Original Research Article

TJ Tumori Journal

Heterogeneous risk profiles among B3 breast lesions of uncertain malignant potential

Tumori Journal
1–11

DOI: 10.1177/0300891619868301
journals.sagepub.com/home/tmj
SAGE

Paolo Orsaria[1], Antonella Grasso[1], Rita Carino[1], Emanuele Caredda[2], Matteo Sammarra[3], Carlo Altomare[3], Carla Rabitti[4], Gabriella Gullotta[4], Giuseppe Perrone[4], Francesco Pantano[5], Oreste Claudio Buonomo[6] and Vittorio Altomare[1]

Abstract

Background: Most cases of breast lesions of uncertain malignant potential (B3) undergo surgical intervention. We aimed to analyze the outcome of B3 lesion subtypes in a large series of screen-detected cases.

Methods: We screened 2,986 core needle biopsies to classify B3 lesions. Positive predictive values (PPVs) for malignancy were calculated for a comprehensive risk characterization according to clinicopathologic and morphologic variables.

Results: B3 lesions comprised 35% atypical ductal hyperplasia (PPV = 20%), 16.7% flat epithelial atypia (PPV = 12%), 22.7% lobular neoplasia (PPV = 16.2%), 9% papillary lesion (PPV = 18.5%), 8.6% phyllodes tumor (PPV = 3.8%), and 8% radial scars (PPV = 4.1%) based on histopathologic diagnosis. Upgrade rates were 15.9% for calcifications, 13.7% for mass lesions, and 16.7% for architectural deformities, with 8.3% of malignant lesions classified as ductal carcinoma in situ and 6.7% as invasive cancers (PPV = 15%).

Conclusion: B3 lesions entail a heterogeneous risk of malignancy, and careful radiologic–pathologic correlation is required for optimal treatment.

Keywords

Breast neoplasm, needle core biopsy, positive predictive value, B3, mammography screening

Date received: 6 March 2019; revised: 9 May 2019; accepted: 20 June 2019

Introduction

Most core needle biopsy (CNB) samples can be readily categorized as normal, benign, or malignant, but a small proportion (probably <10%) of samples cannot.[1] There are 5 reporting categories for screen-detected and symptomatic lesions (e.g. microcalcification, architectural deformities, and mass lesions) similar to those used in fine needle aspiration cytology, but these lesions are not equivalent and potentially identify morphologic criteria of uncertain malignant potential (B3). These include a range of epithelial proliferative lesions, extending from atypical ductal hyperplasia (ADH) over lobular neoplasia (LN) and flat epithelial atypia (FEA) to papillary lesions (PL), radial scars (RS), or potential phyllodes tumors (PT). It has been

[1]Department of Breast Surgery, University Campus Bio-Medico, Rome, Italy
[2]Department of Biomedicine and Prevention, Tor Vergata University Hospital, Rome, Italy
[3]Department of Radiology, University Campus Bio-Medico, Rome, Italy
[4]Department of Human Pathology, University Campus Bio-Medico, Rome, Italy
[5]Department of Medical Oncology, University Campus Bio-Medico, Rome, Italy
[6]Department of Breast Surgery, Tor Vergata University Hospital, Rome, Italy

Corresponding author:
Paolo Orsaria, Department of Breast Surgery, University Campus Bio-Medico, 200 Alvaro de Portillo Street, Rome, 00128, Italy.
Email: orsaria@aol.it

observed that FEA, ADH/low-grade ductal carcinoma in situ (DCIS), LN, and invasive low-grade breast cancer (BC) have similar molecular genetic and immunophenotype characteristics that are distinct from those of high-grade BCs, and they coincide with invasive tubular and lobular carcinoma (ILC).[2] Loss of heterozygosity studies have identified similar genetic lesions in low-grade DCIS and ADH, which suggests that these are clonal processes and fulfil the basic criteria for neoplasia.[3] Nevertheless, this potentially useful classification system is limited by a lack of clear treatment guidelines, with constant modification of current treatment trends and perceived associations with malignancy. For instance, a strong correlation between RS and carcinoma was suggested in earlier reports, but more recent studies focusing on preoperative CNB diagnosis describe low rates of associated malignancy (0% to 8%).[4,5] In contrast, an increasing number of studies support routine excision of LN diagnosed based on CNB because this type of lesion is associated with high rates of malignancy at excision (6% to 53%). In addition, LN are often multicentric and carry a risk of both ductal and lobular invasive carcinoma in the contralateral and ipsilateral breast.[6–8]

Correlation of radiologic findings with histopathologic variables is essential to comprehensively evaluate breast specimens.[9] CNB histopathologic observations such as cellular monotony, lack of myoepithelial cells, and cytological atypia are useful to differentiate papillary lesions, but radiologic imaging characteristics such as well-circumscribed and lobulated irregular masses and associated microcalcifications may aid in the prediction of malignancy.[10] Furthermore, accurate identification of phyllodes neoplasms without surgical intervention is difficult and complicates the nonoperative management of apparently benign lumps. This impacts on the open benign biopsy rate, particularly in case of dense and hypercellular stromal lesions, from which tissue capture may be difficult.[11] Carcinoma arising within fibroadenomas and phyllodes neoplasms have rarely been reported, and there is no convincing evidence that these lesions are precursors of breast carcinoma.[12,13] An ideal classification system for epithelial proliferative diseases of the breast is reproducible between centers and incorporates clinical, morphologic, phenotypic, and genetic evidence. The level of chromosomal alterations and genomic loss determined by molecular analysis correlates with the degree of proliferation, complex architectural patterns, and cytologic atypia in the more advanced lesions.[14] In this context, previous studies demonstrated that these categories, as evaluated by comparative genomic hybridization and immunohistochemistry data, entail distinct risk profiles with divergent molecular pathways of development.[15]

It is important to emphasize that these recommendations cannot exclude a false-negative (FN) diagnosis in the individual patient. Therefore, the evaluation should be performed by a multidisciplinary team on a case-by-case basis, taking into account the patient demographics, patient preference, imaging features, lesion size, and the practicality and technical feasibility of minimally invasive management. If calcification is identified as the main radiologic abnormality, the CNB-based diagnosis is often FEA or LN, which are both associated with variable rates of upgrade or long-term increased risk of BC.[16] Furthermore, cases with demonstrated mass lesions and calcification imaging or radiopathologic discordance are linked to higher malignant rates.

