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Chapter 3

Histopathology of Fibroadenoma of the Breast

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Abstract

Fibroadenoma of the breast is associated with an elevated risk for invasive breast cancer, especially in case of complex changes and epithelial proliferations in adjacent tissue. The aim of this study was, therefore, to make a thorough inventory of the histologic features of epithelium and stroma within and adjacent to breast fibroadenomas in a group of 396 cases.

Breast fibroadenomas appeared to display a wide spectrum of proliferative and non-proliferative histologic changes. Hyperplasia (excluding mild hyperplasia) within the fibroadenoma was found in 32.3% of cases. Carcinoma *in situ* (CIS; five ductal, three lobular) was found in eight fibroadenomas (2.0%) removed from six patients (1.7%), the youngest being 40 years of age. In three cases CIS was not confined to the fibroadenoma, but also involved the adjacent parenchyma. No invasive carcinoma was present within this series of fibroadenomas. Complex histology was seen in 40.4% of cases, mostly at higher age (mean age 35.4 years; $p = 0.009$). Hyperplasia in adjacent tissue was found in 8.8% of cases, usually at higher age (mean age 45.5 years; $p < 0.001$).

In conclusion, known risk-elevating lesions in and around breast fibroadenomas occur frequently and mostly above the age of 35 years. These findings may have consequences for the clinical management of a subgroup of patients with fibroadenoma.

Introduction

Fibroadenoma of the breast is a relatively frequently occurring tumor. Women can present with fibroadenoma at any age, but the peak incidence is in the second and third decade [1]. Although often considered a benign tumor, several reports describe a higher risk of subsequent breast carcinoma in patients diagnosed with fibroadenoma [2-5]. Dupont et al found relative risks (RR) ranging from 2 to 4 depending on presence of complex changes within the fibroadenoma, benign proliferative disease in the surrounding parenchyma and a positive family history for breast cancer [2]. For hyperplasia in the surrounding tissue, this was previously demonstrated by McDivitt and coworkers.⁴ In addition, the development of invasive carcinoma within fibroadenoma has been well documented in literature [6-10].

Fibroadenoma is a biphasic tumor, i.e. it is composed of an epithelial and a stromal component. The epithelial component of fibroadenoma can display similar aberrations as the epithelial component of the normal breast. In a series of 70 tumors, Deschenes et al found 2 carcinomas (one invasive, one *in situ*) arising within a fibroadenoma [7]. Ozello and Gump reported a combined incidence of 0.3% for *in situ* and invasive carcinoma arising within fibroadenomas [9]. The incidence of apocrine metaplasia and sclerosing adenosis inside fibroadenoma has been reported to be 14% and 6%, respectively [11]. Comprehensive studies describing the histologic features of fibroadenomas are not available in literature. Only limited data can be found on the incidence of changes such as squamous metaplasia [12], focal tubular adenoma [13], smooth muscle [14] and, although often mentioned in textbooks, hyperplasia within fibroadenomas [11,15,16]. If hyperplasia behaves in a similar way as in the otherwise normal breast [17], it may contribute to the higher risk of subsequent invasive breast carcinoma.

Since there are clues that fibroadenoma indicates a higher risk of subsequent carcinoma and little is known about lesions occurring within and adjacent to fibroadenomas, the aim of this study was to make a thorough inventory of the histologic features of the epithelium and stroma within and around breast fibroadenomas in a large group of cases.

Materials and Methods

Patients

Excluding consultation and revision cases, a total of 426 lesions originally diagnosed as fibroadenoma between 1984 and 1999 were retrieved from the archives of the Department of Pathology, Free University Hospital Amsterdam, the Netherlands. All these lesions had been removed in our Hospital. A total of 30 cases (7.0%) were on revision not classified as fibroadenoma, since another diagnosis seemed more appropriate (Table 1), leaving 396 fibroadenomas in 358 patients. The average age of the patients was 33.4±12.1 years (range 12-81 years). Size of the

tumors varied between 0.1 and 22 centimeters, with a mean of 1.5 ± 1.4 centimeters. In 7.8% of patients, multiple tumors were found. In 59.3% of patients with multiple tumors the fibroadenomas were located ipsilaterally, in 40.7% the tumors were found in both breasts.

