/m^2 and over or equal to 30 kg/m^2. The former group consisted 411 (63.8%) of subjects, the middle group had 180 (28.0%) members, and the latter one had 47 (7.3%) members. Of the subjects, 36 (5.6%) members were nulliparous women, while 628 (94.4%) had given birth to at least one child. Other characteristic data are also shown in **Table 2**.

Our study conducted on breast intraductal papillary neoplasms and related clinical factors showed that several influencing factors were associated with the ability to accurately identify IPC, which including menopause, age at first child, smoking behavior and palpable mass. Age, tubal ligation, hypertension, complaint, average menstrual cycle and menarche were also significant related factors. The prevalence of IPC (**Table 2**) was not significantly different in occupation, lactation, BMI and so on (*P*>0.05 for all). A multiple logistic regression analysis revealed that the presence of malignant lesions was significantly related to four factors: menstrual status (premenopausal or postmenopausal, *P*=0.007, age at first child (*P*=0.006), smoking habit (*P*=0.013) and physical examination (palpable mass or not, *P*=0.02).

151 nipple discharge samples from 145 women were evaluated for the candidate predictive tumor markers. Nipple aspiration fluid was obtained from both breasts in 6 (6/346) women

Table 3. Sensitivity and specificity of auxiliary examinations

	Mammograpgy	Ultrasonography	Exfoliative Cytology	Ductoscopy	Galactography
Sensitivity (%)	49.3	87	20	33.3	66.7
Specificity (%)	82.2	18.3	97.7	12.8	22.4
PPV (%)	32.2	14.2	50	0.9	10.2
NPV (%)	90.4	90	91.3	88.9	83.6
Accuracy	77.3	27.5	89.6	13.3	27.6

Note: NPV=negative predictive value, PPV=positive predictive value.

and from one breast of 139 (139/346) women, giving a total collection rate of 41.91% (145 of 346). CEA and CA15-3 levels ranged from 0.2 ng/ml to 8736 ng/ml (median-81.6 ng/ml) and 1 U/ml to 14880 U/ml (median-418.8 U/ml), respectively. Median levels of CEA and CA15-3 in nipple discharge exceeded control serum tumor marker levels (0-5 ng/ml and 0-25 U/ml) by approximately 16-fold and 17-fold, respectively. **Figure 3A** shows concentrations of CEA and CA15-3 in nipple discharge in IPC group and IDP group. There were statistically higher concentrations of CEA and CA15-3 in the IPC group.

Based on the previous data from our research group, the cutoff values of CEA and CA15-3 to tell malignant from benign were 224.3 ng/ml and 1368.2 U/ml, respectively. According to the given cutoff values, sensitivity, specificity, positive predictive value, negative predictive value and accuracy of CEA and CA15-3 were shown in **Figure 3B**. CEA has the higher specificity (84.6%), NPV (94%) and accuracy (82.2%) compared with CA15-3. Utilizing the established cutoff levels for CEA and CA15-3 and defining positive as the levels for both tumor markers from the nipple discharge fluid were above the cutoff levels, sensitivity and specificity for detection of breast cancer were 33.3% and 93.8%, respectively. The combination of tumor markers (CEA and CA15-3) demonstrates an increase of accuracy to 85.4% (**Figure 3B**).

The results of preoperative investigations were compared with the end histological diagnosis obtained from surgery to determine their sensitivity and specificity at predicting malignancy. **Table 1** shows the results of mammography, ultrasonography, exfoliative cytology, ductoscopy and galactography compared to histological results. The cytological smears were negative (clear background secretion, benign cells, mildly atypical cells) in 230 cases, severely atypical cells or malignant cells were diagnosed in 10 cases. Mammography was abnormal (BIRADS 4 or 5) in 115 patients (22.5%). Exfoliative cytology and mammography were found to be valuable alternative methods for differentiating IPC from IDP (P<0.001 for both). Exfoliative cytology (20% sensitivity, 97.7% specificity) and mammography (49.3% sensitivity, 82.2% specificity) were significantly predictive of IPC (**Table 3**).

Discussion

This is important that the management of benign and malignant papillary lesions is different, with vastly distinguish prognostic implications. In our opinion, there are cases that are not easy to characterize as IPC or IDP by morphology. Despite the well-described histological features of these two tumors, it is occasionally difficult to distinguish between them because of overlapping characteristics [23]. These 'gray-zone' cases would be diagnostically controversial in clinic. We analyzed samples based on epidemiologic status to determine if these factors had greater predictive ability in patients with breast intraductal papillary neoplasms. Women with IPC who were in an old age >50, P<0.001) were more likely to be post-menopausal (P<0.001) than other subjects in our study. Women reported with a complaint of a palpable mass (P<0.001), hypertension (P<0.001) and a history of tubal ligation (P=0.003) also had a higher incidence of IPC. Delay at menarche (age >14, P=0.01) and a longer menstrual cycling pattern (day >28, P=0.03) were significantly related to a higher risk of IPC (**Table 2**). Also Lau and colleagues found in a study of 116 patients that those found to have malignancy were more frequently post-menopausal [24]. In one previous study, the major finding was the association of larger BMI with epithelial atypia in breast ductal samples [25]; however, our data does not consis-

tent with Djuric's research results. Since the clinical factors might be a related reflection of the activity of breast intraductal papillary neoplasms, it is essential to interpret the screening results and select the high risk women for the next diagnostic procedure. As we learn more about clinical factors and epidemiology, we could screen for patients with risks of breast intraductal papillary neoplasms would become more automatic.