On the other hand, vacuum-assisted biopsy as opposed to surgery may be sufficient for therapeutic excision of many B3 lesions, which benefits the patient and decreases healthcare costs by obliterating the need for operative intervention.[17] A decrease in the positive predictive value (PPV) for malignancy has been observed in the last few years (from 29% to 10%), reflecting a gradual increase in the number of CNBs and their improved performance on screen-detected breast lesions.[18] It is becoming increasingly obvious that these borderline breast lesion categories need to be investigated further to recognize the most suitable therapeutic management option as a part of the screening assessment. This is of particular importance when the lesion was not completely removed after morphologic imaging (e.g. residual calcification) and if the finding was marked using a clip.[19] In addition, nonoperative treatment options of the initial clinicopathologic cases need to be carefully analyzed to determine the prognosis for specific borderline proliferations. In the current retrospective study, we assessed the outcome of lesions diagnosed as B3 between 2003 and 2018 in our institution. We performed a detailed review of the different types of intraductal epithelial atypia and discuss implications for clinical practice and future research. We also assessed the quality of CNB performance to revise evidence-based threshold of accurate measurements and an optimal disease-tailored approach, which may improve both the radiologic evaluation and sampling of breast lesions.

Methods

All CNBs diagnosed as B3 between January 2003 and December 2018 at our institution were included in the study. The reason for CNB was usually the presence of a digital mammographic or clinical abnormality detected by or reported to the radiographer. Only few eligible women from 2016 were recalled for further assessment through breast tomosynthesis within a single compression episode for each projection ($n = 9$, 3%).The potential of magnetic resonance imaging (MRI) for the characterization of borderline lesions was assessed for 86 patients (28.6%). CNBs were performed using either ultrasound-guided core biopsies (14G needle, 3–5 specimens obtained) or stereotactic vacuum-assisted biopsies (11G needle, 12–16 specimens

obtained), without intending complete lesion removal. Only if the entire lesion seen at imaging was removed, a localizing radiopaque marker was placed in order to facilitate identification of the lesion bed before surgery. Adequate tissue samples for histopathologic evaluation were obtained in all cases.

All patients with known histopathologic B3 diagnosis and definitive histology after surgical resection were included ($n = 300$). Histologic agreement between a CNB diagnosis and excision specimen was analyzed to determine associated rates of malignancy and the outcomes of different B3 subtypes. Excision histology findings were categorized as malignant, including invasive carcinoma, DCIS, and other malignant lesions such as sarcomas and lymphomas, or benign, including FEA, ADH, classical lobular neoplasia (atypical lobular hyperplasia and lobular carcinoma in situ), PL, RS, or PT. PPVs for detection of malignancy were calculated for all B3 core cases and for each subcategory as follows: PPV = (number of final malignant diagnoses/total number of subjects with B3 diagnosis × 100%).

All cases were also divided into 4 major categories (PL, PT, RS, and intraepithelial atypical lesions, such as FEA, ADH, or lobular neoplasia) to provide a complementary standardization of the pathologic diagnosis and ensure correct risk characterization and patient management. Quality assurance measurements were performed and correlations between different morphologic variables established in order to determine the quality of CNB performance in the assessment of breast lesions. Tumors were classified based on subsequent malignant excision biopsies according to the American Joint Committee on Cancer staging criteria (8th edition), with BC subtype classification based on the hormone receptor status (estrogen receptor [ER] or progesterone receptor [PR] staining), Ki-67 threshold value (⩾20%), and HER2 amplification. The classification allowed us to determine whether some variables can be considered independently associated with CNB diagnosis without a requirement for molecular diagnostics.[20,21] Patients were also categorized based on the receptor status of their primary tumor as follows: luminal A (ER+ or PR+ and HER2−); luminal B HER2− (ER+, HER2−, and at least one of Ki-67 high or PR negative or low); luminal B HER2+ (ER+, HER2-overexpressed or amplified, any Ki-67, and any PR); HER2 (ER− or PR− and HER2+); and basal (ER− or PR− and HER2−). Tumors were considered HER2-positive only if they were scored 3+ by immunohistochemistry (strong, complete membrane staining in >10% of cancer cells) or showed HER2 amplification (ratio >2) using fluorescence in situ hybridization. The pathologic characterization of steroid hormone receptor status was classified as luminal and nonluminal profile.

The nuclear grade of the invasive BC and axillary lymph node metastases was also examined by histopathology. Patients who underwent surgical excision were reviewed at a weekly multidisciplinary meeting attended by specialist breast histopathologists, radiologists, surgeons, oncologists, and radiotherapists. This meeting served as an opportunity to retrieve follow-up information on the status of all B3 patients with subsequent new primary ipsilateral or contralateral invasive BC occurrence during the study period (median observation time 65.4 ± 42.6 months), and without providing any chemopreventive treatment (e.g. selective ER modulators or aromatase inhibitors) in patients with LN or ADH, since this indication in Europe is still off-label, with the exception of the United Kingdom.[22] We collected data on the primary site, laterality, histology, and extent of any later malignant disease, in order to define the cumulative BC incidence of a patient with a previous primary uncertain subdiagnosis, and to investigate whether the lesion represented a true precursor or a prognostic marker for succeeding tumor development.[8,23]

Statistical analysis

The χ^2 test was used to determine the proportion of definite malignant lesions within the histopathologic and clinicopathologic subcategories. p Values below 0.05 were considered statistically significant. We analyzed sensitivity, specificity, and PPV of the B3 diagnosis for the subcategories included in the study (ADH, FEA, LN, PL, RS, and PT). IBM SPSS Statistics 23 (SPSS Statistics, Chicago, IL) was used for statistical analyses.

To compare specific subcategories of malignant BC occurring after CNB diagnosis, a Mann-Whitney test with exact p values was performed. Moreover, cumulative incidence curves of new primary BC or BC relapses after CNB were estimated with a Kaplan-Meier analysis, and multivariate Cox regression was performed to evaluate the association with BC features.

Results

B3 CNB cases with surgical excision comprised 10.1% (300/2986) of all CNB specimens. Lesion types identified by mammography were mass or dense tissue in 46.3% (139/300) of cases, microcalcifications in 35.7% (107/300), and architectural distortion in 18% (54/300). Ultrasound-guided core biopsies were performed in 61.3% (184/300) of cases for sonographically visible lesions, and stereotactic vacuum-assisted biopsies were performed for lesions invisible in ultrasound or for further evaluation of microcalcifications (38.7% of cases, 116/300). Screen-detected calcifications showed no higher incidence in malignant outcome (15.9%; 17/107) when compared to mass lesions (13.7%, 19/139) or architectural deformities (16.7%, 9/54; χ^2 analysis, $p = 0.828$), with no association between the radiologic finding and the upgrade rate in the final histology. Of the radiologic abnormalities observed in these 45 malignant cases, 37.8% (17/45) were calcifications, 42.2% (19/45) mass lesions, and 20% (9/45) architectural distortion.

