Risk factors of breast intraductal lesions in patients without pathological nipple discharge

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Abstract. The majority of breast cancer arises from the ductal epithelium. It is crucial in the diagnosis and treatment of breast cancer by detecting intraductal lesions at an early stage. The typical clinical characteristic of intraductal lesions is pathological nipple discharge (PND), although many patients with intraductal lesions do not exhibit PND. It is a serious challenge for clinicians to detect patients with intraductal lesions without PND at an early stage. The aim of the present study was to investigate the risk factors associated with intraductal lesions in patients without PND. This retrospective database review, conducted between April 2016 and April 2017, included 370 lesions from 255 patients with intraductal lesions (intraductal papilloma, atypical intraductal hyperplasia, intraductal carcinoma *in situ*) and non-intraductal lesions (fibroadenoma, adenosis, cysts, lobular carcinoma *in situ*), diagnosed through surgical pathology. The patients were divided into two groups based on pathological diagnosis and clinical parameters were evaluated using univariate and multivariate analyses. Univariate analysis revealed that 9 of 14 factors were statistically significant. Five factors were identified to be associated risk factors in patients without PND through the multivariate logistic regression analysis: Age between 35 and 49 years and age ≥50 years [odds ratio (OR)=4.749, 95% confidence interval (CI)=2.371-9.513, P<0.001; OR=2.587, 95% CI=2.587-14.891, P<0.001; respectively], non-menstrual breast pain (OR=1.922, 95% CI=1.037-3.564, P=0.038), breast duct dilatation as seen using ultrasonography (OR=9.455, 95% CI=3.194-27.987, P<0.001), lesion distance from nipple ≤2 cm (OR=2.747, 95% CI=1.668-4.526, P<0.001) and lesion size ≤1 cm (OR=1.903, 95% CI=1.155-3.136, P=0.012). In conclusion, for patients without PND but with risk factors, such as the patient being >35 years, with non-menstrual breast pain, breast duct ectasia, lesion distance from nipple ≤2 cm and lesion size ≤1 cm as seen using ultrasonography, clinicians should be highly concerned about the possibility of intraductal lesions, in order to prevent misdiagnosis and reduce the misdiagnosis rate.

Introduction

Intraductal lesions of the breast, include usual ductal hyperplasia (UDH), atypical ductal hyperplasia (ADH), ductal carcinoma *in situ* (DCIS), benign intraductal papilloma (IDP) with or without atypia, and malignant papillary carcinoma (1). Intraductal lesions are often associated with pathological nipple discharge (PND), with papilloma being the most common cause (40-70%), followed by adenomatous or papillary epithelial proliferation (14%) (2,3). One to 23% of women with PND are diagnosed with invasive breast cancer or ductal carcinoma *in situ* worldwide (4-6). However, intraductal lesions may be asymptomatic and can be detected through routine mammography screening. Sometimes they can be found due to other symptoms such as palpable lump(s), or associated micro-calcification (7).

Fiber-optic ductoscopy is important for the diagnosis of patients with PND, and it is now becoming indispensable (8,9). Women without PND are usually diagnosed through

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ultrasound-guided core needle biopsy (CNB) (7,10). However, it has been reported that physicians fail to obtain the appropriate specimens from atypical or malignant lesions through CNB, due to histological heterogeneity. It has been demonstrated that CNB is not concordant with surgical excision due to high rates of upgrading of precursor lesions into carcinoma (7,10-16). For this reason, numerous authors have advocated surgical excision of intraductal lesions, such as benign papilloma (with or without atypia), but others conclude that CNB would remove all lesions (17,18). Increasingly, the focus of studies has been on patients with intraductal lesions without nipple discharge than with nipple discharge. However, in none of those studies have researchers drawn attention to the importance of PND. There is no consensus on whether such patients should undergo routine ductoscopy examination. Recent research has suggested that precursor lesions of cancer include IDPs and ADH (10,19). Therefore, it is important to identify intraductal lesions in women without PND at an early stage.

