European guidelines for the diagnosis, treatment and follow-up of breast lesions with uncertain malignant potential (B3 lesions) developed jointly by EUSOMA, EUSOBI, ESP (BWG) and ESSO

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Abstract: Introduction: Breast lesions of uncertain malignant potential (B3) include atypical ductal and lobular hyperplasias, lobular carcinoma in situ, flat epithelial atypia, papillary lesions, radial scars and fibroepithelial lesions as well as other rare miscellaneous lesions. They are challenging to categorise histologically, requiring specialist training and multidisciplinary input. They may coexist with in situ or invasive breast cancer (BC) and increase the risk of subsequent BC development. Management should focus on adequate classification and management whilst avoiding overtreatment. The aim of these guidelines is to provide updated information regarding the diagnosis and management of B3 lesions, according to updated literature review evidence. Methods: These guidelines provide practical recommendations which can be applied in clinical practice which include recommendation grade and level of evidence. All sections were written according to an updated literature review and discussed at a consensus meeting. Critical appraisal by the expert writing committee adhered to the 23 items in the international Appraisal of Guidelines, Research and Evaluation (AGREE) tool. Results: Recommendations for further management after core-needle biopsy (CNB) or vacuum-assisted biopsy (VAB) diagnosis of a B3 lesion reported in this guideline, vary depending on the presence of atypia, size of lesion, sampling size, and patient preferences. After CNB or VAB, the option of vacuum-assisted excision or surgical excision should be evaluated by a multidisciplinary team and shared decision-making with the patient is crucial for personalizing further treatment. De-escalation of surgical intervention for B3 breast lesions is ongoing, and the inclusion of vacuum-assisted excision (VAE) will decrease the need for surgical intervention in further approaches. Communication with patients may be different according to histological diagnosis, presence or absence of atypia, or risk of upgrade due to discordant imaging. Written information resources to help patients understand these issues alongside with verbal communication is recommended. Lifestyle interventions have a significant impact on BC incidence so lifestyle interventions need to be suggested to women at increased BC risk as a result of a diagnosis of a B3 lesion. Conclusions: These guidelines provide a state-of-the-art overview of the diagnosis, management and prognosis of B3 lesions in modern multidisciplinary breast practice.

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ABSTRACT

Introduction
Breast lesions of uncertain malignant potential (B3) include atypical ductal and lobular hyperplasias, lobular carcinoma in situ, flat epithelial atypia, papillary lesions, radial scars and fibroepithelial lesions as well as other rare miscellaneous lesions. They are challenging to categorise histologically, requiring specialist training and multidisciplinary input. They may coexist with in situ or invasive breast cancer (BC) and increase the risk of subsequent BC development. Management should focus on adequate classification and management whilst avoiding overtreatment. The aim of these guidelines is to provide updated information regarding the diagnosis and management of B3 lesions, according to updated literature review evidence.

Methods
These guidelines provide practical recommendations which can be applied in clinical practice which include recommendation grade and level of evidence. All sections were written according to an updated literature review and discussed at a consensus meeting. Critical appraisal by the expert writing committee adhered to the 23 items in the international Appraisal of Guidelines, Research and Evaluation (AGREE) tool.

Results
Recommendations for further management after core-needle biopsy (CNB) or vacuum-assisted biopsy (VAB) diagnosis of a B3 lesion reported in this guideline, vary depending on the presence of atypia, size of lesion, sampling size, and patient preferences. After CNB or VAB, the option of vacuum-assisted excision or surgical excision should be evaluated by a multidisciplinary team and shared decision-making with the patient is crucial for personalizing further treatment. De-escalation of surgical intervention for B3 breast lesions is ongoing, and the inclusion of vacuum-assisted excision (VAE) will decrease the need for surgical intervention in further approaches. Communication with patients may be different according to histological diagnosis, presence or absence of atypia, or risk of upgrade due to discordant imaging. Written information resources to help patients understand these issues alongside with verbal communication is recommended. Lifestyle interventions have a significant im*pact on BC incidence so* lifestyle interventions need to be suggested to women at increased BC risk as a result of a diagnosis of a B3 lesion.

Conclusions
These guidelines provide a state-of-the-art overview of the diagnosis, management and prognosis of B3 lesions in modern multidisciplinary breast practice.

INTRODUCTION

Breast lesions of uncertain malignant potential, also known as “B3 lesions”, are composed of a variety of pathological entities with different risks of malignancy. These lesions are being increasingly diagnosed due to the implementation of screening programs, as well as the use of more sensitive imaging techniques. The incidence of B3 lesions varies between 3% and 21%, with higher rates in screening populations (1) (2). Management and diagnosis is complicated because B3 lesions comprise a heterogeneous group of lesions with or without histopathological atypia: atypical ductal hyperplasia (ADH), flat epithelial atypia (FEA), lobular neoplasia (LN), which include lobular carcinoma in situ (LCIS) and atypical lobular hyperplasia (ALH), papillary lesions, radial scars, and other miscellaneous entities such as fibroepithelial lesion (FEL), mucocele-like lesions, and apocrine adenosis. All vary in their risk of upgrade to malignancy at the time of excision and the risk these confer of subsequent in situ or invasive malignancy. The reported potential risk of coexisting associated malignancy after a B3 lesion detected on VAB ranges from 0% to 25% depending on the specific entity according to the Swiss Minimally Invasive Breast Biopsy group (MIBB) database. (2)

The management of B3 lesions has undergone significant change over the last few years. Historically, all B3 lesions were managed with surgical excision, due to the uncertainty regarding malignant potential and the concern about the adequacy of image-guided sampling. (3) However, using larger gauge core needles (14 G) and vacuum-assisted biopsy (VAB) needles (up to 8 or 7 G) in modern practice upgrade 5−20% of all B3 lesions to overtly malignant lesions(4). Improvements in imaging techniques and image-guided interventions, now including vacuum-assisted percutaneous excision (VAE), may allow women to safely avoid surgical excision. (5) VAE aims to obtain a similar amount of tissue as a diagnostic surgical excision, i.e. 4 g of tissue, using the same VAB method to remove the entire B3 lesion. (6)

Risk prediction for women with B3 lesions may be aided by the use of online predictive models, such as the Breast Cancer Risk Assessment Tool (BCRAT, based on the Gail model) (7) or the International Breast Cancer Intervention Study (IBIS Tyrer Cuzick) model. (8) However, the performance of these models may over- or underestimate the risk of subsequent malignancy after the diagnosis of a B3 lesion, so the use of cumulative incidence data or adding the number of foci of atypical hyperplasia may permit further stratification, which may be useful when counseling women about subsequent BC risk. (9)

Multidisciplinary discussion is important to ensure that there is radiological and pathological concordance for the diagnosis of B3 lesions. Careful explanation about the nature of these lesions when communicating with patients is essential to convey the complexities of risk prediction and ideally written information sources in high-quality lay language should be used. Interventional procedures and management need to be discussed with patients in a shared decision-making process.

The following sections describe each of the B3 lesions in detail, followed by specific sections relating to clinical management and risk prediction of future breast malignancy.

Material and Methods

This guideline was developed using the international Appraisal of Guidelines, Research and Evaluation (AGREE) tool (10).

1. A multidisciplinary panel of experts in radiology, pathology and surgery conducted the review.
2. The first stage was a systematic review of the literature. Key words were selected and searched in the following databases: PubMed, Embase, Web of Science, Cochrane Library, and Emcare through to June 2022. Preclinical studies, case reports, images of interest, abstracts-only presented in congresses, and editorials were excluded. Non-English language papers were excluded.
3. Relevant papers were selected based on title and abstract.
4. Papers were critically analyzed for the level of evidence. (Table 1)
5. Factors that increased the certainty of evidence included the following: (1) large magnitude of effect; (2) dose-response gradient; and (3) the effect of plausible residual confounding. The factors that decreased certainty included the following: (1) risk of bias; (2) inconsistency; (3) indirectness; (4) imprecision; and (5) publication bias.
6. Finally, after applying the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) framework (11), and after judgment from the multidisciplinary team of experts, the level of evidence and recommendation grade was established for each pathologic entity. Topics of disagreement and methods used to solve them were detailed in the text.
7. A guidelines development group including Radiologists (F.G, F.S, A.A, N.S, J.C), Pathologists (A.M.S, P.R, D.S, S.Z, Z.V.), Breast Surgeons (I.R, L.W, G.C, M.S, J.D), and Patient Advocates (M.Z) met in Florence, Italy, in December 2022 to review all evidence and draft the guidelines. Draft guidelines were subsequently refined by the group using an iterative process.

Table 1. Levels of evidence and Grades of recommendation

Levels of Evidence	
I	Evidence from at least one large randomized, controlled trial of good methodological quality (low-potential for bias) or meta-analysis of well-conducted randomized trials without heterogeneity
II	Small randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analysis of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinions
Grades of Recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended

B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient benefit for efficacy or benefit does not outweigh the risk or the disadvantages, optional
D	Moderate evidence against efficacy or for adverse outcomes, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended.

Adapted from http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology

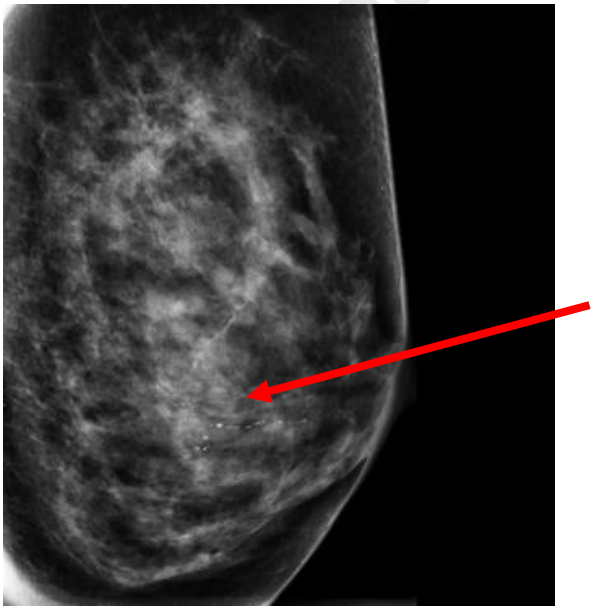
Review of specific B3 lesions

1. ATYPICAL DUCTAL HYPERPLASIA (ADH)

Radiology

ADH is one of the most frequently diagnosed B3 lesions of the breast. It is most commonly associated with clustered calcifications (4, 5), masses or asymmetric densities on mammography (Fig. 1). On ultrasound, ADH may be seen as a mass or an ill-defined hypoechoic area. On magnetic resonance imaging (MRI), ADH has a nonspecific appearance, manifesting as either mass or non-mass enhancement (12). Image-guided biopsy may be with a 14G core needle biopsy (CNB) or a vacuum-assisted biopsy (VAB) using a 14G- to 9G- needle.

Fig. 1 Mammogram with grouped heterogeneous microcalcifications showing linear distribution attributable to ADH



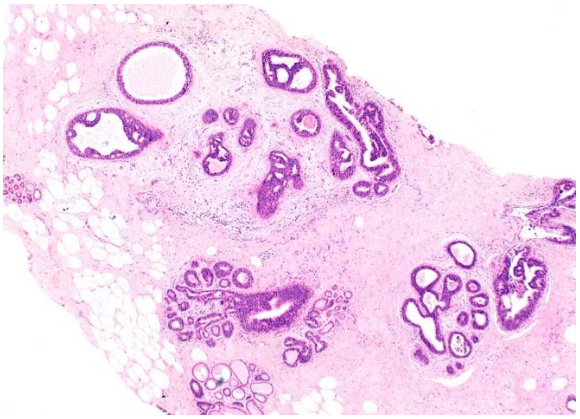
Contrast-enhanced imaging with MRI or contrast enhanced mammography (CEM)

Additional contrast imaging can help in excluding malignancy due to its high negative predictive value (NPV) (and hence avoid surgical excision) as well as diagnosing clinically unsuspected malignancies in areas unrelated to the site of the already detected high-risk lesion. National Comprehensive Cancer Network ® (NCCN) guidelines recommend that at diagnosis of ADH or LN, breast MRI (or CEM should be considered. The recommendation is for screening in those with lifetime risk > 20. In several preliminary studies, MRI has shown promise as a tool to evaluate high-risk lesions to exclude the presence of coexisting malignancy, with negative predictive values between 90% and 98%.(13) When MRI is not available, contrast-enhanced mammography (CEM) may also help in excluding malignant lesions showing the absence of enhancement.(14)

Pathology

ADH is defined as a small focus of a low-grade, monotonous epithelial intraductal proliferation not exceeding a maximum diameter of 2 mm (15, 16) (Fig. 2) Often, but not always, there are associated calcifications (15, 16). The official terminology, as recommended by the 2019 WHO classification of breast tumors (17) is 'atypical ductal hyperplasia' abbreviated as 'ADH'. However, in some countries, an alternative term, 'atypical intraductal epithelial proliferation', abbreviated as 'AIDEP' is also used for CNB and diagnostic VAB samples (16, 18, 19). The latter term more strongly reflects the uncertainty of the lesion, as the distinction of ADH from low grade DCIS solely depends on the size of the lesion with lesions greater than 2 mm called low-grade DCIS. As this cannot be determined on preoperative CNB or VAB with certainty (6, 16) additional sampling of the lesion is required, either with VAE or surgical excision.
ADH is a clonal proliferation in virtually all cases. It overexpresses the estrogen receptor (ER) and has a parallel loss of basal cytokeratins (16, 19). This marker constellation is extremely useful in routine histopathological diagnostics (17), as the main differential diagnosis of ADH, usual type ductal hyperplasia (UDH), can be differentiated from an ADH only by proving the clonal nature of the proliferation with immunohistochemistry.

Fig.2: Photomicrograph showing ADH in a VAB specimen. Stained with H and E. Magnification of X50.



Upgrade rate to malignancy

The rate of ADH upgrade to DCIS or invasive cancer is critical to management but is highly variable and difficult to predict. It is reported at between 5% and 50%. It is higher in cases with discordant imaging and pathology findings, those with mass lesions on imaging and those where only CNB was used for diagnosis (6, 19, 20). A recent meta-analysis regarding VAB of B3 lesions (21) showed that there are considerable differences in the upgrade rate according to B3 subtype. The total upgrade rate of ADH to malignancy was 22%. The pooled positive predictive value of VAB in determining the final histological diagnosis was 79%. (4) In addition, the presence of microcalcifications and multifocality also correlate with a higher upgrade rate on subsequent open excision (6, 19, 20). Use of MRI-guided VAB to determine if these lesions can be spared surgical procedures, showed that complex histologic findings such as ADH and DCIS are characterized more accurately, however, the use of this approach did not alter the upgrade rate. (12) Nomograms of varying levels of complexity, have been evaluated determine whether surgery may be avoided. One involved using three criteria to avoid surgical excision: age, no residual radiologic lesion after biopsy, and radiologic lesion size of less than 16 mm. The area under the curve (AUC) of the resulting model for patients with ADH was only 0.63 (95% CI 0.56–0.70(21)). In another study, prior BC history was the only factor associated with subsequent BC risk (odds ratio 2.25, 95% confidence interval 1.04–4.87) and in those patients surgical excision was always indicated. (22) Machine learning may provide additional information regarding ADH management. Harrington and colleagues developed a series of machine learning models that show promising performance for upgrade prediction with age, lesion size, number of biopsies, needle gauge, and personal and family history of BC being significant risk factors (23). Using this model, 98% of all malignancies would have been diagnosed through surgical biopsies, whereas 16% of unnecessary surgeries on benign lesions could have been avoided (87% sensitivity, 45% specificity) (23). Future work includes incorporation of radiological and histopathological images into these machine learning models.

Management

No combination of factors has been identified which predicts a sufficiently low upgrade rate to obviate additional intervention after the needle biopsy diagnosis of ADH. A meta-analysis of 93 articles attempted to determine which imaging and patient factors provided sufficient confidence of no-upgrade to avoid surgery. The study included 6458 cases of ADH, where 5911 were managed with surgical excision and 547 were managed with imaging follow-up (24). They concluded that excision is recommended for all patients with ADH found at needle biopsy, although the results were extremely heterogeneous.

The main controversy lies in whether these lesions can be treated with vacuum-assisted excision (VAE) instead of surgery. There have been some discrepancies between the published guidelines and consensus. In the guidelines recommended by AGO (Arbeitsgemeinschaft Gynäkologische Onkologie, German Gynecological Oncology Group) Task Force and The Second International Consensus Conference on B3 lesions, surgical excision is the first option to pursue after-needle biopsy returns (2, 25). If excisional surgery is required, a range of effective localization techniques can be applied to guide surgery based on local expertise and resources (26). Intraoperative radiographic evaluation of surgical specimen(s) is suggested for immediate correlation. The recently published 3rd international consensus conference of B3

lesions recommends an open surgical excision after an ADH diagnosis on CNB is delivered and favors this option also as a preferred option if an ADH diagnosis is delivered by VAB. However, in small or focal ADH lesions on imaging, and after discussing the problem at the multidisciplinary discussion, a second VAE can be also considered. (27)
In the guidelines recommended by the UK National Health Service Breast Screening Programme (NHS BSP) Working Group, second-line VAE is the method of choice for the detailed secondary assessment of most B3 lesions, whether initially diagnosed on CNB or primary diagnostic VAB (28). B3 lesions diagnosed on core biopsy (ADH, LN, radial scar, FEA, mucocele-like lesions with or without epithelial atypia) should undergo excision with VAE. Provided 4 g of tissue is obtained, and there is no evidence of malignancy on VAE, these patients will be suitable for annual mammographic surveillance and primary prevention advice (see below).
One important issue to consider is the size of the lesion, with 15 mm broadly accepted as a threshold for VAE, the cut-off where the radiological abnormality is likely to be fully excised with VAE (28) with radiological confirmation of complete removal of the suspicious finding. In larger lesions, surgical excision may be adopted as the best option but VAE may allow for representative sampling of the area. In very extensive cases, the most suspicious areas need to be focally surgically excised to ensure representative sampling and associated malignancy are excluded. (29)
Whether to choose surgical excision or VAE should take into account evidence-based data, country resources, availability of VAE and skills, and follow-up. There is an agreement among the experts that sparing open surgery, when this can be avoided, is desirable, although there is a need for more data on VAE, where actually few countries are performing. (28)
It is also relevant to note that not all ADH cases have associated calcifications, so a proper imaging size assessment remains unreliable in a subset of ADH cases, further supporting the need for surgical excision after needled biopsy diagnosis of ADH (19).
In those patients with a diagnosis of ADH and additional risk factors for developing BC determined by predictive models, different approaches may be undertaken. Contrast-enhanced MRI or CEM may be considered before planning definitive treatment (30).