Table 1. Patient characteristics.

Variables	Number	%
Proportion of B3 lesions	300	100
Benign	255	85
Malignant	45	15
Radiologic findings		
Calcification	107	35.7
Mass	139	46.3
Architectural distortion	54	18.0
Diagnostic B3 category		
ADH	105	35.0
FEA	50	16.7
LN	68	22.7
PL	27	9.0
PT	26	8.6
RS	24	8.0
Histologic findings		
Atypical proliferation	223	74.3
No atypical proliferation	77	25.7
Core biopsy procedure		
Ultrasound	184	61.3
Stereotaxic	116	38.7

ADH: atypical ductal hyperplasia; FEA: flat epithelial atypia; LN: lobular neoplasia; PL: papillary lesions; PT: phyllodes tumors; RS: radial scars.

Overall, 51 of the 86 lesions evaluated by MRI were correctly diagnosed as either malignant (17 true-positive lesions) or benign (34 true-negative lesions). The remaining 35 lesions included 33 false-positive (FP) lesions and 2 FN lesions. The FN rate was 10.5% (2/19) and the FP rate was 42.8% 33/77). The sensitivity, specificity, PPV, and negative predictive value of magnetic resonance imaging of the breast to rule out malignancy overall was 89.4%, 50.7%, 34%, and 94.4%, respectively. The diagnostic accuracy was 59.3%.

The clinicopathologic characteristics of the study participants are listed in Tables 1 and 2. B3 lesions were diagnosed as follows based on the histopathologic features: 35% (105/300) ADH, 16.7% (50/300) FEA, 22.7% (68/300) LN, 9% (27/300) PL, 8.6% (26/300) PT, and 8% (24/300) RS.

Classification of radiopathologic abnormalities into CNB-based histopathologic lesion categories identified intraepithelial atypia such as FEA, ADH, or LN as the most frequent CNB diagnosis for calcifications (92.5%, 99/107; 44.3%, 99/223 of all atypia; odds ratio [OR] 6.886, $p < 0.001$), RS as the most frequent CNB diagnosis for architectural distortions (20.3%, 11/54; 45.8%, 11/24 of all RS), and PT (17.2%, 24/139; 92.3%, 24/26 of all PTs) or PL (16.5%, 23/139; 85.1%, 24/27 of all PLs) as the most frequent CNB diagnosis for mass lesions. A χ^2 test of this distribution reveals a statistically significant noncausal association ($p < 0.001$).

Malignant lesions included 25 (8.3%) cases of DCIS and 20 (6.7%) cases of invasive cancers, associated with a concomitant in situ component in 75% of cases (15/20), yielding an overall PPV of 15% (45/300) based on excision histology. Of all these cases, 84.5% (38/45) were diagnosed as epithelial atypia based on the CNB, of which 55.2% (21/38) were ADH, 15.8% (6/38) FEA, and 28.9% (11/38) LN.

Lesion-specific PPVs for a subsequent diagnosis of carcinoma were as follows: ADH 20% (21/105), FEA 12% (6/50), LN 16.2% (11/68), PL 18.5% (5/27), PT 3.8% (1/26), and RS 4.1% (1/24). Of those epithelial atypia explicitly mentioned in the CNB report, 17.0% (38/223) were finally diagnosed as malignant, whereas when the absence of epithelial atypia was stated, only 9.0% (7/77) were malignant based on definite histology. These results demonstrate a higher but not statistically significant tendency toward lesion upgrade for the 3 major atypical areas, ADH, FEA, and LN (OR 2.05, 95% confidence interval [CI] 0.87–4.81; $p = 0.092$), with a proportionally greatest risk for ADH (OR 1.78, 95% CI 0.94–3.38; $p = 0.075$). Furthermore, these subcategories were characterized by significantly smaller and more homogeneous lesions compared to other B3 subtypes such as PL, PT, and RS (15.31 ± 8.06 mm vs 17.53 ± 11.91 mm, $p = 0.001$).

Tables 3 and 4 summarize the CNB-based histologic categories, radiologic characteristics, excision histology outcomes, and category-specific PPV.

Six of the 45 malignant lesions were visibly completely removed at the end of sonographically guided or vacuum assisted biopsies (mean size 7.1 mm, range 5–9 mm), whereas incomplete removal was confirmed in the remaining 39 lesions (16 mass, 16 microcalcifications, and 7 architectural distortions). Furthermore, among these latter patients with partial initial percutaneous biopsy, the prevalence of the different histopathologic findings showed 17 (43.6%) patients with ADH, 6 (15.4%) patients with FEA, 11 (28.2%) patients with LN, 3 (7.7%) patients with papillary lesions, and 2 (5.1%) patients with histology of a radial scar complex radial and a phyllodes tumor, respectively.

Among all DCIS cases ($n = 25$), 40% (10/25) were diagnosed as ADH and 32% (8/25) as LN based on the CNB, while 55% (11/20) of invasive tumors were diagnosed as ADH and 20% (4/20) as FEA.

For B3 lesions without atypia such as PL, PT, or RS ($n = 77$), the PPV was 7.1% (1/14) if the detected radiologic abnormality was architectural distortion, 12.5% (1/8) if it was calcification, and 9% (5/55) if it was a mass lesion. B3 lesions classified as atypia such as ADH, FEA, or LN ($n = 223$) based on CNB had a PPV of 16.1% (16/99) for calcifications, compared to 16.6% (14/84) for mass lesions and 20% (8/40) for architectural distortions.

Of the invasive tumors ($n = 20$), 16 (80%) were ductal, 3 (15%) were lobular carcinomas, and 1 (5%) was malignant phyllodes; 35% were classified as grade 1, 55% as grade 2,

Table 2. Association between radiologic abnormality and core needle biopsy (CNB)–based diagnosis and final excision.