The objective of the present study was to retrospectively survey potential risk factors associated with intraductal lesions (IDPs, ADH and DCIS) in patients without PND and to provide recommendations for clinicians.

Materials and methods

Study design and patients' information. The histopathology and imaging databases were searched for patients who had been diagnosed with non- or intraductal lesions after post-operative histopathological examination in the 13 month-period from April 2016 to April 2017 at the Department of Breast Surgery within China-Japan Union hospital of Jilin University (Jilin, China). The patients presented in outpatient because of routine physical examination or breast palpable lump(s). The age range of the patients was 12-77 years of age, with a median age of 40 years.

Lesions with mastitis and invasive carcinoma as indicated through post-operative histopathological analysis and patients with PND were excluded. Patients were divided into the following study groups: Intraductal lesions (IDP, ADH and DCIS) and control group: Non-intraductal lesions (fibroadenoma, adenosis, cysts and lobular carcinoma *in situ*). In this study, intraductal papilloma included both central papilloma and peripheral papilloma. Intraductal papilloma with an atypical lesion was defined as ADH. DCIS was categorized as pure DCIS and intraductal papilloma with DCIS. As LCIS arises from the breast lobular epithelium of the breast rather than the breast ductal epithelium, so LCIS was placed under non-intraductal lesions in our study (20,21). Once eligibility was established based on histopathological diagnosis, we extracted data of clinical variables, such as patient age, course of disease (year), menopausal status, age at menarche, number of pregnancies and abortions, non-menstrual breast pain; and imaging features, such as tumor size, number, margin and shape of masses, distance from nipple, masses with or without blood flow, as well as duct ectasia indicated through ultrasound, and calcification indicated through mammography. Breast Imaging Reporting and Data System (BI-RADS) categories were measured using ultrasound.

The study was approved by the China-Japan Union Hospital of Jilin University (included all content related to the patient; project approval no. 201620218). Even though this was a retrospective study, the hospital Ethics Committee evaluated it carefully and suggested it could waive the informed consent (including the 12-year-old patient's guardians), based on our institutional policy of strict maintenance of anonymity.

Table I. Summary of postoperative histopathology findings.

Group	No.
Study	
Papilloma	111
ADH	29
DCIS	16
Overall	156
Control	
Fibroadenoma	101
Cysts	32
Fibroadenoma and cysts	6
Adenosis and and cysts	38
Adenosis	37
Overall	214

ADH, atypical ductal hyperplasia; DCIS, ductal carcinoma *in situ*.

Ultrasonography and pathology assessment. All patients were evaluated using a Philips IU22A Ultrasound Imaging system (line probe, probe frequency 9-15 MHZ) and all ultrasonography examinations were performed by two physicians with 5 years of experience in US diagnosis. Each surgically resected specimen was fixed in formalin and embedded in paraffin for histological analysis, which was performed by three pathologists specialized in breast diagnosis. The pathologists were blinded to the US reports. Diagnosis was made based on the 2012 WHO classification of tumors of the breast (22).

Statistical analysis. Statistical analysis was performed using IBM SPSS Statistics for Windows (version 20.0; IBM Corp., Armonk). First, comparison of categorical data was conducted using the χ^2 test. Then, a multivariate logistic regression analysis was used to determine risk factors that may be associated with intraductal lesions without PND. $P<0.05$ was considered statistically significant.

Results

Postoperative histopathology findings. A total of 370 lesions in 255 patients without PND, and with a postoperative histopathology diagnosis of intraductal lesions (IDP or IDPs, ADH and DCIS) or non-intraductal lesions (fibroadenoma, adenosis, cysts and lobular carcinoma *in situ*), were included in the study. Of the 255 patients, 115 patients had bilateral lesions, while 140 patients had unilateral lesions. ADH was found in 29 cases and DCIS was found in 16 cases. The distribution of the histopathological diagnoses is summarized in Table I.