Diagnosis	No. of cases	%
Fibroadenoma	396	93.0
Sclerosing lobular hyperplasia	5	1.2
Phyllodes tumor	5	1.2
Hamartoma	4	0.9
Tubular adenoma	3	0.7
Pseudoangiomatous stromal hyperplasia	6	1.4
Adenomyoepithelioma	1	0.2
Normal tissue	6	1.4

Table 1. Revised diagnosis of 426 cases originally diagnosed as fibroadenoma.

Histopathology

All available hematoxylin and eosin (H&E) stained slides (on average 4) were thoroughly reviewed by two observers, either AK or EM and PvD, an experienced breast pathologist. Fibroadenomas were screened for proliferative epithelial changes (hyperplasia, carcinoma *in situ* [CIS], invasive carcinoma), fibrocystic epithelial changes (apocrine metaplasia, cysts, squamous metaplasia, sclerosing adenosis, microglandular adenosis, papilloma, lactational changes, calcifications), stromal changes (foci of pseudoangiomatous stromal hyperplasia, presence of smooth muscle), and various other changes such as foci of tubular adenoma and phyllodes tumor.

Complex fibroadenomas were, according to Dupont et al [2], defined as fibroadenomas harboring one or more of the so-called complex features: epithelial calcifications, apocrine metaplasia, sclerosing adenosis and cysts larger than 3 mm.

At least 0.5 cm² of tissue had to be present around the fibroadenoma in order to be evaluable for changes in the surrounding breast parenchyma [2].

In diagnosing hyperplasia and CIS, the criteria as described by Page et al [18] and Holland et al [19] were used. Only the most advanced lesion of the so-called usual ductal hyperplasias (mild, moderate or florid) was scored, i.e. if moderate and florid ductal hyperplasia were both present, only florid ductal hyperplasia was scored. Because the distinction between hyperplastic epithelium and tangential sectioning can be difficult to make, the appearance of myoepithelial cells throughout a duct was used as an additional criterion in favor of tangential sectioning (Fig 1). A pitfall previously described by Rosen [20] is an artificial hyperplasia like pattern caused by detachment of the epithelium with subsequent curling up, leading to a widened duct filled with epithelial strands (Figure 2).

Figure 1. Dispersed myoepithelial cells in this seemingly increased amount of epithelium indicate tangential sectioning and not hyperplasia in a breast fibroadenoma (hematoxylin and eosin, original magnification x200).

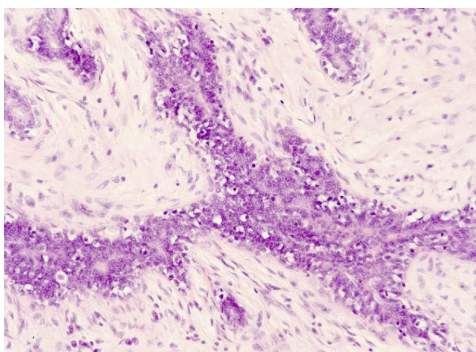
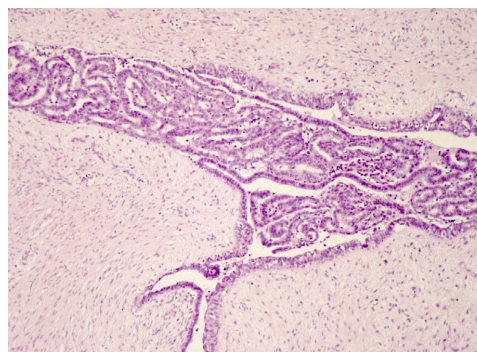


Figure 2. The epithelial pattern observed in this fibroadenoma is due to detachment and curling up of the epithelium and should not be classified as hyperplasia (hematoxylin and eosin, original magnification x100).



