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ORIGINAL ARTICLE – BREAST ONCOLOGY

# Incidence of Breast Cancer in Patients with Pure Flat Epithelial Atypia Diagnosed at Core-Needle Biopsy of the Breast

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## ABSTRACT

**Purpose.** to determine the frequency of malignancy in subsequent breast excisions following core-needle biopsy (CNB) diagnosis of pure flat epithelial atypia (pFEA) and to evaluate the imaging features of the associated tumors.

**Materials and Methods.** Retrospective review of 8,996 image-guided CNB (2002–2010) identified 115 cases of FEA not associated with other atypia. Patients with history of breast cancer or radiation therapy were excluded. One hundred four cases (women) with pFEA (mean age 51 years, range 29–77 years) were reviewed. Stereotactic CNB was performed in 79 (76 %) cases and ultrasound (US)-guided CNB in 25 (24 %) cases. In 99 cases 14G needles were used, and 10G vacuum-assisted devices were used in 5 cases. Ninety-four patients had subsequent excision. Ten patients declined excision, and imaging follow-up (mean of 36 months) is available. The upgrade rate of pFEA was defined as the number of patients diagnosed with invasive carcinoma (IC) or carcinoma in situ (CIS) divided by the total number of patients.

**Results.** 10 of 104 (9.6 %) patients were diagnosed with cancer: 9 presented as calcifications (89 % fine pleomorphic and amorphous) and 1 case as a mammographically occult mass. The size of calcifications was not statistically significant ($P = 0.358$). Five cases had ductal carcinoma in situ (DCIS) and five cases had IC (ductal and lobular) presenting as amorphous and pleomorphic calcifications.

**Conclusions.** The upgrade rate of pFEA in our series was 9.6 %. The presence of 4.8 % of invasive cancers is substantial and warrants continuing management with surgical excision in all cases.

With the increasing use of full-field digital mammography and direct computer-aided detection (CAD) systems in screening for breast cancer, subtle findings are detected with greater frequency. In addition, with the utilization of vacuum-assisted biopsy (VAB) in stereotactic procedures, clinicians are getting increasing numbers of pathologic results that are not cancerous.

The World Health Organization working group on the pathology and genetics of tumors of the breast introduced the term flat epithelial atypia (FEA).[1] This is characterized by replacement of native epithelial cells by one or more layers of mildly atypical cells. The involved terminal ductal lobular units (TDLUs) are variably distended with central flocculent secretions that may be associated with calcifications, which can be the only manifestation on mammography.[1–3] The term encompasses various synonyms such as ductal intraepithelial neoplasia 1A (DIN 1A), atypical cystic lobules, columnar alteration with apical snouts and secretions, columnar cell change with atypia, and columnar cell hyperplasia with atypia.[1] Some of these cases may progress to invasive cancer (IC) with no quantitative epidemiologic data available for risk estimation.[3]



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There are scant data in the literature characterizing radiological findings observed in these cases, including those suggestive of possible upgrade to malignancy. Pandey et al. describe amorphous and fine pleomorphic calcifications as the usual mammographic features of FEA possibly due to development of these lesions in multiple TDLUs with intraluminal calcium deposits.[4,5]

The reported upgrade rate in the literature varies from 6.7 % to 25 %, hence favoring surgical excision.[6–15] However, Senetta and Piubello et al. had no upgraded cases in their patients with pure flat epithelial atypia (pFEA) on CNB.[5,16] They concluded that cases with FEA not associated with other atypia could be spared surgical excision and managed with close radiologic follow-up.

To date, surgical excision is considered the best treatment in these cases because of the risk of upgrade to malignancy.[6–15] However, the published data are limited by the small numbers of pFEA cases. The aim of this study is to determine the upgrade rate of pFEA at CNB and to review their imaging features.

## MATERIALS AND METHODS

Institutional ethical approval was obtained for this study, which did not require informed consent.