Table II. Univariate analysis of characteristics of intraductal lesions patients compared with non-intraductal lesions patients.

Clinical characteristics	Study group no. (%)	Control group no. (%)	χ^2	P-value
Age, years				
≤34	15 (16.7)	75 (83.3)		
35-49	109 (49.8)	110 (50.2)		
≥50	32 (52.5)	29 (47.5)	31.843	<0.001[a]
Course of disease, years				
≤1	124 (45.4)	149 (54.6)		
>1	32 (33.0)	65 (67.0)	4.536	0.033[a]
Age at menarche				
10	0 (0.0)	2 (100.0)		
11	0 (0.0)	3 (100.0)		
12	5 (45.5)	6 (54.5)		
13	25 (33.8)	49 (66.2)		
14	49 (43.8)	63 (56.2)		
15	42 (45.7)	50 (54.3)		
16	14 (37.8)	23 (62.2)		
17	11 (78.6)	3 (21.4)		
18	0 (0.0)	2 (100.0)		
19	2 (100.0)	0 (0.0)	17.114	0.047[a]
Menopausal state				
Non-menopausal	132 (40.9)	191 (59.1)		
Menopausal	24 (51.1)	23 (48.9)	1.749	0.186
Number of pregnancies				
0	11 (20.4)	43 (79.6)		
≥1	145 (45.90)	171 (54.1)	12.313	<0.001[a]
Number of abortions				
0	56 (34.6)	106 (65.4)		
≥1	100 (48.1)	108 (51.9)	6.815	0.009[a]
Non-menstrual breast pain				
No	115 (38.5)	184 (61.5)		
Yes	41 (57.7)	30 (42.3)	8.75	0.003[a]

[a]P<0.05.

Univariate analyses (characteristics of patients). The clinicopathological parameters of the surgical histopathological diagnosis data of 370 lesions were compared based on the presence or absence of intraductal lesions (Table II). The average age of these patients was 43 years (range, 12-77 years), with an average of 54 years in the study group, and 41 years in the control group. We confirmed that there was only one 12-year old patient in the present study, her information was not removed prior to the statistical analysis, and this case did not affect the results. The data in our study demonstrated that age was associated with intraductal lesions (P<0.001). In addition, we found that age at first menstruation was statistically different among patients of each group (P=0.047). In terms of menopausal status, no significant difference was found between the two groups (P=0.186). Regarding the number of pregnancies and abortions, there was a statistically significant difference between the two groups (P=0.009; P<0.001, respectively). Similarly, there was a difference between the groups with regard to the course of disease (P=0.033). We also evaluated non-menstrual breast pain, and the difference was statistically significant between the two groups (P=0.003) (Table II).

Univariate analyses (characteristics of imaging). Table III shows the imaging characteristics of intraductal lesions, compared with non-intraductal lesions, in patients without PND. In terms of breast duct ectasia, lesion size, and distance from nipple, significant differences (all P<0.01) were found. In the 156 samples without PND that were confirmed positive for intraductal lesions, 26 of the samples were found to contain duct ectasia (Fig. 1). However, only 6 samples were found to have duct ectasia in the control group. The lesion size (>1 cm) in the control group was more than that of the study group (68.9 vs. 31.1%), while the distance from nipple (>2 cm) was the same (68.7 vs. 31.3%).

For the other imaging characteristics, BI-RADS, calcification, blood flow, the number of nodules, margin and shape of

Table III. Univariate analysis of imaging (mammography and ultrasonography) characteristics of the patients without PND.