Another difficulty was sometimes the distinction between normal stroma and smooth muscle. When in doubt, immunohistochemical staining for smooth muscle actin was performed.

Phyllodes tumor was distinguished from fibroadenoma using Rosen's criteria, i.e. expansion and increased cellularity of the stromal component with often a leaf-like stromal growth pattern [15]. In phyllodes areas of fibroadenomas, stromal mitoses were counted per 10 high power fields (HPF; 400x magnification, $\pm 1.6\text{mm}^2$).

Finally, fibroadenomas were classified as pericanalicular or intracanalicular when 90% of the tumor displayed that particular type of growth pattern. If neither type could be assigned to a tumor, we diagnosed it as mixed histological type.

Data analysis

Relations between age and histologic findings were investigated using the Student's *t*-test. The chi-square test was used to investigate relations between hyperplasia within the fibroadenoma, hyperplasia in adjacent parenchyma and complexity of the fibroadenoma. *P*-values below 0.05 were regarded as significant.

Table 2. Frequency of histopathological changes in 396 cases of fibroadenoma.

Lesion	No. of cases	%
<i>Proliferative epithelial changes</i>		
Mild ductal hyperplasia	46	11.6
Moderate ductal hyperplasia	106	26.8
Florid ductal hyperplasia	21	5.3
Atypical ductal hyperplasia	1	0.3
Atypical lobular hyperplasia	0	0
Lobular carcinoma in situ	3	0.8
Ductal carcinoma in situ	5	1.3
Invasive carcinoma	0	0
<i>Fibrocystic epithelial changes</i>		
Apocrine metaplasia	111	28.0
Cysts	20	5.1
Sclerosing adenosis	49	12.4
Calcifications	15	3.8
Microglandular adenosis	1	0.3
Papilloma	7	1.8
Pseudolactational changes	2	0.5
Squamous metaplasia	1	0.3
<i>Stromal changes</i>		
Pseudoangiomatous changes	15	3.8
Smooth muscle	11	2.8
<i>Other</i>		
Foci of tubular adenoma	2	0.5
Focal phyllodes tumor	3	0.8

Results

Changes within the fibroadenoma

The frequencies of histopathological changes found within the fibroadenomas are shown in Table 2. 60.2% of fibroadenomas were of the pericanalicular type, 20.8% were classified as intracanalicular and 19.0% were of the mixed histological type.

In this series, hyperplasia was a common feature of fibroadenoma. Mild ductal hyperplasia was found in 11.6% of cases. Moderate ductal hyperplasia was seen in 26.8% and florid ductal hyperplasia in 5.3% of cases (Fig 3). Atypical ductal hyperplasia (ADH) was detected once (Fig 4). All together, in 43.9% of fibroadenomas some form of hyperplasia can be found. However, since in the otherwise normal breast an elevated risk for invasive carcinoma has been proven only for moderate, florid and atypical hyperplasia, we excluded mild ductal hyperplasia from further considerations. Within fibroadenomas, hyperplasia of higher grade than mild was found in 32.3% of fibroadenomas, and was present in all age groups (mean age 32.9 years; n.s.). No relation with hyperplasia in adjacent tissue could be detected. However, complexity of fibroadenomas was significantly associated with the presence of hyperplasia within the fibroadenoma ($p=0.005$).

Figure 3. Usual ductal hyperplasia within a fibroadenoma (haematoxylin and eosin, original magnification x100).

