Araştırma Makalesi (Research Article)

Fibroadenomların İçindeki ve Çevresindeki Histopatolojik Değişikliklerin Karşılaştırılması

Comparison of The Histopathologic Changes Within and Around Fibroadenomas

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Özet

Amaç: Fibroadenom en sık görülen benign meme tümörüdür ancak literatürde fibroadenomların ve bitişik dokuların histolojik özelliklerini tanımlayan az sayıda çalışma bulunmaktadır. Bu çalışmanın amacı fibroadenomların içindeki ve çevresindeki epitelyal ve stromal dokuların histolojik özelliklerini incelemektir.

Gereç ve Yöntemler: Retrospektif olarak patoloji arşivi tarandı ve eksizyonel meme biyopsi tanısı fibroadenom olan kadın hastalar çalışmaya dahil edildi. Tüm hematoksilin eozin boyalı preparatlar iki patolog tarafından yeniden değerlendirildi. Kategorik değişkenler Ki-kare testi ile, kantitatif değişkenler ise Mann-Whitney U veya Kruskal Wallis tesleri ile analiz edildi.

Bulgular: Çalışmaya dahil edilme kriterlerini karşılayan 52 hastada, kompleks fibroadenom ile normal duktal hiperplazi arasında istatistiksel olarak anlamlı bir ilişki saptandı ($p < 0.001$), kompleks fibroadenomların % 55.9'unda duktal hiperplazi mevcuttu. Fibroadenom içindeki ve çevre parankimdeki duktal hiperplazi arasında anlamlı bir ilişki saptanmadı ($p = 0.132$). Duktal hiperplazi içeren fibroadenomların % 26.3'ünde, komşu meme parankiminde de duktal hiperplazi mevcuttu. Kompleks fibroadenom ile çevre parankimdeki duktal hiperplazi veya fibrokistik değişiklikler arasında anlamlı bir ilişki yoktu (sırasıyla $p = 0.438$ ve $p = 0.523$).

Sonuç: Fibroadenom içinde ve çevresinde meme kanseri için bir risk oluşturan proliferatif değişikliklerin oranları genç ve ileri yaşlarda benzer bulunmuştur. Fibroadenomdaki kompleks ve proliferatif değişikliklerin ve çevre meme parankimindeki proliferatif değişikliklerin titizlikle incelenmesi ve raporda tüm bu değişikliklerin belirtilmesi, meme kanseri gelişme riskinin daha doğru bir şekilde belirlenmesini sağlayacaktır.

Anahtar kelimeler: Meme, Fibroadenom, Histopatoloji, Duktal hiperplazi, İn situ karsinom

Abstract

Objective: Fibroadenoma is the most common benign breast tumor but there are a few studies in the literature that describe the histological features of inner and adjacent tissues of fibroadenomas. The aim of the present study is to examine the histological features of the epithelial and stromal tissues within and around fibroadenomas.

Material and Metods: The pathology archive was scanned retrospectively, and female patients with excisional breast biopsy diagnosed fibroadenoma were included in the study. All hematoxylin eosin stained slides were reevaluated by two pathologists. Categorical variables were analyzed using the Chi-square test, and quantitative variables were analyzed with Mann-Whitney U or Kruskal Wallis tests.

Results: In 52 patients who met the inclusion criteria, a statistically significant correlation was detected between complex fibroadenoma and usual ductal hyperplasia ($p < 0.001$), usual ductal hyperplasia was present in 55.9 % of the complex fibroadenomas. No significant association was detected between presence of usual ductal hyperplasia in the surrounding parenchyma and fibroadenoma ($p= 0.132$). In 26.3 % of fibroadenomas containing usual ductal hyperplasia, usual ductal hyperplasia was present in the adjacent breast parenchyma. There was no significant relationship between complex fibroadenoma and usual ductal hyperplasia or fibrocystic changes in the surrounding parenchyma ($p= 0.438$ and $p= 0.523$, respectively).