### *Study Population*

Retrospective chart review of 8,996 cases of image-guided CNB performed in Princess Margaret Hospital (2002–2010) was performed. CNB pathology reports including the word "atypia" were selected. These exams were reviewed by three pathologists (S.J.D., N.M., B.J.Y.) with more than 15, 25, and 21 years of experience in breast pathology sign-out, respectively. FEA was diagnosed following the criteria described by Schnitt et al.[1] pFEA was defined in this study as a case without higher-grade atypia [atypical ductal hyperplasia (ADH), lobular carcinoma in situ (LCIS) or atypical lobular hyperplasia (ALH)]. Patients with prior history of breast cancer, chest wall irradiation, and concomitant high-risk lesions in the ipsilateral or contralateral breast were excluded.

Our population was composed of 104 (1.2 %) patients with pFEA diagnosed on CNB [mean age 51 years, range 29–77 years, standard deviation (SD) 8.4 years]. Fifty-six of 104 (53.8 %) women were premenopausal with 48 (46.2 %) postmenopausal women. Thirty (28.8 %) women had family history of breast cancer. Fourteen (13.5 %) women were under hormone replacement therapy (HRT) at the time of the biopsy, and 90 (86.5 %) women never used HRT. Thirty-eight (36.5 %) women had their imaging abnormalities detected at first screening examination. Ten (9.6 %) patients had prior benign breast surgeries, and 12 (11.5 %) patients had prior CNB biopsy. Nineteen (18.3 %) patients had prior microcalcifications found to be increasing on mammography (Table 1). Ninety-four (90 %) patients with pFEA underwent surgical excision of the sampled area, and 10 (10 %) of 104 patients declined surgical excision and had mean time of follow-up of 35.77 months [95 % confidence interval (CI): 7.17, 53.29] without development of breast cancer.

**TABLE 1** Clinical features in 104 cases of pFEA diagnosed at CNB

| History | No. | % |
|---|---|---|
| Menopausal status | | |
| Premenopausal | 56 | 53.8 |
| Postmenopausal | 48 | 46.2 |
| Family history of breast cancer | | |
| Positive | 30 | 28.8 |
| Negative | 74 | 71.2 |
| Hormone replacement therapy | | |
| Yes | 14 | 13.5 |
| No | 90 | 86.5 |
| First screening mammogram | | |
| Yes | 38 | 36.5 |
| No | 66 | 63.5 |
| Prior benign breast surgery | | |
| Yes | 10 | 9.6 |
| No | 94 | 90.4 |
| Prior benign breast core-needle biopsy | | |
| Yes | 12 | 11.5 |
| No | 92 | 88.5 |
| Previous microcalcifications | | |
| Yes | 19 | 18.3 |
| No | 85 | 81.7 |

### *Imaging Review*

Review of imaging features (calcification, distortion, mass) was performed using dedicated workstations (Advantage GE Workstation; GE Medical Systems, Milwaukee, WI), including two high-resolution 2,000 × 2,500 pixel monitors. Full-field digital mammographic units (Senographe 2000D; GE Medical Systems, Milwaukee, WI) were used in all examinations. Ultrasound (US) examinations were performed by technologists initially using ATL HDI 5000 series (Philips Healthcare) prior to 2007 and later with high-frequency transducers of Aplio series (Toshiba America Medical Systems). All scans were reviewed by staff radiologists or supervised trainees (residents or clinical fellows) at the time of imaging. Images were retrospectively reviewed using the picture archive and communication system (PACS) by a single reader (N.A.K.)

radiologist with 6 years' experience in breast imaging using the American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS) lexicon.[17] Cases found discordant with the report on the patient's electronic records were subsequently reviewed with another radiologist (A.M.S.) with 19 years' experience in breast imaging to reach a consensus.