Radiologic abnormality	CNB B3 diagnosis							Final excision diagnosis, n (%)		
	ADH	FEA	LN	PL	PT	RS	p^a	Benign	Malignant	p^a
Calcification	36	27	36	3	0	5	>0.001	90 (84.2)	17 (15.8)	0.001
Mass	46	16	22	23	24	8		120 (86.4)	19 (13.6)	
Architectural distortion	23	7	10	1	2	11		45 (83.4)	9 (16.6)	
Total	105	50	68	27	26	24		255 (85)	45 (15)	

[a]χ^2 Test used.
ADH: atypical ductal hyperplasia; FEA: flat epithelial atypia; LN: lobular neoplasia; PL: papillary lesions; PT: phyllodes tumors; RS: radial scars.

Table 3. Excision histology outcome and positive predictive value (PPV) of core needle biopsy (CNB)–detected B3 lesion subcategories.

Category of CNB-based B3 diagnosis (number of cases)	Final excision diagnosis, n (%)			
	Benign cases	Malignant in situ cases	Malignant invasive cases	PPV % excision histology (number/total number of cases)
ADH (105)	84	10 (9.5)	11 (10.5)	20.0 (21/105)
FEA (50)	44	2 (4.0)	4 (8.0)	12.0 (6/50)
LN (68)	57	8 (11.8)	3 (4.4)	16.2 (11/68)
PL (27)	22	4 (14.8)	1 (3.7)	18.5 (5/27)
PT (26)	25	0 (0)	1 (3.8)	3.8 (1/26)
RS (24)	23	1 (4.1)	0 (0)	4.1 (1/24)
Total (300)	255	25 (8.3)	20 (6.7)	15 (45/300)

ADH: atypical ductal hyperplasia; FEA: flat epithelial atypia; LN: lobular neoplasia; PL: papillary lesions; PT: phyllodes tumors; RS: radial scars.

and 10% as grade 3. Fifty-six percent of the 25 DCIS cases were low-grade, 32% intermediate grade, and 12% high grade. The median tumor size was 10.9 mm (range 2–50 mm), and a greater proportion of T1 cases ($n = 17$, 85%) occurred compared with T2 cases ($n = 3$, 15%). Of the 17 T1 patients, 3 (17.6%) were pT1a, 8 (47.1%) pT1b, and 6 (35.3%) pT1c, with a tumor size ⩽10 mm in 64.7% (11/17) of cases. In this context, the smallest BCs were identified after a previous CNB diagnosis of PL (6.6 ± 4.219, $p = 0.077$) or FEA (14.583 ± 17.7719, $p = 0.057$).

High ER expression of ⩾50% was detected in 39/45 tumors (86.6%) and high PR expression of ⩾20% in 34/45 tumors (75.5%). Eight patients (17.7%) had high Ki-67 expression (⩾20%), and overexpression of cerbB-2 was detected in 2 out of 19 invasive tumors (10.5%). The incidence of luminal and nonluminal subtypes was 94.7% ($n = 18$) and 5.3% ($n = 1$), respectively, among infiltrating BCs with a well-defined pathologic characterization ($n = 19$). The majority of ductal and lobular cases ($n = 19$) had luminal A tumors (63.1%, 12/19), followed by luminal B (21.1%, 4/19), HER2-positive luminal B (10.5%, 2/19), basal (5.3%, 1/19), and any nonluminal HER2-positive tumors. Of the invasive cancers, only 15% of patients (3/20) had ipsilateral lymph node metastases according to the gold standard diagnosis and were staged as pN1 (2 with micrometastases, pN1mi). There were 25 patients (55.5%) in stage 0, 16 (35.5%) in stage I, and 4 (9%) in stage II.

At the time of analysis, 19/300 cases (6.3%) developed new primary invasive BCs after previous B3 CNB-based diagnosis and subsequent excision histology (10.5% ipsilateral and 89.5% contralateral), 6 (31.5%) of which occurred after a preceding surgical outcome of malignancy, 3 as IDC, 2 as DCIS, and 1 as ILC (16.7% ipsilateral and 83.3% contralateral).

Only 1 of the 2 patients who developed a new ipsilateral tumor during follow-up had an incomplete or equivocal surgical excision in the context of a previous radiologic finding of microcalcifications.

New invasive tumors occurring during the study period most often developed after an earlier epithelial atypia CNB finding ($n = 15/19$, 78.9%), showing a significant association with LN ($n = 8$, 42.1%; OR 2.679, 95% CI 1.031–6.957; $p = 0.037$), but without any statistical difference in the time of development during the observation time ($p = 0.847$). Interestingly, the χ^2 test also revealed a new primary growing risk among patients with previous BC diagnosis (OR 2.864, 95% CI 1.028–7.980; $p = 0.037$, Figure 1).

Discussion

The current belief is that CNB is superior to fine needle aspiration cytology in discriminating between benign and malignant breast lesions; however, borderline core needle histology occurs in a similar or even higher proportion of

Table 4. Clinicopathologic tumor characteristics.

Variables	Number	%
Proportion of malignant lesions	45	100
DCIS	25	55.6
Invasive	5	11.1
Invasive + DCIS	15	33.3
Tumor classification		
Tis	25	55.6
T1a	3	6.7
T1b	8	17.7
T1c	6	13.3
T2	3	6.7
Nuclear grade		
1	21	46.7
2	19	42.2
3	5	11.1
DCIS nuclear grade	25	100
1	14	56.0
2	8	32.0
3	3	12.0
Invasive nuclear grade	20	100
1	7	35.0
2	11	55.0
3	2	10.0
Invasive histology	20	100
IDC	16	80
ILC	3	15
Other	1	1
Nodal metastasis	20	100
Negative	17	85
Positive	3	15
Lymph node classification	20	100
N0	17	85
N1	3	15
Pathologic stage	45	100
0	25	55.5
I	16	35.5
II	4	9
Estrogen receptor	45	100
>50	39	86.6
⩽50	6	13.4
Progesterone receptor	45	100
>20	34	75.5
⩽20	11	24.5
Ki-67 index	45	100
>20	8	17.7
⩽20	37	82.3
c-erbB-2 (HER2)	19	100
0	7	36.9
1+	5	26.3
2+	5	26.3
3+	2	10.5
Breast cancer subtype	19	100
Lum A	12	63.1
Lum B−	4	21.1
Lum B+	2	10.5
HER2	0	0
Basal	1	5.3
Breast cancer profile	19	100
Lum	18	94.7
Not Lum	1	5.3
Subsequent primary BC after B3	19	100
Ipsilateral	2	10.5
Contralateral	17	89.5