Conclusion: The rates of the proliferative changes that create a risk for breast cancer in and around the fibroadenoma in the younger ages were found similar with the older ages. The examination of the complex and proliferative changes in the fibroadenoma and the proliferative changes in the surrounding breast parenchyma meticulously and specification of all those changes in the report will allow determination of the risk for development of breast cancer more accurately.

Keywords: Breast, Fibroadenoma, Histopathology, Ductal hyperplasia, Carcinoma in situ

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INTRODUCTION

Fibroadenoma is the most common benign breast tumor originating from the epithelial and stromal component of the terminal ductal lobular unit. They may occur in females in any age, particularly in 30s (1). The incidence of postmenopausal or older than 50 years is less than 5% (1). It usually presents with the complaint of a painless, firm or rubbery, well-circumscribed, solitary mass noticed by the patient (1). Fibroadenomas are mostly soliter, but multiple fibroadenomas can be seen less frequently (1-3). Fibroadenoma manifests a broad spectrum of cytological and histological variations. The changes that may appear in the normal breast epithelium may occur also in the epithelial component of the fibroadenoma. Mc Divitt et al. in their studies investigating the cancer development risk of benign breast diseases; they stated that cases with hyperplasia without atypia and coexistence of fibroadenoma carry a higher risk than cases with atypical hyperplasia without fibroadenoma, and that the risk is much higher if fibroadenoma is accompanied by hyperplasia with atypia (4). In the literature, several epidemiologic studies have suggested the increased risk for invasive breast cancer in the patients with fibroadenoma compared with various control groups (5-8). Dupont et al. reported that increased risk of breast cancer depended on existence of the positive family history of breast cancer, complex changes in fibroadenoma and benign proliferative disease in the surrounding parenchyma (5). A fibroadenoma that contains at least one of the complex features is defined as a complex fibroadenoma. The complex feature are as follows: Epithelial calcification, papillary apocrine changes, sclerosing adenosis and cysts over 3 mm in diameter (1, 5). There are a few studies in the literature that describe the histological features of inner and adjacent tissues of fibroadenomas.

The aim of the present study is to investigate the histological features of the epithelial and stromal tissues within and around fibroadenomas.

MATERIAL AND METHODS

Patients:

This is a retrospective single-center study on the spectrum of histopathological changes in breast fibroadenomas that were diagnosed between January 2009 and December 2015 at The Department of Pathology of Silifke State Hospital, Mersin, Turkiye. The present study was approved by Hatay Mustafa Kemal University Non-interventional Clinical Research Ethics Committee (Date: 16.01.2020, Approval No: 11). Female patients without known malignancy and non-autolytic samples whose histopathological diagnosis was confirmed as fibroadenoma by excisional biopsy were included in the study. Male gender, patients with known malignancy and autolyzed samples were excluded from the study. All available H&E-stained slides (averagely 4 slides) were meticulously reviewed by two pathologists (İES, DG).

Fibroadenoma is usually 3 cm or less in diameter (2, 3, 9). If it is larger than 5 cm, it is called "giant fibroadenoma" (10). Therefore, the samples were divided into three groups according to the size of the fibroadenoma. Fibroadenomas smaller than 3 cm were grouped as small fibroadenomas. Fibroadenomas ranging in size from 3 cm to 5 cm were considered as large fibroadenomas. Giant fibroadenomas were larger than 5 cm in size.

Histopathological Examination:

We have histopathologically evaluated fibroadenoma types (intracanalicular, pericanalicular and mixed), proliferative epithelial changes in fibroadenomas [usual ductal hyperplasia (UDH), atypical ductal hyperplasia (ADH), atypical lobular hyperplasia, lobular carcinoma in situ (LCIS), ductal carcinoma in situ (DCIS)], fibrocystic epithelial changes (apocrine metaplasia, cyst (larger than 3 mm), microglandular adenosis, sclerosing adenosis, papilloma, squamous metaplasia, pseudolactational changes), and stromal changes (pseudoangiomatous stromal hyperplasia, myxoid change, hyaline and inflammatory changes, adipose metaplasia, smooth muscle change, calcification and infarction).