In a previous study, Dr. Morrogh concluded that mammography and exfoliative cytology are not reliable at diagnosing the etiology [26]. Adepoju and colleagues, too, have emphasized the importance of the surgical approach in their study of 168 cases showing the sensitivity of mammography and ultrasound to be only 10% and 36%, respectively, at detecting malignancy [27, 28]. Compared with other imaging, mammography was a reliable method of diagnosing calcification, irregular mass or spiculated sign of breast carcinoma, playing an important role in diagnosis and differential diagnosis. Mammography for IPC had a high specificity. Although nipple discharge exfoliative cytology is often inadequate for routine assessment but specific in cases of malignancy. In our and Balci's study, ductoscopy [29] and galactography were shown to be accurate in providing the location and depth of ductal abnormalities when a single duct is identified as the source. However, these tests were not able to be used as a diagnostic tool for differentiating IPC from IDP. It should be mentioned that despite being poor predictors of malignant pathology in patients, ultrasound is still vital in the routine work-up of these patients to exclude concomitant pathology in either breast.

Measurement of tumor markers in nipple discharge is a simple, low risk, noninvasive and relatively painless preoperative diagnostic tool. The advantage of nipple discharge tumor marker analysis is the presence of concentrated secreted proteins. Thus, trace amounts were sufficient for analysis of target tumor markers. It has been proposed as an alternative way of establishing a diagnosis of breast malignancy. Previous studies investigated to explore CEA as a single tumor marker in nipple discharge which has the lower sensitivity (35.42-48%) [30, 31]. Based on our data, we recommend the use of CEA and CA15-3 evaluation of nipple discharge. We observed that CEA and CA15-3 levels in nipple discharge can aid in the preoperative confirmation of breast cancer. We examined CEA and CA15-3 in nipple discharge to determine whether these tumor markers might be useful for IPC detection or not. Concentrations of CEA and CA15-3 were significantly higher in samples from IPC than those from IDP. Combination of CA15-3 and CEA had a greater specificity and accuracy than that of CEA or CA15-3 alone but a lower sensitivity and NPV than CEA or CA15-3 alone. It was indicated that the use of combination of CA15-3 and CEA in clinic could increase the number patients with IPC diagnosed for surgery.

Based on immunohistochemistry studies of breast cancer tissues, CEA and CA15-3 expression in breast cancer were variable and heterogeneous. CEA-reactive cells were observed in 45.2% cases and CA15-3 was aberrantly overexpressed in 37.0% of patients [32, 33]. Evaluation of serum tumor markers in the diagnosis of breast malignancy has limitations due to low sensitivity and specificity, varies from 19.6% to 54% [34, 35]. In contrast, we have observed significantly higher levels of CEA and CA15-3 in nipple discharge. These observations suggest the evaluation of nipple discharge tumor marker levels can aid in establishing diagnosis of IPC, and can help guide surgical plan for patients with nipple discharge. Based on our data, patients with nipple discharge could be safely managed with expectant follow-up if diagnostic examination including galactography, exfoliative cytology, and measurement of tumor markers (CEA and CA15-3) in nipple discharge are all negative. Moreover, if levels of CEA and CA15-3 in nipple discharge are abnormal, surgery should be strongly considered.

A retrospective design in a single center was a major limitation of this study, but the number of patients was relatively large. There are several limitations to this study that should be considered: Firstly, the study belongs to the retrospective study. We didn't have a follow-up of the patient's prognosis and survival rates. Secondly, our study was performed in a single center, and further researches including multicenter studies are necessary for better understanding the relationship between multiple clinical factors and intraductal papillary carcinoma. Furthermore, it was unclear if higher tumor marker concentrations in nipple discharge correlated with greater tumor burden, cancer progression or poor outcomes.

As conclusion, each of the epidemiologic features such as complaint, age, menarche, menopause, average menstrual cycle, tubal ligation, hypertension, reproductive age and palpable mass played a predicted role for the diagnosis of DCIS and IDP. As patients with breast intraductal papillary neoplasms can often be a diagnostic challenge, in our study, exfoliative cytology and mammography had a diagnostic role in patients where such an investigation showed the low sensitivity of IPC. Test of CEA and CA15-3 in nipple discharge is a simple, minimally invasive technique that can be used to improve preoperative confirmation of IPC, thereby serving as a tool with which to triage patients for intraductal papilloma.

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Disclosure of conflict of interest

None.

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