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# Histopathology



## Outcome of breast lesions diagnosed as lesion of uncertain malignant potential (B3) or suspicious of malignancy (B4) on needle core biopsy including detailed review of epithelial atypia

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**Revision****Outcome of breast lesions diagnosed as lesion of uncertain malignant potential (B3) or suspicious of malignancy (B4) on needle core biopsy including detailed review of epithelial atypia**

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**Running title:** B3 and B4 breast needle core biopsies

**Keywords:** Breast, needle core biopsy, B3, B4, atypia, positive predictive value

**ABSTRACT**

Aim: To provide updated evidence of the outcome of breast lesions of uncertain malignant potential (B3) and suspicious of malignancy (B4) diagnosed on needle core biopsy (NCB) and analyse the outcome of the different types of intraductal epithelial atypia.

Methods and results: 149 B3 and 26 B4 NCB diagnosed over a 2 year period (2007-2008) were compared to those diagnosed over a previous 2 year period (1998-2000). The proportion of B3 diagnoses increased from 3.1% to 4.5% and the positive predictive value (PPV) of malignancy of a B3 core decreased from 25% to 10%. Increased diagnosis of radial scar and reductions in the PPV of lobular neoplasia and of atypical intraductal proliferation may explain the reduction in the PPV of the B3 group as a whole. There were no significant changes in the proportion of B4 diagnosis (1.1% and 0.8%) or the PPV of B4 (83% and 88%). Review of cores with intraductal atypia showed a wide range of PPVs from 100% for suspicious of DCIS, to 40% for atypical ductal hyperplasia categorised as B3, and 14% for isolated flat epithelial atypia.

Conclusion: The study has found a decrease in the PPV for a B3 diagnosis and suggests possible explanations.

## INTRODUCTION

Needle core biopsy (NCB) is now considered as the method of choice for the triple assessment of breast lesions<sup>1</sup> and the published data suggest that the use of core biopsy has significantly increased the preoperative diagnosis rate.<sup>2-4</sup> The majority of NCB are classified as normal (B1), benign (B2) or malignant (B5).<sup>5</sup> The accuracy of benign and malignant NCB diagnoses is supported by the use of two borderline categories: lesion of uncertain malignant potential (B3) and suspicious of malignancy (B4). The B3 category consists of a heterogeneous group of lesions, which for sampling or other reasons may yield only benign histology on initial NCB sampling but are recognised to show heterogeneity and may harbour malignancy elsewhere or to have an increased risk of associated adjacent malignancy.<sup>2, 5, 6</sup> The B4 category is most commonly used for small fragments of atypical cells separate from the main core, focal atypical intraductal proliferations, which are insufficient for confident diagnosis of DCIS or very small foci of invasive carcinoma in which there is insufficient material for a definite diagnosis.<sup>5, 7</sup> Although the B3 and B4 categories constitute a relatively small proportion of all NCB,<sup>2, 7-9</sup> most cases progress to surgical intervention to establish an excision histology diagnosis.

In a previous study of NCB in the screening setting, we found that the performance of NCB improved over time since its introduction,<sup>2</sup> which may reflect an improvement in the radiological evaluation of breast lesions, sampling technique,<sup>10, 11</sup> publishing of guidelines for assessing breast lesions and reporting of NCB.<sup>5</sup> We also noted a reduction in the positive predictive

value of B3 NCB from 29% in 1997-1998 to 13% in 2006-2007.<sup>2</sup> Therefore, in the current study, we aimed to assess the outcome of lesions recently diagnosed as B3 and B4 categories (2007 to 2008) in our institution and to compare the results with those previously reported over a similar period of time (1998 to 2000).<sup>7</sup> In addition, sections showing intraductal epithelial atypia were reviewed to assess the outcome of the different subtypes of atypia.

## **MATERIALS AND METHODS**

All NCBs reported as B3 or B4 in the 2-year period from January 2007 to December 2008 were studied. NCB results were categorised according to UK guidelines.<sup>5</sup> All patients with a core biopsy diagnosis are discussed at a multidisciplinary meeting, with a breast radiologist, histopathologist and surgeon present, at which decisions on further action are made. Those patients not undergoing an excision biopsy were therefore subject to multidisciplinary discussion to ensure that this conclusion was appropriate. Histology reports of B3 and B4 NCB and the subsequent diagnostic surgical biopsy results of all patients were reviewed. For the purpose of this study, excision histology findings were categorised as a) malignant including invasive carcinoma, ductal carcinoma in situ (DCIS), and other malignant lesions such as sarcomas and lymphomas, and b) benign lesions including atypical ductal hyperplasia (ADH), classical lobular neoplasia (atypical lobular hyperplasia and lobular carcinoma in situ). Positive predictive values (PPV) for detection of malignancy were calculated as recommended by the NHS breast screening programme.<sup>5</sup> The PPV for B3 diagnoses = (number of final

malignant diagnoses / total number of subjects with B3 diagnosis) x 100%. The PPV for B4 diagnoses = (number of final malignant diagnoses / total number of subjects with B4 diagnosis excluding those without further histology) x 100%. Comparisons were made with a previous review of B3 and B4 NCB from July 1998 to June 2000.<sup>7</sup>

In this study, we classified B3 and B4 diagnoses into entities similar to those that we previously used.<sup>7, 12</sup> Cases diagnosed as atypical intraductal epithelial proliferation (AIDEP) or suspicious of DCIS were subjected to histological review by 3 pathologists and classified into different entities according to the subtype of atypia. If a change in diagnosis was being considered, the slides were reviewed by a fourth pathologist. This review was blind to the final diagnosis.

Flat epithelial atypia was defined as dilated acini lined by up to a few layers of cells with round to oval nuclei and apical snouts.<sup>13</sup> The nuclei were typically small and evenly spaced. Occasionally the nuclei were larger with more obvious atypia. Atypical ductal hyperplasia is a diagnosis that strictly should be reserved for surgical specimens. Nevertheless, we used this term for proliferations of cells with small evenly spaced nuclei with solid, cribriform or micropapillary architecture. An important criterion was that low grade DCIS was being considered, but the changes were not sufficient for this diagnosis. We follow the UK guidelines that diagnosis of low or intermediate grade DCIS requires involvement of two duct spaces, whereas high grade DCIS can

diagnosed in one duct.<sup>5</sup> Atypical apocrine proliferations were categorised separately.

## RESULTS

In 2007 and 2008, 149 of 3347 NCB (4.5%) were reported as B3 compared with 3.1% (120 of 3822) in 1998 to 2000 (corrected  $\chi^2 = 8.1$ ,  $P = 0.004$ ). 50 were screen-detected and 99 were symptomatic lesions. 26 of 3347 NCB (0.8%) were reported as B4 compared with 1.1% (43 of 3822) in 1998 to 2000 ( $P = 0.17$ ). 8 were screen-detected and 18 were symptomatic lesions. The excision biopsy findings for these patients are shown in table 1. In each of the categories B3 and B4 no association was found between the final diagnosis (benign versus malignant) and method of presentation (screen detected versus symptomatic), preoperative radiological/clinical diagnosis, method of guidance of the biopsy (free hand versus stereotactic versus ultrasound) or type of biopsy (core biopsy versus vacuum-assisted biopsy).

### *B3 cores*

A comparison of the excision biopsy findings in 2007 to 2008 and 1998 to 2000 is shown in table 2. The main B3 NCB diagnoses in both series were AIDEP, radial scar and papillary lesions. The number of cores showing isolated radial scar nearly doubled; this difference measured as the proportion of all core biopsies was significant (1.8% versus 1.2%,  $\chi^2 = 7.4$ ,  $P = 0.006$ ),

but not when assessed as the proportion of B3 NCB (26% versus 18%,  $\chi^2 = 2.1$ ,  $P = 0.15$ ).

The PPV for B3 lesions was 10%, significantly reduced from 25% in 1998 to 2000 ( $\chi^2 = 9.5$ ,  $P = 0.002$ ). There were clear differences in outcome in the different B3 subtypes in both series. The PPV was highest for AIDEP (23%), but this was less than the figure of 41% in 1998 to 2000, although this difference was not significant ( $P = 0.12$ ). The PPV for lobular neoplasia was much lower in the current series (0% versus 46%,  $\chi^2 = 5.4$ ,  $P = 0.02$ ), but this does not take radiological-pathological discordance into account. Most of the other categories without epithelial atypia had low PPVs. The exceptions were spindle cell lesions (one of five was a spindle cell carcinoma) and mucocoele-like lesions (one of three was a mucinous carcinoma in a symptomatic patient), but the numbers in these categories are small. 11 of 16 (69%) cellular fibroepithelial lesions on NCB were phyllodes tumour on excision (8 benign, 3 borderline).

#### *B4 cores*

The most frequent B4 diagnosis in both series was 'suspicious of DCIS'. The PPV was similar in both, 88% in 2007 to 2008 and 83% in 1998 to 2000.

The total number of biopsies reported as AIDEP or suspicious of DCIS reduced as a proportion of all B3 and B4 biopsies (45% in 1998 to 2000 and 33% in 2007 to 2008,  $\chi^2 = 4.8$ ,  $P = 0.03$ ), but not as a proportion of all core biopsies (1.8% versus 1.7%,  $P = 0.72$ ).

### *Subtypes of atypia*

All biopsies with intraductal epithelial atypia were reviewed. Four biopsies were downgraded to benign: 3 columnar cell lesions initially categorised as B3 and one initially categorised as suspicious of low grade DCIS was downgraded to epithelial hyperplasia of usual type. In some of these the initial sections were not available, so new sections were cut. The excision biopsy findings for those judged to have atypia are shown in table 3. All NCB categorised as suspicious of DCIS were malignant at excision. A NCB diagnosis of atypical ductal hyperplasia-like changes categorised as B3, either on its own with no other risk lesion (40%), which we term 'isolated' or with flat epithelial atypia (29%) had an intermediate risk of malignancy. Isolated flat epithelial atypia (14%) or in combination with lobular neoplasia (0%) had the lowest risk. The single upgraded case of isolated flat epithelial atypia was biopsied for screen-detected calcifications, showed radiological-pathological concordance and revealed low grade DCIS on final histology.

## **DISCUSSION**

In breast cancer screening the use of needle core biopsy (NCB) as part of the triple approach to diagnosis has been standard practice for approximately 10 years in many centres in the UK and elsewhere. According to the current system of NCB categorisation,<sup>5</sup> a diversity of lesions can result in borderline categories; lesion of uncertain malignant potential (B3) or suspicious of malignancy (B4). Previous studies have reported PPVs for B3 lesions from

20% to 35% and PPVs for B4 lesions from 83% to 90%.<sup>7,9,12,14-17</sup> In a previous study of screen detected B3 lesions we noted a reduction in the PPV in recent years.<sup>2</sup> Therefore, in this study we compared B3 and B4 NCBs diagnosed in our institution in 2007 and 2008 with those diagnosed in 1998 to 2000.

The proportion of NCBs reported as B3 increased from 3.1% to 4.5%. A near doubling of the diagnosis of radial scar contributed to this. The most striking result was the decrease in the PPV for B3 diagnoses as a whole from 25% to 10% consistent with the reduction seen in a recent audit of Trent Breast screening NCB.<sup>2</sup> The increase in the diagnosis of radial scar was a contributory factor. This increase is likely to be the result of detection of more subtle lesions following the introduction of digital mammography and improvements in the resolution of ultrasound. Increasing use of vacuum-assisted biopsies, yielding more tissue for diagnosis, may also have helped. Most individual lesions had a similar PPV in both periods, but there was a dramatic reduction in the PPV for lobular neoplasia and a non-significant reduction for AIDEP. An important consideration in analysing the PPV for lobular neoplasia is whether the pathology explains the radiological and clinical features. Lobular neoplasia very rarely causes a mass. In a previous audit of lobular neoplasia on NCB from 1998 to 2006 we found that the majority of patients with malignancy identified in the surgical specimen had radiological-pathological discordance, particularly a mass that was not explained by the NCB histology.<sup>18</sup> Such discordances were more common in the earlier part of this previous study.<sup>18</sup> Improvements in localising the lesion by radiologists may explain this reduction in discordance. We therefore

consider that the most likely explanation for the change in the PPV for lobular neoplasia between the two periods in the present study is more accurate targeting of the lesions by the radiologist taking the NCB. We suspect that, although not statistically significant, the reduction in the PPV for AIDEP from 41% to 23% was an important contributor to the overall reduction in the PPV of all B3 NCBs, as in both series this was the group in which the largest number of cases of malignancy was identified. The recognition of flat epithelial atypia (with its lower PPV) in the more recent series, will have contributed to the reduction in the PPV for all AIDEPs. Despite the diagnosis of the newly recognised flat epithelial atypia in the later series, the total number of diagnoses of AIDEP or of 'suspicious of DCIS' dropped as a proportion of the total of B3 and B4 cores. We suspect that more definite diagnoses of DCIS have been made following the introduction of vacuum-assisted biopsies and plan to investigate this.

In agreement with previous studies,<sup>7-9,12,15,19</sup> our results showed that AIDEP is one of the most frequent B3 lesions, and the PPV for detection of malignancy is about 30%. Similarly, in agreement with our previous study of screen detected B3 lesions in the Trent region<sup>12</sup> and with other authors,<sup>20,21</sup> the results of the current study showed that when papillary lesions or radial scars are detected on NCB without associated epithelial atypia, the PPV for malignancy is low (7% and 3% respectively). Therefore, removal by vacuum

assisted biopsy appears to be a safe alternative to surgical excision if there is no associated epithelial atypia.<sup>22</sup>

The high PPV of 33% for mucocoele-like lesions is most probably not an accurate assessment of the risk of malignancy associated with this lesion in view of the small sample. Four larger studies have found only one malignancy in 30 patients after a core biopsy showing a mucocoele-like lesion without epithelial atypia.<sup>12,23</sup>

It is important to emphasise that the B3 category is not solely used for identifying lesions with an increased risk of epithelial malignancy. For example 69% of the lesions categorised as cellular fibroepithelial lesion on NCB were phyllodes tumour on excision, although none were malignant.

By contrast with the results for B3 NCBs, the proportion of NCBs reported as B4 showed a non-significant reduction from 1.1% to 0.8% and the PPV for a B4 diagnosis was similar in both periods (83% and 88%).

The review of cores with intraductal atypia showed a wide range of PPVs. All those categorised as suspicious of DCIS after review were malignant on excision. The numbers are low and in our previous audit the PPV was less than 100%. We therefore consider that repeat NCB or diagnostic surgical biopsy, rather than therapeutic excision, is still appropriate. The PPVs were

lower following a NCB diagnosis of atypical ductal hyperplasia-like changes categorised as B3, either isolated (40%) or with flat epithelial atypia (29%), or isolated flat epithelial atypia (14%). Some categories with few biopsies had no malignancy on excision, but all categories with at least 6 biopsies had at least one patient with malignancy. The figures for 'suspicious of DCIS' and atypical ductal hyperplasia are similar to previous studies. Flat epithelial atypia is a recently recognised entity and the literature suggests that the risk for isolated flat epithelial atypia is low with PPVs varying between 0 and 20%.<sup>13,24-26</sup> However, the risk on current evidence, is not sufficiently low for multidisciplinary discussion and diagnostic surgical biopsy to be safely avoided.

In conclusion, our results show a significant reduction in the PPV for B3 diagnoses as a group. The increase in the diagnosis of benign radial scar and the reduced PPV for lobular neoplasia contribute to this fall. The potential role of the reduction of the PPV of AIDEP is worthy of further investigation. The different categories of intraductal atypia showed a wide range of PPVs. The PPV for isolated flat epithelial atypia in the current series was not sufficiently low to avoid diagnostic surgical biopsy, but further larger studies would be useful to clarify this. This audit has not resulted in a change to our routine practice as the PPVs for individual lesions has not changed much apart from the reduction for lobular neoplasia. It would be interesting to know whether other centres have also seen a reduction in the PPV for B3 lesions and the reasons for any reduction.

For Peer Review

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**Table 1:** Excision biopsy diagnoses of the different groups of B3 and B4 lesions reported on NCB (based on initial histological reports of the NCB)

Reason for B3/B4 diagnosis on NCB	No	Final excision diagnosis				No excision histology
		Malignant invasive	DCIS	Benign	PPV	
<b>B3</b>						
AIDEP	31	3	4	22	23%	2
Isolated LN	11	0	0	7	0%	4
Isolated papillary lesion	29	1	1	17	7%	10
Papillary + AIDEP	6	0	2	3	33%	1
Isolated RS	39	0	1	29	3%	9
RS +AIDEP	2	0	0	2	0%	0
RS +LN	2	0	0	1	0%	1
Cellular fibroepithelial lesions	16	0	0	15	0%	1
Spindle cell lesion	5	1	0	4	20%	0
Mucocoele-like	3	1	0	1	33%	1
B3 miscellaneous	5	0	1	2	0%	2
B3 total	149	6	9	103	10%	30
<b>B4</b>						
Suspicious of DCIS	18	4	13	1	94%	0
Suspicious of invasive	5	3	1	1	80%	0
Other	3	1	1	1	67%	0
B4 total	26	8	15	3	88%	0

AIDEP= Atypical intraductal epithelial proliferation, LN = Lobular neoplasia (ALH and LCIS), RS = Radial scar/complex sclerosing lesion.

**Table 2:** Comparison of histological outcome of the main groups of B3 and B4 lesions reported on NCB with previous audit

Reason for B3/B4 diagnosis on NCB	Final excision diagnosis					
	2007-2008			1998-2000		
	No	Malignant	PPV	No	Malignant	PPV
<b>B3</b>						
AIDEP*	39	9	23%	46	19	41%
LN*	13	0	0	13	6	46%
Isolated papillary lesion	29	2	7%	22	1	5%
Isolated RS	39	1	3%	21	1	5%
Cellular fibroepithelial lesions	16	0	0	8	1	12%
B3 miscellaneous	13	2	15%	6	1	17%
B3 total	149	15	10%	116	29	25%
<b>B4</b>						
Suspicious of DCIS	18	17	94%	24	19	83%
Suspicious of invasive carcinoma	5	4	80%	4	4	100%
Other	3	2	67%	12	9	75%
B4 total	26	23	88%	40	33	85%
Total core biopsies	3347			3822		

\*AIDEP and LN include biopsies which also contain a radial scar or papillary lesion

Table 3. Atypical intraductal epithelial proliferations (categorised at histological review) and malignancy at excision.

Core diagnosis	Final excision diagnosis					
	Total	Invasive	DCIS	Benign	PPV	No excision
<b>B3</b>						
FEA	7	0	1	6	14%	0
FEA + LN	3	0	0	2	0%	1
FEA + ADH	7	2	0	5	29%	0
ADH	16	1	5	9	40%	1
Apocrine atypia	3	0	0	2	0%	1
Uncategorised	1	0	1	0	100%	0
<b>B4</b>						
FEA + suspicious of low grade DCIS	3	2	1	0	100%	0
Suspicious of low grade DCIS	7	1	6	0	100%	0
Suspicious of intermediate / high grade DCIS	6	1	5	0	100%	0

FEA = flat epithelial atypia, LN = lobular neoplasia, ADH = atypical ductal hyperplasia, DCIS = ductal carcinoma in situ

**Revision with changes marked**

**Outcome of breast lesions diagnosed as lesion of uncertain malignant potential (B3) or suspicious of malignancy (B4) on needle core biopsy including detailed review of epithelial atypia**

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**ABSTRACT**

Aim: To provide updated evidence of the outcome of breast lesions of uncertain malignant potential (B3) and suspicious of malignancy (B4) diagnosed on needle core biopsy (NCB) and analyse the outcome of the different types of intraductal epithelial atypia.

Methods and results: 149 B3 and 26 B4 NCB diagnosed over a 2 year period (2007-2008) were compared to those diagnosed over a previous 2 year period (1998-2000). The proportion of B3 diagnoses increased from 3.1% to 4.5% and the positive predictive value (PPV) of malignancy of a B3 core decreased from 25% to 10%. Increased diagnosis of radial scar and reductions in the PPV of lobular neoplasia and of atypical intraductal proliferation may explain the reduction in the PPV of the B3 group as a whole. There were no significant changes in the proportion of B4 diagnosis (1.1% and 0.8%) or the PPV of B4 (83% and 88%). Review of cores with intraductal atypia showed a wide range of PPVs from 100% for suspicious of DCIS, to 40% for atypical ductal hyperplasia categorised as B3, and 14% for isolated flat epithelial atypia.

Conclusion: The study has found a decrease in the PPV for a B3 diagnosis and suggests possible explanations.

## INTRODUCTION

Needle core biopsy (NCB) is now considered as the method of choice for the triple assessment of breast lesions<sup>1</sup> and the published data suggest that the use of core biopsy has significantly increased the preoperative diagnosis rate.<sup>2-4</sup> The majority of NCB are classified as normal (B1), benign (B2) or malignant (B5).<sup>5</sup> The accuracy of benign and malignant NCB diagnoses is supported by the use of two borderline categories: lesion of uncertain malignant potential (B3) and suspicious of malignancy (B4). The B3 category consists of a heterogeneous group of lesions, which for sampling or other reasons may yield only benign histology on initial NCB sampling but are recognised to show heterogeneity and may harbour malignancy elsewhere or to have an increased risk of associated adjacent malignancy.<sup>2, 5, 6</sup> The B4 category is most commonly used for small fragments of atypical cells separate from the main core, focal atypical intraductal proliferations, which are insufficient for confident diagnosis of DCIS or very small foci of invasive carcinoma in which there is insufficient material for a definite diagnosis.<sup>5, 7</sup> Although the B3 and B4 categories constitute a relatively small proportion of all NCB,<sup>2, 7-9</sup> most cases progress to surgical intervention to establish an excision histology diagnosis.

In a previous study of NCB in the screening setting, we found that the performance of NCB improved over time since its introduction,<sup>2</sup> which may reflect an improvement in the radiological evaluation of breast lesions, sampling technique,<sup>10, 11</sup> publishing of guidelines for assessing breast lesions and reporting of NCB.<sup>5</sup> We also noted a reduction in the positive predictive

value of B3 NCB from 29% in 1997-1998 to 13% in 2006-2007.<sup>2</sup> Therefore, in the current study, we aimed to assess the outcome of lesions recently diagnosed as B3 and B4 categories (2007 to 2008) in our institution and to compare the results with those previously reported over a similar period of time (1998 to 2000).<sup>7</sup> In addition, sections showing intraductal epithelial atypia were reviewed to assess the outcome of the different subtypes of atypia.

## **MATERIALS AND METHODS**

All NCBs reported as B3 or B4 in the 2-year period from January 2007 to December 2008 were studied. NCB results were categorised according to UK guidelines.<sup>5</sup> All patients with a core biopsy diagnosis are discussed at a multidisciplinary meeting, with a breast radiologist, histopathologist and surgeon present, at which decisions on further action are made. Those patients not undergoing an excision biopsy were therefore subject to multidisciplinary discussion to ensure that this conclusion was appropriate. Histology reports of B3 and B4 NCB and the subsequent diagnostic surgical biopsy results of all patients were reviewed. For the purpose of this study, excision histology findings were categorised as a) malignant including invasive carcinoma, ductal carcinoma in situ (DCIS), and other malignant lesions such as sarcomas and lymphomas, and b) benign lesions including atypical ductal hyperplasia (ADH), classical lobular neoplasia (atypical lobular hyperplasia and lobular carcinoma in situ). Positive predictive values (PPV) for detection of malignancy were calculated as recommended by the NHS breast screening programme.<sup>5</sup> The PPV for B3 diagnoses = (number of final

malignant diagnoses / total number of subjects with B3 diagnosis) x 100%. The PPV for B4 diagnoses = (number of final malignant diagnoses / total number of subjects with B4 diagnosis excluding those without further histology) x 100%. Comparisons were made with a previous review of B3 and B4 NCB from July 1998 to June 2000.<sup>7</sup>

In this study, we classified B3 and B4 diagnoses into entities similar to those that we previously used.<sup>7, 12</sup> Cases diagnosed as atypical intraductal epithelial proliferation (AIDEP) or suspicious of DCIS were subjected to histological review by 3 pathologists and classified into different entities according to the subtype of atypia. If a change in diagnosis was being considered, the slides were reviewed by a fourth pathologist. This review was blind to the final diagnosis.

Flat epithelial atypia was defined as dilated acini lined by up to a few layers of cells with round to oval nuclei and apical snouts.<sup>13</sup> The nuclei were typically small and evenly spaced. Occasionally the nuclei were larger with more obvious atypia. Atypical ductal hyperplasia is a diagnosis that strictly should be reserved for surgical specimens. Nevertheless, we used this term for proliferations of cells with small evenly spaced nuclei with solid, cribriform or micropapillary architecture. An important criterion was that low grade DCIS was being considered, but the changes were not sufficient for this diagnosis. We follow the UK guidelines that diagnosis of low or intermediate grade DCIS requires involvement of two duct spaces, whereas high grade DCIS can

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diagnosed in one duct.<sup>5</sup> Atypical apocrine proliferations were categorised separately.

## RESULTS

In 2007 and 2008, 149 of 3347 NCB (4.5%) were reported as B3 compared with 3.1% (120 of 3822) in 1998 to 2000 (corrected  $\chi^2 = 8.1$ ,  $P = 0.004$ ). 50 were screen-detected and 99 were symptomatic lesions. 26 of 3347 NCB (0.8%) were reported as B4 compared with 1.1% (43 of 3822) in 1998 to 2000 ( $P = 0.17$ ). 8 were screen-detected and 18 were symptomatic lesions. The excision biopsy findings for these patients are shown in table 1. In each of the categories B3 and B4 no association was found between the final diagnosis (benign versus malignant) and method of presentation (screen detected versus symptomatic), preoperative radiological/clinical diagnosis, method of guidance of the biopsy (free hand versus stereotactic versus ultrasound) or type of biopsy (core biopsy versus vacuum-assisted biopsy).

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### *B3 cores*

A comparison of the excision biopsy findings in 2007 to 2008 and 1998 to 2000 is shown in table 2. The main B3 NCB diagnoses in both series were AIDEP, radial scar and papillary lesions. The number of cores showing isolated radial scar nearly doubled; this difference measured as the proportion of all core biopsies was significant (1.8% versus 1.2%,  $\chi^2 = 7.4$ ,  $P = 0.006$ ),

but not when assessed as the proportion of B3 NCB (26% versus 18%,  $\chi^2 = 2.1$ ,  $P = 0.15$ ).

The PPV for B3 lesions was 10%, significantly reduced from 25% in 1998 to 2000 ( $\chi^2 = 9.5$ ,  $P = 0.002$ ). There were clear differences in outcome in the different B3 subtypes in both series. The PPV was highest for AIDEP (23%), but this was less than the figure of 41% in 1998 to 2000, although this difference was not significant ( $P = 0.12$ ). The PPV for lobular neoplasia was much lower in the current series (0% versus 46%,  $\chi^2 = 5.4$ ,  $P = 0.02$ ), but this does not take radiological-pathological discordance into account. Most of the other categories without epithelial atypia had low PPVs. The exceptions were spindle cell lesions (one of five was a spindle cell carcinoma) and mucocoele-like lesions (one of three was a mucinous carcinoma in a symptomatic patient), but the numbers in these categories are small. 11 of 16 (69%) cellular fibroepithelial lesions on NCB were phyllodes tumour on excision (8 benign, 3 borderline).

#### *B4 cores*

The most frequent B4 diagnosis in both series was 'suspicious of DCIS'. The PPV was similar in both, 88% in 2007 to 2008 and 83% in 1998 to 2000.

The total number of biopsies reported as AIDEP or suspicious of DCIS reduced as a proportion of all B3 and B4 biopsies (45% in 1998 to 2000 and 33% in 2007 to 2008,  $\chi^2 = 4.8$ ,  $P = 0.03$ ), but not as a proportion of all core biopsies (1.8% versus 1.7%,  $P = 0.72$ ).

### *Subtypes of atypia*

All biopsies with intraductal epithelial atypia were reviewed. Four biopsies were downgraded to benign: 3 columnar cell lesions initially categorised as B3 and one initially categorised as suspicious of low grade DCIS was downgraded to epithelial hyperplasia of usual type. In some of these the initial sections were not available, so new sections were cut. The excision biopsy findings for those judged to have atypia are shown in table 3. All NCB categorised as suspicious of DCIS were malignant at excision. A NCB diagnosis of atypical ductal hyperplasia-like changes categorised as B3, either on its own with no other risk lesion, (40%), which we term 'isolated' or with flat epithelial atypia (29%) had an intermediate risk of malignancy. Isolated flat epithelial atypia (14%) or in combination with lobular neoplasia (0%) had the lowest risk. The single upgraded case of isolated flat epithelial atypia was biopsied for screen-detected calcifications, showed radiological-pathological concordance and revealed low grade DCIS on final histology.

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## **DISCUSSION**

In breast cancer screening the use of needle core biopsy (NCB) as part of the triple approach to diagnosis has been standard practice for approximately 10 years in many centres in the UK and elsewhere. According to the current system of NCB categorisation,<sup>5</sup> a diversity of lesions can result in borderline categories; lesion of uncertain malignant potential (B3) or suspicious of malignancy (B4). Previous studies have reported PPVs for B3 lesions from

20% to 35% and PPVs for B4 lesions from 83% to 90%.<sup>7,9,12,14-17</sup> In a previous study of screen detected B3 lesions we noted a reduction in the PPV in recent years.<sup>2</sup> Therefore, in this study we compared B3 and B4 NCBs diagnosed in our institution in 2007 and 2008 with those diagnosed in 1998 to 2000.

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The proportion of NCBs reported as B3 increased from 3.1% to 4.5%. A near doubling of the diagnosis of radial scar contributed to this. The most striking result was the decrease in the PPV for B3 diagnoses as a whole from 25% to 10% consistent with the reduction seen in a recent audit of Trent Breast screening NCB.<sup>2</sup> The increase in the diagnosis of radial scar was a contributory factor. This increase is likely to be the result of detection of more subtle lesions following the introduction of digital mammography and improvements in the resolution of ultrasound. Increasing use of vacuum-assisted biopsies, yielding more tissue for diagnosis, may also have helped.

Most individual lesions had a similar PPV in both periods, but there was a dramatic reduction in the PPV for lobular neoplasia and a non-significant reduction for AIDEP. An important consideration in analysing the PPV for lobular neoplasia is whether the pathology explains the radiological and clinical features. Lobular neoplasia very rarely causes a mass. In a previous audit of lobular neoplasia on NCB from 1998 to 2006 we found that the majority of patients with malignancy identified in the surgical specimen had radiological-pathological discordance, particularly a mass that was not explained by the NCB histology.<sup>18</sup> Such discordances were more common in the earlier part of this previous study.<sup>18</sup> Improvements in localising the lesion by radiologists may explain this reduction in discordance. We therefore

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consider that the most likely explanation for the change in the PPV for lobular neoplasia [between the two periods in the present study](#) is more accurate targeting of the lesions by the radiologist taking the NCB. We suspect that, although not statistically significant, the reduction in the PPV for AIDEP from 41% to 23% was an important contributor to the overall reduction in the PPV of all B3 NCBs, as in both series this was the group in which the largest number of cases of malignancy was identified. [The recognition of flat epithelial atypia \(with its lower PPV\) in the more recent series, will have contributed to the reduction in the PPV for all AIDEPs. Despite the diagnosis of the newly recognised flat epithelial atypia in the later series, the total number of diagnoses of AIDEP or of 'suspicious of DCIS' dropped as a proportion of the total of B3 and B4 cores. We suspect that more definite diagnoses of DCIS have been made following the introduction of vacuum-assisted biopsies and plan to investigate this.](#)

In agreement with previous studies,<sup>7-9,12,15,19</sup> our results showed that AIDEP is one of the most frequent B3 lesions, and the PPV for detection of malignancy is about 30%. Similarly, in agreement with our previous study of screen detected B3 lesions in the Trent region<sup>12</sup> and with other authors,<sup>20,21</sup> the results of the current study showed that when papillary lesions or radial scars are detected on NCB without associated epithelial atypia, the PPV for malignancy is low (7% and 3% respectively). Therefore, removal by vacuum

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assisted biopsy appears to be a safe alternative to surgical excision if there is no associated epithelial atypia.<sup>22</sup>

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The high PPV of 33% for mucocoele-like lesions is most probably not an accurate assessment of the risk of malignancy associated with this lesion in view of the small sample. Four larger studies have found only one malignancy in 30 patients after a core biopsy showing a mucocoele-like lesion without epithelial atypia.<sup>12,23</sup>

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It is important to emphasise that the B3 category is not solely used for identifying lesions with an increased risk of epithelial malignancy. For example 69% of the lesions categorised as cellular fibroepithelial lesion on NCB were phyllodes tumour on excision, although none were malignant.

By contrast with the results for B3 NCBs, the proportion of NCBs reported as B4 showed a non-significant reduction from 1.1% to 0.8% and the PPV for a B4 diagnosis was similar in both periods (83% and 88%).

The review of cores with intraductal atypia showed a wide range of PPVs. All those categorised as suspicious of DCIS [after review](#) were malignant on excision. The numbers are low and in our previous audit the PPV was less than 100%. We therefore consider that repeat NCB or diagnostic surgical biopsy, [rather than therapeutic excision](#), [is](#) still appropriate. The PPVs were

lower following a NCB diagnosis of atypical ductal hyperplasia-like changes categorised as B3, either isolated (40%) or with flat epithelial atypia (29%), or isolated flat epithelial atypia (14%). Some categories with few biopsies had no malignancy on excision, but all categories with at least 6 biopsies had at least one patient with malignancy. The figures for 'suspicious of DCIS' and atypical ductal hyperplasia are similar to previous studies. Flat epithelial atypia is a recently recognised entity and the literature suggests that the risk for isolated flat epithelial atypia is low with PPVs varying between 0 and 20%.<sup>13,24-26</sup>

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However, the risk on current evidence, is not sufficiently low for multidisciplinary discussion and diagnostic surgical biopsy to be safely avoided.

In conclusion, our results show a significant reduction in the PPV for B3 diagnoses as a group. The increase in the diagnosis of benign radial scar and the reduced PPV for lobular neoplasia contribute to this fall. The potential role of the reduction of the PPV of AIDEP is worthy of further investigation. The different categories of intraductal atypia showed a wide range of PPVs. The PPV for isolated flat epithelial atypia in the current series was not sufficiently low to avoid diagnostic surgical biopsy, but further larger studies would be useful to clarify this. [This audit has not resulted in a change to our routine practice as the PPVs for individual lesions has not changed much apart from the reduction for lobular neoplasia. It would be interesting to know whether other centres have also seen a reduction in the PPV for B3 lesions and the reasons for any reduction.](#)

For Peer Review

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**Table 1:** Excision biopsy diagnoses of the different groups of B3 and B4 lesions reported on NCB (based on initial histological reports of the NCB)

Reason for B3/B4 diagnosis on NCB	No	Final excision diagnosis				No excision histology
		Malignant invasive	DCIS	Benign	PPV	
<b>B3</b>						
AIDEP	31	3	4	22	23%	2
Isolated LN	11	0	0	7	0%	4
Isolated papillary lesion	29	1	1	17	7%	10
Papillary + AIDEP	6	0	2	3	33%	1
Isolated RS	39	0	1	29	3%	9
RS +AIDEP	2	0	0	2	0%	0
RS +LN	2	0	0	1	0%	1
Cellular fibroethelial lesions	16	0	0	15	0%	1
Spindle cell lesion	5	1	0	4	20%	0
Mucocoele-like	3	1	0	1	33%	1
B3 miscellaneous	5	0	1	2	0%	2
B3 total	149	6	9	103	10%	30
<b>B4</b>						
Suspicious of DCIS	18	4	13	1	94%	0
Suspicious of invasive	5	3	1	1	80%	0
Other	3	1	1	1	67%	0
B4 total	26	8	15	3	88%	0

AIDEP= Atypical intraductal epithelial proliferation, LN = Lobular neoplasia (ALH and LCIS), RS = Radial scar/complex sclerosing lesion.

**Table 2:** Comparison of histological outcome of the main groups of B3 and B4 lesions reported on NCB with previous audit

Reason for B3/B4 diagnosis on NCB	Final excision diagnosis					
	2007-2008			1998-2000		
	No	Malignant	PPV	No	Malignant	PPV
<b>B3</b>						
AIDEP*	39	9	23%	46	19	41%
LN*	13	0	0	13	6	46%
Isolated papillary lesion	29	2	7%	22	1	5%
Isolated RS	39	1	3%	21	1	5%
Cellular fibroepithelial lesions	16	0	0	8	1	12%
B3 miscellaneous	13	2	15%	6	1	17%
B3 total	149	15	10%	116	29	25%
<b>B4</b>						
Suspicious of DCIS	18	17	94%	24	19	83%
Suspicious of invasive carcinoma	5	4	80%	4	4	100%
Other	3	2	67%	12	9	75%
B4 total	26	23	88%	40	33	85%
Total core biopsies	3347			3822		

\*AIDEP and LN include biopsies which also contain a radial scar or papillary lesion

Table 3. Atypical intraductal epithelial proliferations (categorised at histological review) and malignancy at excision.

Core diagnosis	Final excision diagnosis					
	Total	Invasive	DCIS	Benign	PPV	No excision
<b>B3</b>						
FEA	7	0	1	6	14%	0
FEA + LN	3	0	0	2	0%	1
FEA + ADH	7	2	0	5	29%	0
ADH	16	1	5	9	40%	1
Apocrine atypia	3	0	0	2	0%	1
Uncategorised	1	0	1	0	100%	0
<b>B4</b>						
FEA + suspicious of low grade DCIS	3	2	1	0	100%	0
Suspicious of low grade DCIS	7	1	6	0	100%	0
Suspicious of intermediate / high grade DCIS	6	1	5	0	100%	0

FEA = flat epithelial atypia, LN = lobular neoplasia, ADH = atypical ductal hyperplasia, DCIS = ductal carcinoma in situ