DCIS: ductal carcinoma in situ; BC: breast cancer; IDC: invasive ductal carcinoma; ILC: invasive lobular carcinoma.

cases than atypical or borderline cytology.[24,25] Most B3 cases progress to surgical intervention, which has significant implications for diagnosis and treatment and potentially prevents excision in select cases.[26] Therefore, careful correlation between radiologic and pathologic parameters is required to guide risk stratification and ensure appropriate patient management. Furthermore, it would be useful to verify correction of surgical pathology with initial imaging, identify the indication of MRI scan, and correlate this with upgraded data, detailing the presence or absence of sonographic or mammographic correlation (since this series showed that the specificity [50.7%] and PPV [34%] of MRI for detection of primary BC are low) and no studies have attempted to identify predictive morphologic or kinetic characteristics for high-risk lesions.[27,28]

In our study, there was no association between radiologic finding and outcome, but calcification was more likely to be associated with epithelial atypia, particularly ADH and LN, compared to mass lesions or architectural distortions, while it was rare in PL and RS. In agreement with previous results, we showed that the most frequent B3 lesion was atypical proliferation, and the PPV for detection of malignancy for this diagnosis was 17.0%.[24,29–31] Nonetheless, the PPV also varied among the different subtypes of epithelial atypia, with the highest rate detected for ADH and lower rates for lobular neoplasia and FEA.

ADH and low nuclear grade DCIS exhibit not only morphologic similarities (e.g. cytologic and architectural features) but also immuno–phenotypic overlap as both are ER- and PR-positive and HER2-negative with particular genomic alterations.[32] This supports the standard clinical practice of performing excision biopsy of all lesions with a diagnosis of epithelial atypia, taking into consideration parameters such as the number of cores, type of needle used, lesion biology, and diameter before resection.[33]

Furthermore, the PPV for FEA was 12%, which was lower than that for ADH, but 5 out of 6 malignant lesions occurring after FEA presented with calcification (OR 12.5, 95% CI 1.28–120.85; $p = 0.01$). Recent studies suggest that some cases of FEA are associated with ADH and several

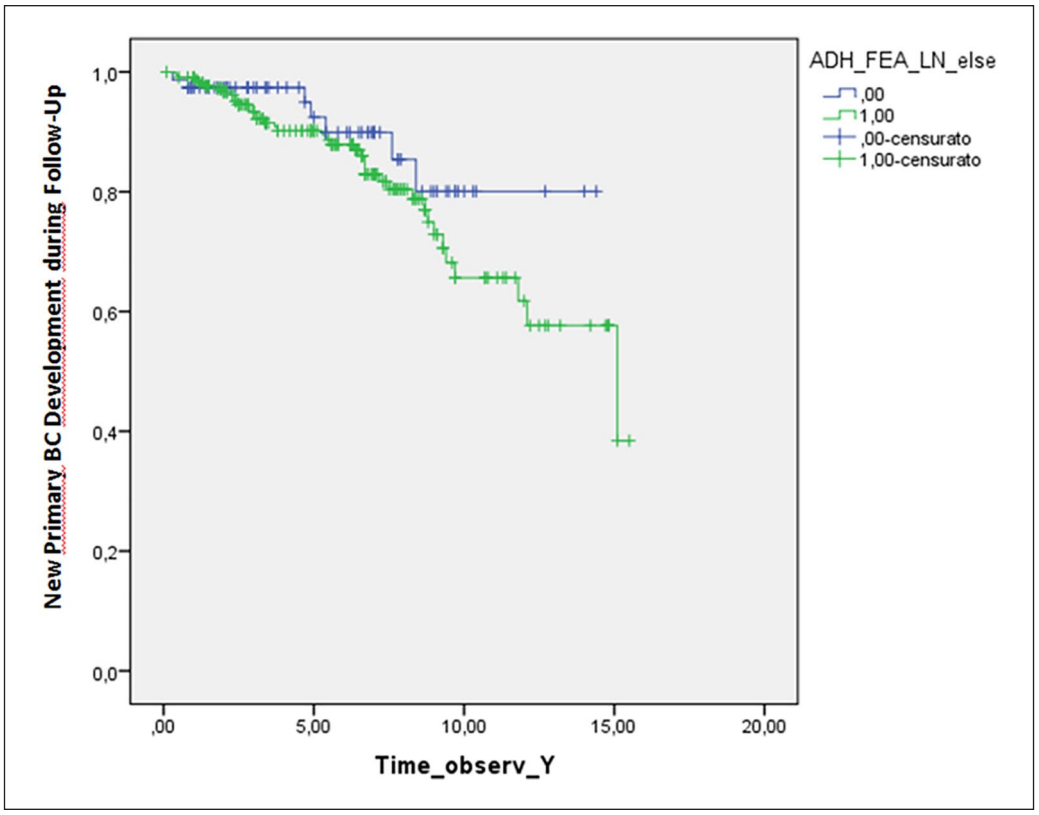

Figure 1. Kaplan-Meier analysis of new primary breast cancer incidences among patient subgroups adjusted for presence of atypia (atypical ductal hyperplasia [ADH], flat epithelial atypia [FEA], and lobular neoplasia [LN] vs others [papillary lesions, phyllodes tumors, radial scars]).

types of low-grade invasive carcinoma, particularly tubular and invasive lobular carcinoma. These findings imply a similar pathogenesis of FEA and ADH, which presents a management dilemma for pathologists and clinicians.[34–36] Future studies of FEA diagnosed in CNBs are expected to include larger case numbers, as recognition and classification of the spectrum of columnar cell lesions by surgical pathologists improves. This will facilitate determination of the BC risk and the clinical outcomes associated with this diagnosis.[37]

The proportion of PLs that later proved to be malignant was 18.5%, which falls in the range of 7%–26% reported in most other cohorts. This suggests that the frequency of histologic underestimation was similar to that of the other atypical findings in the CNB.[38] There were no statistically significant associations between lesions manifesting as a mass, calcification, or architectural distortion and subsequent DCIS or invasive carcinoma revealed by the excisional biopsy, and the sufficient accuracy of CNB in the diagnosis of benign pathology remains controversial. Nevertheless, both the predominantly papillary pattern and the associated solid or cribriform architecture, which is generally indicative of slow-growing potential and good prognosis, were more likely present in CNB specimens from malignant lesions; nevertheless, discordant imaging and histologic findings should prompt a repeat biopsy and a case review.[39]