Recommendations

1. ADH diagnosed by CNB or VAB in a lesion that is visible on imaging, surgical excision is the preferred option (evidence/grade I/A); imaging-guided vacuum-assisted procedure (VAE) might be undertaken with the aim of excision if less than 15 mm in size. (evidence/grade III/B)
2. ADH diagnosed by CNB or VAB and larger than 15 mm might undergo surgical excision (evidence/grade I/A). Image-guided vacuum assisted excision (VAE) may be considered (evidence/grade III/B)

2. LOBULAR CARCINOMA IN SITU AND ATYPICAL LOBULAR HYPERPLASIA

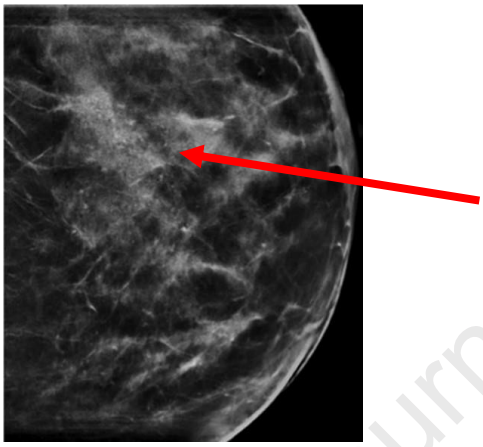
Classical lobular neoplasia (LN) is categorized as a B3 lesion and classified by the WHO as classical LCIS or atypical lobular hyperplasia (ALH). Pleomorphic LCIS (PLCIS) and florid-LCIS are regarded as comparable to DCIS. Both entities are risk factor lesions (increased risk of BC

developing in either breast) and are nonobligate precursor lesions (increased risk of cancer) conferring a 8−10 times relative risk compared to the general population. (31)

Radiology

Some authors consider that LCIS is usually mammographically occult. When microcalcifications are seen, they are generally found in adjacent benign tissue separate from the lobular neoplastic architecture, making LN an incidental finding in the great majority of cases. Other authors have found that microcalcifications are common (27) (Fig. 3) Upgrade rates are higher (13−18%) for LN associated with mass lesions and calcifications (8, 9). When found on MRI or CEM, the characteristic finding is non-mass enhancement. The preceding comments are relevant regarding the role for MRI and CEM in exclusion of malignancy in ADH and LN.

Fig.3: Amorphous microcalcifications with a segmental distribution typical of lobular neoplasia



Pathology

Histologically, the lobular cells are dis-cohesive, often with eccentric nuclei and some show intracytoplasmic vacuoles. The distinction between ALH and LCIS is quantitative and hence the generic term “lobular neoplasia, LN” can be used in the limited core/diagnostic VAB biopsy. The classic lobular neoplasia cells are of either type A (small uniform nuclei with inconspicuous nucleoli and scanty cytoplasm) (Fig. 4) or type B (larger nuclei with more conspicuous nucleoli and moderate cytoplasm) (Fig. 5) ; neither is high-grade. Florid LCIS comprises a proliferation of type A or type B classic LCIS cells involving large acini or ducts (>40−50 cells in largest diameter of an acinus and/or minimal intervening stroma between acini). (2, 28)The lesion in its pure form on core biopsy is categorized as either B4 (UK) or B5a. PLCIS is diagnosed when the lesion comprises high-grade nuclei and is categorized as B5a. Classical LCIS can be associated with luminal calcification and comedo-necrosis and hence identified mammographically. Calcification is even more likely with PLCIS and florid LCIS. While classic LCIS is strongly and uniformly positive for ER and negative for HER2, PLCIS can be ER-negative and HER2-positive, a feature that can help distinguishing both lesions in difficult cases (32-34).

LN can be multifocal and/or bilateral. It has long been thought the lesion confers an equal risk for subsequent malignancy in both breasts (35) (36). Recent evidence however, showed that the risk associated with ALH is 3 times higher in the same breast compared with the contralateral breast (37).
One of the hallmarks of LN is the inactivation of the E-cadherin gene leading to diminished or absent E-cadherin expression by immunohistochemistry (38). In some cases, E-cadherin expression can be preserved, heterogeneous or aberrant, and other markers such as β-catenin and p120 can be used to confirm the lobular phenotype. In those cases, confirmation of the lobular phenotype can be confirmed by negative β-catenin or cytoplasmic p120 staining (39, 40).

Fig 4. Photomicrograph of breast tissue containing LCIS type A (H and E staining, magnification X100. A terminal duct lobular unit distended by monotonous discohesive lobular cells with hyperchromatic nuclei, inconspicuous nucleoli and minimal cytoplasm.

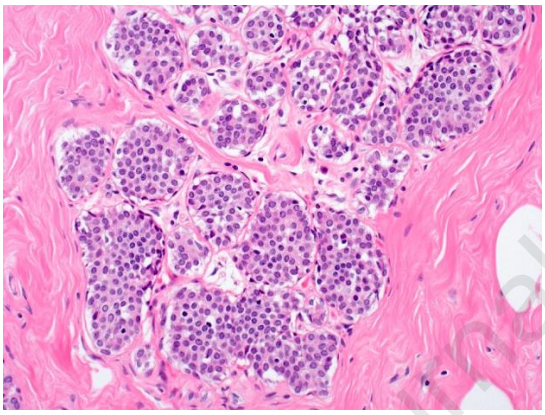
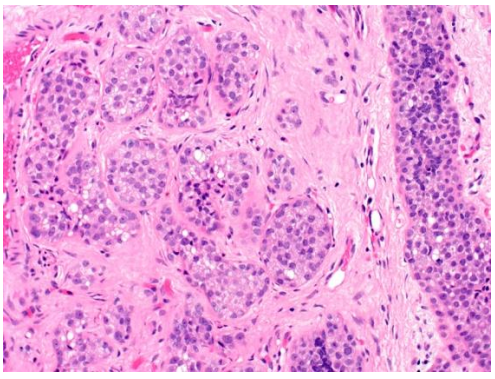


Fig 5. Photomicrograph of breast tissue containing LCIS type B (H and E staining, magnification X100.. There is a solid proliferation of discohesive cells showing slightly enlarged nuclei with, some variation in nuclear size and shape and moderate eosinophilic cytoplasm



Upgrade rate to malignancy

The upgrade rate to malignancy following the diagnosis of LN varies in the literature (41, 42). On average, it is 27% for LN (range 0-40%), 12% for ALH, and 22% for LCIS. (43) The upgrade rate for PLCIS can be over 40% (range 0-60%) (33) (44). This rate of upgrade was reduced in a recent meta-analysis that identified 16 studies that fulfilled the criteria for analysis. The pooled risks for upgrade to any malignancy following the diagnosis of LN, ALH or LCIS were 3.1%, 2.5% and 5.8%, respectively (43).

Management

Once a diagnosis of LCIS is established with CNB, whether or not further excision is necessary is a matter of debate. Several recent studies suggest that when a CNB based diagnosis of LN is made, no other lesions requiring excision (ADH, papilloma, radial scar) are present and radiological–pathological concordance is present, upgrade rates are less than 5%. (45)
In a prospective multi-institutional trial (TBCRC 20) to determine the rate of upgrade to cancer after excision for pure LCIS on CNB, women diagnosed with LCIS who received no further surgery (as reported to the SEER registry) had a subsequent 10-year incidence of cancer development of 13.9%, and BC specific survival was not impacted by the choice of surgical procedure (46). For these reasons, it is advocated not to perform routine surgical excision of ALH or LCIS when the radiological and pathological diagnoses are concordant and no other lesions requiring excision are present (45, 46). Over time, the surgical management of patients with LCIS has changed substantially. While in the 1960s–70s most patients with classical LCIS underwent mastectomy, often bilateral, in the past few decades, 50–80% of women with classical LCIS had a surgical excision, and mastectomy was performed only in 10–20% of cases (47).

In a SEER population-based study, Cheng and colleagues showed that patients diagnosed with LCIS receiving lumpectomy formed the majority (68.1%) of patients, while mastectomy, once the first choice, made up only 21.4%. This indicated that, for patients with LCIS, most clinicians are now inclined to perform limited surgery rather than offer non-operative management or mastectomy (48). Taylor and colleagues, reported a study using data from the USA National Cancer Data Base (NCDB), including women with a diagnosis of LCIS from 2004 to 2013. They found that only 5.4% of women did not receive surgery, 84.8% underwent surgical excision, 4% underwent unilateral mastectomy, and 5.1% underwent bilateral mastectomy as the definitive surgical treatment. On multivariate analysis, patients were more likely to undergo either unilateral or bilateral mastectomy (compared with no surgery or surgical excision) if they were younger, white, insured, or had greater comorbidity. It is important that a shared decision-making process is used and patients are adequately informed of the risks and benefits of surgery (49).

Van Maaren and colleagues, using the Netherlands Cancer Registry (NCR), (50) also showed rates of mastectomy were higher than expected. They found 26.7 % of women diagnosed with

LCIS received no surgery, 50.5% breast-conserving surgery (BCS), 10.2% mastectomy and 12.6% an unknown type of surgery (mainly in earlier years). Most invasive BCs presented ipsilaterally, and the contralateral BC risk was still higher than the BC risk in the general population. Survival was very high and most patients did not develop subsequent invasive BC and if so, they generally had a good prognosis, supporting the recommendation for active surveillance (50) In the majority of population-based studies, limitations exist related to information about family history, prior radiation exposure, or genetic mutations such as BRCA 1/2. In addition, some studies do not distinguish between classical and PLCIS, at least in the most historic publications, which limits their applicability (49, 50)

Margins

Classical LCIS does not require clear margins or re-excision for positive margins. The majority of publications report no increased risk of recurrence regardless of margin involvement, although two papers did report increased recurrence rates, however with low sample sizes. (51-53).

Recommendations

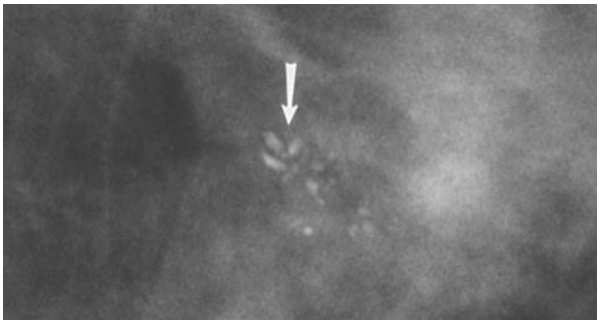
1. When a core needle biopsy returns classical LCIS on histopathology in a lesion that is visible on imaging, it is recommended to perform VAB/VAE. Thereafter, if there is pathological–radiological concordance and no residual lesion, surgery is not required and surveillance is justified. (evidence/grade II/B)
2. If there is radiological-pathological discordance after CNB /VAB diagnosis, further tissue examination by the second line, surgical excision, or VAE is recommended. (evidence/grade III/B)
3. Unilateral or bilateral mastectomy is no longer recommended in classical LCIS unless additional high-risk factors are identified on formal risk assessment such as a significant family history or a known pathogenic gene mutation. (evidence/grade III/B)
4. Patient information and shared decision-making are needed when agreeing management

3. FLAT EPITHELIAL ATYPIA

Radiology

Flat epithelial atypia (FEA) is a B3 breast lesion found in approximately 5% of percutaneous breast biopsies that typically presents on mammography as grouped amorphous calcifications and on ultrasound as an irregular hypoechoic mass (54) (Fig 6).

Fig. 6 Grouped coarse heterogeneous microcalcifications.



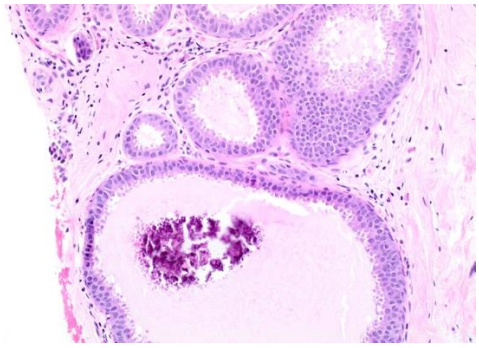
Pathology

The current WHO classification includes FEA among columnar cell lesions (CCL). Columnar cell lesions include columnar cell change (CCC) and columnar cell hyperplasia (CCH), both without atypia; when atypia is present, it is called flat epithelial atypia (FEA). CCLs are clonal alterations of the terminal duct lobular unit (TDLU) characterized by enlarged, variably dilated acini lined by columnar epithelial cells. According to the definition, CCC and CCH show elongated nuclei with evenly dispersed chromatin and inconspicuous nucleoli, oriented perpendicular to the basement membrane, lack nuclear cytological atypia and are designated as B2 lesions, without the need for further evaluation. (Fig.7)

FEA is characterized by low-grade (monomorphic) cytological atypia with one to several layers of mildly atypical cuboid to columnar cells in a flat architecture. Nuclei are round and uniform with inconspicuous nucleoli, similar to the nuclei that characterize low-grade DCIS, resembling the monomorphic cytological atypia of low-grade DCIS (17). FEA is often associated with intraluminal secretions and calcifications in dilated TDLU. The distinction between FEA, CCC and CCH is performed only on hematoxylin and eosin histology since all lesions share the same immunoreactive profile: strong clonal ER-positivity, CK5-negativity (except myoepithelial cells), and a low Ki-67 labeling index.

FEA shares molecular changes of the so-called low-grade molecular pathway with other lesions like ADH, low-grade DCIS, or classical LN, and even with tubular carcinoma, invasive cribriform carcinoma, classical ILC and low-grade invasive ductal carcinoma. It is frequently associated with these lesions (17, 55).

Fig 7. Photomicrograph of breast tissue containing FEA with microcalcifications on VAB (H and E staining, magnification X100. A dilated terminal duct lobular unit lined by bland columnar cells with apical snouts and associated luminal secretion and calcification



Reproducibility of pathology readings for FEA lesions

It is important that pathologists adhere to the strict definition of FEA to make an accurate diagnosis at CNB. Both under- and over-reporting of FEA with ADH at CNB occurs (56-59). Darvishian and colleagues and O'Malley and colleagues have demonstrated acceptable interobserver agreement after training and tutorials for pathologists (56, 57).

Upgrade rate to malignancy

For pure FEA the risk of local recurrence and progression to carcinoma is low. Some cases of pure FEA progress to invasive breast carcinoma, although the risk of progression appears to be very low and this lesion is not associated with the same level of BC risk seen with ALH and ADH. When FEA is associated with other lesions like ADH, DCIS and LN, the risk associated with the higher risk lesion should be adopted when counselling the patient about treatment options. The evidence on the biological behavior of pure FEA is limited and varies highly among individual studies. The largest meta-analysis and systematic review of 42 studies with 2482 FEA cases without other concomitant risk lesions, calculated a pooled upgrade rate for pure FEA on CNB after surgical excision or 2-year imaging follow-up to be 5% (CI: 3-6%) for BC, 1% (CI: 0-2%) as invasive carcinoma, and 2% (CI: 1-3%) as DCIS (60) Several other, mostly earlier, meta-analyses found that the upgrade rate following surgical excision was different, ranging from 1% to 16% (2, 4, 61, 62).

Wahab and colleagues examined 1502 cases from 25 studies for the co-occurrence of ADH at surgical excision after a diagnosis of pure FEA, with observed proportions for the co-occurrence ranging from 0% to 42%. The pooled co-occurrence rate for ADH was 17% (CI: 12-21%). They concluded the high coincidence rate would be an argument for surgical excision of pure FEA to identify the risk for these women (60). Similar to other B3 lesions, FEA diagnosed on needle biopsy needs additional sampling because identification of co-existent ADH increases the upgrade rate. Removal of more than 90% of the target lesion at CNB (the majority with a 12-G or larger needle) was reported for 312 cases of pure FEA in 11 studies and it was found that when more than 90% of targeted calcifications were removed by core needle biopsy (CNB), the pooled upgrade rate to BC was 0%.(60) However, this study only reported on microcalcifications, and other radiological findings such as distortions or masses cannot be commented on.

Another meta-analysis by Rudin and colleagues (62) reporting the frequency of upgrade to cancer or ADH at surgical excision of FEA found the cancer upgrade pooled estimate of 7.5% (95% CI, 5.4–10.4%), with a rate of invasive cancer of 3% (95% CI 1.9–4.5%). For upgrade to ADH, data from 22 studies including 937 patients were analyzed. The proportion of patients upgraded to ADH ranged from 0 to 60%, with a pooled estimate of 17.9% overall and 18.6% among high-quality studies. They found that at least 20% of patients with pure FEA on CNB will upgrade at surgical excision to cancer or a high-risk lesion that may change patient management. Regarding those patients without surgical excision, 10 studies reported follow-up evaluation (from 6 months to 5 years) for 300 patients with FEA and only 2% experienced invasive cancer at the core biopsy site. It is likely that these women had lower risk features that

contributed to the omission of surgical excision. Women who have FEA without ADH do not have an increased long-term risk of BC. (62)

Management

Radiological follow-up is the preferred course of action proposed by several independent research bodies and worldwide guidelines for FEA diagnosed on VAB. Only instances with pathological-radiological discordance, mass lesions, or cases with residual calcifications after biopsy should be offered surgical excision (2, 63-68). In addition to radiological-pathological correlation, age, other BC risk factors and the size of lesions are also key aspects for informed decision-making (69).