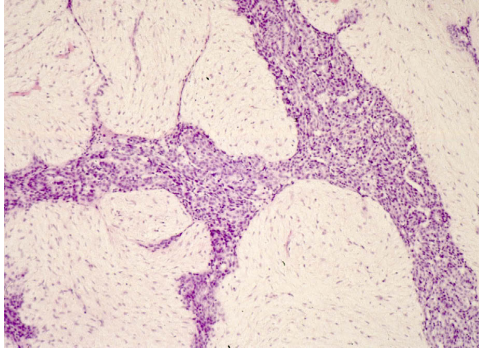
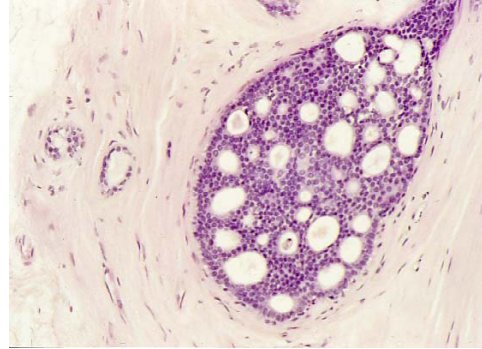


Figure 4. Atypical ductal hyperplasia found in a heavily sclerosed fibroadenoma (haematoxylin and eosin, x200).



Lobular carcinoma *in situ* (LCIS) was found three times (0.8%) (Fig 5). Ductal carcinoma *in situ* (DCIS) was seen five times (1.3%) (Fig 6). Mean age of these patients was 51.7 years, which is significantly older than those without this lesion ($p < 0.001$). The youngest patient with this lesion was 40 years of age. CIS arising within fibroadenoma was accompanied by CIS in adjacent tissue in three of eight cases (37.5%). Invasive carcinoma within fibroadenoma was not seen in this series.

Figure 5. Fibroadenoma with extensive lobular carcinoma *in situ* in a 46-year-old patient (haematoxylin and eosin, original magnification x200).

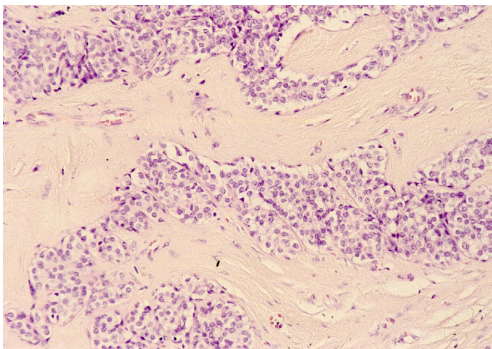
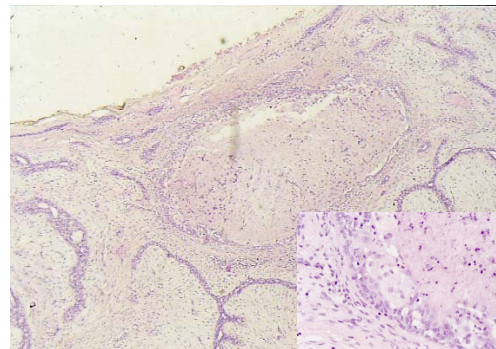


Figure 6. A small focus of poorly differentiated ductal carcinoma *in situ* detected in a fibroadenoma removed from a 40 year old patient (haematoxylin and eosin, original magnification x50; insert: cellular details at original magnification x400).



The so-called complex features were frequently seen, apocrine metaplasia being most frequent (28.0%). Taken together, 40.4% of fibroadenomas in this series were complex. 18.4% of the complex fibroadenomas harbored more than one complex feature, 2.5% harbored more than two complex features. Complex

fibroadenomas were seen more often at higher age (mean age 35.4 years; $p=0.009$). No relation between complexity and hyperplasia in adjacent tissue was detected.

Focal pseudoangiomatous stromal changes could be detected in 3.8% of cases. In two cases we observed foci of tubular adenoma. In three fibroadenomas we detected a part of the tumor which had to be classified as a focal phyllodes tumor. Two of these foci were benign, but one had a mitotic count of 8 per 10 HPF (see Figure 2, Chapter 2).

Table 3. Frequency of histopathological changes in the adjacent parenchyma of 317 cases of fibroadenoma.