Imaging characteristics	Study group no. (%)	Control group no. (%)	χ^2	P-value
Duct ectasia				
No	130 (38.5)	208 (61.5)		
Yes	26 (81.2)	6 (18.8)	21.947	<0.001[a]
The number of nodules				
Single	58 (39.7)	88 (60.3)		
Multiple	98 (43.8)	126 (56.2)	0.587	0.444
Distance from nipple and areola, cm				
≤2 cm	104 (51.2)	99 (48.8)		
>2 cm	52 (31.1)	115 (68.9)	15.171	<0.001[a]
Lesion size, cm				
≤1 cm	100 (52.4)	91 (47.6)		
>1 cm	56 (31.3)	123 (68.7)	16.824	<0.001[a]
Margin and shape				
Indistinct/irregular	68 (45.3)	82 (54.7)		
Clear/regular	88 (40.0)	132 (60.0)	1.040	0.308
Blood flow				
No	120 (43.2)	158 (56.8)		
Yes	36 (39.1)	56 (60.9)	0.462	0.497
BI-RADS category				
≤3	112 (41.3)	159 (58.7)		
≥4	44 (44.4)	55 (55.6)	0.289	0.591
Calcification				
No	21 (31.3)	46 (68.7)		
Yes	59 (36.9)	101 (63.1)	0.633	0.426

[a]P<0.05.

masses, no significant difference was found between the study and control groups (P>0.05) (Table III).

Risk factors for intraductal lesions. Nine out of 14 factors were found to be statistically different as shown by the univariate analyses (Tables II and III). Five factors were identified as relative risk factors through multivariate logistic regression analysis (Table IV). The predominant relative risk of intraductal lesions for women without PND but with duct ectasia of breast was found to be 9.455 times higher than that for women without duct ectasia of the breast (95% CI=3.194-27.987, P<0.001). The second highest relative risk for intraductal lesions was found to be patients aged over 50 years (OR=6.207, 95% CI=2.587-14.891, P<0.001). Age between 35 and 50 years also constituted a risk factor. The data confirm that the relative risk for older patients was higher than that of younger patients. The relative risk of having intraductal lesions ≤2 cm (Fig. 2) from the nipple was 2.745-fold higher than that of patients who have intraductal lesions at a distance >2 cm from the nipple (95% CI=1.668-4.526, P<0.001). The multivariate analysis also shows that non-menstrual breast pain (OR=1.922, 95% CI=1.037-3.564, P=0.038), and a lesion size of ≤1 cm (Fig. 3) (OR=1.903, 95% CI=1.155-3.136, P=0.012) were more highly associated with intraductal lesions than non-intraductal lesions (Table IV).

Discussion

Along with the increase in the knowledge of breast cancer, it is a generally accepted consensus that early detection and early treatment is of great benefit to patients. To the best of our knowledge, DCIS is considered a true precursor lesion for invasive cancer (19), as well as ADH. In addition, all IDPs are considered cancer precursor lesions (10), so all precursor lesions are intraductal lesions (10,19). However, there is no generally accepted consensus regarding criteria used to distinguish between intraductal and non-intraductal lesions.

It has been demonstrated that clinical parameters, such as age, estrogen levels, a history of family genetics, including HER-2 overexpression and BRCA1/2 mutations, increase the risk of breast cancer. Although technology used for gene mutation detection is highly advanced, it is very expensive. Therefore, it is important to identify relative risk factors for precursor lesions, which may provide guidance for clinicians. Although many investigators have assessed risk factors for malignancies in benign papilloma of breast in CNB, the results remain conflicting (7,10-13,23-27).

PND is an important common symptom seen in intraductal lesions and has been confirmed as a risk factor for breast cancer in many studies (4-6). However, a recent study