In this context, RS were predominant among the architectural distortions (45.8%, 11/24), with no cases of BC upgrade as suggested by earlier reports of low malignancy rates. These findings therefore delineate a potential spectrum of lesions to be monitored by subcategorization criteria and managed safely by regular mammographic surveillance.[40] It has been suggested that the association between RS and BC could result from an unrepresentative core biopsy, rather than reflecting evolution from premalignant to malignant disease over time. In this equivocal setting, as in patients with ADH, the differentiation of breast carcinoma could be a critical question related to the extension of the lesion and its localization at the time of surgery. Thus, percutaneous biopsy sampling may spare a patient from surgical excision because it can be more representative of the lesion.[41]

Carcinomas detected after a B3 diagnosis often showed favorable histopathologic features, with 55.5% comprising DCIS and only 10% high-grade invasive tumors. Most carcinomas were small (64% ⩽10 mm) with prevailing hormone receptor positivity (71.1%) or low Ki-67 labeling index (82.3%), and only 15% of invasive cancers showed lymph node metastases. The limited available molecular data support the concept that overlapping morphologic and immunohistochemical features of these uncertain malignant lesions make these precursors for the progression

to low-grade DCIS and invasive carcinoma with specific consequences for the clinical outcome, which is mostly true for lesions of the luminal phenotype and negative for HER2.[42–44] The molecular genetic profiles including comparative genomic hybridization data and divergent chromosomal alterations closely reflect the degree of proliferation and atypia in the B3 categories, rendering some of these proliferations a nonobligate, intermediary step in the development of certain forms of malignancies.[45]

Such genetic features may thus influence the stratification of the molecular evolution of differentiated versus poorly differentiated tumors. This implicates a potential evolutionary relationship between the level of genetic instability and the morphologic complexity, which may aid in characterization of tumor biology and ultimately result in better management of the more advanced lesions.[46] The association of a concomitant in situ component with invasive carcinoma detected in our study seems to correlate with less aggressive disease and metastatic potential according to distinct prognostic factors (lower ki67 index, fewer involved nodes), with an observed trend towards superior overall survival.[47] Hence, given that fast-replicating (high Ki-67) cancers might be expected to contain more dysfunctional tumor suppressor genes, our study results support the possibility that pure invasive ductal carcinomas arise as a result of more drastic suppressor gene defects, eventually favoring the therapeutically challenging basaloid phenotype in the BC progression pathways.[48] If multiple neoplastic or atypical lesions are detected by high-resolution imaging, more recent generation sequencing approaches of carcinoma and concurrent B3 lesions might change the direction of patient management by treating or removing not only cancerous lesions but also the reservoir of genetically diverse neoplasias to prevent recurrence.[49] Alternatively, these borderline histologic findings and other benign proliferations could be the result of a field effect, where nonrelated tumors are colocated within a cancer-prone tissue, or of additional microenvironmental risk factors (e.g. alcohol consumption, smoking, or obesity).[50]

In this context also the effectiveness of preventive strategies with therapeutic agents like tamoxifen or exemestane could be a risk reduction option for women who have an increased risk of BC, including those with ADH or LN, but several concerns remain on related adverse events risk ratio or adequate levels of uptake and adherence in clinical practice.[51,52]

Our results show a significant reduction in the PPV for B3 diagnoses as a group (14.2%) compared to previous studies reporting PPVs ranging from 20% to 35%.[24,29,31] CNB performance has improved over time, which likely reflects detection of more subtle lesions with introduction of digital mammography, advanced ultrasound resolution, and increasing use of vacuum-assisted biopsy yielding more tissue for diagnosis.[53] In agreement with other studies, this hand-held device can be a useful technique in patients who desire removal of the breast lesion as an alternative to open surgical biopsy because they do not accept the follow-up recommendation.[54] Moreover, percutaneous procedures carried out through a meticulous technique are well accepted for several reasons including no scarring at subsequent mammography or physical examinations, no discomfort, good cosmetic results, and no stay in hospital or serious complications, with theoretical cost savings.[55] The consequence should be the integration of this new tool into screening programs as a safe therapeutic option for breast lesions presumed to be benign.

However, it is important to emphasize that the B3 category is not only used to identify lesions with an increased rate of epithelial malignancy, but also to recognize predisposing risk factors for the subsequent development of BC, potentially leading to several clinical consequences.[56] The minimum cumulative risk of new primary invasive BC occurrence during the study period was 6.3%, with greater incidence in the contralateral breast. This was particularly true after previous epithelial atypia in the CNB, implying this lesion as a prognostic marker and a true precursor lesion for which close follow-up may be required.[8,23] LN is generally considered a risk indicator for invasive disease, with an increase in the rate of invasive carcinoma of about 1%–2% per year, a lifetime risk of 30%–40%, and equal chances for both breasts.[57] Investigating the association of atypia with these distinct low- and high-grade multistep models of BC progression could help to identify patients with a high risk of recurrence, for whom intensified subsequent surveillance and management may be warranted.[58] Specific molecular events attributed to tumor progression are not consistent and may reflect intertumoral heterogeneity. Alternatively, this could mean that the number and combination of tumor promoters is equally important for the cancer phenotype, independent of gene amplification.[59]

Our study is limited by the relatively rare diagnosis of B3 lesions and by its retrospective design. In addition, the different use of diagnostic terms for identical pathologic lesions aggravates a clear comparison of pathologic diagnoses.

Conclusion

BC is a heterogeneous disease, and much research has been directed towards identifying subtypes to aid risk stratification. The paradigm of early BC management is thus shifting towards personalizing therapy as a function of morphologic, biological, and molecular disease variables. This study proposes that the association of B3 lesions with a malignancy category could be factored into future therapies. This distinction would in turn suggest a molecular basis for the divergent clinical behavior of these uncertain potential breast lesion subtypes. The

strategy is to define subgroups and determine for which of these subgroups surgical intervention may or may not be appropriate.

Our data corroborate the heterogeneity of B3 lesions diagnosed by CNB and their risk for associated malignancies. Radiologic evaluation provides useful information regarding the nature and outcome of these screen-detected lesions. Further research is needed to confirm our observations and to explore molecular explanations for the differences between lesion subtypes.