### *Sampling Technique, Adequacy, and Upgrade Rate Definitions*

Stereotactic CNB was performed in 79 (76 %) cases, and US-guided CNB was performed in 25 (24 %) cases. Disposable needles (14-gauge, Bard Magnum Reusable Core Biopsy System; Bard Peripheral Technologies, Tempe, AZ) were used in 99 cases, and 10-gauge vacuum-assisted device (Vacora® Breast Biopsy System, Bard Biopsy Systems, Tempe, AZ) in 5 cases. Adequacy of sampling of microcalcifications was confirmed by visualizing calcifications on specimen radiographs. The CNB and postoperative surgical pathology results were obtained from the electronic patient records (EPR) in our institution.

The upgrade rate was defined as the total number of patients who received the diagnosis of IC or DCIS after surgical excision divided by the total number of patients.

### *Statistical Analysis*

The sampled lesions were categorized into four main groups: calcification, architectural distortion, mass with associated calcifications, and mass without calcifications.

The microcalcifications were grouped by morphology into: amorphous, coarse heterogeneous, punctate, and fine pleomorphic. Masses seen on sonography were grouped into circumscribed and noncircumscribed ones, with and without calcifications.

Statistical analyses were performed using SPSS software version 20 (IBM SSPS, Chicago, IL). Continuous variables were described using mean ± SD and categorical variables using frequency and percentage. Fisher's exact test was used to examine the association between upgrade to malignancy, morphology and distribution of microcalcifications. Further, the mean size of calcification in the cancer group was compared with that of the noncancer group using a two-sample $t$ test.

A $p$ value less than 0.05 was considered significant throughout this study.

## RESULTS

For the 104 patients, 104 mammograms and 80 breast ultrasound exams were available for imaging pathology correlation. US-guided CNB was performed in 25 (24 %) patients for 21 (84 %) masses and 4 (16 %) masses associated with calcifications. Stereotactic CNB was performed in 79 of 104 (76 %) cases targeting 78 (98.7 %) cases of microcalcifications and 1 (1.3 %) case of architectural distortion. Adequate sampling of microcalcification was confirmed on specimen radiography in all cases.

Ten (9.6 %) of 104 patients were diagnosed with breast cancer following surgical excision: 5 with in situ carcinoma and 5 with invasive cancers. Nine of these ten (90 %) patients presented with calcifications (11 % punctate, 33 % amorphous, and 56 % fine pleomorphic) (Table 2) and one (10 %) with a hypoechoic noncircumscribed mass not visualized on mammography (Table 3). There was no statistically significant association ($P = 0.681$) between imaging abnormality and cancer upgrade, i.e., mass versus calcifications.

The mean size of calcifications in cancer patients was 24.4 mm (95 % CI: 3, 70), and 12.81 mm (95 % CI: 3, 60)

**TABLE 2** Morphology and outcome of cases presenting with microcalcifications

| Calcification | Surgical outcome | | Follow-up[b] | Total |
|---|---|---|---|---|
| | Malignant[a] | Benign[a] | | |
| Amorphous | 3 (33) | 11 (17) | 1 (12.5) | 15 (19) |
| Fine pleomorphic | 5 (56) | 14 (22) | 4 (50) | 23 (28) |
| Coarse heterogeneous | 0 (0) | 20 (31) | 1 (12.5) | 21 (26) |
| Punctate | 1 (11) | 19 (30) | 2 (25) | 22 (27) |
| Total | 9 (100) | 64 (100) | 8 (100) | 81 (100) |

[a] Numbers in parenthesis are percentages

[b] Numbers of patients presenting with microcalcifications who declined surgical excision and had imaging follow-up

**TABLE 3** Morphology and outcome of cases presenting with masses

| Masses | Surgical outcome | | Follow-up[b] | Total |
|---|---|---|---|---|
| | Malignant[a] | Benign[a] | | |
| Noncircumscribed mass without calcifications | 1 (100) | 1 (5) | 0 (0) | 2 (9) |
| Noncircumscribed mass with calcifications | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| Circumscribed mass without calcifications | 0 (0) | 3 (16) | 2 (100) | 5 (23) |
| Circumscribed mass with calcifications | 0 (0) | 15 (79) | 0 (0) | 15 (68) |
| Total | 1 (100) | 19 (100) | 2 (100) | 22 (100) |