Lesion	No. of cases	%
<i>Proliferative epithelial changes</i>		
Mild ductal hyperplasia	16	5.1
Moderate ductal hyperplasia	22	6.9
Florid ductal hyperplasia	3	1.0
Atypical ductal hyperplasia	2	0.6
Atypical lobular hyperplasia	2	0.6
Lobular carcinoma in situ	1	0.3
Ductal carcinoma in situ	6	1.9
Invasive carcinoma	3	1.0
<i>Fibrocystic epithelial changes</i>		
Apocrine metaplasia	75	23.7
Cysts	8	2.5
Sclerosing adenosis	46	14.5
Calcifications	11	3.5
Microglandular adenosis	6	1.9
Papilloma	1	0.3
Pseudolactational changes	4	1.3
Squamous metaplasia	0	0
<i>Stromal changes</i>		
Pseudoangiomatous changes	0	0
Smooth muscle	0	0
<i>Other</i>		
Foci of tubular adenoma	0	0
Focal phyllodes tumor	0	0

Changes in the adjacent parenchyma

Lesions found in the adjacent parenchyma of the fibroadenoma are displayed in Table 3. Seventy-nine fibroadenomas had less than 0.5 cm² of surrounding tissue, leaving 317 cases with sufficient adjacent breast tissue to be evaluable.

Mild ductal hyperplasia was seen in 5.1% and moderate and florid ductal hyperplasia in 6.9% and 1.0% of cases, respectively. ADH and atypical lobular hyperplasia (ALH) were both seen twice (mean age 43.8 years; n.s.). Therefore, in 13.9% of cases, some form of hyperplasia could be observed in the surrounding tissue (one ALH coexisted with a moderate ductal hyperplasia). To be consistent with Dupont et al [2], we excluded mild hyperplasia from further considerations, leaving 8.8% of fibroadenomas with hyperplasia in surrounding tissue. Hyperplasia in adjacent parenchyma was seen significantly more often at higher age (mean age

45.5 years; $p < 0.001$). There were no significant correlations with hyperplasia within the fibroadenoma and complexity.

LCIS was detected once, synchronous with a lobular invasive carcinoma. DCIS was seen six times, twice synchronous with an invasive ductal carcinoma. Mean age of cases with CIS in adjacent tissue was 43.3 years. Invasive carcinoma was seen three times in the surrounding parenchyma of the fibroadenoma, without involvement of the fibroadenoma itself (mean age 48.3 years).

As within the fibroadenoma, apocrine metaplasia was the most common of the fibrocystic epithelial changes in the surrounding tissue (23.7% of cases).

Discussion

This is the first study reviewing in detail the histologic features of a large group of 396 fibroadenomas. Although fibroadenoma is associated with a higher risk for invasive breast cancer [2-5], few data on histological changes adjacent to and inside fibroadenomas were available in literature. We found that the fibroadenoma displays a large variety of histological changes, some of which are expected to be of importance.

In some cases, the diagnosis fibroadenoma can be difficult to make (Table 1). Various benign lesions had been mistaken for fibroadenomas, such as pseudoangiomatous stromal hyperplasia (6x) and sclerosing lobular hyperplasia (5x). This is of little practical consequence. However, 5 phyllodes tumors were originally classified as fibroadenomas. This distinction can be of importance, particularly if the tumor was only partially excised. Phyllodes tumors have the tendency to recur and may then be of a higher grade than the primary tumor [21]. Histopathological criteria for the distinction between fibroadenoma and phyllodes tumor can be difficult to apply [15,16]. On several occasions, we experienced difficulty in differentiating between benign phyllodes tumor and fibroadenoma. Therefore, in case of doubt one has to make sure that resection was complete. In addition, in three cases part of the fibroadenoma could only be interpreted as phyllodes tumor. This has been described by Rosen [15] and Elston and Ellis [16]. Further, progression of fibroadenoma to phyllodes tumor was demonstrated by Noguchi and coworkers by means of clonal analysis [22]. This underlines that phyllodes tumors may derive from fibroadenomas by clonal expansion of the stromal compartment.

Hyperplasia within fibroadenoma was frequently seen in this series, even when excluding mild ductal hyperplasia, it was present in 32.3% of cases. It can be found at all ages. We cannot exclude the possibility of observer subjectivity, but we have been strict in using Page's criteria for hyperplasia and included an additional feature (dispersed myoepithelial cells) which, in our opinion, denies hyperplasia. Further, we excluded a hyperplasia like pattern which is caused by curling up of the epithelium of larger ducts when it is disrupted and detached. Dupont et al gave relative risks for

hyperplasia in breast parenchyma ranging from 2 to 5 [17]. It is tempting to apply these relative risks to hyperplasia found within fibroadenomas, but nothing has been proven regarding this matter. However, if hyperplasia within fibroadenoma behaves in the same way as in the otherwise normal breast, it could make a contribution to the increased relative risk associated with fibroadenoma and may be a reason for excision. It is conceivable that part of the increased relative risk associated with complexity of the fibroadenoma, as described by Dupont et al [2], can be attributed to hyperplasia within the fibroadenoma since the presence of the former was correlated with presence of the latter in our study. No correlation with hyperplasia in the surrounding tissue was found. Therefore, the meaning of hyperplasia within fibroadenomas in terms of progression risks remains to be determined.

8.8% of fibroadenomas were associated with hyperplasia in the adjacent parenchyma. Dupont et al found an incidence of 13.7%, which was associated with a relative risk of 3.9 [2]. Likewise, McDivitt et al reported an odds ratio of 3.7 [4]. Mean age of patients with fibroadenomas with hyperplasia in the adjacent parenchyma was significantly older than mean age of those without this feature. Frequencies of both usual ductal and atypical hyperplasia (7.9% and 1.2%) are somewhat lower in our study than those found by Dupont et al (13.7 % and 1.7%) [2]. Although in 80.1% of cases the requirement of 0.5 cm² of surrounding tissue was met, in most cases not much more tissue was present. Possibly, minimal surgery provided us with less surrounding tissue and therefore lower chances of finding epithelial proliferations compared with Dupont et al, who studied fibroadenomas which were removed four decades ago [2]. In order to identify women with this risk factor, it would be preferable to include, if possible, a small rim of surrounding tissue when resecting a fibroadenoma.

A frequency of 2.0% for CIS within fibroadenoma was found. Five cases of DCIS and three cases of LCIS were detected in our series. However, from one patient three CIS lesions arising within three fibroadenomas were removed. Thus, CIS arising within fibroadenoma was detected in six patients (1.7%). Few heterogeneous figures describing the occurrence of *in situ* and invasive carcinoma within fibroadenoma exist. Ozello and Gump [9]. found an incidence of 0.3% for invasive and *in situ* carcinoma taken together and Deschenes et al [7] found one carcinoma *in situ* and one invasive carcinoma in 70 fibroadenomas (1.4% each). Further, Buzanowski et al reported five cases of LCIS in 4000 fibroadenomas (0.1%) [6]. Our percentage seems somewhat higher, but this figure is nevertheless realistic in view of the fact that we excluded revision and consultation cases. Three of eight cases also had CIS in the adjacent breast tissue; two fibroadenomas with DCIS were accompanied by DCIS, one fibroadenoma with DCIS by LCIS. Therefore, if CIS is detected in an enucleated fibroadenoma, the surrounding tissue should be explored as well. It is hard to say if these CIS lesions occur synchronously or metachronously. The former, however, seems more likely and may reflect the genetic relationships

(and thus susceptibility to progression) between fibroadenoma epithelium and adjacent epithelium. In our series, mean age of patients with CIS within fibroadenoma was relatively high (51.7 years), comparable to the study by Diaz et al [8].

In seven cases, CIS (six ductal, one lobular) was found in the surrounding tissue. Invasive carcinoma was found three times in the adjacent parenchyma, all three without involvement of the fibroadenoma. Therefore, there is no reason to assume that the relationship between both lesions is anything but coincidental. Again, both lesions were found in elder women.