Understanding the genetics of B3 lesions might lead to effective strategies to prevent development and progression of associated BC, particularly non-low-grade and ER− carcinoma, and identify the respective malignant progression model. The improvement of next-generation sequencing technologies may allow for the careful selection of a larger cohort of uncertain histologic findings and may provide early diagnosis and preventive therapeutic strategies, thereby potentially preventing overtreatment.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Paolo Orsaria https://orcid.org/0000-0002-6224-7784

References

1. Ellis IO. Intraductal proliferative lesions of the breast: morphology, associated risk and molecular biology. *Mod Pathol* 2010; 23: 1–7.
2. Abdel-Fatah TM, Powe DG, Hodi Z, et al. High frequency of coexistence of columnar cell lesions, lobular neoplasia and low grade ductal carcinoma in situ with invasive tubular carcinoma and invasive lobular carcinoma. *Am J Surg Pathol* 2007; 31: 417–426.
3. Lakhani SR, Collins N, Stratton MR, et al. Atypical ductal hyperplasia of the breast: clonal proliferation with loss of heterozygosity on chromosomes 16q and 17p. *J Clin Pathol* 1995; 48: 611–615.
4. Douglas AG and Pace DP. Pathology of R4 spiculated lesions in the breast screening programme. *Histopathology* 1997; 30: 214–220.
5. Cawson JN, Malara F, Kavanagh A, et al. Fourteen-gauge needle core biopsy of mammographically evident radial scars: is excision necessary? *Cancer* 2003; 97: 345–351.
6. Arpino G, Allred DC, Mohsin SK, et al. Lobular neoplasia on core needle biopsy: clinical significance. *Cancer* 2004; 101: 242–250.
7. Elsheikh TM and Silverman JF. Follow up surgical excision is indicated when breast core needle biopsies show atypical lobular hyperplasia or lobular carcinoma in situ: a correlative study of 33 patients with review of the literature. *Am J Surg Pathol* 2005; 29: 534–543.
8. Page DL, Schuyler PA, Dupont WD, et al. Atypical lobular hyperplasia as a unilateral predictor of breast cancer risk: a retrospective cohort study. *Lancet* 2003; 361: 125–129.
9. Cardenosa G and Eklund GW. Benign papillary neoplasms of the breasts: mammographic findings. *Radiology* 1991; 181: 751–755.
10. Ivan D, Selinko V, Sahin AA, et al. Accuracy of core needle biopsy diagnosis in assessing papillary breast lesions: histologic predictors of malignancy. *Modern Pathol* 2004; 17: 165–171.
11. Dillon MF, Quinn CM, McDermott EW, et al. Needle core biopsy in the diagnosis of phyllodes neoplasm. *Surgery* 2006; 140: 779–784.
12. Parfitt JR, Armstrong C, O'Malley F, et al. In-situ and invasive carcinoma within a phyllodes tumor associated with lymph node metastases. *World J Surg Oncol* 2004; 15: 46.
13. Franco N, Arnould L, Mege F, et al. Comparative analysis of molecular alterations in fibroadenomas associated or not with breast cancer. *Arch Surg* 2003; 138: 291–295.
14. Roylance R, Gorman P, Harris W, et al. Comparative genomic hybridization of breast tumors stratified by histological grade reveals new insights into the biological progression of breast cancer. *Cancer Res* 1999; 59: 1433–1436.
15. Schnitt SJ and Vincent-Salomon A. Columnar cell lesions of the breast. *Adv Anat Pathol* 2003; 10: 113–124.
16. Rakha EA, Lee AH, Jenkins JA, et al. Characterization and outcome of breast needle core biopsy diagnoses of lesions of uncertain malignant potential (B3) in abnormalities detected by mammographic screening. *Int J Cancer* 2011; 129: 1417–1424.
17. Alonso-Bartolome P, Vega-Bolivar A, Torres-Tabanera M, et al. Sonographically guided 11-G directional vacuum-assisted breast biopsy as an alternative to surgical excision: utility and cost study in probably benign lesions. *Acta Radiol* 2004; 45: 390–396.
18. El-Sayed ME, Rakha EA, Reed J, et al. Audit of performance of needle core biopsy diagnoses of screen detected breast lesions. *Eur J Cancer* 2008; 44: 2580–2586.
19. Saladin C, Haueisen H, Kampmann G, et al.; MIBB Group. Lesions with unclear malignant potential (B3) after minimally invasive breast biopsy: evaluation of vacuum biopsies performed in Switzerland and recommended further management. *Acta Radiol* 2016; 57: 815–821.
20. Amin MB, Edge S, Greene F, et al.; American Joint Committee on Cancer (AJCC). *Cancer Staging Manual, eighth edition*. New York: Springer; 2017.
21. Goldhirsch A, Winer EP, Coates AS, et al. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the primary therapy of early breast cancer. *Ann Oncol* 2013; 24: 2206–2223.
22. Smith SG, Sestak I, Forster A, et al. Factors affecting uptake and adherence to breast cancer chemoprevention: a systematic review and meta-analysis. *Ann Oncol* 2016; 27: 575–590.
23. Haagensen CD, Lane N, Lattes R, et al. Lobular neoplasia (so-called lobular carcinoma in situ) of the breast. *Cancer* 1978; 42: 737–769.