As with other B3 lesions, the presence of ADH in the biopsy was the only predictor of histological upgrade to malignancy (P = 0.04). Nonoperative management of biopsy-proven FEA can be considered in the absence of both ADH and radiology-pathology discordance (69). In the study by Di Pasquale and colleagues (70), all 24 patients who underwent radiological observation did not show malignant upgrade with an average of 36 months of follow-up. Patients undergoing radiological follow-up were less likely to have concurrent ADH (p=0.053) and more likely to receive a VAB (p=0.001). All patients undergoing radiological follow-up also had concordant imaging.

According to the German Gynecological Oncology Group (AGO) guidelines, when FEA is found at CNB or VAB, surgery can be avoided in the following situations: small lesion (< 2 TDLU involved at VAB) or near complete (> 90%) removal of microcalcifications after VAB at imaging. In contrast, surgical intervention is mandatory if the lesion is detected as a wide area of microcalcifications or in the case of discrepancy between pathology and radiology. If FEA is detected within surgical resection margins, no other treatment is recommended unless microcalcifications have not been completely removed. (63)

The NHS BSP recommends a similar approach although is in favor of VAE for FEA lesions diagnosed on CNB or on diagnostic VAB. In the presence of a large area of calcification, more than one area can be sampled and managed accordingly. Surgery should be considered only in cases of radio-pathological discordance or upgrade to DCIS or invasive cancer (28)

The third International Conference on B3 lesions suggested that, if FEA is identified on CNB, depending on the clinical presentation and the size of the lesion at imaging, either VAE or surgical excision should be performed. Afterwards, if FEA is returned on VAB and >90% of the targeted lesion, such as calcifications, has been eliminated, surveillance and radiological follow-up is suggested (27)

Recommendations

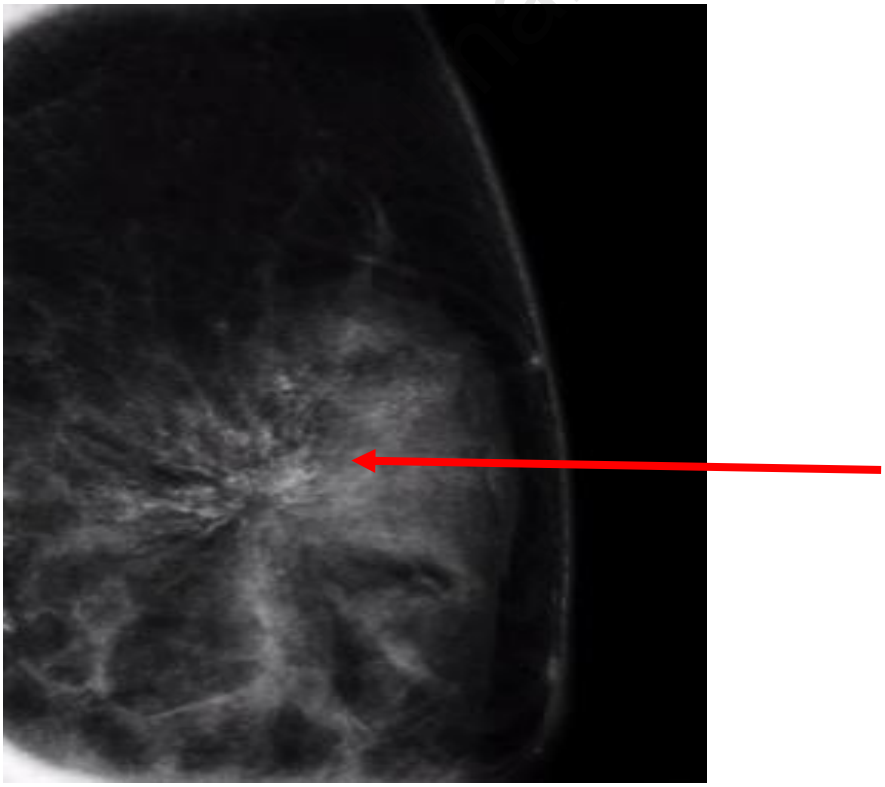
1. FEA diagnosed on CNB/VAB without ADH and concordant with imaging can be managed with surveillance. (evidence/grade II/B)
2. FEA concomitant with ADH diagnosed by CNB has a higher risk of upgrade to BC so additional intervention is recommended (surgical excision or VAE) (evidence/grade II/B)
3. FEA with ADH diagnosed by VAB, if not all calcifications are excised, and concordant imaging cannot be assured, may benefit from surgical excision or VAE (evidence/grade III/B)

4. RADIAL SCAR/COMPLEX SCLEROSING LESION (RS/CSL)

Radiology

RS/CSL are typically seen on mammography and tomosynthesis as areas of architectural distortion or stellate lesions with a radiolucent center. The spicules can be quite long and isodense to the adjacent parenchyma. Change of this distorted area between different mammographic views is indicative of RS. Associated microcalcifications are frequent. Small RS can sometimes be an incidental histological finding in biopsies. (Fig.8) The ultrasound appearance of RS/CSL is variable, ranging from no clear correlate to an hypoechoic, irregular mass with indistinct margins or focal area of shadowing with no associated mass.
MRI appearance can also be variable and non-specific. They can lack any MRI correlate and show no enhancement after intravenous injection of gadolinium-based contrast agent or they can present as mass lesions with irregular margins or non-mass enhancement. Enhancement kinetics can also be variable with slow uptake benign, indeterminate plateau or rapid uptake and wash out malignant curves encountered. (2, 71, 72) CNB under ultrasound guidance or VAB under stereotactic or tomosynthesis guidance (especially if microcalcifications are associated) can be safely used to establish the diagnosis of RS/CSL.

Fig. 8: Mammographic image showing architectural distortion with a radiolucent center and associated amorphous microcalcifications



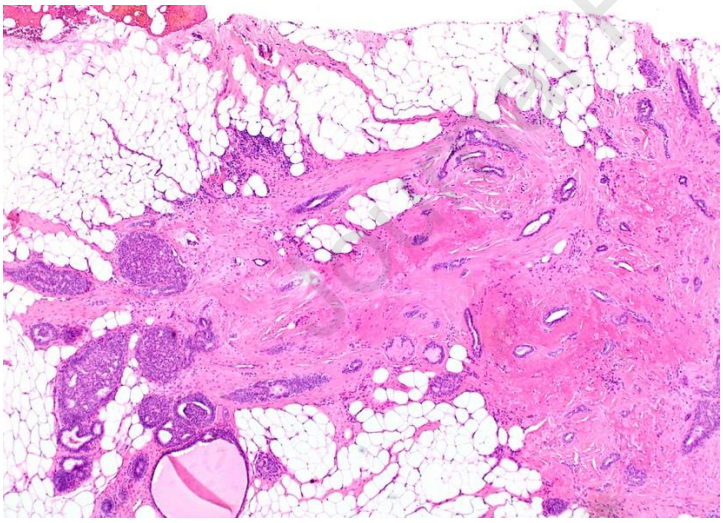
Contrast imaging with MRI and CEM as a diagnostic tool.

MRI can be used to exclude underlying invasive malignancy associated with RS/CSL due to its excellent negative predictive value (NPV), approaching 99%). It can less reliably distinguish RS/CSL with and without atypia (73-75). At present, there is only scarce literature on the role of CEM in this setting (76).

Pathology

Radial scar (RS) and complex sclerosing lesions (CSL), according to the WHO classification, are the same entity, with a stellate configuration and a central fibro-elastotic core lacking a reactive fibroblastic stroma, as well as peripherally entrapped glandular structures and cysts that are often radially orientated. These lesions are frequently associated with calcifications and sclerosing adenosis. RS is often compact, less than 10 mm in size, with a stellate form, in contrast to CSL, which are bigger and more disorganized. Apocrine metaplasia and usual type ductal hyperplasia frequently coexist. In a small percentage of cases, RS are accompanied with ADH or malignancy that can be accurately identified and verified by the use of immunohistochemistry for basal cells (17) (Fig. 9).

Fig.9: Photomicrograph showing radial scar with hyperplasia on VAE (H and E staining, magnification 60X. The radial scar comprised central fibroelastosis with entrapped benign ductal structures and peripheral usual ductal hyperplasia



Reproducibility of pathology readings for RS / CSL lesions

Up till now, no reproducibility studies exist for RS/CSL. Pathologists must take care in establishing the differential diagnosis. In some areas of sclerosing adenosis, luminal cells disappear due to atrophy within the fibro-elastotic core. This might give rise to concern regarding monotypical cell proliferation and might even be confused with invasion. In such situations immunohistochemistry for luminal and myoepithelial cells is very helpful.

Upgrade rate to malignancy

Reported data on the conversion rates of RS to DCIS or invasive carcinoma range widely, from 0 to nearly 40% (28, 77-79). The number and size of biopsy specimens impacts the rate of histopathological upgrading at surgical excision, similar to other B3 lesions. The presence of atypia (ADH) and the needle caliper of the core biopsy (as a marker of the degree of tissue excision) on the likelihood of upgrade were investigated by Farshid and colleague in a systematic review and meta-analysis of 49 studies that comprised 3,163 RS cases with surgical outcomes (including both invasive carcinoma and DCIS) (78). When stratified by atypia (ADH) and needle biopsy gauge, upgrade rates in RS were consistent and predictable. RS assessed by VABs and lacking atypia (resp. ADH) have a 1% (95% CI 0, 4%) upgrade rate to DCIS at surgical excision. Other assessment groups (smaller needles used or with associated atypia) have upgrade rates of 2-28% on surgical excision. This risk may be reduced by VAB excision (78). Ferreira and colleagues (80) showed similar results, with the use of VAB reducing the upgrade rate by 87%, or 3 times less than that of 14G CNB. They also found the presence of atypia was the only significant predictor of malignancy in RS, increasing the upgrade rate ten-fold.

Other studies also found that RS upgrade rates were greater if atypia (ADH) was present. According to the NHS BSP Guidelines upgrade occurs in 36% of cases with atypia (ADH) versus 10% without atypia (ADH) (28). Similar findings were made by Groen and colleagues on a large patient cohort, which indicated that RS without atypia (ADH) had an upgrade rate of 9%, whereas RS with atypia had an upgrade rate of 33% (81). The Swiss Minimally Invasive Breast Biopsy group (MIBB) database showed a relatively low RS upgrade rate (8%) in successive surgical excision specimens, primarily with DCIS (2).

Management

The correlation between histology and radiology remains the key element in the final management decision. CNB diagnosis alone seems to underestimate the cancer risk, because of a relatively high probability of association with ADH.

The AGO recommends no operative excision if the lesion is smaller than 5 mm or if the lesion is nearly completely excised by VAB. If the lesion is at the resection margin, then no further re-excision is needed (63).

The 3rd International Consensus Conference stated that after the identification of RS without atypia on CNB, in correlation with the imaging size, 58% of the panel supported therapeutic VAE. If the target lesion was entirely removed, the majority of the panel (82%) favored radiological follow-up after diagnostic VAB or VAE (27).

The NHSBSP recommends thorough sampling with VAE (> 4 g of tissue) and, depending on the results, RS/CSL without atypia, no additional surveillance is required and patients go back to routine 3 yearly mammographic follow-up (routine mammographic screening). For RS/CSL with atypia, either open excision or yearly mammographic follow-up should be offered, depending on the multidisciplinary team decision (28)

Recommendations

1. RS without atypia (without ADH) diagnosed by CNB is best managed by VAE. (evidence/grade III/B)
2. RS with atypia (with ADH) increases the risk of upgrading to BC. In those cases, if diagnosed by VAB, surgical excision is recommended but VAE could be considered. (evidence/grade II/B)

5. PAPILLARY LESIONS

Radiology

Mammography may be normal or can show dilated ducts, a well-defined retroareolar mass or clustered calcifications in 25% of cases. The calcifications are often pleomorphic in character. The presence of suspicious microcalcifications makes malignancy more likely. Solitary lesions are often in the retroareolar area or centrally but can be anywhere within the breast (82). Multiple lesions are typically found in the periphery.

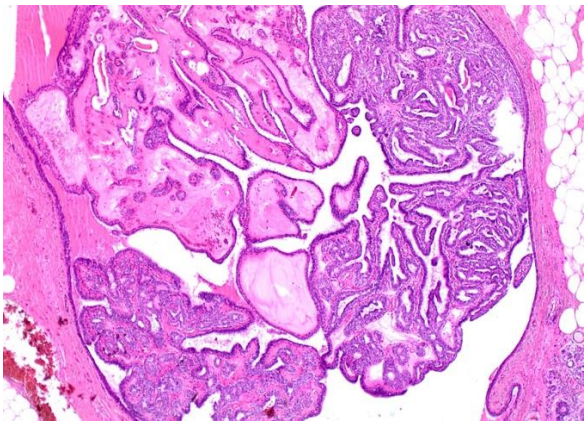
Ultrasound usually shows a well-defined nodule with or without cystic components or a small mass within a dilated duct. Color Doppler may demonstrate internal vascularization or a typical a vascular stalk (83).

On MRI, papillary lesions may appear as circumscribed enhancing masses or irregular masses associated with dilated ducts. Multiple lesions can be present. It is difficult to distinguish benign lesions from those with atypia or malignancy (84)

Pathology

An intraductal papilloma (IDP) is a benign lesion of papillary architecture comprising fibrovascular cores covered by benign luminal epithelium with associated myoepithelium. The lesion can be associated with hyperplasia, apocrine metaplasia, squamous metaplasia (85), infarction or fibrosis with distortion. The lesion can be heterogeneous and superimposed ADH can be seen. DCIS in a papilloma is diagnosed when non-high-grade ADH measures 3 mm or more (86). Therefore, assessment of the extent of the ADH, where present, is critical to differentiate between a papilloma with ADH and DCIS in a papilloma. Features supportive of ADH within a papilloma include abnormal architecture (e.g. solid, cribriform), lack of a myoepithelial layer within the fibrovascular cores and demonstration of a monomorphous cell population by basal cytokeratin immunohistochemistry (Fig. 10). Multiple peripheral papillomas are more likely to be associated with ADH and/or DCIS compared with solitary intraduct papillomas (87).

Fig.10. Photomicrograph showing a papilloma (H and E staining, magnification X50. A large dilated ducta shows a benign intraduct papilloma comprising well defined fibrovascular cores covered by benign bilayer epithelium



The combination of basal cytokeratins (CK5, CK14), myoepithelial (SMM) and ER immunohistochemistry can help distinguish benign papillomas from those with ADH and /or papillary DCIS. Lobular neoplasia cells can also colonise papillomas and these can be highlighted by their dis-cohesive nature and negative E-cadherin immunohistochemistry.

Upgrade rate to malignancy

The presence of ADH is the strongest predictor of upgrade of IDP to in situ or invasive carcinoma, with upgrade to malignancy seen in less than 10% for papillomas without atypia or ADH and increasing to 27-36% for lesions with ADH (88-90).The risk is local, within the region of the original papilloma (91). All papillomas, with or without ADH, are categorized as B3 lesions. The presence or absence of ADH, however, should be stated as the former is associated with a higher upgrade rate and is managed differently.

In a recent meta-analysis by Zhang and colleagues (92), among the 44 relevant studies, 14 reported the prevalence of papillomas (including non-atypical and atypical papillomas) ranging from 1.8 to 9.3%, and the pooled estimate of the prevalence of IDP was 4.6% (95% CI 4.4–4.7%). The majority of IDP cases diagnosed at biopsy were without ADH, and the proportion of atypical IDPs in VAB-based studies was significantly higher than in CNB-based studies (19.6 vs. 12.8%, $p < 0.001$). They identified 10 predictive factors for upgrade, including assigned BI-RADS 4C or 5 category, mass or calcifications on mammography, bloody nipple discharge, radio-pathological discordance, peripheral location, palpable mass, assigned BI-RADS 4B category, microcalcifications, and lesion size of over 1 cm. The upgrade rates associated with these predictive factors ranged from 7.3 to 31.1%. The upgrade rate of IDP diagnosed by VAB was significantly lower than that of IDP diagnosed by CNB. Other authors have identified bloody nipple discharge, size on imaging ≥15 mm, BI-RADS ≥ 4B, peripheral location, and lesion palpability as independent predictors of malignancy at follow-up surgical excision in benign papilloma without atypia. The area under the receiver operating characteristic (ROC) curve was 0.947 (95% CI: 0.913–0.981, $p < 0.001$) and the negative predictive value of the absence of these predictors was 100%.(93)

Management

In the presence of pathological nipple discharge (unilateral, uniductal or bloody) and/or a lesion on mammography or ultrasound with papillary features (solid-cystic mass, small mass within a dilated duct), VAB is the procedure of choice. When a CNB yields an IDP with no atypia or ADH, VAB is an acceptable strategy. The majority of retrospective studies have shown that using VAB, the accuracy of diagnosis was improved, and women could be offered imaging surveillance after VAB resulting into benign pathology (94, 95).
If a CNB or a VAB yields a papilloma with ADH, surgical excision is indicated (83) although the low risk of upgrade may pave the way to avoid surgical excision in some cases after MDT consultation. This is to examine the lesion intact and assess the extent of the ADH in continuity using the 3-mm cutoff value to diagnose DCIS. (83)
Large papillary lesions without atypia or lesions where VAB is not technically feasible should be surgically excised.
The 2019 consensus on lesions of uncertain malignant potential concluded that imaging surveillance is sufficient for IDP fully removed by VAB. For larger lesions, surgical excision is recommended followed by continued surveillance (2) As multiple papillomas have a three-fold increased risk of invasive cancer and a seven-fold risk if ADH or LN is present, long term imaging surveillance is recommended (27)

Recommendations
1. IDP without concomitant ADH can be managed safely with VAB and, if fully excised, imaging surveillance is sufficient. (evidence/grade II/B)
2. In IDP with concomitant ADH, surgical excision is recommended. (evidence/grade II/B)

6. MISCELLANEOUS

Miscellaneous lesions contain rare entities, also classified as B3 lesions, which encompass a broad spectrum of lesions (such as atypical apocrine adenosis, mucocele-like lesions as well as several stromal spindle and myofibroblastic proliferations), which all need to be discussed at the preoperative board as often individual management strategies will be necessary.