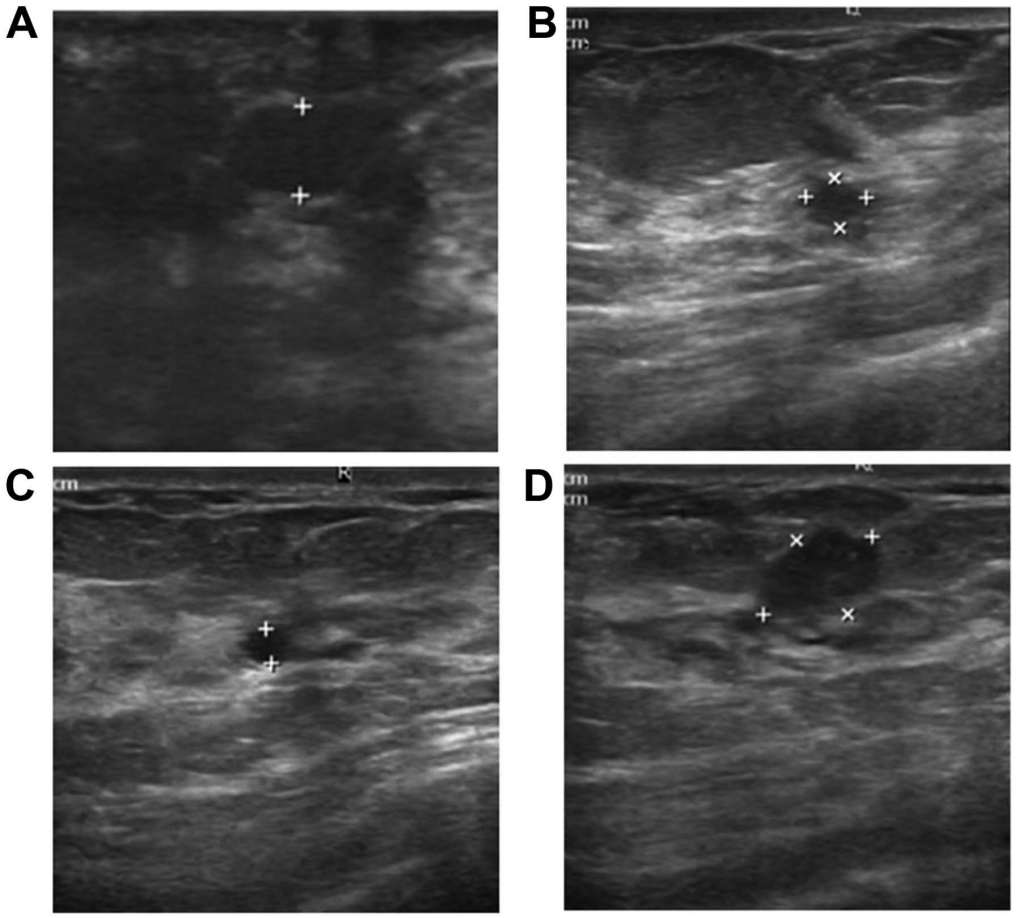

Figure 1. A representative sample of duct ectasia. A 48-year-old woman without PND with breast non-menstrual pain who underwent bilateral breast ultrasonography. Post-operative pathology showed intraductal papilloma in left and right breast. (A) US demonstrates duct ectasia in left breast. (B) US demonstrates a low echoic tumor in left breast, the lesion size is 0.46x0.39 cm. (C) US demonstrates duct ectasia in right breast. (D) US demonstrates a low echoic tumor in right breast, the lesion size is 1.02x0.68 cm.

confirmed that the frequency of intraductal lesions without PND is much higher than that with PND (28). Pareja *et al* reported that only 8 out of 166 women with nipple discharge in their study were diagnosed with IDP (29). A number of cases have reported similar findings (Table V). Our findings confirm that the number of intraductal lesions is similar to that of non-intraductal lesions (156 vs. 214), which indicates that there may be many intraductal lesions in patients without PND. Although many studies have investigated risk factors associated with malignant changes in intraductal lesions, they have not specifically separated patients with PND from those without PND. Therefore, we studied risk factors associated with intraductal lesions in patients without PND, whose diagnosis was confirmed through histopathological methods. In addition, in our study, non-intraductal lesions were considered as the control group, and their characteristics were compared with precursor lesions.

We studied clinical and imaging variables to analyze risk factors of intraductal lesions. We found clinical parameters, including age, non-menstrual breast pain, breast duct ectasia, distance from nipple and lesion size to be related to the risk of intraductal lesions.

