

## Fibroepithelial Tumors of Female Breast: A Review of 250 Cases of Fibroadenomas and Phylloides Tumors.

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### ABSTRACT:

#### BACKGROUND:

Fibroepithelial tumors of the breast including fibroadenomas and phylloides tumors arise from epithelial and stromal components of the terminal duct-lobular unit. Fibroadenoma is the commonest benign neoplasm of the female breast. These tumors are found as early as puberty. Mammary phylloides tumors are uncommon stromal-epithelial neoplasms and are divided into benign, borderline malignant and frankly malignant groups on the basis of their histological features.

#### OBJECTIVE:

The aim of this study is to evaluate the role of morphologic diagnosis in a series of fibroepithelial (biphasic) tumors of the breast including fibroadenoma and phylloides tumor, highlighting the morphological and Histopathological variants of fibroadenoma, and the most recent histological classification criteria of phylloides tumors.

#### PATIENTS AND METHODS:

This is a retrospective study including 250 cases of fibroepithelial tumors of the female breast, from October 2007 to September 2008. Cases were taken from private laboratories. All cases were excisional biopsy, the specimens were already fixed in 10% formalin and paraffin embedded. Sections of 4 microns were made from the paraffin blocks and stained with hematoxyllin and eosin stain and examined microscopically.

#### RESULTS:

Two-hundred and fifty cases of mammary fibroepithelial tumors were reviewed in this study. The age of the patients ranged between 14-49 years, and the tumor size ranged between 1.5-20 cm. The cases were histologically classified into: 220(88%) cases of fibroadenoma(FA) and 30(12%) cases of phylloides tumor(PT). Additional morphological features of fibroadenoma were: fifteen(6.8%)cases juvenile fibroadenoma, infarction in eight(3.6%) cases, lactational changes in ten(4.5%) cases, multinucleated giant cells in the stroma in six(2.7%) cases, prominent myxoid changes in three(1.4%) cases, features of fibrocystic changes in the surrounding in 14(6.4%) cases, cellular stroma in eight(3.6%) cases, apocrine metaplasia in 26(11.9%) cases, hyalinization and calcification of the stroma in 14(6.4%) cases, presence of adipose tissue , muscle or cartilage in 18(8.2%) cases, atypical epithelial hyperplasia in four(1.8%) cases, and ordinary fibroadenomas (non-otherwise specific) in 94(42.7%) cases. Multiple fibroademnomas were found in 20(9.1%) cases. Histological classification of the phylloides tumors showed 20(66.7%) benign cases, six(20%) cases borderline malignant and four(13.3%) malignant cases.

#### CONCLUSION:

Fibroadenoma is the commonest fibroepithelial tumor of female breast, phylloides tumor is an uncommon neoplasm which is usually benign but malignant variant exists.

**KEYWORDS:** fibroepithelial tumors, fibroadenoma, phylloides tumor.

### INTRODUCTION:

Periductal stromal tumors of the breast including fibroadenomas and phylloides tumors arise from epithelial and stromal component of the terminal duct-lobular unit. <sup>(1, 2, 3)</sup>Fibroadenoma is the most common benign neoplasm of the female breast. These estrogen-sensitive tumors are found as

early as puberty, have the highest age incidence between 20-35 years. <sup>(4)</sup> During pregnancy the lesion may develop secretory changes and after menopause sclerosis and regression occur, less than 5% of women with fibroadenomas are older than 50 years or postmenopausal. <sup>(3, 4)</sup> This slowly growing tumor is usually single, but as many as 20% are multiple either in the same breast or in the contralateral breast. <sup>(3)</sup>.

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Mammary phylloides tumor is an uncommon fibroepithelial neoplasm with a prominent stromal component, accounting for 2.5% of all fibroepithelial tumors of the breast and 0.3-0.5% of all breast tumors. <sup>(5)</sup> It has been reported the incidence of this tumor is 1 in 100.000; it is a very rare neoplasm in adolescent girls and young women. <sup>(6)</sup> Currently phylloides tumors are classified as benign, borderline malignant, and malignant based on histological features. <sup>(5, 6, 7, 8)</sup> It affects women between 30-70 years, the lesion is sharply circumscribed, round or bosselated and contain slit like or cystic spaces. <sup>(5, 6, 9, 10)</sup>

### PATIENTS AND METHODS:

Two-hundred and fifty cases of fibroepithelial (biphasic stromal/epithelial) tumors were included in this study. All cases were collected from private laboratories from October 2007 to September 2008.