Apocrine adenosis
An atypical apocrine adenosis represents a glandular proliferation often with the full spectrum of apocrine features resembling a low-grade apocrine DCIS (implying a B5a category); the distinction between the two entities is often problematic and can be definitely determined only by assessing the surgical specimen (16) Immunohistochemistry is not helpful in most cases, as ER and basal cytokeratins are negative and androgen receptors are positive both in adenosis and in low to intermediate grade apocrine DCIS. However, a 3+ score in HER2 expression is strong evidence for high-grade apocrine DCIS. (16) Atypical apocrine adenosis usually behaves differently from high-grade DCIS, however its exact relationship to low-intermediate DCIS is unclear and underestimation of the rate of upgrade is common (16). urrent literature suggest that an open excision is necessary to determine the real biological nature of this lesion (16) The upgrade rate of those rare lesions have been reported to range from 16.7-25% . (96)

Mucocele-like lesions

A mucocele-like lesion is defined as free mucus pools within the stroma of the breast tissue, devoid of any epithelial structures inside the pools, often in the vicinity of ruptured ducts (16). The main differential diagnosis is a mucinous carcinoma, which needs to be excluded morphologically and immunhistochemically (16). Cytokeratins are useful to exclude carcinomatous cells. Without epithelial cells within the mucus pools, the upgrade rate is very low (<2%) (16, 97). If imaging and pathology findings are concordant, and a mucinous carcinoma has been excluded with immunhistochemistry, both an open excision or a therapeutic VAB can be avoided (98).

Fibroepithelial lesions (FEL)

Fibroepithelial lesions are composed of both epithelial and stromal components, comprising the common fibroadenoma and the less frequently occurring phyllodes tumour (PT). It can be difficult to distinguish fibroadenomas from PT on CNB due to overlapping histological features, even when strict histopathological criteria are applied. (28) Some guidelines recommend excision of FEL over 3 cm in size, to rule out PT, while others do not support that recommendation. There seems to be an emerging consensus that the growth rate of FA may be a more useful criterion for excision. Although further sampling such as larger gauge CNB or VAB could be considered to try to differentiate PT from fibroadenomas, excision is appropriate for lesions where PT cannot be excluded regardless of size due to the high chance of diagnosing PT. (99)

Table 2. Summary of rates of upgrade to malignancy of commonest B3 lesions

B3 lesion	Total upgrade to malignancy	Upgrade to DCIS	Upgrade to Invasive
Atypical ductal hyperplasia (ADH) (17-19)	0-50% (22%)	20%	5%
Atypical lobular hyperplasia (ALH) (42)	12%	9%	2%
Classical lobular neoplasia (cLCIS) (41,42)	22%	15%	7%
Flat epithelial atypia (FEA) (60,61)	0-5%	1%	2%
Radial scar/Complex sclerosing lesions (RS/CSL) (77,78)	1-10%	1-5%	1%
Intraductal papilloma (IDP) (87,89)	< 10%	5%	2%

THE ROLE OF PRIMARY PREVENTION IN B3 LESIONS

Primary prevention of BC is the use of medical or radiation therapy to reduce the risk of invasive BC in women who have never been diagnosed with the disease. The term primary prevention is preferable to chemoprevention, as the latter may be confused with chemotherapy/systemic therapy and deter uptake. This concept has been around for many decades, based on historic observations that women on adjuvant tamoxifen have a much-reduced risk of developing a second primary (100). The majority of the data available relates to women at increased risk due

to their family history but there are a small number of studies that include subgroups of women diagnosed with B3 lesions.

The majority of primary prevention strategies are only effective against ER-positive cancers. They work by either reducing estrogen levels and hence estrogenic stimulation to breast tissue (oophorectomy, aromatase inhibitors) or by antagonizing the ER by use of drugs such as selective ER modulators (SERMs) such as tamoxifen and raloxifene. A large SEER database study conducted before and after the advent of primary prevention demonstrated that women with atypia and LCIS reduced their 10-year BC risk from 21% to 7.5%.(101) There are experimental primary prevention strategies that may be effective against non-estrogen sensitive cancers but none are in routine use and none have been evaluated specifically in the context of B3 lesions, for example, drugs like metformin, retinoids and NSAIDs. (102)

The majority of B3 lesions, such as ADH and FEA, express the ER (103, 104) and are therefore sensitive to these antiestrogenic strategies.

Selective ER Modulator (SERM) studies

Tamoxifen

There have been 4 major randomized trials to assess primary prevention with tamoxifen. (105-108). These are summarized in Table 3.

The first trial started in 1986, and recruited women with elevated BC risk due to their family history, but very few with atypia or LCIS (0.3%) were included and therefore this study is not helpful to the management of B3 lesions. (105, 109) The NSABP P1 RCT (106, 110) The NSABP P1 RCT recruited over 13 000 (randomized to 6599 in the placebo arm and 6576 in the tamoxifen arm) women at elevated risk based on the Gail criteria or age over 60 and found that 5 years of tamoxifen reduced breast cancer risk by 49%. Of more interest is that the trial contained a small cohort of women with high-risk lesions (~15%). The study found a lower rate of breast cancer in those with LCIS (18/411 in the placebo versus 8/415 in the tamoxifen arm), representing a 56% reduction (RR: 0.44, 95%CI 0.16-1.06) although this was not statistically significant. In those with atypical hyperplasia risk reduction was greater at 86% (23/614 in the placebo arm versus 3/ 579 in the Tamoxifen arm, RR: 0.14, 95% CI 0.03-0.47) which was statistically significant. Based on the data in this trial, tamoxifen prophylaxis was approved by the US FDA in 1998 for high-risk women The IBIS-I RCT also recruited high-risk women and randomized them to 5 years of tamoxifen versus placebo. It showed a reduction in the risk of BC for all women. (108) The cohort contained 4% of women with atypia or LCIS but no subgroup analysis was presented, so it is not possible to determine whether there was any differential efficacy for these women.

More recently, a smaller RCT randomized women with either DCIS, LCIS or atypical hyperplasia to either low-dose tamoxifen for 3 years (5 mg as opposed to the standard dose of 20 mg used in the above trials) or placebo. For the group overall they found a reduced risk of invasive cancer (RR: 0.48, 95%CI 0.26-0.92) and an even more pronounced impact on the rate of contralateral events (RR: 0.25, 95%CI: 0.07-0.88). Rates of toxicity were lower than reported in the full-dose trials with a similar efficacy.(111)

There have also been non-randomized studies that have confirmed efficacy. A large US multi-institutional study of 2459 women between 1999 and 2010 who either did (466) or did not (1472) receive chemoprevention (largely tamoxifen) and who all had either AH, LCIS or high risk ADH also found a significant reduction in the 10 - year risk of invasive cancer when all lesion types were analyzed together ($P < 0.001$). No subgroup analysis by type of lesion was reported and would probably have been individually non-significant due to smaller numbers.

In summary, Tamoxifen at both 20-mg and 5-mg doses is effective at risk reduction in high-risk women. All studies that have included women with B3 lesions have shown similar levels of efficacy, although smaller numbers of this subgroup of high-risk women have prevented the RCTs from finding statistical significance. In a non-randomized study, a statistically significant difference was shown (although this study did include women with DCIS). (101) It is therefore likely that tamoxifen is effective in women with B3 lesions.

Raloxifene

Studies comparing raloxifene with placebo are not available for high-risk women. The trials that did evaluate this drug recruited women for osteoporosis risk or cardiac risk (112) and all found that BC risk was reduced by approximately one third. The STAR RCT compared tamoxifen and raloxifene in high-risk women, including approximately one third of the population with either LCIS or AH, and found that both drugs were equally effective at preventing invasive disease but tamoxifen had a slight, non-significant, advantage for preventing DCIS. (113) The side effect profile of raloxifene was better than tamoxifen, in particular with a lower rate of uterine cancers and thromboembolic side effects.

Aromatase Inhibitors

In postmenopausal women there have also been two large, randomized trials of aromatase inhibitors for primary prevention, both of which included over 8% of their population with AH or LCIS as a risk factor for cancer. The IBIS II trial (114) used 5 years of anastrozole compared to placebo and the MAP.3 trial (115) which used exemestane. Both populations were very similar, and both showed significant efficacy in reducing the risk of both DCIS and invasive cancers not just in the population overall, but also on subgroup analysis of the populations with atypia and LCIS.

In all of the above studies, both those using tamoxifen and aromatase inhibitors, the drugs only prevent ER-positive BC and even with long-term follow up, no survival benefit has been seen. This suggests that anti-oestrogen therapy is selectively preventing development of good prognosis cancers which would have minimal impact on mortality rather than that follow-up duration has not yet been long enough to see a survival impact. This is reinforced by the very long follow-up available for most of these trials now.

The data from the above studies are summarised in Table 2.

Uptake and compliance

One of the main limitations of these therapies is poor uptake and compliance. In the IBIS II trial compliance was about 75%.(114) However, in the real-world rates of uptake and compliance

are low. (116) Uptake rates are only 4% in high-risk women when offered primary prevention. (117) Therefore, despite good quality data suggesting these are highly effective in reducing BC risk in women with atypias and LCIS, few women benefit from this. Patient education, dedicated clinics and decision aids may help. For women taking tamoxifen, who tolerate it poorly, there is evidence that use of a lower dose may have similar efficacy when compared in a group of women with either AH, LCIS or DCIS (5 mg compared to 20 mg). (111) The side effect profile of the lower dose was lower and the rate of compliance was increased. (118, 119) Use of anastrozole may also be offered to postmenopausal women as this does not increase risks of endometrial cancer, thromboembolic disease and has a slightly better rate of hot flushes. Hot flushes may be actively managed, and bone density loss may be monitored and fully abrogated by use of bisphosphonates.

Clearly the above issues are complex and require expertise on the part of the health professional to explain the complex pros and cons of primary prevention and to select and manage therapy and any side effects.

Current guidelines

Current USA guidelines, (120) UK NICE guidelines (121) and ESMO guidelines (122) recommend that women at increased BC risk should be offered the option of primary medical prevention therapy, although often in the context of increased familial risk rather than due to the presence of atypias where the evidence base is less strong due to smaller numbers in trials. Women with LCIS and atypical lesions be protected from developing invasive BC by use of SERMs such as tamoxifen and raloxifene, and aromatase inhibitors. The risk of BC development is roughly halved after 5 years of treatment and side effects are generally mild and can be managed. Most of the evidence is inferred from studies that have recruited high familial risk women with women with B3 lesions forming smaller cohorts in these studies. Consequently, statistical significance is lacking in the SERM studies but is present in the AI trials. In light of these data women with AH or LCIS should be offered primary prevention. The evidence base relating to other B3 lesions is lacking at present but it is biologically plausible that the protective effects will also apply to these lesions and they should be considered, taking into account the relative cancer risk of each lesion.

Table 3. Table summarizing trials that have evaluated primary prevention of BC

Trial name	Reported follow up	Patient population	Total sample size on active therapy	Total sample size on placebo	% LCIS or ADH	Relative risk reduction (95% CI)	Risk reduction in atypia patients
SERMS							
Royal Marsden (104)	20 years	High familial risk	1238 on tamoxifen	1233 on placebo	0.3%	0.78 (0.58-1.04)	Not reported
NSABP Prevention 1 (109)	7 years	High risk (age over 60 or family history or atypia	6576 on tamoxifen	6599 on placebo	16%	0.57, (0.46 to 0.70) for invasive disease	LCIS: 0.44(0.16-1.06) AH: 0.14(0.03-0.47)
IBIS I(107)	96 months	High risk family history, AH or LCIS	3579 on tamoxifen	3575 on placebo	4%	0.73, (0.58 to 0.91) for invasive and DCIS	Not reported separately
STAR Trial(112)	72 months	High risk family history, AH and LCIS	9726 on tamoxifen	9745 on raloxifene	9% with LCIS and 22-23% with AH	1.02, (0.82-1.28) Not significant for invasive disease. Trend in favour of Tamoxifen for DCIS prevention	LCIS 0.98 (0.58-1.63) AH 1.12 (0.72-1.74)
Low dose tamoxifen trial(110)	61 months	Women with DCIS, LCIS and AH	253 on 5mg tamoxifen	247 on placebo	20% AH 10-11% LCIS	0.48 (0.26-0.92) for invasive disease	AH 0.50 (0.05-5.47) LCIS 0.31 (0.06-1.51)

					(90% of cases ER+)		
Aromatase inhibitors							
IBIS II (113)	131 months	High risk family history, AH or LCIS	1920 (anastrozole)	1944	8% AH plus LCIS in anastrozole group, 10% in placebo group	0.51 (0.39-0.66) for invasive and DCIS	AH plus LCIS: 0.31(0.12-0.84)
MAP 3 (114)	35 months	High risk family history, AH or LCIS	2285 (exemestane)	2275	8.1% AH plus LCIS in anastrozole group, 8.3% in placebo group	0.47 (0.27-0.79) for invasive and DCIS	AH plus LCIS: 0.26(0.11-0.64)

Recommendations

1. Women at increased BC risk should be offered the option of primary medical prevention therapy. (evidence/grade I/A)
2. Before deciding on primary prevention, a detailed medical history should be taken, including familial and other risk factors for cancer (using online models such as Gail CanRISK or IBIS II) and any medical conditions. (evidence/grade I/A)
3. Women with B3 lesions conferring a significantly increased risk of BC should all be counselled by a clinician with expertise in risk management strategies (evidence/grade III/B)
4. Premenopausal women may be offered 5 mg oral tamoxifen as primary prevention for up to 5 years if they have no risk factors for thromboembolic disease or endometrial cancer. (evidence/grade I/A)
5. Postmenopausal women may be offered 5 years of treatment with either anastrozole or exemestane with appropriate bone density monitoring. (evidence/grade I/A)

Lifestyle interventions for patients at increased risk of BC

Lifestyle interventions (e.g. smoking cessation, reducing alcohol consumption, increasing physical activity, weight reduction) not only have a positive effect on a patient's psychological well-being (123, 124), but also have a significant impact on BC incidence and treatment outcomes. Danaei and colleagues demonstrated that 21% of BC related deaths are caused by the detrimental effects of alcohol consumption, obesity and

lack of physical activity (125). For this reason, lifestyle intervention(s) should be suggested to women at increased BC risk as a result of a diagnosis of a B3 lesion, although specific evidence in this population is lacking.

Smoking

Smoking affects a patient's endocrine system; in particular androgens are affected by nicotine which triggers an increase in production of adrenal androgens via adrenocorticotropic hormones (e.g. ACTH) (126). In addition, smoking slows aromatase activity thereby preventing the conversion from androgens to oestrogens (126-129). In 2005, a large cohort study of 65,000 postmenopausal women in Sweden demonstrated that active smoking was associated with high serum levels of testosterone (odds ratio 1.85; 95% CI 1.06-3.23) and that for every 10 cigarettes a day the risk of BC was increased by 1.55 (130). Elevated serum levels of androgens have been positively associated with the risk of primary BC in both pre- and postmenopausal women (129, 131, 132). The metabolites of carcinogenic substances from tobacco smoke cause an increased risk of developing BC as the mammary tissue stores these lipogenic substances (133). The link between smoking and BC is therefore biologically plausible. From an epidemiologic point of view, the increased risk of developing primary BC by smoking has been demonstrated in many studies, (133-136). A publication in 2014, studied a cohort of nearly 186,000 women of whom 7500 developed BC (mean follow-up of 9.6 years) (137). In this cohort, it was concluded that active- and former smokers had an increased risk of developing BC with a risk of HR 1.19 (95% CI 1.10-1.28) and 1.07 (95% CI 1.01-1.13) respectively (137). All the above meta-analyses and large cohort studies show a strikingly consistent increase in risk of approximately 1.1 to 1.2 for developing invasive BC for both active and former smoking. It can be concluded that, in addition to the previously described biological explanation, this association has also been demonstrated epidemiologically.

Obesity

Obesity is associated with an increased risk of BC caused by a number of local and systemic factors including an increase in circulating insulin, glucose and oestrogens from fat cells (adipocytes), as well as adipokines and a range of inflammatory mediators (138). The risk varies according to menopausal status and tumour biology. In premenopausal women, there is an increased risk of developing ER-negative and triple-negative BC. In triple-negative BC, two meta-analyses show an increased risk of up to 80% (139). Conversely, it protects against ER-positive BC in premenopausal women (140, 141).

In postmenopausal women, obesity increase the risk of ER-positive BC by up to 30% (142) but not ER-negative BC (142). After BC diagnosis, independent of menopausal status and hormonal receptor status, obesity is an independent risk factor for BC-specific and all-cause mortality, due to the increased risk of recurrence and decreased overall health (143). Therefore, women with B3 lesions who are overweight or obese should be advised to lose weight.

Physical activity

Several meta-analyses have been conducted to explore the link between physical activity and BC risk. A meta-analysis of various risk factors for BC, including exercise (144) found an RR of 0.90 (95% CI 0.86-0.95) for developing BC for women taking at least 30 minutes of moderate-to-vigorous physical activity per day or 150 minutes per week compared to those not taking exercise. Another meta-analysis of prospective studies specifically on physical activity and BC (145) and a more recent study (146) did distinguish between the type, amount and timing of physical activity and BC subtypes. These studies reported an RR of 0.88 (95% CI 0.85-0.91) (145) and 0.87 (95% CI 0.84-0.90) (146) for adequate physical activity on the risk of developing invasive BC. Wu and colleagues described a lower RR in case of physical activity in premenopausal women (RR 0.77, 95% CI 0.72-0.84), women with a BMI < 25 kg/m^2 (RR 0.72, 95% CI 0.65-0.81) and on the risk of ER/PR-negative tumours (RR 0.80, 95% CI 0.73-0.87) (145). Physical activity during all life stages (≤25 years, 26-50 years and >50 years) was associated with a reduced risk of BC (145).

In summary, meta-analyses of prospective observational studies show that adequate physical activity (by most definitions 30 min per day or 150 min per week of moderate-to-vigorous exercise) is associated with a lower risk of BC, with an RR of approximately 0.88. There is a dose-effect relationship: an increase in intensity, length (per week) and duration (in years) of exercise leads to a further reduction in the risk of BC. This probably accounts for all age groups, in obese and non-obese people, in pre- and postmenopausal status, and for both ER/PR-positive and negative BC. A causal relationship (i.e., exercise independent of other (lifestyle) factors) remains difficult to prove.