Clinically, intraductal papilloma could occur at any age, but the majority of patients are 40-50 years of age when it occurs (23). We reported that a more advanced age is associated with a higher risk of intraductal lesions. Some studies have indicated that age is correlated with the severity of intraductal lesions (12,14,17,28,30,31). Those studies have demonstrated that the older the patient, the higher the degree of severity of the intraductal lesions. In contrast to that, another study reported that age is not significantly related to the severity of intraductal lesions, but they found that all patients with carcinoma were aged over 50, and 34.9% of the patients in their study had prior or concurrent breast carcinoma (29). Therefore, their research, to a certain extent, does not provide clinical guidance for the early detection of intraductal lesions.

We also observed that the occurrence rate of both pregnancies and abortions, but not menopausal state was associated with intraductal lesions in the univariate analysis. However, in the multivariate logistic regression analysis, they were found to be confounding factors. Unlike in this study, a previous study by Shiino *et al* (10) founded that menopausal status (menopause) is a relative risk factor for precursors and carcinoma. One major reason for menopausal state not reaching statistical significance (P=0.186) in our study is that most patients were diagnosed with benign lesions at a younger age, at which they were still menstruating. Another reason is that the age factor may be more important when compared with menstrual and reproductive history. Although in this study menstrual and reproductive history was found to have no

Table IV. Multivariate analysis of characteristics of intraductal lesions compared with non-intraductal lesions.

Factors	P-value	OR	EXP (B) 95% C.I. Lower limit	EXP (B) 95% C.I. Upper limit
Age, years				
≤34	<0.001			
35-49	<0.001	4.749	2.371	9.513
≥50	<0.001	6.207	2.587	14.891
Number of pregnancies (≥1)	0.724	0.832	0.299	2.314
Number of abortions (≥1)	0.401	1.272	0.726	2.227
Non-menstrual breast pain (present)	0.038	1.922	1.037	3.564
Breast duct ectasia (present)	<0.001	9.455	3.194	27.987
Distance from nipple, cm (≤2 cm)	<0.001	2.747	1.668	4.526
Lesion size, cm (≤1 cm)	0.012	1.903	1.155	3.136

OR, odds ratio; 95% C.I., confidence interval.

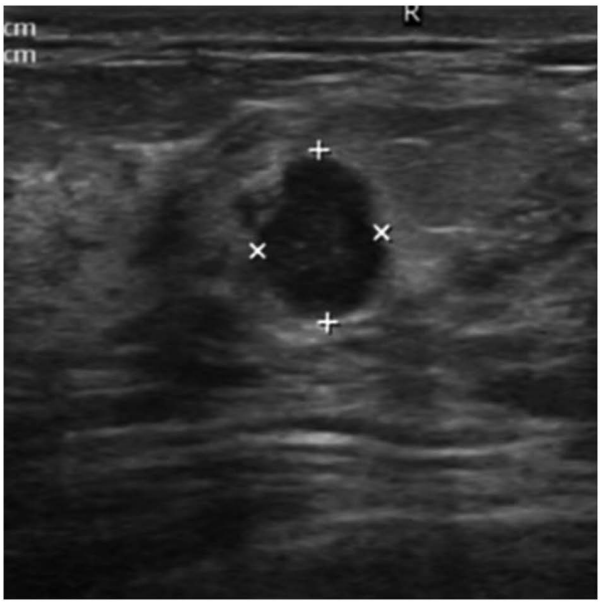

Figure 2. A 38-year-old woman without PND who underwent bilateral breast ultrasonography. Post-operative pathology diagnosed as ADH in right breast. US demonstrates a low echoic tumor in right breast, the lesion size is 1.00x0.71 cm, the lesion distance from nipple is 0.73 cm.