UDH was diagnosed according to Rosen's criteria and scored as mild, moderate or florid. Mild hyperplasia (Figure 1) is characterized by three to four cells layers of epithelial cells, moderate hyperplasia involves more than four cells of epithelium in thickness and florid hyperplasia **(Figure 2)** is termed if the duct lumen is enlarged and possibly obliterated or distended with cells (11). Scoring was based on the most developed lesion, for instance; only florid ductal hyperplasia was scored if moderate and florid ductal hyperplasias are both present. The presence of myoepithelial cells along the duct was interpreted in favor of tangential sectioning if differentiation between hyperplastic epithelium and tangential sectioning was challenging **(Figure 3)** (2).

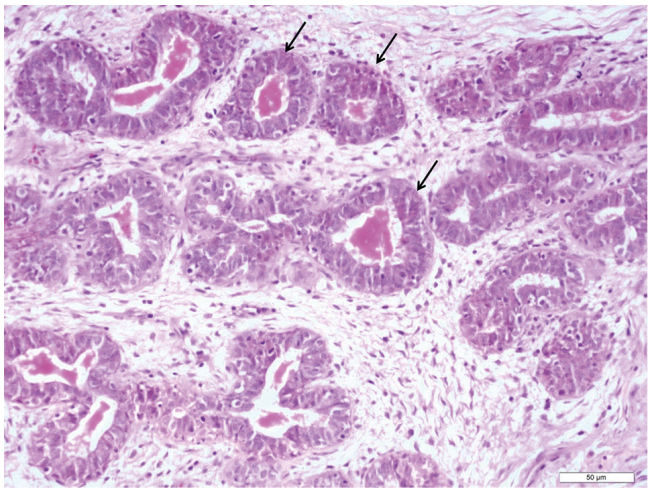

Figure 1. Mild ductal hyperplasia within a fibroadenoma, ductal epithelial cells appear to have three to four rows (arrows). (H&E, original magnification x 200)

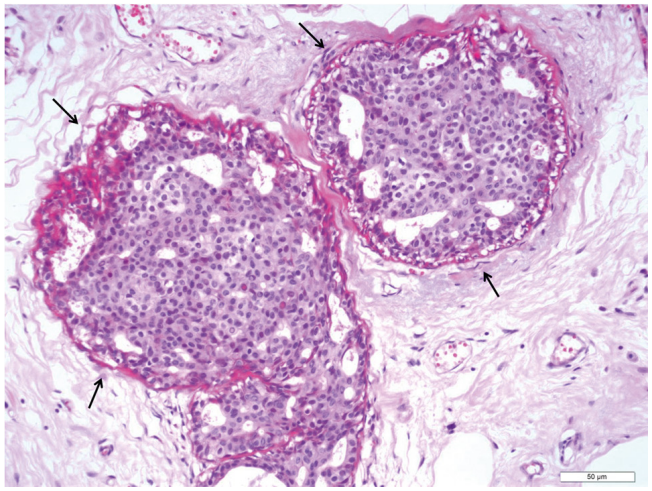

Figure 2. Florid ductal hyperplasia within a fibroadenoma, epithelial cells are observed to fill and expand the entire ductus lumen (arrows). (H&E, original magnification x 200)

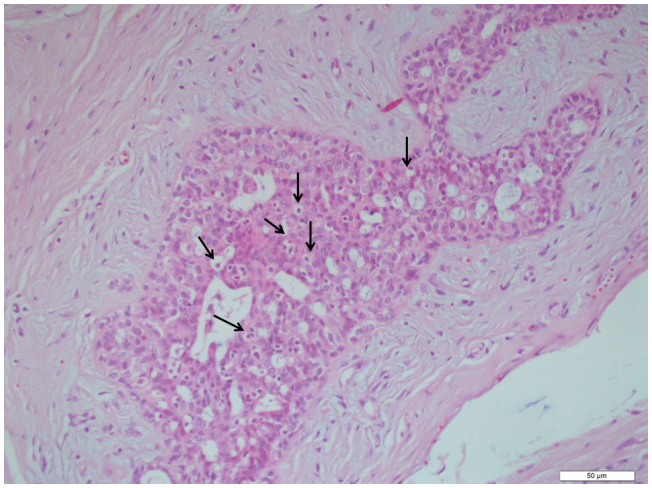

Figure 3. The presence of myoepithelial cells (arrows) along the duct was interpreted in favor of tangential sectioning not usual ductal hyperplasia (H&E, original magnification x 200)

Fibroadenomas were classified as pericanalicular, intracanalicular or mixed fibroadenoma (containing both components and none constitutes over 90 %) (1).