Therefore, women with a recent B3 diagnosis should be encouraged to increase their exercise levels.

Alcohol consumption

Alcohol consumption increases the risk of BC (147-152) in both pre- and postmenopausal women with the strongest evidence for postmenopausal BC (153). It is not clear whether there is any differential impact for different tumour biological subtypes with conflicting findings (154-157). The more alcohol a person consumes during their lifetime, the higher the risk of BC (150). When drinking one unit per day, the lifetime risk is increased by 7 to 10% (152). However, in patients with BRCA1 or BRCA2 gene mutations, there is no additional increased risk of BC from alcohol consumption (158).

Again, there are no data specific to women with B3 lesions but the evidence would suggest that reducing alcohol consumption is likely to be beneficial.

Recommendations

1. Smoking, obesity, a sedentary lifestyle and alcohol consumption are all associated with an increased risk of BC development in women. (II/B)
2. There is no evidence specific to women with B3 lesions nor is there ever likely to be, however the evidence available suggests there is likely to be some benefit in lifestyle modification for these women. (IV/C)

2. Education of patients about the increased risk of BC due to these factors should be given at the time of a B3 diagnosis and the risks explained in lay language.

COMMUNICATION

Patients diagnosed with B3 lesions face two types of risk, the risk of immediate upgrade to BC diagnosis and the long-term risk of developing a BC. B3 lesions include a highly heterogeneous group of lesions associated to different risk levels and uncertainties. Thus, communication with patient may be different according to histological diagnosis, presence or absence of atypia or imminent risk of upgrade due to discordant imaging.

Communication can be verbal during patients' consultation, but it is advisable to design specific decision aids for B3 lesions. Several models of risk communication are available, the International Patient Decision Aid Standards (IPDAS) Collaboration aims to enhance the quality and effectiveness of patient decision aids (PtDAs) by establishing a shared, evidence-informed framework to guide developers and researchers in their development, content, evaluation, and implementation. (159)

Quantitative information using numerical factors (versus verbal terms only) has been demonstrated to increase trust and transparency in outcomes communication. Numerical information is a current quality indicator for decision aids. However, interpretation of statistics can be difficult especially in fields of large uncertainty as in the case of B3 lesions. Including labels, symbols or colours in decision aids contributes to risk understanding.

It may be helpful to assess patients' numeracy beforehand, acknowledging that data available about risk are often reported in different formats (relative, absolute, hazard ratio).

For example:

- Present the chance an event will occur (immediate or long-term upgrade) using percentages or, better, natural frequencies in a specific time-frame (e.g., 15 out of 100 who had a diagnosis of lobular neoplasia, 15 women will develop BC in the same breast within 15 years)
- use consistent denominators identifying the population to whom the risk applies (e.g., ADH is diagnosed in 3.3 out of 10,000 screening mammograms).

It is also important to know how to communicate results derived from predictive risk models. Consider providing comparative risks or reference standards. Select accurately choice comparators to prevent bias or influence beliefs (e.g., upgrade rates using VAB vs. CNB, observation vs. excision and risk of long-term malignancy). In this regard, using validated predictive models for personalized risk estimates, which include the patients' previous history of breast biopsies positive for B3 (such as the Gail Model or the Tyrer Cuzick model) can be helpful. These tools can also be useful to understand risk in different time frames.

How to deal with uncertainty when communicating with patients

Uncertainty dominates the discussion of B3 lesions, especially following ~~a~~ tissue sampling (with a certain degree of invasiveness) allowing histopathological analysis, which does NOT result in a final diagnosis. The long name of these entities – lesions with "uncertain malignant potential" – may explain the dilemma.

In addition, evidence is of low level and poor quality. It is rather difficult to extrapolate consistent information (e.g., upgrade rates to carcinoma for ADH found on CNB have been reported to vary from 10 to 50%). Patients often struggle to understand uncertainty regarding future events and this may increase stress.

In this context, it is important to recognize limitations of our current biological and medical knowledge but also to put the data into perspective by reassuring that life-threatening risk is minimal and that a key issue is to avoid unnecessarily aggressive treatment. For example, a SEER Database study relating to LCIS found the 1-, 5- and 10-year estimated overall survival rates were 99.7%, 96.7% and 91.7%, respectively. ((160)

Ideally Breast Centers should develop their own written information resources to help patients understand these issues using native language and terminology. These should be used alongside verbal communication. These may be adapted from existing resources: (https://breastcancernow.org/sites/default/files/publications/pdf/bcc78_hyperplasia_dl_2018_web.pdf; https://breastcancernow.org/information-support/publication/lobular-neoplasia-bcc126)

These recommendations do not have any level of evidence as there is not enough data and it is more a strategy needed in patient centered cancer care.

Recommendations

1. The explanation about the impact of B3 lesions on actual and future BC risk, the uncertainty and the range of management options is complex and often involves dealing with uncertainty.
2. Time, patience and expertise in risk communication and general communication skills are required and more than one visit may be needed.
3. The time frame should be tailored to patient characteristics taking into account patient literacy, numeracy and preferences.
4. The patient should be referred to accurate reliable information hubs and additional sources of information (such as printed leaflets, websites, when available).
5. Clinicians should allow for a follow-up meeting in the short term, to respond to any questions raised by patient after they have had time to consider initial information.
6. The aim should be a shared decision-making process tailored to the patient's needs and wishes.
7. Patients should be encouraged to bring a friend or relative to these consultations to provide support.

CONCLUSION

Diagnosis and management of B3 lesions have changed due to improvements in radiological imaging and more adequate image-guided sampling. Further evaluation and potential interventions based on each lesion are better managed by a multidisciplinary team that will ensure a comprehensive evaluation and individualized care depending on the patient´s risks, wishes, and characteristics of the lesion. Adequate communication with the patient is necessary for shared decision-making as an essential aspect of managing B3 lesions

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References

1. Rakha EA, Lee AH, Jenkins JA, Murphy AE, Hamilton LJ, Ellis IO. 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(6):1417-24.
2. Rageth CJ, O'Flynn EAM, Pinker K, Kubik-Huch RA, Mundinger A, Decker T, et al. Second International Consensus Conference on lesions of uncertain malignant potential in the breast (B3 lesions). Breast Cancer Res Treat. 2019;174(2):279-96.
3. Bianchi S, Caini S, Renne G, Cassano E, Ambrogetti D, Cattani MG, et al. Positive predictive value for malignancy on surgical excision of breast lesions of uncertain malignant potential (B3) diagnosed by stereotactic vacuum-assisted needle core biopsy (VANCB): a large multi-institutional study in Italy. Breast. 2011;20(3):264-70.
4. Cullinane C, Byrne J, Kelly L, M OS, Antony Corrigan M, Paul Redmond H. The positive predictive value of vacuum assisted biopsy (VAB) in predicting final histological diagnosis for breast lesions of uncertain malignancy (B3 lesions): A systematic review & meta-analysis. Eur J Surg Oncol. 2022;48(7):1464-74.
5. McMahon MA, Haigh I, Chen Y, Millican-Slater RA, Sharma N. Role of vacuum assisted excision in minimising overtreatment of ductal atypias. Eur J Radiol. 2020;131:109258.
6. Catanzariti F, Avendano D, Cicero G, Garza-Montemayor M, Sofia C, Rullo EV, et al. High-risk lesions of the breast: concurrent diagnostic tools and management recommendations. Insights Imaging. 2021;12(1).
7. Gail MH, Brinton LA, Byar DP, Corle DK, Green SB, Schairer C, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. J Natl Cancer Inst. 1989;81(24):1879-86.
8. Tyrer J, Duffy SW, Cuzick J. A breast cancer prediction model incorporating familial and personal risk factors. Stat Med. 2004;23(7):1111-30.
9. Hartmann LC, Degnim AC, Santen RJ, Dupont WD, Ghosh K. Atypical hyperplasia of the breast--risk assessment and management options. N Engl J Med. 2015;372(1):78-89.
10. Brouwers MC, Kerkvliet K, Spithoff K. The AGREE Reporting Checklist: a tool to improve reporting of clinical practice guidelines. Bmj. 2016;352:i1152.

11. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383-94.
12. Liberman L, Holland AE, Marjan D, Murray MP, Bartella L, Morris EA, et al. Underestimation of atypical ductal hyperplasia at MRI-guided 9-gauge vacuum-assisted breast biopsy. AJR Am J Roentgenol. 2007;188(3):684-90.
13. Berg WA, Zhang Z, Lehrer D, Jong RA, Pisano ED, Barr RG, et al. Detection of breast cancer with addition of annual screening ultrasound or a single screening MRI to mammography in women with elevated breast cancer risk. Jama. 2012;307(13):1394-404.
14. Cozzi A, Schiaffino S, Fanizza M, Magni V, Menicagli L, Monaco CG, et al. Contrast-enhanced mammography for the assessment of screening recalls: a two-centre study. Eur Radiol. 2022;32(11):7388-99.
15. Rageth CJ, O'Flynn EAM, Pinker K, Kubik-Huch RA, Mundinger A, Decker T, et al. Second International Consensus Conference on lesions of uncertain malignant potential in the breast (B3 lesions). Breast Cancer Res Tr. 2019;174(2):279-96.
16. WHO. Breast Tumours WHO Classification of Tumours, 5th Edition2019.
17. WHO Classification of Tumours, WHO. Breast Tumours 5th Edition ed: International Agency for Research of Cancer; 2019.
18. Royal College of Pathologists, Guidelines for non-operative diagnostic procedures and reporting in breast cancer screening [Internet]. 2021. Available from: https://www.rcpath.org/uploads/assets/4b16f19c-f7bd-456c-b212f557f8040f66/G150-Non-op-reporting-breast-cancer-screening.pdf.
19. Rageth CJ, Rubenov R, Bronz C, Dietrich D, Tausch C, Rodewald AK, et al. Atypical ductal hyperplasia and the risk of underestimation: tissue sampling method, multifocality, and associated calcification significantly influence the diagnostic upgrade rate based on subsequent surgical specimens. Breast Cancer. 2019;26(4):452-8.
20. Nicosia L, Latronico A, Addante F, De Santis R, Bozzini AC, Montesano M, et al. Atypical Ductal Hyperplasia after Vacuum-Assisted Breast Biopsy: Can We Reduce the Upgrade to Breast Cancer to an Acceptable Rate? Diagnostics (Basel). 2021;11(6).
21. Uzan C, Mazouni C, Rossoni C, De Korvin B, de Lara CT, Cohen M, et al. Prospective Multicenter Study Validate a Prediction Model for Surgery Uptake Among Women with Atypical Breast Lesions. Ann Surg Oncol. 2021;28(4):2138-45.
22. Kilgore LJ, Yi M, Bevers T, Coyne R, Lazzaro M, Lane D, et al. Risk of Breast Cancer in Selected Women with Atypical Ductal Hyperplasia Who do not Undergo Surgical Excision. Ann Surg. 2021.
23. Harrington L, diFlorio-Alexander R, Trinh K, MacKenzie T, Suriawinata A, Hassanpour S. Prediction of Atypical Ductal Hyperplasia Upgrades Through a Machine Learning Approach to Reduce Unnecessary Surgical Excisions. JCO Clin Cancer Inform. 2018;2:1-11.
24. Schiaffino S, Calabrese M, Melani EF, Trimboli RM, Cozzi A, Carbonaro LA, et al. Upgrade Rate of Percutaneously Diagnosed Pure Atypical Ductal Hyperplasia: Systematic Review and Meta-Analysis of 6458 Lesions. Radiology. 2020;294(1):76-86.
25. Ditsch N, Wocke A, Untch M, Jackisch C, Albert US, Banys-Paluchowski M, et al. AGO Recommendations for the Diagnosis and Treatment of Patients with Early Breast Cancer: Update 2022. Breast Care (Basel). 2022;17(4):403-20.
26. Ahmed M, Rubio IT, Klaase JM, Douek M. Surgical treatment of nonpalpable primary invasive and in situ breast cancer. Nature Reviews Clinical Oncology. 2015;12(11):645-63.
27. Elfgen C, Leo C, Kubik-Huch RA, Muenst S, Schmidt N, Quinn C, et al. Third International Consensus Conference on lesions of uncertain malignant potential in the breast (B3 lesions). Virchows Arch. 2023;483(1):5-20.

28. Pinder SE, Shaaban A, Deb R, Desai A, Gandhi A, Lee AHS, et al. NHS Breast Screening multidisciplinary working group guidelines for the diagnosis and management of breast lesions of uncertain malignant potential on core biopsy (B3 lesions). Clin Radiol. 2018;73(8):682-92.
29. Ahmed M, Rubio IT, Klaase JM, Douek M. Surgical treatment of nonpalpable primary invasive and in situ breast cancer. Nat Rev Clin Oncol. 2015;12(11):645-63.
30. NCCN. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology. Breast Cancer.2023 [Available from: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1419.
31. King TA, Pilewskie M, Muhsen S, Patil S, Mautner SK, Park A, et al. Lobular Carcinoma in Situ: A 29-Year Longitudinal Experience Evaluating Clinicopathologic Features and Breast Cancer Risk. J Clin Oncol. 2015;33(33):3945-52.
32. Carder P, Shaaban A. Pleomorphic lobular carcinoma in situ
Diagnostic Histopathology
2012;18(3):119-23.
33. Masannat YA, Husain E, Roylance R, Heys SD, Carder PJ, Ali H, et al. Pleomorphic LCIS what do we know? A UK multicenter audit of pleomorphic lobular carcinoma in situ. Breast. 2018;38:120-4.
34. Zhong E, Solomon JP, Cheng E, Baum J, Song W, Hoda SA. Apocrine Variant of Pleomorphic Lobular Carcinoma In Situ: Further Clinical, Histopathologic, Immunohistochemical, and Molecular Characterization of an Emerging Entity. The American journal of surgical pathology. 2020;44(8):1092-103.
35. Anderson JA. Multicentric and bilateral appearance of lobular carcinoma in situ of the breast. Acta Pathol Microbiol Scand A. 1974;82(6):730-4.
36. Chuba PJ, Hamre MR, Yap J, Severson RK, Lucas D, Shamsa F, et al. Bilateral risk for subsequent breast cancer after lobular carcinoma-in-situ: analysis of surveillance, epidemiology, and end results data. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2005;23(24):5534-41.
37. Page DL, Schuyler PA, Dupont WD, Jensen RA, Plummer WD, Jr., Simpson JF. Atypical lobular hyperplasia as a unilateral predictor of breast cancer risk: a retrospective cohort study. Lancet. 2003;361(9352):125-9.
38. Berx G, Cleton-Jansen AM, Strumane K, de Leeuw WJ, Nollet F, van Roy F, et al. E-cadherin is inactivated in a majority of invasive human lobular breast cancers by truncation mutations throughout its extracellular domain. Oncogene. 1996;13(9):1919-25.
39. Dabbs DJ, Bhargava R, Chivukula M. Lobular versus ductal breast neoplasms: the diagnostic utility of p120 catenin. The American journal of surgical pathology. 2007;31(3):427-37.
40. Dabbs DJ, Schnitt SJ, Geyer FC, Weigelt B, Baehner FL, Decker T, et al. Lobular neoplasia of the breast revisited with emphasis on the role of E-cadherin immunohistochemistry. The American journal of surgical pathology. 2013;37(7):e1-11.
41. El-Sayed ME, Rakha EA, Reed J, Lee AH, Evans AJ, Ellis IO. Predictive value of needle core biopsy diagnoses of lesions of uncertain malignant potential (B3) in abnormalities detected by mammographic screening. Histopathology. 2008;53(6):650-7.
42. Hussain M, Cunnick GH. Management of lobular carcinoma in-situ and atypical lobular hyperplasia of the breast--a review. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2011;37(4):279-89.
43. Shehata MN, Rahbar H, Flanagan MR, Kilgore MR, Lee CI, Ryser MD, et al. Risk for Upgrade to Malignancy After Breast Core Needle Biopsy Diagnosis of Lobular Neoplasia: A Systematic Review and Meta-Analysis. J Am Coll Radiol. 2020;17(10):1207-19.
44. Foschini MP, Miglio R, Fiore R, Baldovini C, Castellano I, Callagy G, et al. Pre-operative management of Pleomorphic and florid lobular carcinoma in situ of the breast: Report of a large multi-institutional series and review of the literature. European journal of surgical oncology : the journal of the

European Society of Surgical Oncology and the British Association of Surgical Oncology. 2019;45(12):2279-86.
45. Morrow M, Schnitt SJ, Norton L. Current management of lesions associated with an increased risk of breast cancer. Nat Rev Clin Oncol. 2015;12(4):227-38.
46. Nakhlis F, Gilmore L, Gelman R, Bedrosian I, Ludwig K, Hwang ES, et al. Incidence of Adjacent Synchronous Invasive Carcinoma and/or Ductal Carcinoma In-situ in Patients with Lobular Neoplasia on Core Biopsy: Results from a Prospective Multi-Institutional Registry (TBCRC 020). Ann Surg Oncol. 2016;23(3):722-8.
47. Brogi E. The morphologic spectrum of lobular carcinoma in situ (LCIS) observations on clinical significance, management implications and diagnostic pitfalls of classic, florid and pleomorphic LCIS. Virchows Archiv. 2022.
48. Cheng P, Huang Q, Shou J, Hu G, Han M, Huang J. Treatment and survival outcomes of lobular carcinoma in situ of the breast: A SEER population based study. Oncotarget. 2017;8(61):103047-54.
49. Taylor LJ, Steiman J, Schumacher JR, Wilke LG, Greenberg CC, Neuman HB. Surgical Management of Lobular Carcinoma In Situ: Analysis of the National Cancer Database. Annals of Surgical Oncology. 2018;25(8):2229-34.
50. van Maaren MC, Ávila AO, van Manen JG, Menke-Pluijmers MB, Veltman J, Bart J, et al. Trends in incidence, treatment, survival and subsequent breast cancer in lobular carcinoma in situ in the Netherlands: A population-based analysis. Breast. 2021;59:376-82.
51. Nakhlis F, Katlin FD, Grossmith SC, DiPasquale A, Harrison BT, Schnitt SJ, et al. Presence of Non-classic LCIS Is Not a Contraindication to Breast Conservation in Patients with Concomitant Invasive Breast Cancer or DCIS. Ann Surg Oncol. 2022;29(12):7696-702.
52. Sadek BT, Shenouda MN, Abi Raad RF, Niemierko A, Keruakous AR, Goldberg SI, et al. Risk of local failure in breast cancer patients with lobular carcinoma in situ at the final surgical margins: is re-excision necessary? Int J Radiat Oncol Biol Phys. 2013;87(4):726-30.
53. Hoffman DI, Zhang PJ, Tchou J. Breast-conserving surgery for pure non-classic lobular carcinoma in situ: A single institution's experience. Surg Oncol. 2019;28:190-4.
54. Solorzano. Flat epithelial atypia of the breast: pathological-radiological correlation 2011 [
55. Leibl S, Regitnig P, Moinfar F. Flat epithelial atypia (DIN 1a, atypical columnar change): an underdiagnosed entity very frequently coexisting with lobular neoplasia. Histopathology. 2007;50(7):859-65.
56. Darvishian F, Singh B, Simsir A, Ye W, Cangiarella JF. Atypia on breast core needle biopsies: reproducibility and significance. Ann Clin Lab Sci. 2009;39(3):270-6.
57. O'Malley FP, Mohsin SK, Badve S, Bose S, Collins LC, Ennis M, et al. Interobserver reproducibility in the diagnosis of flat epithelial atypia of the breast. Modern pathology : an official journal of the United States and Canadian Academy of Pathology, Inc. 2006;19(2):172-9.
58. Gomes DS, Porto SS, Balabram D, Gobbi H. Inter-observer variability between general pathologists and a specialist in breast pathology in the diagnosis of lobular neoplasia, columnar cell lesions, atypical ductal hyperplasia and ductal carcinoma in situ of the breast. Diagn Pathol. 2014;9:121.
59. Tan PH, Ho BC, Selvarajan S, Yap WM, Hanby A. Pathological diagnosis of columnar cell lesions of the breast: are there issues of reproducibility? Journal of clinical pathology. 2005;58(7):705-9.
60. Wahab RA, Lee SJ, Mulligan ME, Zhang B, Mahoney MC. Upgrade Rate of Pure Flat Epithelial Atypia Diagnosed at Core Needle Biopsy: A Systematic Review and Meta-Analysis. Radiol Imaging Cancer. 2021;3(1):e200116.
61. Ferre R, Kuzmiak CM. Upgrade rate of percutaneously diagnosed pure flat epithelial atypia: systematic review and meta-analysis of 1,924 lesions. Journal of osteopathic medicine. 2022;122(5):253-62.