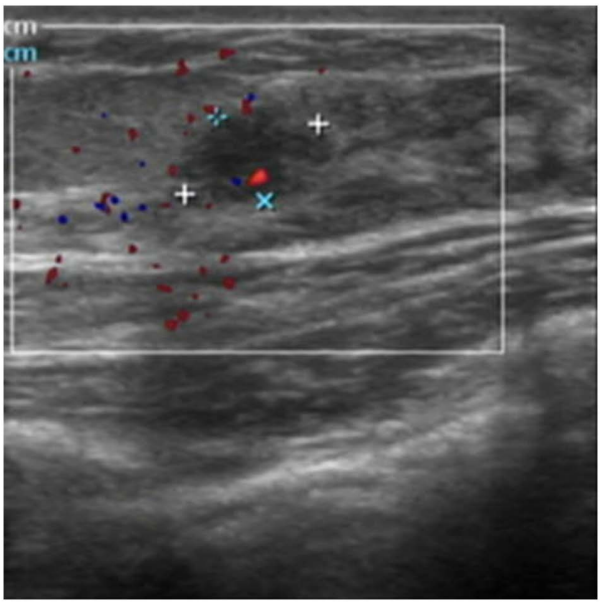

Figure 3. A 35-year-old woman without PND who underwent bilateral breast ultrasonography. Post-operative pathology showed presence of IDP in right breast. US demonstrates a low echoic tumor in right breast, the lesion size is 0.87x0.56 cm.

statistical significance, they should be taken into consideration when evaluating clinical cases, since many recent studies have shown that these factors are associated with an increased risk of breast cancer (32-35). Therefore, further investigations are required to explore the mechanisms that underlie the association between menstrual and reproductive histories and the risk of breast cancer.

Over half of the patients with intraductal lesions in our study (57.7%), had suffered non-menstrual breast pain, a statistically significant difference was found among clinical characteristics between lesions with and those without intraductal lesions. A recent study reported that breast pain may be associated with breast cancer and it has been suggested that clinicians and radiologists should remain attentive to female patients who complain of breast pain (36). Similarly, Preece *et al* (37) cautioned that focally isolated pain can be a presenting symptom of cancer. When the symptom of breast pain is present, further imaging examinations should be suggested.

Furthermore, there are clear trends towards an increased risk of intraductal lesions with duct ectasia, as shown through ultrasound in the present study. In our study, duct ectasia has been demonstrated to be a predominant risk factor for intraductal lesions in women without PND (OR=9.455, P<0.01). Hsu *et al* (38) studied 172 patients with duct ectasia through ultrasound and found that there is a relationship between

Table V. The number of patients with PND and without PND in recently published studies.

Study	Total	PND	no-PND	Journal	Year	(Refs.)
Pareja *et al*	166	8	158	Cancer	2016	(29)
Chang *et al*	38	16	22	European Radiology	2010	(13)
Glenn *et al*	179	14	165	Annals of Surgical Oncology	2015	(28)
Shiino *et al*	145	30	115	Pathology International	2015	(10)
Zhu *et al*	44	7	37	American Journal of Roentgenology.	2012	(23)
Swapp *et al*	224	61	163	Annals of Surgical Oncology	2013	(11)
Sakr *et al*	130	59	71	European Journal of Surgical Oncology	2008	(14)
Yi *et al*	136	28	113	World Journal of Surgery	2013	(17)
Rizzo *et al*	276	58	218	American College of Surgeons	2012	(31)

PND, pathological nipple discharge.

ductal ectasia and intraductal lesions, especially non-invasive cancerous lesions. However, they did not categorize the lesions as with or without nipple discharge. Therefore, it is not possible to determine the relationships between nipple discharge, duct ectasia and intraductal lesions using this study. Since our study was a preliminary study on risk factors for intraductal lesions in patients without PND, no categorization of the specific types of duct ectasia was made and further analysis of categories is required in future studies. Intraductal lesions originate from the ductal epithelium, therefore, regardless of the presence of PND, it is commonly accepted that ductal ectasia indicates intraductal lesions, which was confirmed by the results of our study, in which ductal ectasia was found to be statistically significant. Duct ectasia with a well-defined hypoechoic solid mass is a typical sonographic characteristic of intraductal tumors (23,39,40). Therefore, these findings support the results of our study.