Masson's Trichrome staining was applied if distinction between normal hyalinized or collagenized stroma and smooth muscle changes was challenging.

Rosen's criteria were used to differentiate phyllodes tumor from fibroadenoma. Stromal enlargement, increased cellularity and leaf-like stromal growth pattern were interpreted in favor of phyllodes (1).

The changes in the adjacent breast parenchyma were evaluated in the samples containing at least 0.5 cm2 of parencyhma or five lobular units adjacent to fibroadenoma (5).

Statistical Analysis

All data were analyzed with Statistical Package for the Social Sciences v.21.0 software package (SPSS IBM Corp; Armonk, NY, USA). Quantitative variables were expressed as median and interquartile range (IQR), categorical variables were expressed as number (n) and percentage (%). With the "Shapiro Wilk test", it was found that our variables were not normally distributed. "Chi-square test" was used to compare qualitative data. The difference in quantitative data between the paired groups was analyzed with the "Mann-Whitney U test" and in those of the three and more groups with the "Kruskal Wallis test". $p<0.05$ was considered significant.

RESULTS

The present study included the formalin-fixed excisional breast biopsies of 52 patients that were histopathologically diagnosed with fibroadenoma. The median age of the patients was 31years (IQR: 22.3 to 43). Age distribution was shown in Table 1. Fifth decade age group included the maximum number of patients (28.8 %, n=15). The minimum number of the patients (3.8 %, n=2) were assigned to the group above 50 years of age.

Table 1. Age distrubition

Age group (year)	No. of patients	Percentage
15-20	9	17.3 %
21-30	14	26.9 %
31-40	12	23.1 %
41-50	15	28.8 %
> 50	2	3.8 %

Tumor sizes varied between 0.5 and 8 cm in diameter (median: 2.5 cm, IQR: 1.5 to 3.4). Small fibroadenomas were found in the maximum number (63.3 %, n=38) of the patients. Giant fibroadenomas represented the minimum number (8.3 %, n=5) of the patients. The rate of large fibroadenomas was 28.3 % (n=17) in the patients. There was no significant difference in age value between tumor size groups ($p = 0.06$).

Five patients (9.6 %) were found to have multiple tumors. Multiple fibroadenomas were located unilaterally in 3 (60 %) whereas fibroadenomas were found bilaterally in 2 (40 %) patients.

The frequencies of histopathological changes in the fibroadenomas were shown in **Table 2.** 20 % (n=12) of fibroadenomas were pericanalicular, 36.7 % (n= 22) were intracanalicular and 43.3 % (n= 26) were in mixed histological morphology. Apocrine metaplasia (38.3 %, n= 23) was the most common form of fibrocystic epithelial changes. The most common proliferative epithelial change was mild UDH (20 %, n= 12). No LCIS or invasive carcinoma was encountered, the rates of DCIS **(Figure 4)** and ADH were both 1.7 %, and they were 31 and 15 years old, respectively.

Table 2. Distrubition of histopathologic changes found within 60 cases of fibroadenoma.