62. Rudin AV, Hoskin TL, Fahy A, Farrell AM, Nassar A, Ghosh K, et al. Flat Epithelial Atypia on Core Biopsy and Upgrade to Cancer: a Systematic Review and Meta-Analysis. Annals of surgical oncology. 2017;24(12):3549-58.
63. Arbeitsgemeinschaft Gynäkologische Onkologie. **Empfehlungen gynäkologische Onkologie Kommission Mamma** 2022 [Available from: https://www.ago-online.de/leitlinien-empfehlungen/leitlinien-empfehlungen/kommission-mamma.
64. Batohi B, Fang C, Michell MJ, Morel J, Shah C, Wijesuriya S, et al. An audit of mammographic screen detected lesions of uncertain malignant potential (B3) diagnosed on initial image guided needle biopsy: how has our practice changed over 10 years? Clin Radiol. 2019;74(8):653.e19-.e25.
65. Grabenstetter A, Brennan S, Salagean ED, Morrow M, Brogi E. Flat Epithelial Atypia in Breast Core Needle Biopsies With Radiologic-Pathologic Concordance: Is Excision Necessary? The American journal of surgical pathology. 2020;44(2):182-90.
66. Lucioni M, Rossi C, Lomoro P, Ballati F, Fanizza M, Ferrari A, et al. Positive predictive value for malignancy of uncertain malignant potential (B3) breast lesions diagnosed on vacuum-assisted biopsy (VAB): is surgical excision still recommended? European radiology. 2021;31(2):920-7.
67. Mariscotti G, Durando M, Ruggirello I, Belli P, Caumo F, Nori J, et al. Lesions of uncertain malignant potential of the breast (B3) on vacuum-assisted biopsy for microcalcifications: Predictors of malignancy. European journal of radiology. 2020;130:109194.
68. Mohrmann S, Maier-Bode A, Dietzel F, Reinecke P, Krawczyk N, Kaleta T, et al. Malignancy Rate and Malignancy Risk Assessment in Different Lesions of Uncertain Malignant Potential in the Breast (B3 Lesions): An Analysis of 192 Cases from a Single Institution. Breast Care (Basel). 2022;17(2):159-65.
69. Chan PMY, Chotai N, Lai ES, Sin PY, Chen J, Lu SQ, et al. Majority of flat epithelial atypia diagnosed on biopsy do not require surgical excision. Breast. 2018;37:13-7.
70. DiPasquale A, Silverman S, Farag E, Peiris L. Flat epithelial atypia: are we being too aggressive? Breast Cancer Res Treat. 2020;179(2):511-7.
71. Choudhery S, Johnson MP, Larson NB, Anderson T. Malignant Outcomes of Architectural Distortion on Tomosynthesis: A Systematic Review and Meta-Analysis. AJR Am J Roentgenol. 2021;217(2):295-303.
72. Cohen MA, Newell MS. Radial Scars of the Breast Encountered at Core Biopsy: Review of Histologic, Imaging, and Management Considerations. AJR Am J Roentgenol. 2017;209(5):1168-77.
73. Hammersley JA, Partridge SC, Blitzer GC, Deitch S, Rahbar H. Management of high-risk breast lesions found on mammogram or ultrasound: the value of contrast-enhanced MRI to exclude malignancy. Clin Imaging. 2018;49:174-80.
74. Amitai Y, Scaranelo A, Menes TS, Fleming R, Kulkarni S, Ghai S, et al. Can breast MRI accurately exclude malignancy in mammographic architectural distortion? Eur Radiol. 2020;30(5):2751-60.
75. Alsharif S, Aldis A, Subahi A, Khoury ME, Mesurolle B. Breast MRI Does Not Help Differentiating Radial Scar With and Without Associated Atypia or Malignancy. Can Assoc Radiol J. 2021;72(4):759-66.
76. Patel BK, Naylor ME, Kosiorek HE, Lopez-Alvarez YM, Miller AM, Pizzitola VJ, et al. Clinical utility of contrast-enhanced spectral mammography as an adjunct for tomosynthesis-detected architectural distortion. Clin Imaging. 2017;46:44-52.
77. Rakha E, Beca F, D'Andrea M, Abbas A, Petrou-Nunn W, Shaaban AM, et al. Outcome of radial scar/complex sclerosing lesion associated with epithelial proliferations with atypia diagnosed on breast core biopsy: results from a multicentric UK-based study. Journal of clinical pathology. 2019;72(12):800-4.
78. Farshid G, Buckley E. Meta-analysis of upgrade rates in 3163 radial scars excised after needle core biopsy diagnosis. Breast cancer research and treatment. 2019;174(1):165-77.
79. Kraft E, Limberg JN, Dodelzon K, Newman LA, Simmons R, Swistel A, et al. Radial Scars and Complex Sclerosing Lesions of the Breast: Prevalence of Malignancy and Natural History Under Active Surveillance. Annals of surgical oncology. 2021;28(9):5149-55.

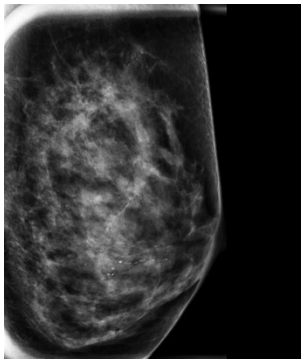
80. Ferreira AI, Borges S, Sousa A, Ribeiro C, Mesquita A, Martins PC, et al. Radial scar of the breast: Is it possible to avoid surgery? Eur J Surg Oncol. 2017;43(7):1265-72.
81. Groen EJ, Hudecek J, Mulder L, van Seijen M, Almekinders MM, Alexov S, et al. Prognostic value of histopathological DCIS features in a large-scale international interrater reliability study. Breast cancer research and treatment. 2020.
82. Eiada R, Chong J, Kulkarni S, Goldberg F, Muradali D. Papillary lesions of the breast: MRI, ultrasound, and mammographic appearances. AJR Am J Roentgenol. 2012;198(2):264-71.
83. Kulka J, Madaras L, Floris G, Lax SF. Papillary lesions of the breast. Virchows Arch. 2022;480(1):65-84.
84. Berger N, Luparia A, Di Leo G, Carbonaro LA, Trimboli RM, Ambrogi F, et al. Diagnostic Performance of MRI Versus Galactography in Women With Pathologic Nipple Discharge: A Systematic Review and Meta-Analysis. AJR Am J Roentgenol. 2017;209(2):465-71.
85. Ginter PS, Hoda SA, Ozerdem U. Exuberant squamous metaplasia in an intraductal papilloma of breast. International journal of surgical pathology. 2015;23(2):125-6.
86. Guidelines Working Group of the UK National Coordinating Committee for Breast Pathology. Pathology reporting of breast disease in surgical excision specimens incorporating the dataset for histological reporting of breast cancer. https://www.rcpath.org/profession/guidelines/cancer-datasets-and-tissue-pathways.html (Accessed 1 September 2022): The Royal College of Pathologists; 2016.
87. Jacobs TW, Connolly JL, Schnitt SJ. Nonmalignant lesions in breast core needle biopsies: to excise or not to excise? The American journal of surgical pathology. 2002;26(9):1095-110.
88. Shouhed D, Amersi FF, Spurrier R, Dang C, Astvatsaturyan K, Bose S, et al. Intraductal papillary lesions of the breast: clinical and pathological correlation. The American surgeon. 2012;78(10):1161-5.
89. Lin LH, Ozerdem U, Cotzia P, Lee J, Chun J, Schnabel F, et al. Upgrade rate of intraductal papilloma diagnosed on core needle biopsy in a single institution. Human pathology. 2021;110:43-9.
90. Khan S, Diaz A, Archer KJ, Lehman RR, Mullins T, Cardenosa G, et al. Papillary lesions of the breast: To excise or observe? The breast journal. 2018;24(3):350-5.
91. Page DL, Salhany KE, Jensen RA, Dupont WD. Subsequent breast carcinoma risk after biopsy with atypia in a breast papilloma. Cancer. 1996;78(2):258-66.
92. Zhang X, Liu W, Hai T, Li F. Upgrade Rate and Predictive Factors for Breast Benign Intraductal Papilloma Diagnosed at Biopsy: A Meta-Analysis. Ann Surg Oncol. 2021;28(13):8643-50.
93. Ahn SK, Han W, Moon HG, Kim MK, Noh DY, Jung BW, et al. Management of benign papilloma without atypia diagnosed at ultrasound-guided core needle biopsy: Scoring system for predicting malignancy. Eur J Surg Oncol. 2018;44(1):53-8.
94. Kuehner G, Darbinian J, Habel L, Axelsson K, Butler S, Chang S, et al. Benign Papillary Breast Mass Lesions: Favorable Outcomes with Surgical Excision or Imaging Surveillance. Ann Surg Oncol. 2019;26(6):1695-703.
95. Choi HY, Kim SM, Jang M, Yun B, Kang E, Kim EK, et al. Benign Breast Papilloma without Atypia: Outcomes of Surgical Excision versus US-guided Directional Vacuum-assisted Removal or US Follow-up. Radiology. 2019;293(1):72-80.
96. Chang Sen LQ, Berg WA, Carter GJ. Upgrade Rate and Imaging Features of Atypical Apocrine Lesions. Breast J. 2017;23(5):569-78.
97. AGO German Commission Breast SoAG. AGO German Commission Breast, State of Art Guidelines 2022 2022 [Available from: https://www.ago-online.de/en/leitlinien-empfehlungen/leitlinien-empfehlungen/kommission-mamma.
98. S3-Richtlinien. Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF. S3-Leitlinie Früherkennung, Diagnose, Therapie und Nachsorge des Mammakarzinoms, Version 4.4. Mai 2021 2021 [Available from: https://www.awmf.org/uploads/tx_szleitlinien/032-045OLl_S3_Mammakarzinom_2021-07.pdf.

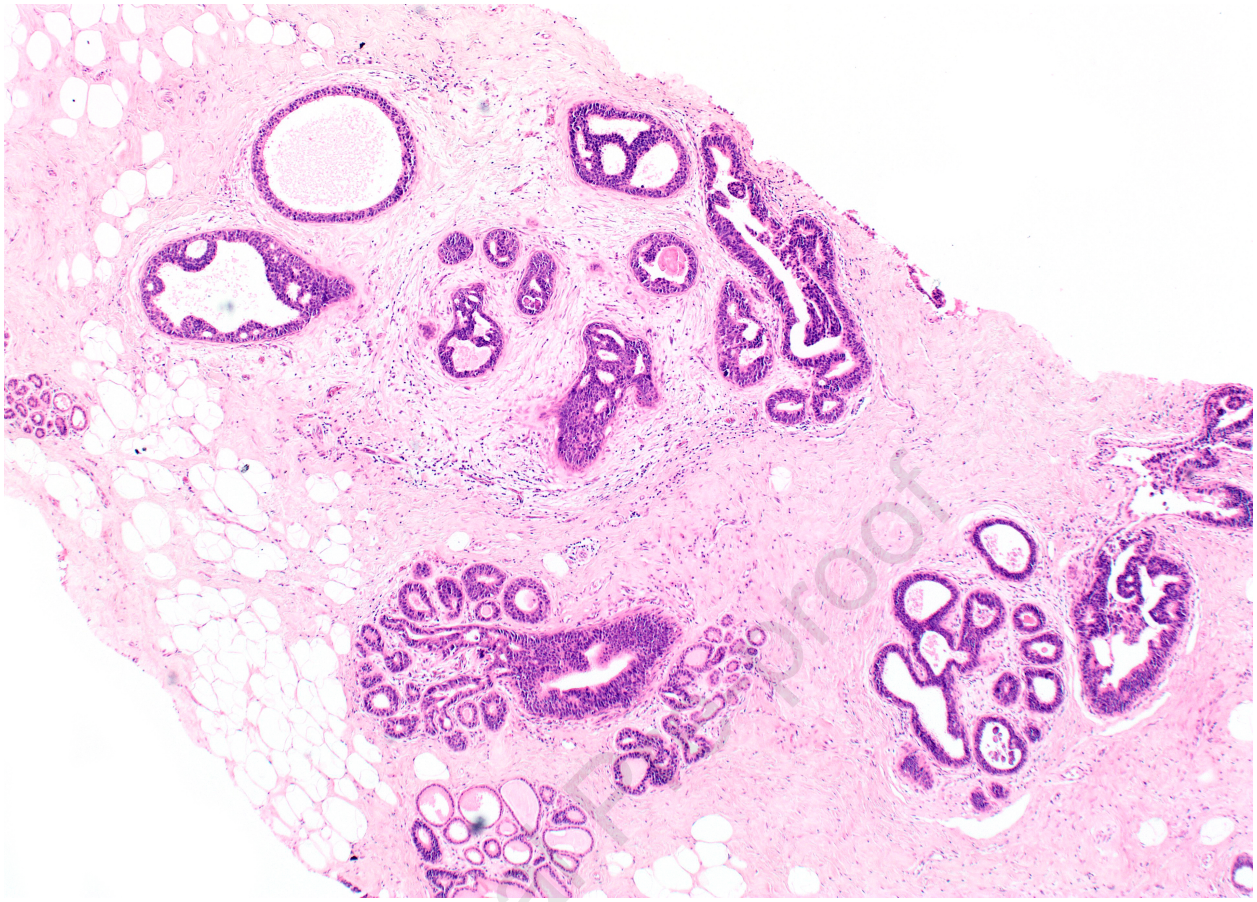
99. Mousa-Doust D, Dingee CK, Chen L, Bazzarelli A, Kuusk U, Pao JS, et al. Excision of breast fibroepithelial lesions: when is it still necessary?-A 10-year review of a regional centre. Breast Cancer Res Treat. 2022;194(2):307-14.
100. Davies C, Godwin J, Gray R, Clarke M, Cutter D, Darby S, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet. 2011;378(9793):771-84.
101. Coopey SB, Mazzola E, Buckley JM, Sharko J, Belli AK, Kim EM, et al. The role of chemoprevention in modifying the risk of breast cancer in women with atypical breast lesions. Breast Cancer Res Treat. 2012;136(3):627-33.
102. Litzenburger BC, Brown PH. Advances in Preventive Therapy for Estrogen-Receptor-Negative Breast Cancer. Curr Breast Cancer Rep. 6. United States2014. p. 96-109.
103. Shoker BS, Jarvis C, Clarke RB, Anderson E, Hewlett J, Davies MP, et al. Estrogen receptor-positive proliferating cells in the normal and precancerous breast. Am J Pathol. 1999;155(6):1811-5.
104. Mao X, Qiao Z, Fan C, Guo A, Yu X, Jin F. Expression pattern and methylation of estrogen receptor α in breast intraductal proliferative lesions. Oncol Rep. 2016;36(4):1868-74.
105. Powles TJ, Ashley S, Tidy A, Smith IE, Dowsett M. Twenty-year follow-up of the Royal Marsden randomized, double-blinded tamoxifen breast cancer prevention trial. J Natl Cancer Inst. 2007;99(4):283-90.
106. Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin WM, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst. 1998;90(18):1371-88.
107. Veronesi U, Maisonneuve P, Rotmensz N, Bonanni B, Boyle P, Viale G, et al. Tamoxifen for the prevention of breast cancer: late results of the Italian Randomized Tamoxifen Prevention Trial among women with hysterectomy. J Natl Cancer Inst. 2007;99(9):727-37.
108. Cuzick J, Forbes J, Sestak I, Cawthorn S, Hamed H, Holli K, et al. Long-term results of tamoxifen prophylaxis for breast cancer--96-month follow-up of the randomized IBIS-I trial. J Natl Cancer Inst. 2007;99(4):272-82.
109. Powles T, Eeles R, Ashley S, Easton D, Chang J, Dowsett M, et al. Interim analysis of the incidence of breast cancer in the Royal Marsden Hospital tamoxifen randomised chemoprevention trial. Lancet. 1998;352(9122):98-101.
110. Fisher B, Costantino JP, Wickerham DL, Cecchini RS, Cronin WM, Robidoux A, et al. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst. 2005;97(22):1652-62.
111. DeCensi A, Puntoni M, Guerrieri-Gonzaga A, Caviglia S, Avino F, Cortesi L, et al. Randomized Placebo Controlled Trial of Low-Dose Tamoxifen to Prevent Local and Contralateral Recurrence in Breast Intraepithelial Neoplasia. J Clin Oncol. 2019;37(19):1629-37.
112. Cuzick J, Sestak I, Bonanni B, Costantino JP, Cummings S, DeCensi A, et al. Selective oestrogen receptor modulators in prevention of breast cancer: an updated meta-analysis of individual participant data. Lancet. 2013;381(9880):1827-34.
113. Vogel VG, Costantino JP, Wickerham DL, Cronin WM, Cecchini RS, Atkins JN, et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. JAMA. 2006;295(23):2727-41.
114. Cuzick J, Sestak I, Forbes JF, Dowsett M, Cawthorn S, Mansel RE, et al. Use of anastrozole for breast cancer prevention (IBIS-II): long-term results of a randomised controlled trial. Lancet. 2020;395(10218):117-22.
115. Goss PE, Ingle JN, Ales-Martinez JE, Cheung AM, Chlebowski RT, Wactawski-Wende J, et al. Exemestane for breast-cancer prevention in postmenopausal women. N Engl J Med. 2011;364(25):2381-91.