[a] Numbers in parenthesis are percentages

[b] Numbers of patients presenting with masses who declined surgical excision and had imaging follow-up

in patients with benign results. The difference in mean size (11.63 mm) between the two groups was not statistically significant ($P = 0.385$). However, the difference in morphology was statistically significant ($P = 0.021$). Eighty-six percent of the punctate and 95 % of the coarse heterogeneous calcifications had a benign outcome (Table 2). There was no statistically significant difference in the distribution of calcifications, where 33.3 % of the segmental calcifications had a malignant outcome ($P = 0.071$).

There was no significant association between age and malignant outcome. The mean age of the group with malignant outcome was 52 years compared with 51.07 years in those with benign outcome (SD 8.53) ($P = 0.988$). There was no significant association between family history and malignant outcome. Four out of 27 (14.8 %) cases with positive family history had malignant outcome ($P = 0.465$). Similarly, no significant association was noted between menopausal status and cancer upgrade. Seven out of 53 (13.2 %) premenopausal women had malignant outcome compared with 3 out of 41 (7.3 %) postmenopausal women ($P = 0.505$). No significant association was found between use of HRT and malignant outcome. Three out of 14 patients (21.4 %) used HRT and were upgraded to cancer compared with 7 out of 80 (8.8 %) women upgraded to cancer who never used HRT ($P = 0.167$). Similarly, 2 out of 12 (16.7 %) women with prior breast biopsy had malignant outcome compared with 8 out of 82 (9.8 %) women with no prior biopsy and malignant outcome ($P = 0.611$). One out of 17 (5.9 %) women with prior microcalcification developed cancer ($P = 0.683$). Similarly, one out of ten (10 %) patients with prior breast surgery was upgraded to malignancy ($P = 1$). Four out of 34 (11.8 %) women with abnormalities detected on the first screening examination were upgraded to malignancy ($P = 1$) (Table 4).

Atypical ductal hyperplasia (ADH) was found in 20 (19.2 %) patients following excision; all presented as calcifications: 45 % were coarse heterogeneous in morphology. Five (4.8 %) of 104 patients had atypical lobular hyperplasia (ALH); three of them presented with calcifications and the remaining two as masses. Three of 104 (2.9 %) patients had lobular carcinoma in situ (LCIS); two presented with microcalcifications and one as a mass.

Twenty-three of 25 (92 %) lesions sampled under US had subsequent surgical excision; 19 (83 %) of 23 cases had benign surgical findings and had presented as follows: 15 cases of hypoechoic circumscribed masses without calcifications, 3 as hypoechoic circumscribed masses with calcifications, and 1 as hypoechoic noncircumscribed mass without calcifications. Of the 25 lesions, only 1 case, presenting as a hypoechoic noncircumscribed mass not visualized on mammography, was upgraded to malignancy (Table 3).

**TABLE 4** Correlation between clinical status and surgical outcome

| Clinical status | Benign | Upgrade to cancer | % | *P* Value |
|---|---|---|---|---|
| Menopausal status | | | | |
| Premenopausal | 46 | 7 | 13.2 | 0.505 |
| Postmenopausal | 38 | 3 | 7.3 | |
| Family history of breast or ovarian cancer | | | | |
| Present | 23 | 4 | 14.8 | 0.465 |
| Absent | 61 | 6 | 9 | |
| Hormonal replacement treatment | | | | |
| Yes | 11 | 3 | 21.4 | 0.167 |
| No | 73 | 7 | 8.8 | |
| Previous breast biopsy | | | | |
| Yes | 10 | 2 | 16.7 | 0.611 |
| No | 74 | 8 | 9.8 | |
| Previous calcifications | | | | |
| Yes | 16 | 1 | 5.9 | 0.683 |
| No | 68 | 9 | 11.7 | |
| Previous surgery | | | | |
| Yes | 9 | 1 | 10 | 1 |
| No | 75 | 9 | 10.7 | |
| Abnormality detected at first screening exam | | | | |
| Yes | 30 | 4 | 11.8 | 1 |
| No | 54 | 6 | 10 | |