24. Lee AHS, Denley HE, Pinder SE, et al. Nottingham Breast Team: Excision biopsy findings of patients with breast needle core biopsies reported as suspicious of malignancy (B4) or lesion of uncertain malignant potential (B3). *Histopathology* 2003; 42: 331–336.
25. Ciatto S, Houssami N, Ambrogetti D, et al. Accuracy and underestimation of malignancy of breast core needle biopsy: the Florence experience of over 4,000 consecutive biopsies. *Breast Cancer Res Treat* 2006; 3: 291–297.
26. Jacobs TW, Connolly JL and Schnitt SJ. Nonmalignant lesions in breast core needle biopsies: to excise or not to excise? *Am J Surg Pathol* 2002; 26: 1095–1110.
27. Crystal P, Sadaf A, Bukhanov K, et al. High-risk lesions diagnosed at MRI-guided vacuum-assisted breast biopsy: can underestimation be predicted? *Eur Radiol* 2011; 21: 582–589.
28. Malhaire C, El Khoury C, Thibault F, et al. Vacuum-assisted biopsies under MR guidance: results of 72 procedures. *Eur Radiol* 2010; 20: 1554–1562.
29. Dillon MF, McDermott EW, Hill AD, et al. Predictive value of breast lesions of "uncertain malignant potential" and "suspicious for malignancy" determined by needle core biopsy. *Ann Surg Oncol* 2007; 14: 704–711.
30. Harvey JM, Sterrett GF and Frost FA. Atypical ductal hyperplasia and atypia of uncertain significance in core biopsies from mammographically detected lesions: correlation with excision diagnosis. *Pathology* 2002; 34: 410–416.
31. El-Sayed ME, Rakha EA, Reed J, et al. Predictive value of needle core biopsy diagnoses of lesions of uncertain malignant potential (B3) in abnormalities detected by mammographic screening. *Histopathology* 2008; 53: 650–657.
32. Lopez-Garcia MA, Geyer FC, Lacroix-Triki M, et al. Breast cancer precursors revisited: molecular features and progression pathways. *Histopathology* 2010; 57: 171–192.
33. Walia S, Ma Y, Lu J, et al. Pathology and current management of borderline breast epithelial lesions. *Am J Hematol Oncol* 2017; 14: 24–31.
34. Kunju LP and Kleer CG. Significance of flat epithelial atypia on mammotome core needle biopsy: should it be excised? *Hum Pathol* 2007; 38: 35–41.
35. Abdel-Fatah TMA, Powe DG, Hodi Z, et al. High frequency of coexistence of columnar cell lesions, lobular neoplasia, and low grade ductal carcinoma in situ with invasive tubular carcinoma and invasive lobular carcinoma. *Am J Surg Pathol* 2007; 31: 417–426.
36. Collins LC, Achacoso NA, Nekhlyudov L, et al. Clinical and pathologic features of ductal carcinoma in situ associated with the presence of flat epithelial atypia: an analysis of 543 patients. *Mod Pathol* 2007; 20: 1149–1455.
37. Schnitt SJ. The diagnosis and management of pre-invasive breast disease: flat epithelial atypia: classification, pathologic features and clinical significance. *Breast Cancer Res* 2003; 5: 263–268.
38. Sydnor MK, Wilson JD, Hijaz TA, et al. Underestimation of the presence of breast carcinoma in papillary lesions initially diagnosed at core-needle biopsy. *Radiology* 2007; 242: 58–62.
39. Ivan D, Selinko V, Sahin AA, et al. Accuracy of core needle biopsy diagnosis in assessing papillary breast lesions: histologic predictors of malignancy. *Mod Pathol* 2004; 17: 165–171.
40. Cawson JN, Malara F, Kavanagh A, et al. Fourteen-gauge needle core biopsy of mammographically evident radial scars: is excision necessary? *Cancer* 2003; 97: 345–351.
41. Brenner RG, Jackman RJ, Parker SH, et al. Percutaneous core needle biopsy of radial scars of the breast. When is excision necessary? *AJR Am J Roentgenol* 2002; 179: 1179–1184.
42. Moinfar F, Man YG, Bratthauer GL, et al. Genetic abnormalities in mammary ductal intraepithelial neoplasia-flat type (clinging ductal carcinoma in situ): a simulator of normal mammary epithelium. *Cancer* 2000; 88: 2072–2081.
43. Otterbach F, Bankfalvi A, Bergner S, et al. Cytokeratin 5/6 immunohistochemistry assists the differential diagnosis of atypical proliferations of the breast. *Histopathology* 2000; 37: 232–240.
44. Buonomo OC, Caredda E, Portarena I, et al. New insights into the metastatic behavior after breast cancer surgery, according to well-established clinicopathological variables and molecular subtypes. *PLoS One* 2017; 12: e0184680.
45. Simpson PT, Gale T, Reis-Filho JS, et al. Columnar cell lesions of the breast: the missing link in breast cancer progression? A morphological and molecular analysis. *Am J Surg Pathol* 2005; 29: 734–746.
46. Buerger H, Otterbach F, Simon R, et al. Comparative genomic hybridization of ductal carcinoma in situ of the breast: evidence of multiple genetic pathways. *J Pathol* 1999; 187: 396–402.
47. Wong H, Lau S, Yau T, et al. Presence of an in situ component is associated with reduced biological aggressiveness of size-matched invasive breast cancer. *Br J Cancer* 2010; 102: 1391–1396.
48. Gao Y, Niu Y, Wang X, et al. Genetic changes at specific stages of breast cancer progression detected by comparative genomic hybridization. *J Mol Med* 2009; 87: 145–152.
49. Birkbak NJ, Eklund AC, Li Q, et al. Paradoxical relationship between chromosomal instability and survival outcome in cancer. *Cancer Res* 2011; 71: 3447–3452.
50. Collins LC, Aroner SA, Connolly JL, et al. Breast cancer risk by extent and type of atypical hyperplasia: an update from the Nurses' Health Studies. *Cancer* 2016; 122: 515–520.
51. Smith SG, Sestak I, Forster A, et al. Factors affecting uptake and adherence to breast cancer chemoprevention: a systematic review and meta-analysis. *Ann Oncol* 2016; 27: 575–590.
52. Noonan S, Pasa A, Fontana V, et al. A survey among breast cancer specialists on the low uptake of therapeutic prevention with tamoxifen or raloxifene. *Cancer Prev Res* 2018; 11: 38–43.
53. Rakha EA, Ho BC, Naik V, et al. Outcome of breast lesions diagnosed as lesion of uncertain malignant potential (B3) or suspicious of malignancy (B4) on needle core

biopsy, including detailed review of epithelial atypia. *Histopathology* 2011; 58: 626–632.
54. Alonso-Bartolomé P, Vega-Bolívar A, Torres-Tabanera M, et al. Sonographically guided 11-G directional vacuum-assisted breast biopsy as an alternative to surgical excision: utility and cost study in probably benign lesions. *Acta Radiol* 2004; 45: 390–396.
55. Huber S, Wagner M, Medl M, et al. Benign breast lesions: minimally invasive vacuum-assisted biopsy with 11-gauge needles: patient acceptance and effect on follow-up imaging findings. *Radiology* 2003; 226: 783–790.
56. Haagensen CD, Bodian C and Haagensen DE. *Lobular Neoplasia (Lobular Carcinoma in Situ) Breast Carcinoma: Risk and Detection*. Philadelphia: WB Saunders; 1981: 238.
57. Andersen JA. Lobular carcinoma in situ: a long-term follow-up in 52 cases. *Acta Pathol Microbiol Scand* 1974; 82: 519–533.
58. Bombonati A and Sgroi DC. The molecular pathology of breast cancer progression. *J Pathol* 2011; 223: 307–317.
59. Brunner AL, Li J, Guo X, et al. A shared transcriptional program in early breast neoplasias despite genetic and clinical distinctions. *Genome Biol* 2014; 15: 1–16.