Lesions	Frequence	Percentage (%)
Proliferative epithelial changes		
Mild ductal hyperplasia	12	(20)
Moderate ductal hyperplasia	8	(13.3)
Florid ductal hyperplasia	2	(3.3)
Atypical ductal hyperplasia	1	(1.7)
Atypical lobular hyperplasia	0	(0.0)
Lobular carcinoma in situ	0	(0.0)
Ductal carcinoma in situ	1	(1.7)
Invasive carcinoma	0	(0.0)
Fibrocystic epithelial changes		
Apocrine metaplasia	23	(38.3)
Cyst	10	(16.7)
Sclerosing adenosis	21	(35.0)
Calcification	12	(20.0)
Papilloma	3	(5.0)
Microglandular adenosis	0	(0.0)
Pseudolactational changes	1	(1.7)
Squamous metaplasia	0	(0.0)
Stromal changes		
Myxoid changes	10	(16.7)
Hyaline changes	33	(55.0)
Pseudoangiomatous changes	0	(0.0)
Inflammatory changes	8	(13.3)
Smooth muscle changes	3	(5.0)
Adipous metaplasia	3	(5.0)
Multinuclear giant cell	0	(0.0)
Infarct	0	(0.0)

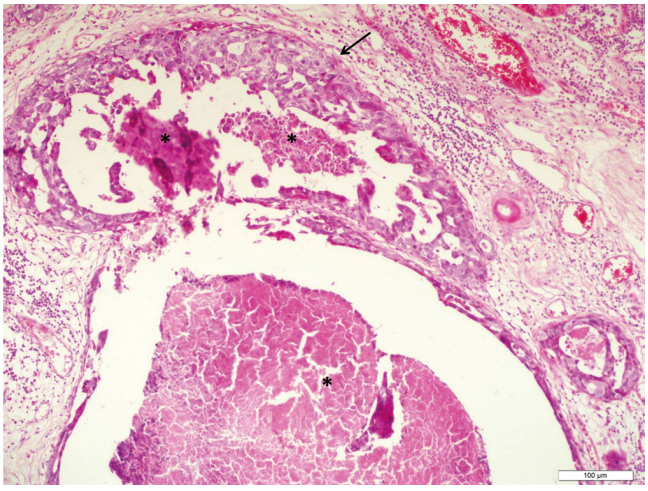

Figure 4. Ductal carcinoma in situ with comedo necrosis is observed (arrow). Necrosis are marked with the asterisks (H&E, original magnification x 100)

Sixty percent (n=36) of the fibroadenomas were complex **(Figure 5)**. No statistically significant difference was found between complex and non-complex fibroadenomas in terms of age and tumor size (p= 0.420, p= 0.569, respectively). No statistically significant difference was determined between fibroadenomas with and without usual hyperplasia in terms of age and tumor size (p= 0.89; p= 0.26, respectively). The median age of the fibroadenoma cases with and without UDH were 31 and 31.5 years, respectively.

A statistically significant relationship was detected between complex fibroadenoma and UDH ($p < 0.001$), UDH was present in 55.9 % of the complex fibroadenomas.

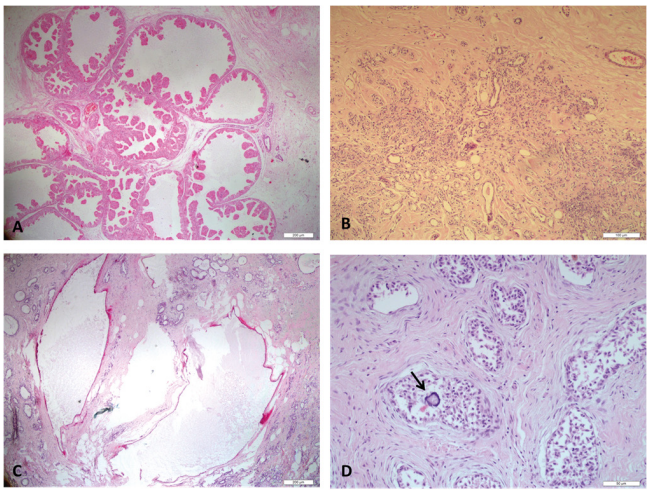

Figure 5. Complex Fibroadenomas. A: Papillary apocrine metaplasia within a fibroadenoma (H&E, original magnification x 40). **B:** Sclerosing adenosis within a fibroadenoma (H&E, original magnification x 100). **C:** Cyst within a fibroadenoma (H&E, original magnification x 40). **D:** Epithelial calcification (→) within a fibroadenoma (H&E, original magnification x 200).