The samples were excisional biopsy specimens. The specimens were already fixed in 10% formalin and paraffin embedded. Sections of 4 microns were made from paraffin blocks and stained with hematoxyllin and eosin stain and examined (re-evaluated) under light microscopy. Clinopathological analysis of these 250 tumors was done, taking in consideration the age of the female patients, the size of the tumors, and the status of the surgical margins. The 250 tumors were histologically classified into two large

groups including fibroadenomas and phylloides tumors.

Fibroadenomas were re-evaluated for specific morphological features including: (evidence of apocrine metaplasia, stromal cellularity, infarction, lactational changes, multinucleated giant cells in the stroma, prominent myxoid changes of the stroma, and atypical epithelial hyperplasia,...). Phylloides tumors were classified into benign, borderline and malignant, taking into consideration the presence of stromal overgrowth, and mitotic activity.

### RESULTS:

1- Age distribution of the patients:

Age ranged between 14-49 years, the mean age was 21.6 years, 53.2% of the cases belonged to the age group 20-29 years. Table (1) shows the age distribution of the cases. (cases were histologically classified into: 220(88%) cases of fibroadenomas, and 30(12%) cases of phylloides tumors).

The age range of fibroadenomas was between 14-49 years, while the age range of phylloides tumor was between 27-46 years.

The youngest patient was a 14 years old female, who presented with fibroadenoma, and the oldest patient was a 49 years old female who presented with phylloides tumor.

Table 1: Age distribution of the patients

Age	Fibroadenoma		Phylloides tumor		Total	
	No	%	No	%	No	%
10-19	15	6	-	-	15	6
20-29	130	52	3	1.2	133	53.2
30-39	50	20	10	4	60	24
40-49	25	10	17	6.8	42	16.8
Total	220	88	30	12	250	100

2- Size of the tumors:

All cases presented as excisional biopsies. The size of the tumors ranged between 1.5-20 cm. The smallest tumor was a fibroadenoma which measured 1.5cm in largest diameter, and the largest tumor was a phylloides tumor which measure 20cm in largest diameter.

Fibroadenoma sizes ranged between 1.5-10cm, while the phylloides tumor sizes ranged between 2-20cm.

3- Histopathological evaluation:

A- Fibroadenoma: (fig 1)

All cases were sharply circumscribed grossly, non-encapsulated lesions consisting of epithelial

and stromal components. The epithelial element most commonly forms slit-like canalicular (intracanalicular type) spaces in 180 cases, or less often forms rounded or irregularly shaped tubules (pericanalicular type) in 40 cases, these are surrounded by large amounts of loose myxoid, moderately cellular stroma (fibroadenomas with these criteria designated as ordinary fibroadenomas or non-otherwise specified fibroadenomas). Morphological variants in fibroadenoma were plentiful in our study (as shown in table 2) including:

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**Table 2: Morphological variants of fibroadenoma**

Morphological variant	No	%
Juvenile fibroadenoma	15	6.8
Infarction	8	3.6
Lactational changes	10	4.5
Multinucleated giant cells in the stroma	6	2.7
Prominent myxoid changes of the stroma	3	1.4
Features of fibrocystic changes	14	6.4
Cellular stroma	8	3.6
Apocrine metaplasia	26	11.9
Hyalinization, calcification of the stroma	14	6.4
Mature adipose tissue or cartilage in the stroma	18	8.2
Atypical epithelial hyperplasia	4	1.8
Ordinary non-otherwise specific fibroadenoma	94	42.7
Total	220	100

Fifteen (6.8%) cases were juvenile fibroadenomas; occurring in young age group and showing epithelial and stromal hypercellularity, eight(3.6%) cases showed infarction, all these cases presented in pregnant females, ten(4.5%) cases showed lactational changes (as clearing of the epithelial cells), six(2.7%) cases showed multinucleated giant cells in the stroma, three(1.4%) cases showed prominent myxoid changes of the stroma, fourteen(6.4%) cases showed features of fibrocystic changes, eight(3.6%) cases showed cellular stroma, twenty six(11.9%) cases showed apocrine metaplasia, fourteen(6.4%) cases showed hyalinization and calcification of the stroma, eighteen (8.2%) cases showed mature adipose tissue and cartilage metaplasia of the stroma, four(1.8%) cases showed atypical epithelial hyperplasia, and ninety four(42.7%)

cases were ordinary fibroadenomas. Multiple fibroadenomas were found in twenty(9.1%) cases.