Thirty-six (34.6 %) of the 104 cases of pFEA on CNB had no change in the pathology diagnosis postexcision. Other benign surgical pathology diagnoses, including fibrocystic changes, apocrine metaplasia, fibroadenomatoid changes, and pseudoangiomatous stromal hyperplasia, were found in 21 % of the surgical specimens. The surgical outcome in our series is presented in Table 5. The ten patients who declined surgery have a mean imaging follow-up of 36 months and remain free of malignancy.

**TABLE 5** Histopathology results in the 94 patients who underwent surgical excision

| Histopathology | Cases[a] |
|---|---|
| Invasive ductal carcinoma (IDC) | 3 (3) |
| Invasive lobular carcinoma (ILC) | 2 (2) |
| Ductal carcinoma in situ (DCIS) | 5 (5) |
| Lobular carcinoma in situ (LCIS) | 3 (3) |
| Atypical ductal hyperplasia (ADH) | 20 (21) |
| Atypical lobular hyperplasia (ALH) | 5 (5) |
| Flat epithelial atypia (FEA) | 36 (38) |
| Benign results[b] | 20 (21) |
| Total | 94 (100) |

[a] Numbers in parenthesis are percentages

[b] Fibrocystic changes, apocrine metaplasia, fibroadenomatoid changes, and pseudoangiomatous stromal hyperplasia

**TABLE 6** Reported upgrade rate of pure flat epithelial atypia and histopathology diagnosis found on surgical excision

| Authors | No. of pFEA | ADH *N* (%) | LN *N* (%) | DCIS *N* (%) | Invasive *N* (%) | DCIS + IC *N* (%) |
|---|---|---|---|---|---|---|
| Senetta et al.[5] | 36 | 5 (13) | 8 (23) | 0 (0) | 0 (0) | 0 (0) |
| Noske et al.[6] | 30 | NA | NA | 2 (6.7) | 0 (0) | 2 (6.7) |
| De Mascarel et al.[7] | 84 | 0 (0) | 1 (1) | 12 (12) | 0 (0) | 12 (12) |
| Guerra-Wallace et al.[8] | 31 | 0 (0) | 0 (0) | 3 (10) | 1 (3) | 4 (13) |
| Lavoue et al.[9] | 60 | 10 (17) | 2 (3.3) | 6 (10) | 2 (3) | 8 (13) |
| Chivukula et al.[10] | 35 | 10 (29) | 8 (23) | 3 (9) | 2 (6) | 5 (14) |
| Lee et al.[11] | 7 | NA | NA | 1 (14) | 0 (0) | 1 (14) |
| Solorzano et al.[12] | 28 | 6 (11) | 3 (11) | 4 (14) | 0 (0) | 4 (14) |
| David et al.[13] | 40 | 5 (12.5) | 0 (0) | 3 (7.5) | 4 (10) | 7 (17.5) |
| Ingegnoli et al.[14] | 15 | NA | NA | 1 (7) | 2 (13) | 3 (20) |
| Kunju et al.[15] | 12 | 5 (41) | 1 (8) | 1 (8) | 2 (17) | 3 (25) |
| Piubello et al.[16] | 33 | 1 (3) | 5 (20) | 0 (0) | 0 (0) | 0 (0) |
| This study | 104 | 20 (20) | 8 (7.7) | 5 (4.8) | 5 (4.8) | 10 (9.6) |