No significant association was detected between presence of UDH in the surrounding parenchyma and within the fibroadenoma (p= 0.132). In 26.3% of fibroadenomas containing UDH, UDH was present in the adjacent breast parenchyma. There was no significant relationship between complex fibroadenoma and UDH or fibrocystic changes in the surrounding parenchyma (p= 0.438 and p= 0.523, respectively). The median ages of the patients with and without UDH in the surrounding parenchyma were 26.5 and 33.5 years, respectively. No statistically significant difference was present between the median ages of patients with and without UDH in the surrounding parenchyma (p= 0.224). The histopathological findings in the adjacent breast parenchyma were summarized in **Table 3**.

Table 3. Distribution of various histopathological changes in adjacent parenchyma of fibroadenoma.

Lesions	Frequence	Percentage (%)
Usual ductal hyperplasia	8	(16.3)
Atypical ductal hyperplasia	0	(0.0)
Atypical lobular hyperplasia	0	(0.0)
Lobular carcinoma in situ	0	(0.0)
Ductal carcinoma in situ	0	(0.0)
Invasive carcinoma	0	(0.0)
Fibrocyctic changes	35	(58.3)
Papilloma	2	(3.3)
Fat necrosis	1	(1.7)
Granulation tissue	0	(0.0)
Infarct	0	(0.0)

DISCUSSION

This study was designed to evaluate detailed histomorphological features of fibroadenomas. Various epithelial and stromal changes are common in fibroadenomas. In the literature, fibroadenomas with complex features and proliferative lesions have been reported to carry a relatively higher risk for the development of invasive carcinoma (5-8, 12). However, limited data are available on the statistical analysis of histopathological changes in fibroadenoma and adjacent breast parenchyma.

Fibroadenomas are mostly single and unilateral however they may be also multiple and bilateral, although rare (1). Kujiper et al. have detected multiple fibroadenomas in 28 (7.8 %) of 358 patients while 11 of those were multiple bilateral fibroadenomas in their study (2). On the other hand, Laxman et al. have determined bilateral fibroadenomas in 7 (14 %) cases in their case series of 50 patients (3). Multiple tumors were detected in 5 (9.6 %) cases in the present study compatibly with the literature, 3 (60 %) and 2 (40 %) of those cases were unilateral and bilateral, respectively.

In the present study, median age was 31 years compatibly with the literature data (1, 2, 13-15). However, although incidence of fibroadenomas is expected to decrease in the fifth decade (1, 3), contrarily, the maximum number of our cases (28.8 %) were in the fifth decade age group.

Fibroadenoma is usually 3 cm in diameter or smaller (2, 3, 9). It is termed as "giant fibroadenoma" if it is larger than 5 cm in diameter and/or 500 gr in weight or replaces at least 80 % of the breast (10). In also this study; median size was 2.5 cm in diameter and 63.3 % of the cases were smaller than 3 cm in diameter. Eight-point-three percent of the fibroadenoma cases were giant fibroadenomas. There was no significant difference in age value between tumor size groups ($p = 0.06$).

Fibroadenoma with UDH was encountered in 36.6 % of the cases. We have found that mild ductal hyperplasia was detected in maximum number of the cases and followed by moderate ductal hyperplasia and florid ductal hyperplasia. Most authors have reported predominantly mild and moderate UDH in fibroadenomas similarly to our study (7, 13, 16-17), whereas, a higher rate of moderate UDH than mild type was reported in another study (2). We should take into account the subjectivity of the observer in the evaluation of hyperplasia, however, we used Rosen's exact diagnostic criteria (11) and myoepithelial cells that extend to the lumen as a clue for differentiation (2). No statistically significant difference was found between fibroadenomas with and without usual hyperplasia in terms of age and tumor size ($p= 0.89$; $p = 0.26$, respectively).