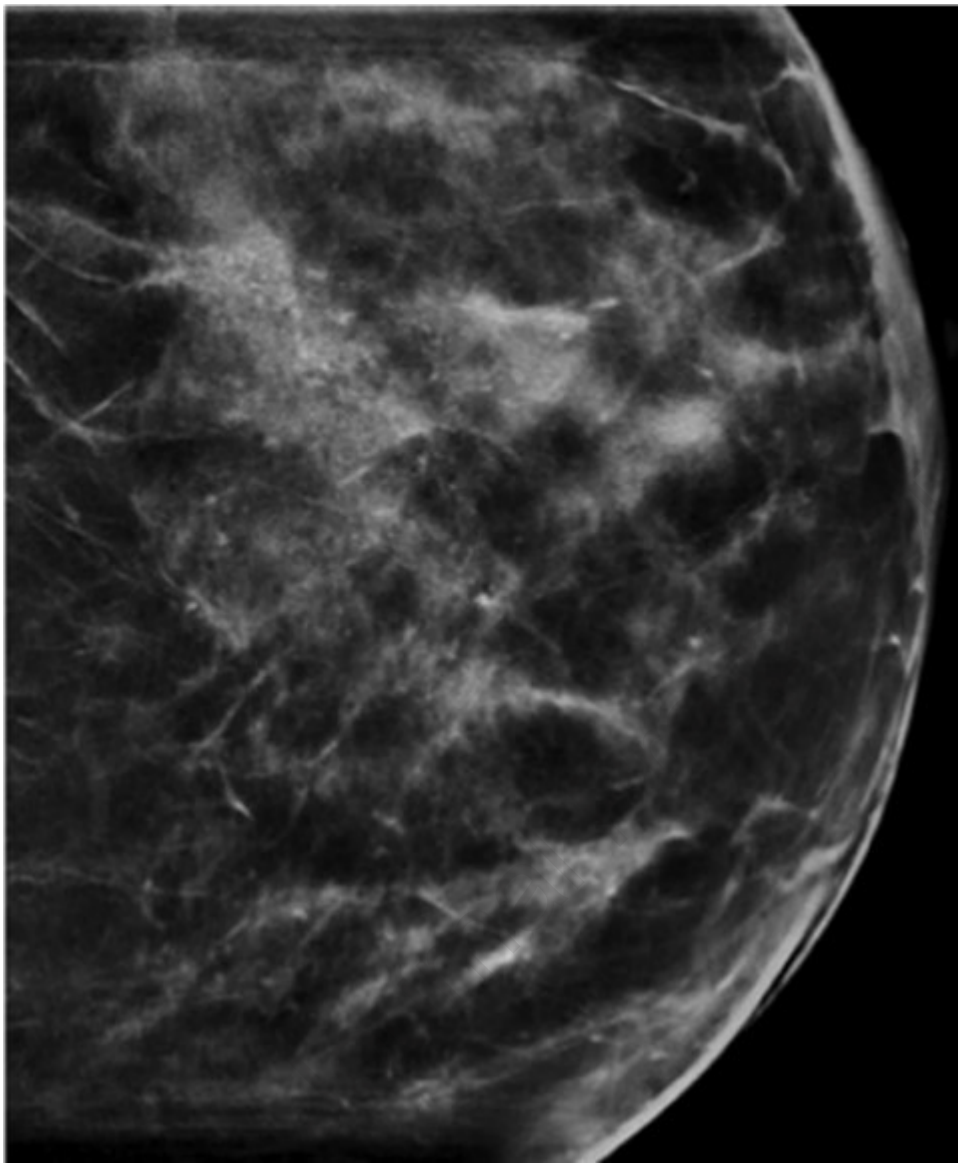
116. Smith SG, Sestak I, Forster A, Partridge A, Side L, Wolf MS, et al. Factors affecting uptake and adherence to breast cancer chemoprevention: a systematic review and meta-analysis. Ann Oncol. 2016;27(4):575-90.
117. Ropka ME, Keim J, Philbrick JT. Patient decisions about breast cancer chemoprevention: a systematic review and meta-analysis. J Clin Oncol. 2010;28(18):3090-5.
118. Bychkovsky B, Laws A, Katlin F, Hans M, Knust Graichen M, Pace LE, et al. Initiation and tolerance of chemoprevention among women with high-risk breast lesions: the potential of low-dose tamoxifen. Breast Cancer Res Treat. 2022;193(2):417-27.
119. Gnant M, Mlineritsch B, Stoeger H, Luschin-Ebengreuth G, Heck D, Menzel C, et al. Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 62-month follow-up from the ABCSG-12 randomised trial. Lancet Oncol. 2011;12(7):631-41.
120. Owens DK, Davidson KW, Krist AH, Barry MJ, Cabana M, Caughey AB, et al. Medication Use to Reduce Risk of Breast Cancer: US Preventive Services Task Force Recommendation Statement. Jama. 2019;322(9):857-67.
121. (NICE) NIoHaCE. Familial breast cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer. 2019:1.7.20-1.7.9.
122. Sessa C, Balmaña J, Bober SL, Cardoso MJ, Colombo N, Curigliano G, et al. Risk reduction and screening of cancer in hereditary breast-ovarian cancer syndromes: ESMO Clinical Practice Guideline. Ann Oncol. 2023;34(1):33-47.
123. Shaikh H, Bradhurst P, Ma LX, Tan SYC, Egger SJ, Vardy JL. Body weight management in overweight and obese breast cancer survivors. Cochrane Database Syst Rev. 2020;12(12):CD012110.
124. Lahart IM, Metsios GS, Nevill AM, Carmichael AR. Physical activity for women with breast cancer after adjuvant therapy. Cochrane Database Syst Rev. 2018;1(1):CD011292.
125. Danaei G, Vander Hoorn S, Lopez AD, Murray CJ, Ezzati M, Comparative Risk Assessment collaborating g. Causes of cancer in the world: comparative risk assessment of nine behavioural and environmental risk factors. Lancet. 2005;366(9499):1784-93.
126. Baron JA, La Vecchia C, Levi F. The antiestrogenic effect of cigarette smoking in women. Am J Obstet Gynecol. 1990;162(2):502-14.
127. MacMahon B, Trichopoulos D, Cole P, Brown J. Cigarette smoking and urinary estrogens. N Engl J Med. 1982;307(17):1062-5.
128. Khaw KT, Tazuke S, Barrett-Connor E. Cigarette smoking and levels of adrenal androgens in postmenopausal women. N Engl J Med. 1988;318(26):1705-9.
129. Ihenacho U, Sriprasert I, Mack WJ, Hamilton AS, Unger JB, Press MF, et al. A Systematic Review and Meta-Analysis of Smoking and Circulating Sex Hormone Levels Among Premenopausal Women. Nicotine Tob Res. 2022;24(11):1705-13.
130. Manjer J, Johansson R, Lenner P. Smoking as a determinant for plasma levels of testosterone, androstenedione, and DHEAs in postmenopausal women. Eur J Epidemiol. 2005;20(4):331-7.
131. Key T, Appleby P, Barnes I, Reeves G, Endogenous H, Breast Cancer Collaborative G. Endogenous sex hormones and breast cancer in postmenopausal women: reanalysis of nine prospective studies. J Natl Cancer Inst. 2002;94(8):606-16.
132. Endogenous H, Breast Cancer Collaborative G, Key TJ, Appleby PN, Reeves GK, Travis RC, et al. Sex hormones and risk of breast cancer in premenopausal women: a collaborative reanalysis of individual participant data from seven prospective studies. Lancet Oncol. 2013;14(10):1009-19.
133. Gaudet MM, Gapstur SM, Sun J, Diver WR, Hannan LM, Thun MJ. Active smoking and breast cancer risk: original cohort data and meta-analysis. J Natl Cancer Inst. 2013;105(8):515-25.
134. Morabia A. Smoking (active and passive) and breast cancer: epidemiologic evidence up to June 2001. Environ Mol Mutagen. 2002;39(2-3):89-95.

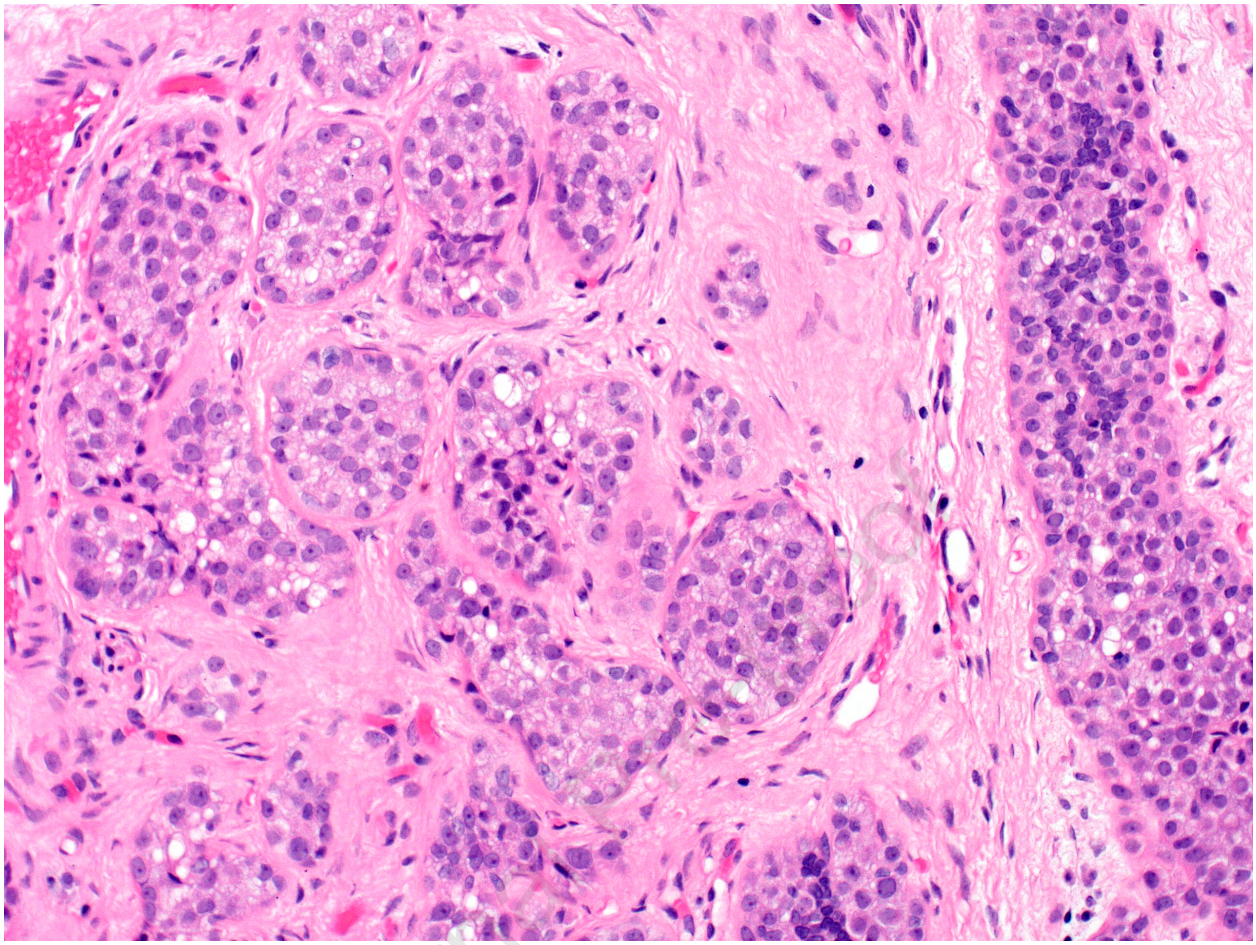
135. Hamajima N, Hirose K, Tajima K, Rohan T, Calle EE, Heath CW, Jr., et al. Alcohol, tobacco and breast cancer--collaborative reanalysis of individual data from 53 epidemiological studies, including 58,515 women with breast cancer and 95,067 women without the disease. Br J Cancer. 2002;87(11):1234-45.
136. Macacu A, Autier P, Boniol M, Boyle P. Active and passive smoking and risk of breast cancer: a meta-analysis. Breast Cancer Res Treat. 2015;154(2):213-24.
137. Nyante SJ, Gierach GL, Dallal CM, Freedman ND, Park Y, Danforth KN, et al. Cigarette smoking and postmenopausal breast cancer risk in a prospective cohort. Br J Cancer. 2014;110(9):2339-47.
138. Brown KA. Metabolic pathways in obesity-related breast cancer. Nat Rev Endocrinol. 2021;17(6):350-63.
139. Picon-Ruiz M, Morata-Tarifa C, Valle-Goffin JJ, Friedman ER, Slingerland JM. Obesity and adverse breast cancer risk and outcome: Mechanistic insights and strategies for intervention. CA Cancer J Clin. 2017;67(5):378-97.
140. Yang XR, Chang-Claude J, Goode EL, Couch FJ, Nevanlinna H, Milne RL, et al. Associations of breast cancer risk factors with tumor subtypes: a pooled analysis from the Breast Cancer Association Consortium studies. J Natl Cancer Inst. 2011;103(3):250-63.
141. Munsell MF, Sprague BL, Berry DA, Chisholm G, Trentham-Dietz A. Body mass index and breast cancer risk according to postmenopausal estrogen-progestin use and hormone receptor status. Epidemiol Rev. 2014;36(1):114-36.
142. Reeves GK, Pirie K, Beral V, Green J, Spencer E, Bull D, et al. Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. BMJ. 2007;335(7630):1134.
143. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med. 2003;348(17):1625-38.
144. Poorolajal J, Heidarimoghis F, Karami M, Cheraghi Z, Gohari-Ensaf F, Shahbazi F, et al. Factors for the Primary Prevention of Breast Cancer: A Meta-Analysis of Prospective Cohort Studies. J Res Health Sci. 2021;21(3):e00520.
145. Wu Y, Zhang D, Kang S. Physical activity and risk of breast cancer: a meta-analysis of prospective studies. Breast Cancer Res Treat. 2013;137(3):869-82.
146. Chen X, Wang Q, Zhang Y, Xie Q, Tan X. Physical Activity and Risk of Breast Cancer: A Meta-Analysis of 38 Cohort Studies in 45 Study Reports. Value Health. 2019;22(1):104-28.
147. Suzuki R, Ye W, Rylander-Rudqvist T, Saji S, Colditz GA, Wolk A. Alcohol and postmenopausal breast cancer risk defined by estrogen and progesterone receptor status: a prospective cohort study. J Natl Cancer Inst. 2005;97(21):1601-8.
148. Agabio R, Madeddu C, Contu P, Cosentino S, Deiana M, Massa E, et al. Alcohol Consumption Is a Modifiable Risk Factor for Breast Cancer: Are Women Aware of This Relationship? Alcohol Alcohol. 2022;57(5):533-9.
149. Zhou X, Yu L, Wang L, Xiao J, Sun J, Zhou Y, et al. Alcohol consumption, blood DNA methylation and breast cancer: a Mendelian randomisation study. Eur J Epidemiol. 2022;37(7):701-12.
150. Donat-Vargas C, Guerrero-Zotano A, Casas A, Baena-Canada JM, Lope V, Antolin S, et al. Trajectories of alcohol consumption during life and the risk of developing breast cancer. Br J Cancer. 2021;125(8):1168-76.
151. Freudenheim JL. Alcohol's Effects on Breast Cancer in Women. Alcohol Res. 2020;40(2):11.
152. Howell A, Anderson AS, Clarke RB, Duffy SW, Evans DG, Garcia-Closas M, et al. Risk determination and prevention of breast cancer. Breast Cancer Res. 2014;16(5):446.
153. Research. WCRFAIfC. Diet, Nutrition, Physical Activity and Cancer: a Global Perspective.Continuous Update Project Expert Report 2018.