We could classify more than twice as many fibroadenomas as complex in comparison with Dupont et al [2]. This is mainly due to the high incidences found for sclerosing adenosis and apocrine metaplasia. This may be contributed to the large amount of slides available per case, as Azzopardi already stated; "no doubt more extensive sampling would reveal its (apocrine metaplasia) presence even more (i.e. more than 14%) frequently" [11]. There is a tendency for complex fibroadenomas to occur at higher age. Since no correlation with hyperplasia in the surrounding tissue was found, it seems that the elevated risk associated with complexity cannot be explained by a higher incidence of epithelial proliferation in the surrounding breast.

Several authors have opted for conservative management of the fibroadenoma below a certain age. 25 years [23], 35 years [24] and 40 years [25] have been suggested as age thresholds. Another study demonstrated that a large proportion of fibroadenomas in women under 20 years of age will resolve [26]. In dealing with fibroadenoma, two problems need to be acknowledged. First, stroma and epithelium of the fibroadenoma itself can undergo malignant transformation. As underlined by this study, CIS arising within fibroadenoma is found mostly at older age. In our study the youngest patient with this lesion was 40 years of age. Therefore, removal of fibroadenomas in women over the age of 35 tackles the problem of epithelial progression. However, no relation with age was found in the four cases of stromal expansion (mean age 31 years; n.s.). A criterion to distinguish between fibroadenoma and phyllodes tumor is rapid growth. Therefore, rapid growth in a tumor previously diagnosed as fibroadenoma should raise suspicion of stromal transformation (and possibly epithelial transformation). Malignancy arising within fibroadenoma should be treated as in the otherwise normal breast [9,10]. Second, fibroadenoma is associated with a long-standing increased risk of invasive breast cancer [2]. Depending on presence of hyperplasia in adjacent tissue, complexity of the fibroadenoma and a positive family history for breast cancer the RR may rise to 4, nearly twice the RR for women with a first degree relative with breast cancer [27]. Since 45.0% of fibroadenomas harbor either complex features or hyperplasia in adjacent tissue, it would be ideal to remove all fibroadenomas in order to identify all women at increased risk for breast cancer. However, since fibroadenoma is a frequently occurring tumor often only seen on ultrasonography, this has major clinical

implications. As long as it is unclear whether the indicated RR is high enough to have clinical consequences such as intensive follow-up or chemoprevention, there are no clear-cut arguments to advise removal of all fibroadenomas.

Of course, the diagnosis of fibroadenoma first needs to be established before a wait-and-see approach can be advised in individual cases. To this end, a triple diagnostic procedure including clinical investigation, mammography/ sonography and fine needle aspiration (FNA)/ needle core biopsy (NCB) can be useful. The advantage of NCB over FNA may be that it more easily reveals complex changes and epithelial proliferations. Excision of fibroadenomas above the age of 35 years will remove all malignant lesions arising within fibroadenomas. Surveillance may be warranted for women with a known family history for breast cancer diagnosed with fibroadenoma with complex features or hyperplasia in adjacent tissue on NCB or excision. For this group, removal may not be necessary since the RR associated with such lesions appears to be bilateral and not specific to the site or the fibroadenoma.