Kuijper et al. have determined 2 % carcinoma in situ (CIS) (5 cases DCIS; 3 cases LCIS) and 0.9 % invasive carcinoma in the fibroadenoma (2). Ansari et al. have detected no accompanying CIS or invasive carcinoma in the case series of 317 patients with fibroadenoma (13). In the recent time, Krishnamurtyhy et al. have found atypical epithelial proliferation in 30 (1.97 %) cases in the case series of 1523 patients with fibroadenoma involving LCIS, ADH, DCIS and invasive carcinoma in 8, 6, 10 and 6 cases, respectively (18). No LCIS or invasive carcinoma was encountered in the present study, the rates of DCIS and ADH were both 1.7 %. It has been stated in the literature that fibroadenomas with atypical proliferative epithelial changes are encountered in more advanced ages (2, 5, 18), however, our cases with ADH and DCIS were 15 and 31 years old, respectively. That may be resulting from that our cases series included a limited number of cases and that each of ADH and DCIS were found in only case. Nevertheless, it may be expected that atypical proliferative changes may be identified in earlier ages taking into consideration that breast cancer onset age in Mediterian countries is lower than many western countries.

The incident rates of the findings for fibroadenoma complexity were reported ranging between 3.6 %-72.8 % (2, 5, 8, 13, 19). In the present study, 56.7 % of the cases were complex fibroadenomas. Similarly to many studies, apocrine metaplasia (38.3 %) was the most common finding among the fibrocystic epithelial changes. This was followed by sclerosing adenosis, calcifications, papilloma, cyst and pseudo-lactational changes. Incidence variability of complexity in the fibroadenomas may be caused by the differences between sample sizes per case. However, sample sizes were not stated in many studies while only Kuijper et al. have noted that they took averagely 4 samples for each case in the study that they have identified 40.4 % complexity (2). It has been denoted in the literature that risk for development of breast cancer relatively increases in the fibroadenoma cases with proliferative epithelial and complex changes (5, 8). A statistically significant relationship was detected between complex fibroadenoma and UDH ($p< 0.001$), UDH was present in 55.9 % of complex fibroadenomas. The complex changes were present in the fibroadenoma cases with either ADH and CIS. There was no significant relationship between complex fibroadenoma and UDH or fibrocystic changes in the surrounding parenchyma ($p= 0.438$ and $p= 0.523$, respectively). The pre-

vious studies have reported that complex fibroadenoma is determined in older women (2, 20). In the present study, no statistically significant difference was found between complex and non-complex fibroadenoma in terms of age and tumor size (p= 0.420, p= 0.569, respectively).

In the present study, 16.3 % UDH was detected in the adjacent breast parenchyma whereas no ADH was encountered. No statistically significant association was found between the presence of UDH in the surrounding parenchyma and fibroadenoma (p= 0.132). UDH was located in the adjacent breast parenchyma in 26.3 % of the fibroadenomas involving UDH. Similarly, Kuijper et al. have determined no correlation between the localization of UDH in the fibroadenoma and surrounding breast parenchyma (2). The incidence rates of UDH in the adjacent parenchyma were slightly higher than those in the studies of Dupont et al. (UDH; 13.7 %, ADH; 1.7 %) and Kuijper et al. (UDH; 7.9 %, ADH; 1.2 %) (2, 5). The differences between the rates may be resulting from the differences between the sizes of imageable surrounding parenchyma. Indeed, Kuijper et al. have denoted that the 80 % of the adjacent parenchyma they have explored was at the lower limit of the adequacy criteria determined for imaging (2). In fibroadenoma surgery, the excision of fibroadenoma including an amount of surrounding parenchyma may be helpful in exposing the proliferative changes in the surrounding breast parenchyma and identification of the risk factors.

The limitations of our study are the small sample size, the unknown family history of breast cancer and the lack of follow-up.

In conclusion, proliferative change rates in and around fibroadenoma that pose a risk for breast cancer at younger ages were found to be similar to those of advanced ages. It is known that breast cancer in our country is seen at a younger age compared to European countries, so the diagnosis of fibroadenoma should not be taken lightly as both pathologists and surgeons. The examination of the complex and proliferative changes in the fibroadenoma and the proliferative changes in the surrounding breast parenchyma meticulously and specification of all those changes in the report will allow determination of the risk for development of breast cancer more accurately.

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