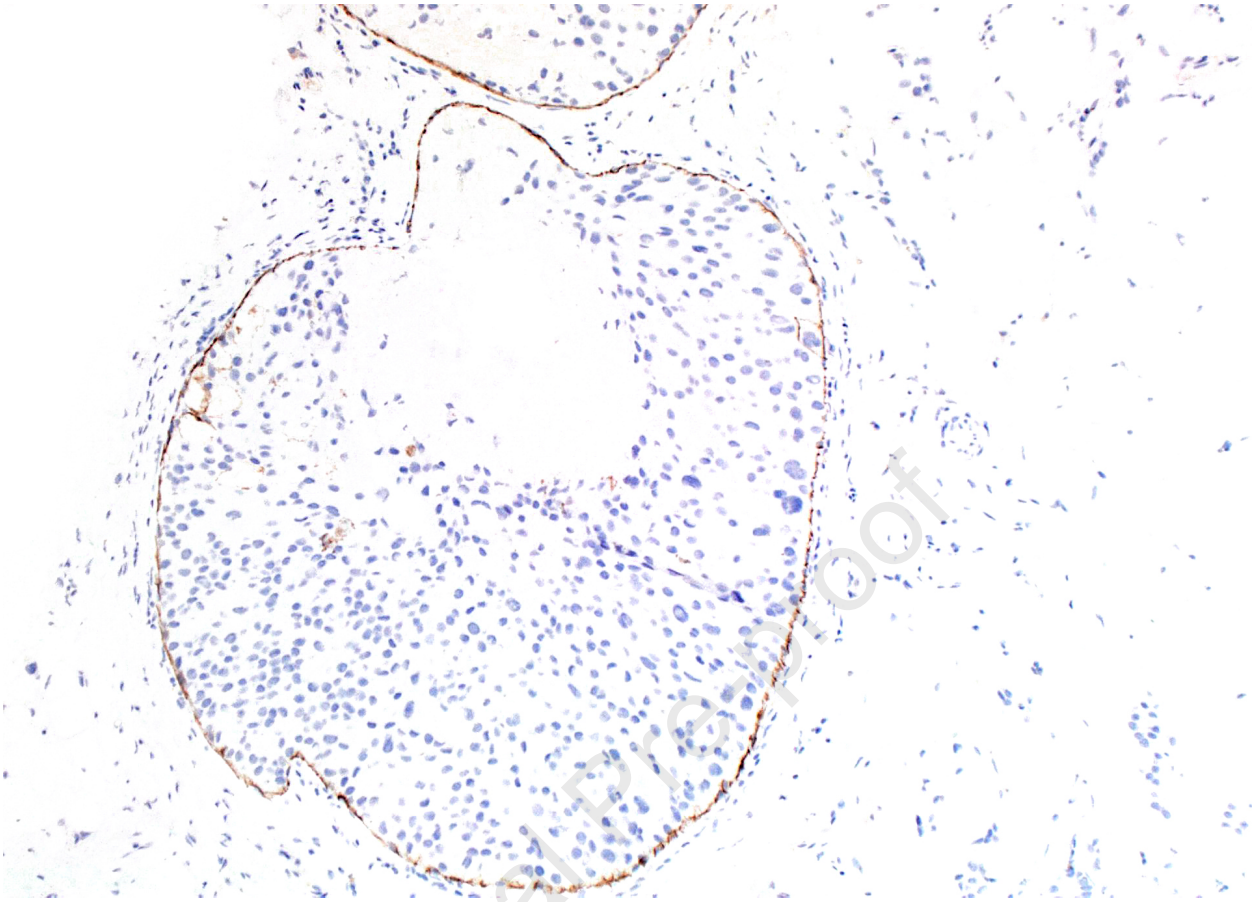
154. Key TJ, Balkwill A, Bradbury KE, Reeves GK, Kuan AS, Simpson RF, et al. Foods, macronutrients and breast cancer risk in postmenopausal women: a large UK cohort. Int J Epidemiol. 2019;48(2):489-500.
155. Baglia ML, Cook LS, Mei-Tzu C, Wiggins C, Hill D, Porter P, et al. Alcohol, smoking, and risk of Her2-overexpressing and triple-negative breast cancer relative to estrogen receptor-positive breast cancer. Int J Cancer. 2018;143(8):1849-57.
156. Jung S, Wang M, Anderson K, Baglietto L, Bergkvist L, Bernstein L, et al. Alcohol consumption and breast cancer risk by estrogen receptor status: in a pooled analysis of 20 studies. Int J Epidemiol. 2016;45(3):916-28.
157. Assi N, Rinaldi S, Viallon V, Dashti SG, Dossus L, Fournier A, et al. Mediation analysis of the alcohol-postmenopausal breast cancer relationship by sex hormones in the EPIC cohort. Int J Cancer. 2020;146(3):759-68.
158. Cybulski C, Lubinski J, Huzarski T, Lynch HT, Randall SA, Neuhausen SL, et al. Prospective evaluation of alcohol consumption and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. Breast Cancer Res Treat. 2015;151(2):435-41.
159. Stacey D, Volk RJ, Leads IEU. The International Patient Decision Aid Standards (IPDAS) Collaboration: Evidence Update 2.0. Med Decis Making. 41. United States2021. p. 729-33.
160. Wong SM, King T, Boileau JF, Barry WT, Golshan M. Population-Based Analysis of Breast Cancer Incidence and Survival Outcomes in Women Diagnosed with Lobular Carcinoma In Situ. Annals of Surgical Oncology. 2017;24(9):2509-17.

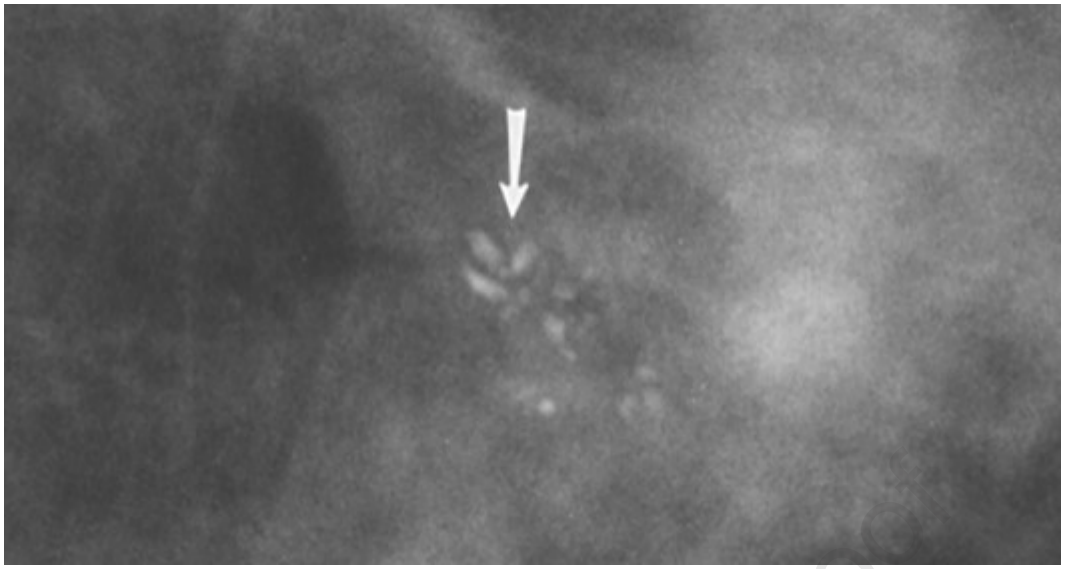


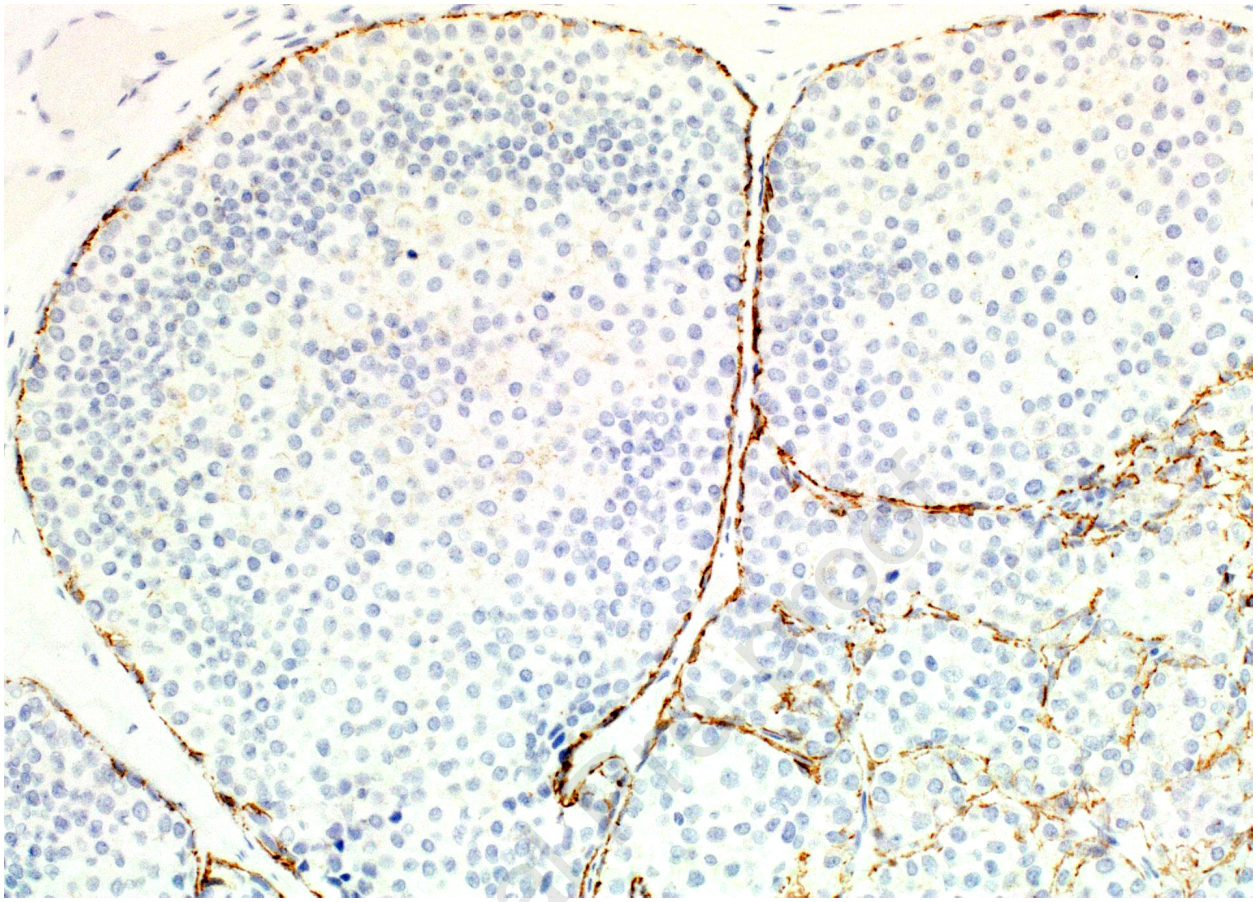


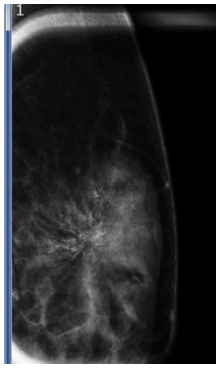


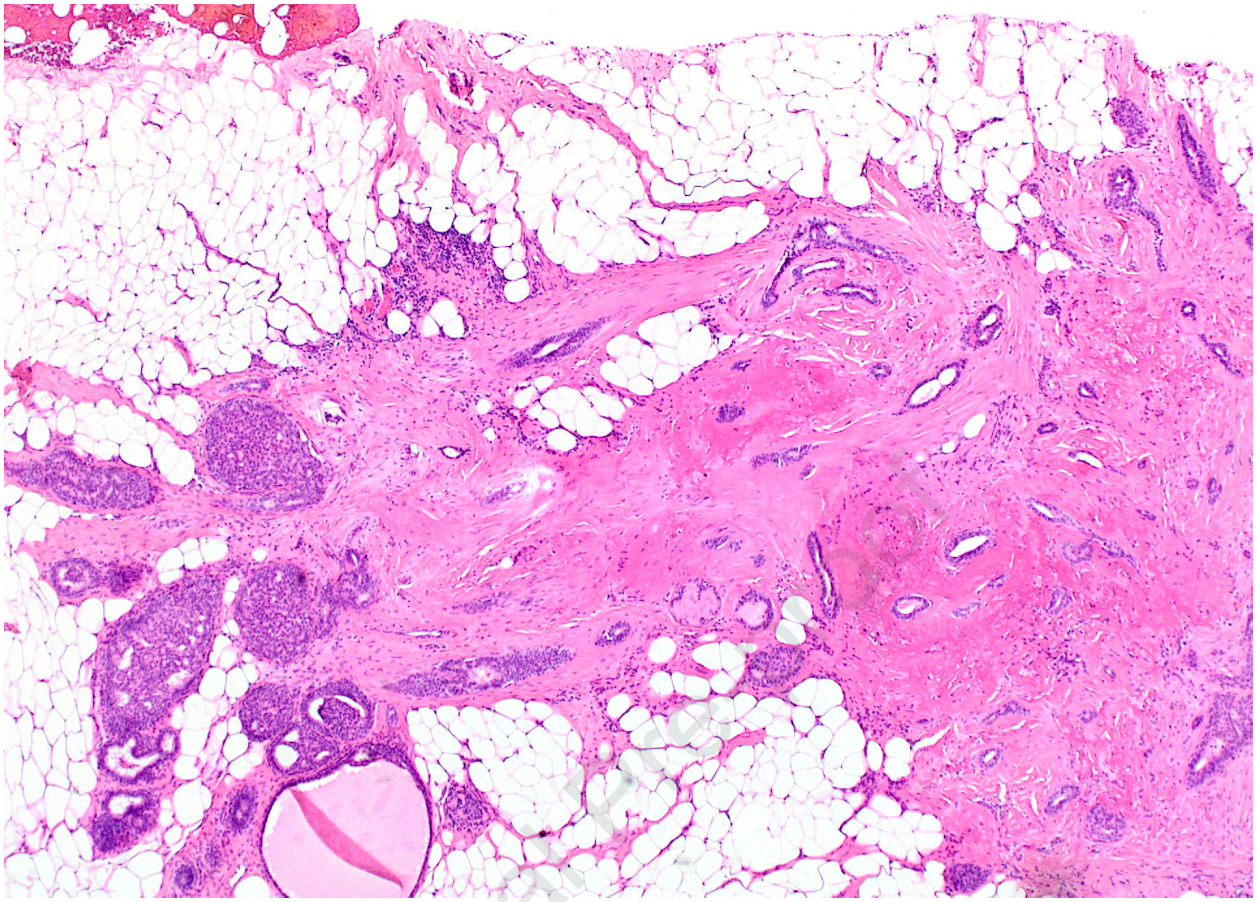


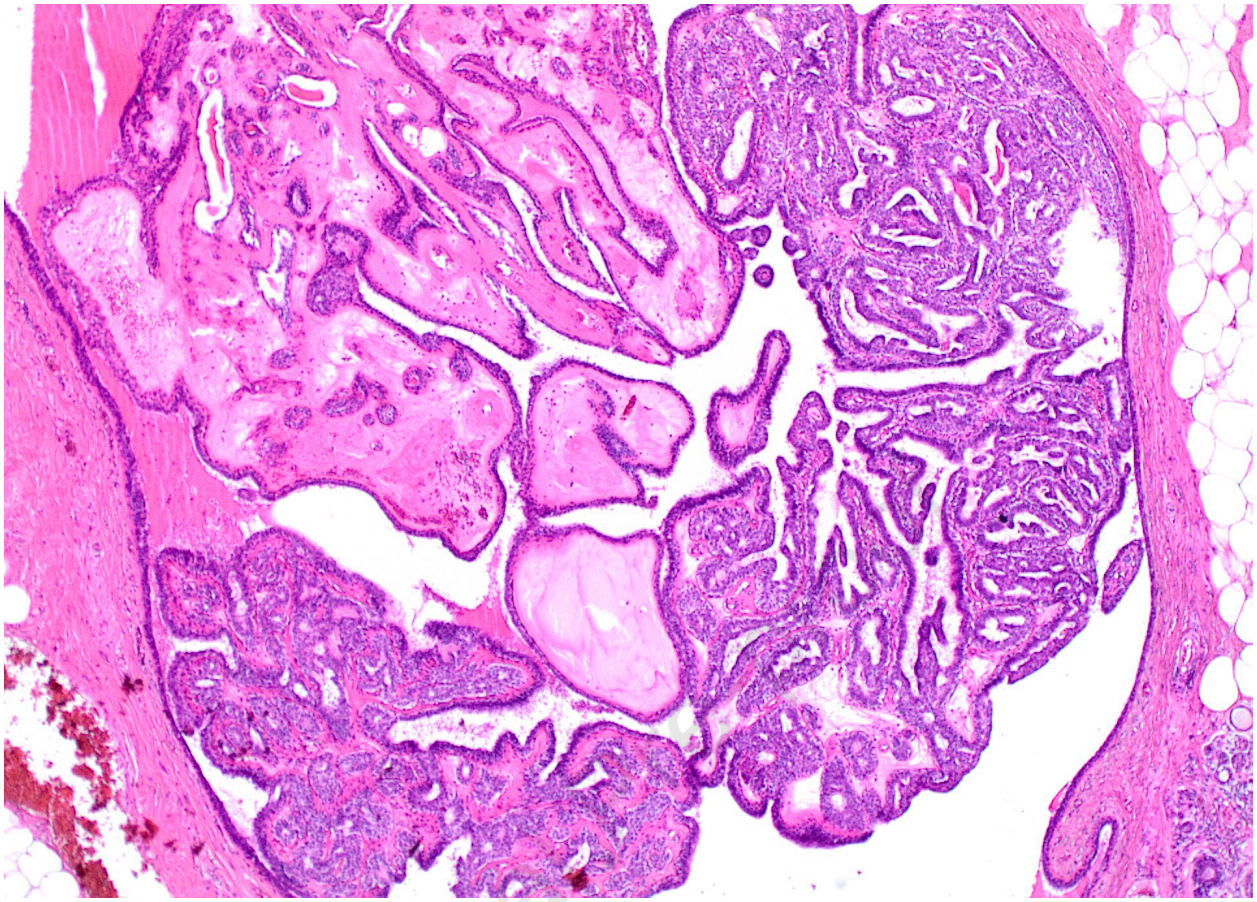












Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: