Large volume "mammotome" biopsy may reduce the need for diagnostic surgery in papillary lesions of the breast

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ABSTRACT

Background: There is currently debate as to whether all papillary lesions diagnosed on breast needle core biopsy (BNCB) require surgical excision. The development of large volume "mammotome" biopsy now permits non-operative removal. Few studies have assessed the usefulness of this approach.

Aim: To review the pathological and radiological findings in a series of B3 and B4 papillary lesions identified on conventional BNCB with a view to assessing the usefulness of mammotome biopsy as a means of avoiding diagnostic surgery.

Methods: All BNCBs from 23 June 2005 to 14 August 2007 that contained a B3 or B4 papillary lesion were identified by searching the pathology department records. Follow-up histology and radiological details were obtained.

Results: 34 papillary BNCBs were included in this study: 21 from screen-detected lesions and 13 from patients presenting symptomatically. 31 were classified B3 and three were B4. Four cases included an atypical ductal epithelial proliferation (three B4, one B3). 14 patients had undergone open surgical biopsy, 15 had undergone mammotome excision, and five had had no subsequent procedure. All cases that had undergone mammotome biopsy had not shown atypia on the core, and 13 (87%) proved benign. In two cases the mammotome biopsy was either atypical or malignant, prompting surgery; the biopsy changes deriving from areas of ductal carcinoma in situ arising in the context of multiple intraduct papillomas and both were distinctive mammographically in presenting with large areas of segmental calcification. 11/14 cases that had undergone surgical excision had not shown atypia on the core, and proved benign. All three cases with atypia on the core proved malignant.

Conclusion: In selected cases, mammotome biopsy may improve sampling of papillary lesions such that malignancy may be excluded without recourse to diagnostic surgery. Mammotome in such cases effectively acts as a therapeutic procedure. This has important implications for symptomatic and breast screening services.

Papillary lesions are encountered in up to 4% of percutaneous breast needle core biopsies[1] and, while infrequent, can be among the most challenging breast lesions to interpret histologically. They comprise a heterogeneous group of benign, atypical and malignant conditions that include papilloma (single or multiple, including so-called "papillomatosis"), papilloma with atypical ductal hyperplasia (ADH) (or "atypical papilloma"), papillary ductal carcinoma in situ (DCIS) (including the solid endocrine variant), intracystic, encysted or "encapsulated" papillary carcinoma, and invasive papillary carcinoma. Tissue fragmentation and inconsistent terminology compound the difficulties in biopsy diagnosis. In view of the potential for papillomas to harbour atypia or malignancy, the UK National Health Service Breast Screening Programme (NHSBSP) pathology reporting guidelines suggest that the majority of papillary lesions diagnosed on needle core biopsy should be categorised B3 (of uncertain malignant potential) or B4 if there is atypia suggesting malignancy.[2] A B2 category may be used if the lesion is benign and "adequately sampled".

Recent reports suggest that the diagnosis of a benign papillary lesion on needle core biopsy implies a very low risk of associated malignancy—possibly as low as 3%—and that surgical excision may be unnecessary in some cases (reviewed by Ashkenazi *et al*[3]). A number of authors have suggested that mammographic follow-up may provide a safe alternative providing that the radiological and pathological features are concordant and the lesion has been adequately sampled,[4–7] although others have advised caution.[8–10] In the absence of atypia, the reported risk of malignancy on excision varies from 0% to 20%.[3] However, most of the literature derives from the USA, and many series include only small numbers of cases. There have been only two UK-based studies,[6 7] both of which have advocated a selective approach to surgery. The risks of a conventional needle core biopsy failing to sample atypical or malignant areas within an otherwise benign papilloma may be minimised by more extensive sampling. Histological assessment may be facilitated by immunohistochemistry.[7]

The recent introduction of vacuum-assisted large volume "mammotome" biopsy provides an opportunity to further sample papillary lesions diagnosed on conventional core biopsy, such that a benign diagnosis may be accepted more confidently. The mammotome, used in this way, offers an alternative to diagnostic excision and, if the lesion has been entirely removed, effectively becomes a therapeutic procedure. Since January 2006, we have used the mammotome to further sample non-atypical papillary lesions in screening and symptomatic populations. Here we present our early results, which confirm the usefulness of this approach.

METHODS

The pathology computer records from the Bradford Teaching Hospitals NHS Foundation Trust were searched for all breast needle core biopsies taken

between the dates 23 June 2005 and 14 August 2007 and classified as B3 or B4, with the words "papillary" or "papilloma" in the final diagnosis. Cases with a malignant diagnosis (B5a, b or c), cases coded as B1 or B2, and cases with a diagnosis of papillary apocrine hyperplasia were excluded. Follow-up histology was traced from the pathology computer records or from the Pennine Breast Screening Unit or the radiology department records. For each case patient age, whether screen-detected or symptomatic, pathological NHSBSP B category and the histological findings on core, mammotome and open biopsy were recorded. The mammographic and ultrasound findings and the radiological R and U categories were retrieved from the screening and radiology records. All core biopsies had been performed under either ultrasound or stereotactic guidance using 14 gauge needles. Large volume biopsy had been performed using the mammotome vacuum-assisted biopsy system (Ethicon Endo-Surgery, Cincinnati, Ohio, USA) with either 11 or 8 gauge needles.

RESULTS

Thirty-four "non-diagnostic" papillary lesions identified on breast needle core biopsies were diagnosed during the study period. Twenty-one cases presented via the Pennine Breast Screening Unit and 13 cases were symptomatic. Thirty had been categorised B3, one had been categorised B2/B3 (the pathologist was uncertain whether the lesion was "adequately sampled") and three had been categorised B4.Twenty-five had been diagnosed as a papilloma on the core biopsy and five had been described as including a lesion that was at least in part papillary. Four of the 34 non-diagnostic papillary core biopsies (three B4 and one B3) included an atypical papillary proliferation raising the possibility of papillary carcinoma. Fourteen patients had undergone open surgical biopsy, 15 had undergone mammotome excision, and five had had no subsequent procedure. In four cases this was because the initial lesion was no longer visible (three were calcification, one was a complex cyst), and in one case because the patient was unfit for the mammotome procedure

Core biopsies with atypia

Four cases included an atypical papillary epithelial proliferation on the core (table 1). One was described as an "intraductal papillary proliferation with atypia—DCIS not excluded—B3" (fig 1) and one was reported as an "atypical papillary proliferation—B4" following review prior to multidisciplinary team (MDT) meeting (having initially been reported as a benign papilloma) (fig 2). Two cases were reported as suspicious of papillary DCIS.

Three of these four cases had undergone open biopsy and all three (100%) proved malignant. The two suspicious cases were confirmed as papillary carcinoma in situ. These two cases were new mass lesions radiologically that had been detected on incident round screening mammograms. The B4 atypical papillary proliferation diagnosed on review was from a clinical lump in a patient with a contralateral breast cancer and proved to represent part of an area of low-grade papillary DCIS within which was found a 1.5 mm focus of grade 1 invasive carcinoma.

There were an additional two cases where a core biopsy diagnosis of benign papilloma was accompanied by a comment in the pathology report suggesting the possibility of associated lobular in situ neoplasia (LISN) amounting to atypical lobular hyperplasia (ALH) (fig 3). Unfortunately immunohistochemistry for E-cadherin was unhelpful in both cases as the relevant areas were not represented on the relevant slides. The two cases had undergone surgical excision, which confirmed intraduct papillomata but no evidence of LISN.

Core biopsies without atypia

All 11 cases without atypia on the core undergoing open surgical biopsy proved benign. Ten of 11 proved to derive from solitary papillomas, and one from an area of benign breast change, which included papilloma formation, radial scar formation, epithelial hyperplasia of usual type and focal LISN amounting to ALH.

Of the 15 cases without atypia on the core who had undergone mammotome rather than surgery, two were atypical or malignant on the mammotome (table 2). The remaining 13 cases demonstrated benign changes only. The diagnosis of benign papilloma was confirmed in 11 cases (adenoma/papilloma in one of these). In one case the mammotome contained only residual cyst wall, and in one there was no residual papilloma, with the radiological lesion considered removed by the core biopsy.

In one case the core contained a fragmenting, focally hyalinised papillary lesion, with the mammotome containing an atypical epithelial proliferation amounting to low-grade micropapillary and cribriform DCIS. Occasional duct profiles contained a benign papillary proliferation suggesting associated multiple intraduct papillomas or papillomatosis. Ultrasound appearances were normal but mammographically there were indeterminate segmental calcifications extending over approximately 6 cm on a prevalent round screen (fig 4). A subsequent mastectomy revealed multiple intraduct papillomata and extensive low-grade DCIS (fig 5). In the other case, the initial core biopsy findings suggested multiple intraduct papillomata with the mammotome revealing a papillary lesion associated with an atypical epithelial proliferation (fig 6). Incident round

Table 1 Core biopsies of papillary lesions with atypia: radiological and pathological findings

Case	Mammography	Ultrasound	R/U	B*	Core biopsy	Excision biopsy
1	5 mm, new cluster calcifications	NA	R3	B3	Intraductal papillary proliferation, DCIS not excluded	Not fit for surgery
2	8 mm mass and calcification	8 mm mass and calcification	R3U3	B4	Suggestive of intraduct papillary carcinoma	6 mm high-grade papillary and cribriform DCIS
3	8 mm mass	19 mm area of altered echogenicity	R2U3	B4	Intraduct papilloma; atypia on review for MDT	20 mm low-grade papillary/micropapillary and flat DCIS with 1.5 mm focus of invasive carcinoma
4	6 mm, new, well-defined mass	6 mm, new, well-defined mass	R2U3	B4	Papillary lesion with atypia? papillary DCIS	6 mm low-grade papillary/cribriform DCIS

*UK National Health Service Breast Screening Programme categorisation.
DCIS, ductal carcinoma in situ; MDT, multidisciplinary team; NA, not applicable.

Table 2 Cases without atypia on the core proving atypical or malignant on mammotome

Mammography	Ultrasound	R/U	B	Core	Mammotome	Excision biopsy	Mastectomy
60 mm segmental calcification	"Fibrocystic change"	RU/U1	B3	Papillary lesion	Low-grade DCIS with possible papillomatosis		70 mm low-grade DCIS arising in context of multiple papillomas
30 mm segmental calcification upper outer quadrant – increased in size	7 mm altered echogenicity with nodules	R3/U3	B3	Papillary lesion with ADH and possible papillomatosis	"Atypical proliferation in relation to a papillary lesion"	×2 excision biopsies with 16 mm and 30 mm low-grade DCIS and adjacent papilloma	×3 papillomas, no residual DCIS

*UK National Health Service Breast Screening Programme categorisation.
ADH, atypical ductal hyperplasia; DCIS, ductal carcinoma in situ.

mammography revealed a 3 cm area of segmental indeterminate calcification, which had increased since the previous screen, and a 7 mm area of altered echogenicity with multiple nodules (fig 7). Diagnostic open biopsy revealed low-grade DCIS extending over 16 mm with an adjacent papilloma. Further DCIS and multiple papillomas were found following two subsequent wide local excisions and a completion mastectomy.

Radiological findings

Eleven of the 21 screen-detected lesions presented solely with mammographic calcification that was new or on prevalent round screen in six and increasing in five. Two had mammographic changes that included a mass with calcification, and one was an area of calcification that was unchanged but in a patient with a newly diagnosed contralateral breast cancer. One had a mass with calcification as well as a separate cluster of calcification. Six were new mass lesions.

Eight of the 13 cases presenting symptomatically had mass lesions radiologically. Five of these had mass lesions on mammography with a corresponding abnormality on ultrasound; three had normal mammograms with an ultrasound-detected mass varying from 4 to 11 mm. One had a mass lesion with calcification, one had a dilated duct on mammography with a corresponding intraductal mass on ultrasound and one had an area of asymmetry and a mass. Two had foci of calcification measuring 5 mm or less

Thirty-three cases were classified as radiologically indeterminate on either mammography, ultrasound or both. One—a 12 mm cluster of calcification—was coded as radiologically benign.

Follow-up

Fourteen patients had undergone surgical excision. Of those with prior non-atypical core biopsies, four were before mammotome became available. Two had two lesions thought to represent multiple papillomata, one had a large lobulated intraductal mass possible representing more than one papilloma, one was too large for mammotome measuring 30 mm on ultrasound, one patient was already planned for surgery with a contralateral breast cancer, and one patient preferred a surgical procedure.

Fifteen patients had had papillary lesions removed by vacuum-assisted mammotome. Ten of these were screen-detected lesions and five were in patients presenting symptomatically. Eight (including all five symptomatic patients) were performed under ultrasound guidance and seven were performed under stereotactic guidance. One mammotome failed as the lesion was very vascular and it was situated immediately beneath the nipple.

In all except three cases, the lesions undergoing mammotome measured 15 mm or less in maximum dimension. In these cases the procedure was effectively a therapeutic rather than a diagnostic procedure. The three larger lesions were the two cases of segmental calcification discussed previously and a symptomatic patient with a 60 mm lobulated mass in which mammotome revealed only residual cyst wall and in whom follow-up mammography was normal.

One patient re-presented 9 months after mammotome excision of a subareolar papilloma with a further papilloma in a similar area. This was removed surgically. Subsequent histology revealed an intraduct papilloma, but it was uncertain

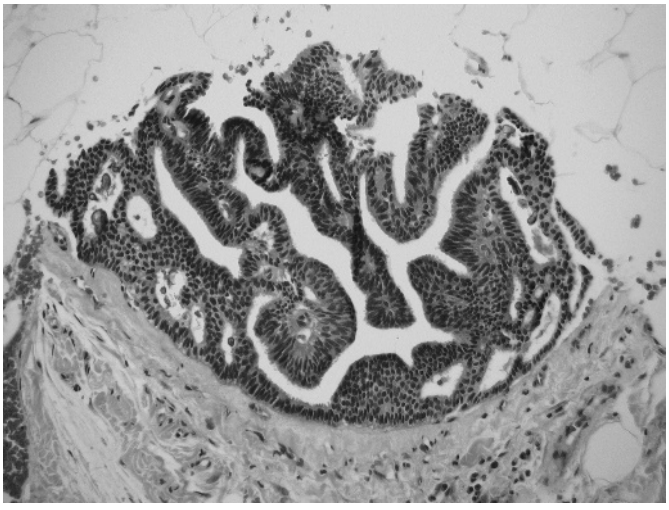

Figure 1 Conventional core biopsy reported as "intraductal papillary proliferation with atypia, DCIS not excluded, B3" (H&E ×100).

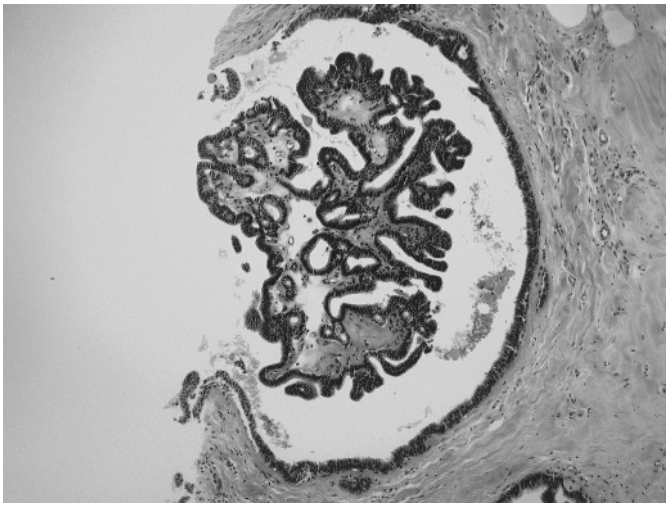

Figure 2 Core biopsy reported as "atypical papillary proliferation, B4" following review prior to multidisciplinary team meeting (H&E ×100).

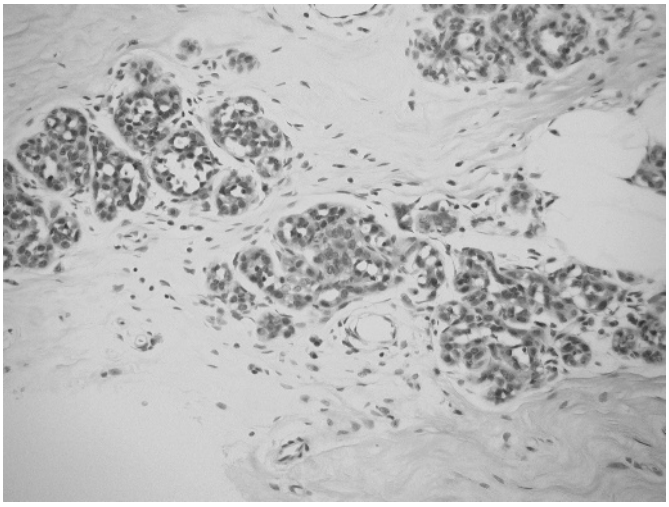

Figure 3 Core biopsy reported as "possible lobular in situ neoplasia amounting to atypical lobular hyperplasia" (H&E ×100).

whether this was a new lesion in a patient with multiple papillomas or a recurrence of the original lesion.

DISCUSSION

Numerous published series suggest that the risk of malignancy following a core biopsy containing a benign papilloma is low[11–17] raising the possibility that some may not require diagnostic surgery. It is not always easy to compare published series, however, as many are small, most derive from the USA, terminology varies, and the B categorisation system used in the UK is not universally employed. Mammographic follow-up may be a safe alternative to surgery providing that radiological and pathological features are concordant, but this approach has not been widely adopted. The recently developed mammotome device permits more extensive sampling of papillary lesions, thus providing additional reassurance that a lesion is wholly benign. Our results confirm that further sampling by mammotome following a conventional core biopsy can reduce the need for surgery.

In our series, 13 out of 15 (87%) non-atypical papillary lesions diagnosed on conventional core biopsy were confirmed as benign on subsequent mammotome and therefore avoided a surgical procedure. None of these cases have developed malignancy or presented with an interval cancer to date. The two cases where the mammotome findings "upgraded" the core biopsy by revealing either atypia or malignancy were the only two cases in this series where the mammographic calcification was segmental and extensive. In both cases the final diagnosis of malignancy was related to a background of multiple intraduct papillomas (or papillomatosis), suggesting the need for a higher incidence of suspicion and perhaps a less conservative approach if this diagnosis is suspected. Multiple papillomas are associated with a higher risk of malignancy[18] and patients with these lesions may be best served by wide excision with clear margins and annual follow-up mammography.

The presence of "atypia" in association with a papillary lesion in general corresponds to a UK NHSBSP B4 category and is an important predictor of subsequent malignancy. Identification of an atypical epithelial proliferation can, however, be challenging histologically and there is thus a degree of interobserver variation in biopsy categorisation. A population of monomorphic cells with rounded evenly spaced nuclei or a uniform

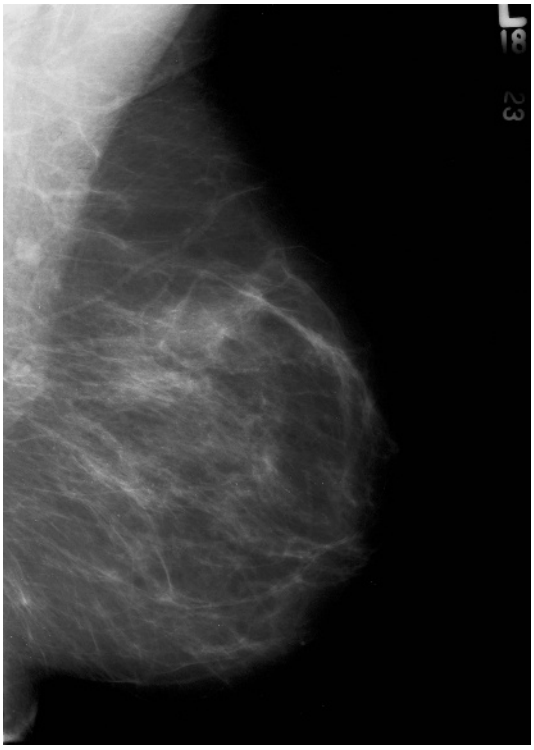

Figure 4 Indeterminate segmental calcification extending over approximately 6 cm on prevalent round screen.

columnar cell population may be seen as part of an intracystic (or encysted) papillary carcinoma, as part of papillary DCIS or as part of ADH/DCIS arising within an otherwise typical papilloma.[1] Immunohistochemistry for cytokeratin 5/6 can be invaluable in highlighting such uniformly negative cells and can be particularly useful in distinguishing between solid papillary endocrine DCIS and severe usual-type epithelial hyperplasia in the context of a papilloma.[19] Myoepithelial markers (eg, smooth muscle myosin or p63) may be useful but may be absent at the periphery of an encapsulated papillary carcinoma[20] The presence of myoepithelium surrounding a duct supports a diagnosis of

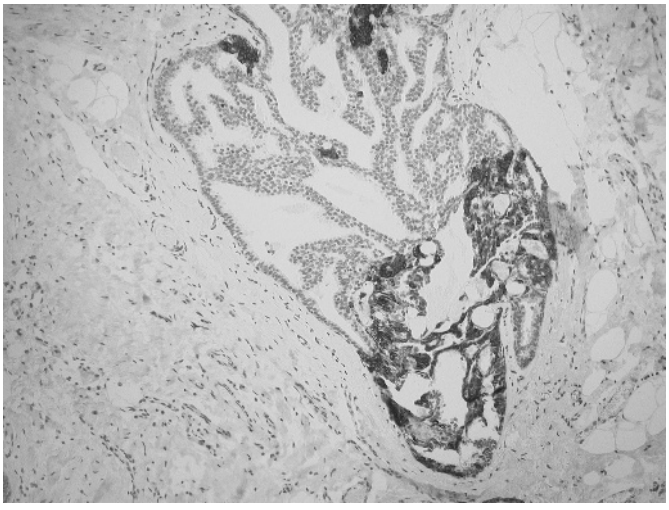

Figure 5 Mastectomy specimen containing multiple intraduct papillomata and extensive low-grade ductal carcinoma in situ. Here the clonal low-grade proliferation is highlighted by negative staining for cytokeratin 5/6 (×100).

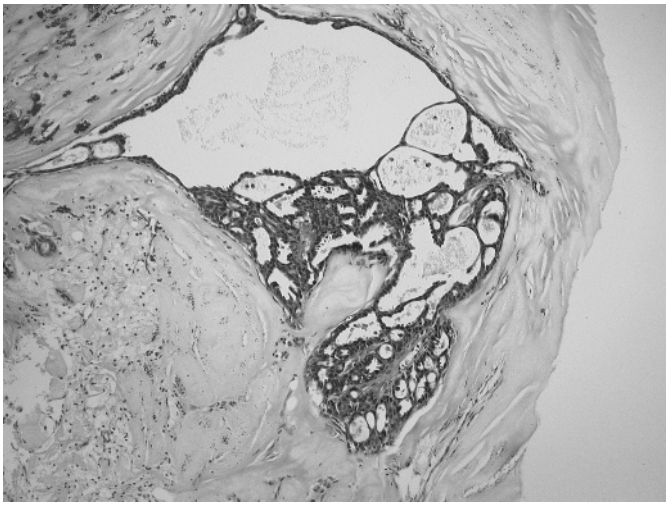

Figure 6 Mammotome biopsy containing a papillary lesion associated with an atypical apocrine proliferation, B4 (H&E ×100).

benign papilloma but does not exclude the possibility of an associated atypical epithelial proliferation.