Central intraductal lesions arise in the large mammary duct, typically at a distance of less than 2 cm from the nipple. By contrast, peripheral intraductal lesions arise in the terminal duct lobular units, typically at a distance of more than 2 cm from the nipple (12). Some authors argue that the distance from the nipple is not associated with intraductal breast lesions (12,13,23,29,30,41). However, the results of our study indicate that a distance of ≤2 cm from the nipple increases the relative risk of intraductal lesions. However, other authors have concluded that lesions 3 cm or more away from the nipple are more likely to be atypical. The differences between patient groups may account for these conflicting results.

Most intraductal papilloma are small (<5 mm). Zhu *et al* (23) reported that 32 of 44 intraductal papilloma analyzed were <1.0 cm in diameter. Similarly, we found that a higher number (52.4%) of intraductal lesion were <1.0 cm in diameter. Chang *et al* (13) demonstrated that a size >1.5 cm appears to be significantly associated with malignancy, which is consistent with our results (lesion ≤1 cm is a risk factor for intraductal lesions). Although sizes larger than 3-4 cm have been reported by Wang *et al* (24), no clinical significance has been found based on larger diameter tumors, both benign and malignant, which indicate that surgery may be required.

Our study found that calcification is not significantly related to a risk of intraductal lesions because we excluded invasive breast cancer patients and only examined characteristics of mammography, with or without calcification. Similarly, in the study by Pareja *et al* (29), the authors confirmed that there is no statistically significant difference in radiological characteristics of intraductal lesions. However, Li *et al* (12) confirmed that micro-calcification is a risk factor for the degree of severity of tumors (P=0.002). Maxwell *et al* (7) and Sakr *et al* (14) have reported similar results. Therefore, further studies are required to determine whether micro-calcifications or calcifications can be used as an indication of the relative risk of intraductal lesions.

To the best of our knowledge, one of the strengths of the present study is that it is the first to study risk factors of patients without PND but diagnosed with intraductal lesions, and all lesions were removed through surgical excision, assuring the accuracy of their pathological diagnosis.

However, our study also has some limitations. First, our study is a purely retrospective study with selection bias. Second, the number of cases included in the current study is limited, and a majority of cases in the control contained lesions that were not clear precursors. Furthermore, our observations of the associated risk factors of intraductal lesions should be regarded as preliminary, since no relevant studies exist to confirm that these factors can help clinicians to improve the early detection rate of breast cancer. Furthermore, large samples of a variety of population studies are needed to confirm our results. We are currently conducting this scale of research with intraductal lesions that have PND, non-intraductal lesions that have PND, intraductal lesions that do not have PND and non-intraductal lesions that do not have PND.

Our study results demonstrate that there is a statistically significant difference in clinical features and imaging between intraductal and non-intraductal lesions in patients without PND. Our data indicate that an age >35 years, non-menstrual breast pain, breast duct ectasia, distance from nipple of ≤2 cm and lesion size of ≤1 cm are risk factors of intraductal lesions in patients without PND. Since the vast majority of intraductal

lesions are associated with PND, and usually only in the presence of this symptom do clinicians and imaging physicians attach more importance to a lesion, we suggest that patients without PND but with the above-mentioned risk factors require investigation, in order to prevent misdiagnosis and improve early detection rates of breast cancer.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YY, ZY and LS conceived and designed the study and drafted the manuscript. LS, ZK and JW collected the data. XL and WL performed the statistical analysis and helped to draft the manuscript. SY contributed to obtaining the pathological materials and pathology assessment. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was conducted in accordance with the amended Declaration of Helsinki. The approval of the Ethical Committee of China-Japan Union Hospital of Jilin University (Jilin, China) was obtained (project approval no. 201620218). We waived the need for ethical approval and informed consent of patients, based on our institutional policy, strict maintenance of anonymity and the observational nature of the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no conflict of interests.

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