B- Phylloides tumor: (figure 2)

Thirty (12%) cases were diagnosed as phylloides tumors. These cases presented as well-circumscribed lesions consisting of epithelial and stromal elements. The stroma was far more cellular than fibroadenoma and the epithelial clefts were more patent and may be cystically dilated; projecting into these spaces are broad-blunt ended epithelial lined stromal papillae producing the characteristic leaf-like pattern of phylloides tumors.

Depending on histological appearance and mitotic counts, and based on Nottingham practice<sup>(11)</sup> (as shown in table 3) phylloides tumors were classified into benign, borderline malignant, and frankly malignant.

**Table 3: Histological criteria of Nottingham practice**

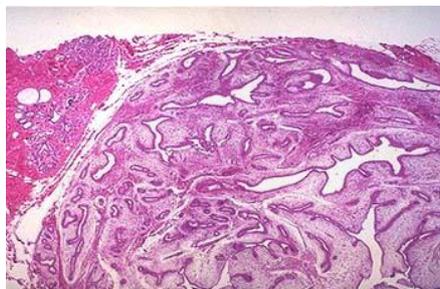
Histological classification	Histological criteria
Benign	Less than 5 mitosis per 10 high power fields lacks sarcomatous foci.
Borderline malignant	Shows 5-9 mitosis per 10 high power fields, and may show a fibrosarcomatous foci
Malignant	Shows more than 10 mitosis per 10 high power fields, and often contains foci of other sarcomatous elements.

In this study twenty (66.7%) cases were classified as benign, six(20%) cases were borderline malignant, and four(13.3%) cases were malignant.

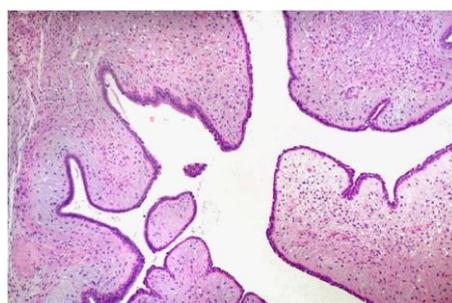
All specimens were excisional biopsies showing free surgical margins. Table 4 shows the histological classification of phylloides tumor.

**Table 4: Histological classification of phylloides tumor**

Histological classification	Number	%
Benign	20	66.7
Borderline malignant	6	20
Malignant	4	13.3
Total	30	100



**Figure 1: Fibroadenoma**



**Figure 2: Phylloides tumor**

**DISCUSSION:**

Phylloides tumor and fibroadenoma are two types of fibroepithelial tumors of the breast that are usually not easy to differentiate (histologically and grossly).<sup>(12)</sup>

Fibroadenoma is common benign breast lesion, arising by proliferation of mammary stroma and epithelial elements.<sup>(10, 13)</sup> The tumors mainly occur in young women aged 20-30 years, but also occur in adolescence as juvenile fibroadenoma, and rarely in postmenopausal women.<sup>(10, 11, 12, 13)</sup> In this study age frequency of patients with fibroadenoma ranged between 14-49 years, 52% of those between 20-29 years.

Fibroadenoma is a painless tumor that can be multiple and bilateral<sup>(10)</sup>. In this study 20(9.1%) cases were multiple.

The size of this tumor varies from a few to several centimeters in diameter. When larger than 8-10cm it is referred to as giant fibroadenoma<sup>(10)</sup>. In this study the size of the tumors ranged between 1.5-20cm. Some rapidly growing fibroadenomas are referred as giant,

juvenile or fetal fibroadenoma, where the patients are generally young and tumors may become as large as 19cm in diameter.<sup>(3)</sup> In this study 15(6.8%) cases were juvenile fibroadenomas.

Other Histopathological features can be seen in association with fibroadenoma such as sclerosing adenosis, duct ectasia, apocrine metaplasia in 15% of cases, florid fibrocystic disease, and other features as infarction, calcification, epithelial metaplasia, and inflammatory reaction may sometimes be present.<sup>(3, 10, 11)</sup> In this study eight(3.6%) cases showed changes of infarction, ten(4.5%) cases with lactational changes, six(2.7%) cases with multinucleated giant cells in the stroma, twenty six(11.9%) cases with apocrine metaplasia, three(1.4%) cases with prominent myxoid changes, fourteen(6.4%) cases with features of fibrocystic changes, eight(3.6%) cases with cellular stroma, fourteen(6.4%) cases with hyalinization and calcification, eighteen(8.2%) cases with mature adipose tissue,

four(1.8%) cases with atypical epithelial hyperplasia, while ninety four(42.7%) cases were ordinary fibroadenomas.

It has been reported that malignant changes in fibroadenoma are found in only 0.1% of cases, usually involving the epithelial component, and the large majority are in situ lesions<sup>(10, 11, 14)</sup>, while sarcomatous transformation of the stroma of fibroadenoma is believed to be an even rare phenomenon.<sup>(11)</sup>

Cytogenetically, approximately 20% of fibroadenomas have been found to have clonal chromosome aberration.<sup>(15)</sup> A lineage-restricted analysis has shown that these clonal aberrations are present in the stromal component suggesting that fibroadenoma is a benign neoplasm of the specialized stroma of the breast with an accompanying epithelial component.<sup>(10, 15)</sup>

Phylloides tumor is an unusual neoplasm resembling the fibroadenoma, clinically, microscopically, and by fine needle aspiration cytology (only in benign cases).<sup>(3, 16)</sup>

This neoplasm occurs most frequent in middle aged females but appears from adolescent to senescence. Its classical presentation is a rapid growth with overlying tense, prominently veined skin.<sup>(2)</sup>

In this study the age frequency ranged between 27-46 years, with 17(6.8%) cases age group 40-49 years.

It is reported that the tumor is spherical and relatively well circumscribed, measuring from 1.0-30.0cm in diameter.<sup>(9, 12, 17)</sup> In this study the size ranged between 2-20cm.

It is the amount of the stromal component that determines whether a breast neoplasm should be called fibroadenoma or phyllodes tumor.<sup>(10)</sup>

Although having a marked similarity to a giant fibroadenoma its most important differentiating feature is the dense stromal component, almost overwhelming the few requisite ductal element.<sup>(10, 11)</sup>

Two recent studies have described features useful in the distinction of phylloides tumor and fibroadenoma on core biopsy, including increased cellularity, mitosis and overgrowth of stroma, adipose tissue in the stroma and fragmentation of the biopsy specimen.<sup>(16)</sup>

It has been displayed that in the majority of the cases this tumor is benign, though some are malignant and show distant metastasis, others have a biological behavior which is intermediate between the two (borderline malignant) these

may recur but rarely metastasize.<sup>(8, 12)</sup> The frequency of malignant lesions varies in different series from 5%-30%.<sup>(18)</sup> In this study four (13.3%) cases were malignant, twenty (66.7%) cases were benign, and six (20%) cases were borderline malignant.

Phylloides tumors require complete excision with free margins, even when pathological features suggest benignity because of a liability to local recurrence.<sup>(8, 12, 18)</sup> After local excision 21%, 46%, and 65% of patients with benign, borderline, and malignant phyllodes tumors, respectively recur in the breast. Malignant phylloides tumors are more likely to recur than benign ones in the breast after breast conserving surgery.<sup>(12)</sup>

Other rare stromal/epithelial tumors of the breast include: myoepitheliosis which is a rare benign lesion adequately treated by local excision, adenomyoepitheliomas (myoepitheliomas) are very rare breast lesions classified as low grade malignant tumors that may recur and rarely metastasize, and myoepithelial carcinoma which is an infiltrative lesion that may show variable appearance.<sup>(19, 20)</sup>

### CONCLUSION:

The commonest fibroepithelial tumor in the female breast in the present study was fibroadenoma, while phylloides tumor was an uncommon neoplasm which was benign in twenty (66.7%) cases and malignant in four(13.3%) cases.

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