In this series there were two core biopsies containing papillomas with possible ALH, which was not confirmed on subsequent excision. It is uncertain whether LISN in association with an otherwise benign papillary lesion has the same implications as an atypical ductal epithelial proliferation. Dyscohesion and tissue disruption can produce potentially misleading histological appearances and immunohistochemistry for E-cadherin can be a useful diagnostic aid. Current recommendations that LISN diagnosed on needle core biopsy should prompt open surgical biopsy are based on an underestimation of carcinoma in up to 33% of cases.[21] More thorough sampling with the mammotome might provide sufficient reassurance to avoid the need for surgery in some of these cases also.

In conclusion, large volume (mammotome) biopsy has the potential to improve sampling of non-atypical papillary lesions diagnosed on conventional core biopsy such that malignancy may be excluded without recourse to diagnostic surgery in a significant proportion of cases. The presence of an atypical papillary proliferation in either a core or a mammotome biopsy, however, is a strong predictor of malignancy. We believe that mammotome excision biopsy should be the management option of choice in selected papillary lesions of the breast. Small, solitary, screen-detected benign papillary lesions—ideally confirmed using immunohistochemistry and on pathological review—would seem ideal candidates for this approach. Selective use of the mammotome device has the potential to significantly reduce the need for diagnostic surgery in the screening and the symptomatic populations.

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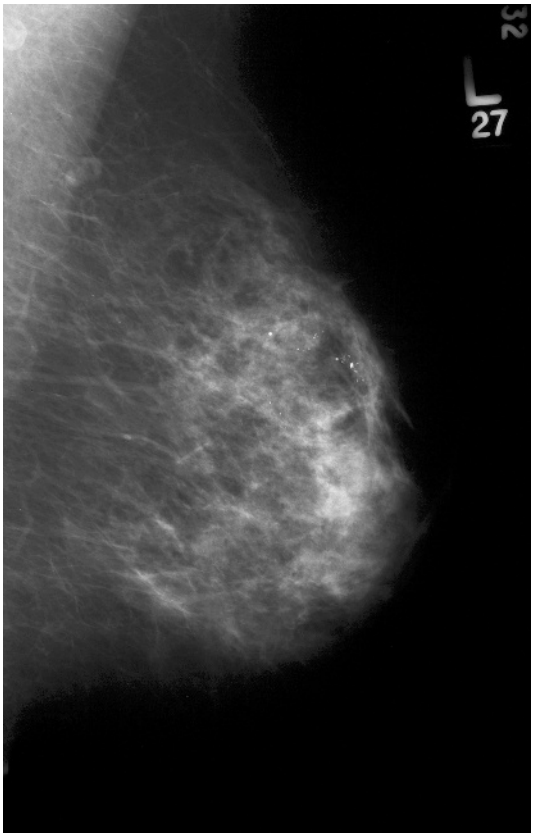

Figure 7 Incident round mammography revealed a 3 cm area of segmental indeterminate calcification that had increased since the previous screen.

Take-home messages

- A core biopsy containing benign papilloma without atypia is rarely associated with malignancy on subsequent excision.
- Selected benign papillary lesions may be removed non-operatively by mammotome excision.
- Small, screen-detected benign papillary lesions confirmed by immunohistochemistry and on pathological review are ideal candidates for mammotome excision.
- A core biopsy containing a papillary lesion with atypia is very likely to prove malignant and should be removed surgically.

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