References

1. Foster ME, Garrahan N, Williams S. Fibroadenoma of the breast. *J Roy Coll Surg, Edinb* 1988;33:16-19.
2. Dupont WD, Page DL, Parl FF, et al. Long-term risk of breast cancer in women with fibroadenoma. *N Engl J Med* 1994;331:10-15.
3. Carter CL, Corle DK, Micozzi MS, et al. A prospective study of the development of breast cancer in 16,692 women with benign breast disease. *Am J Epidemiol* 1988;128:467-477.
4. McDivitt RW, Stevens JA, Lee NC, et al. Histologic types of benign breast disease and the risk for breast cancer. *Cancer* 1992;69:1408-1414.
5. Moskowitz M, Gartside P, Wirman JA, et al. Proliferative disorders of the breast as risk factors for breast cancer in a self-selected screened population: pathologic markers. *Radiology* 1980;134:289-291.
6. Buzanowski-Konakry K, Harrison Jr EG, Payne WS. Lobular carcinoma arising in fibroadenoma of the breast. *Cancer* 1975;35:450-456.
7. Deschenes L, Jacob S, Fabia J, et al. Beware of breast fibroadenomas in middle-aged women. *Can J Surg* 1985;28:372-374.
8. Diaz NM, Palmer JO, McDivitt RW. Carcinoma arising within fibroadenomas of the breast: a clinicopathologic study of 105 patients. *Am J Clin Pathol* 1991;95:614-622.
9. Ozello L, Gump FE. The management of patients with carcinomas in fibroadenomatous tumors of the breast. *Surg Gynecol Obstet* 1985;160:99-104.
10. Pick PW, Iossifides IA. Occurrence of breast carcinoma within a fibroadenoma. *Arch Pathol Lab Med* 1984;108:590-594.
11. Azzopardi JG. Fibroadenoma. In: Bennington JL, ed. *Problems in breast pathology*. Philadelphia: WB Saunders Co., 1979;39-56.
12. Salm R. Epidermoid metaplasia in mammary fibro-adenoma with formation of keratin cysts. *J Pathol Bacteriol* 1957;74:221-223.
13. O'Hara MF, Page DL. Adenomas of the breast and ectopic breast under lactational influences. *Hum Pathol* 1985;16:707-712.
14. Shimizu T, Ebihara Y, Serizawa H, et al. Histopathological study of stromal smooth muscle cells in fibroadenoma of the breast. *Pathol Int* 1996;46:442-449.
15. Rosen PP. Fibroepithelial neoplasms. In: Rosen PP, ed. *Breast pathology*. Philadelphia, PA: Lippincott-Raven, 1997;143-175.
16. Elston CW and Ellis IO. Fibroadenoma and related conditions. In: Symmers WStC, ed. *The breast*. Edinburgh, Scotland: Churchill Livingstone, 1998;147-186.
17. Dupont WD, Page DL. Risk factors for breast cancer in women with proliferative breast disease. *N Engl J Med* 1985;312:146-151.

18. Page DL, Anderson TJ, Rogers LW. Epithelial hyperplasia, and carcinoma in situ (CIS). In: Page DL, Anderson TJ, eds. Diagnostic histopathology of the breast. Edinburgh, Scotland: Churchill Livingstone, 1987;120-192.
19. Holland R, Peterse JL, Millis RR, et al. Ductal carcinoma in situ: a proposal for a new classification. *Semin Diagn Pathol* 1994;11:167-180.
20. Rosen PP. Pathological examination of breast specimens. In: Rosen PP, ed. Breast pathology. Philadelphia, PA: Lippincott-Raven, 1997;837-872.
21. Grimes MM. Cystosarcoma phyllodes of the breast: histologic features, flow cytometry analysis, and clinical correlations. *Mod Pathol* 1992;5:232-239.
22. Noguchi S, Yokouchi H, Aihara T, et al. Progression of fibroadenoma to phyllodes tumor demonstrated by clonal analysis. *Cancer* 1995;76:1779-1785.
23. Cant PJ, Madden MV, Close PM, et al. Case for conservative management of fibro-adenomas of the breast. *Br J Surg* 1987;74:857-859.
24. Wilkinson S, Anderson TJ, Rifkind E, et al. Fibroadenoma of the breast: a follow-up of conservative management. *Br J Surg* 1989;76:390-391.
25. Dixon JM, Dobie V, Lamd J, et al. Assessment of the acceptability of conservative management of fibroadenoma of the breast *Br J Surg*. 1996;83:264-265.
26. Cant PJ, Madden MV, Coleman MG, et al. Non-operative management of breast masses diagnosed as fibroadenoma. *Br J Surg* 1995;82:792-794.
27. Pharoah PDP, Day NE, Duffy S, et al. Family history and the risk of breast cancer: a systematic review and meta-analysis. *Int J Cancer* 1997;71:800-809.