Numbers in parenthesis are percentages

*NA* not available

## DISCUSSION

Flat epithelial atypia is increasingly found on CNB. In our series, pFEA was found in 104 of 8,996 (1.2 %) procedures over an 8-year period. In the literature, the lowest reported prevalence is 1.5 %, going higher to 3.7 %, with the highest reported prevalence of 35.2 %.[6,9,18] The clinical significance of this entity has been hampered by variation in terminology and the limited number of cases that have been studied in a systematic fashion in the presurgical setting.[5] It is thought of as a precursor to, or risk factor for, low-grade DCIS.[19] Very few data are available related to the radiologic presentation, with microcalcification appearing to be the main imaging feature of FEA.[4,14] In our series, microcalcification represents 87 % (82 out of 104) of our sample. We found a statistically significant association between the morphology of calcification and the upgrade to malignancy, with 89 % of upgraded cases demonstrated amorphous and fine pleomorphic calcification; this is consistent with the findings of Penday et al.[4]

Our results showed 9.6 % upgraded cases of pFEA to invasive and in situ cancer on surgical excision. We found no statistically significant association between age, family history, menopausal status, hormone replacement therapy, prior microcalcifications, prior biopsies or surgeries with malignant outcome. Five cases (4.8 %) had invasive cancer of lobular and ductal types including tubular subtype. This is consistent with observations reported in the literature.[7–9,11,20] The presence of 4.8 % invasive cancers in our largest series (Table 6) warrants continuing management with surgical excision in all cases of pFEA on CNB.

Previous studies have observed coexistence of FEA with other forms of atypia and low-grade cancer.[7–16,18–20] In our series, high-risk lesions [ADH and lobular neoplasia (LN)] were found in 28 of 94 cases (29.5 %). Kunju et al. described the highest reported upgrade rate of 25 % that may be related to small sample size (3 out of 12 cases of pFEA).[15] David et al., using a VAB device in 40 cases of pFEA, reported an upgrade rate of 17.5 %.[13] On the other hand, studies with 36 and 33 cases of pFEA in their series using VAB had 0 % upgrade following surgery.[5,16] They concluded that patients with pFEA on VAB could be spared surgical excision and managed with close radiologic follow-up.

The amount of tissue obtained on CNB may be related to the upgrade rate: Kunju and Kleer found a higher upgrade rate compared with other studies and attributed this to the use of 14-gauge VAB probes compared with 11-gauge in other studies.[7,15,18] This cannot be assessed in our study due to the small number of cases done with VAB.

The upgrade rate in our study is comparable to the published literature despite the fact that we used 14-gauge automated devices in most of our cases. Review of specimen radiographs confirmed retrieval of calcifications in all cases. The use of spring-loaded devices implies more flexibility when sampling different areas in the same biopsy procedure compared with using a rigid (not mobile) probe in the VAB technique. The 99 cases of pFEA sampled without VAB in our series showed an upgrade rate of 10 %, less than the published series where VAB was used.[7–12]

David et al. recommended surgical excision when a cluster greater than 10 mm is found on VAB or is incompletely removed.[13] Clusters less than 10 mm or

totally removed may obviate systematic surgery. In our series, 5 of 29 (17 %) cases with clusters larger than 10 mm were upgraded to malignancy with no statistically significant association between size of calcifications and cancer upgrade ($P = 0.195$).

Ten out of 104 (10 %) women declined surgical excision. None of them developed malignancy after 36 months (3 years) mean time of imaging follow-up.

Our study has a few limitations. These include retrospective design. An element of selection bias was unavoidable, as ten patients had no surgery. Lesions identified on both modalities (ultrasound and mammography) were sampled under the attending radiologists' discretion, not always following the same criteria; e.g., calcifications seen on ultrasound were sampled under sonographic rather than stereotactic guidance. The small number of upgraded cases limited adequate statistical assessment.

In conclusion, the upgrade rate of pFEA in our series was 9.6 %. The presence of 4.8 % invasive cancers is substantial and warrants continuing management with surgical excision in all cases. Adequate sampling including retrieval of calcifications and pathologic correlation including multidisciplinary discussion is crucial to plan further management. Subsequently, complete excision of calcification is extremely important in planning further follow-up. Better understanding of the molecular and cytogenetic make-up of pFEA with a larger study including imaging features correlating with the outcome after surgical excision is recommended to better understand this entity.

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