Fibroadenoma of the Breast: Analysis of Associated Pathological Entities – A Different Risk Marker in Different Age Groups for Concurrent Breast Cancer

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Abstract

Background: Fibroadenoma, one of the most common benign breast lesions, has a characteristic age-specific incidence and is associated with other pathological entities in 50% of cases. The clinical or imaging diagnosis of fibroadenoma may be erroneous, and in some cases is found to be invasive cancer. The clustering of such entities, their correlation with age, and the risk of synchronous breast malignancy are uncertain.

Objective: To explore the possibility of any significant clustering of fibroadenoma-associated benign breast diseases and to assess the possible risk of concomitant breast cancer.

Methods: We analyzed the pathological results of 147 women undergoing excisional biopsies for fibroadenoma diagnosed pre-operatively either by clinical examination and imaging (n = 117) or by radiology alone (n = 30). The interrelationships among all entities associated with fibroadenoma were studied by hierarchical cluster analysis. The correlation of the various pathologies with the risk of invasive breast cancer in relation to the patient's age was also evaluated.

Results: Fibroadenoma-associated pathologies were found in 48% of the cases: sclerosing adenosis (23%), duct ectasia (17.7%), apocrine metaplasia (15.6%), florid fibrocystic disease (12.9%), duct papillomatosis (11.6%), infiltrating duct carcinoma (5.4%), duct carcinoma *in situ* (3.4%), and 1 case of lobular carcinoma *in situ* (0.6%). An orderly internal hierarchy and three significant clusters emerged: a) epithelial apocrine metaplasia, duct ectasia and sclerosing adenosis (similarity coefficients 16.0, 11.0 and 8.0 respectively); b) papillomatosis, florid fibrocystic disease and calcifications (similarity coefficients of 6.0, 4.0 and 2.0 respectively); and c) infiltrating duct carcinoma and duct carcinoma *in situ* (similarity coefficients of 1.8 and 1.6 respectively). Seven of the eight patients with breast cancer were older than 40 years.

Conclusions: In about half of the cases fibroadenoma was associated with other pathological entities clustered in an orderly hierarchy. The rarity of synchronous breast cancer in the younger age group and its more common association with fibroadenoma in the older age groups dictate a different approach to each. The finding of fibroadenoma in women older than 40 indicates the need for surgical excision.

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Fibroadenoma of the breast is a benign tumor [1] and one of the most commonly encountered breast lesions [2,3]. It constitutes one of several pathological entities within the broader definition of benign fibrocystic breast disorders [4]. Although much more common in the young age group [5], fibroadenoma can occur in older women as well [6]. The clinical significance of fibroadenoma, the distribution of associated benign pathology and the risk of concurrent malignant disease in younger and older women have been the subject of diverging opinions. While some studies did not find fibroadenoma to be a risk factor for breast cancer [7,8], others reported an alarming association of fibroadenoma with malignant breast disease [9,10]. Furthermore, an erroneous diagnosis of fibroadenoma arrived at clinically can occur in up to 50% of cases [11].

The present study attempted to evaluate whether an orderly hierarchy exists within fibroadenoma-associated pathological entities, and whether it correlates with the risk of concomitant breast cancer in two different age groups. By applying hierarchical cluster analysis to the data obtained by elaborate pathological examination, it may be possible to define a potential significant association between such entities and to observe whether an organized internal structure exists among such entities. In addition, it permits an assessment of the difference in risk of fibroadenoma-associated breast cancer between younger women and those above the age of 40. In agreement with other studies [12,13], it may be advisable to adopt a different approach in different age groups for managing solid lesions diagnosed as fibroadenoma.

Materials and Methods

The study group comprised 147 women, all with a clinical preoperative diagnosis of fibroadenoma that was arrived at either by the presence of a palpable mass consistent with such a lesion and further confirmed by imaging radiology (n=117), or by imaging radiology alone (n=30). Imaging consisted of ultrasonography, mammography, or both, depending on the patient's age. In patients older than 35–40 years, imaging included both mammography and ultrasonography. In younger patients only ultrasonography was performed. All patients underwent wide excisional biopsy – under local anesthesia in

those with palpable lesions, and general anesthesia in those with non-palpable lesions localized by guide wire under mammography or ultrasonography. The specimens, imbedded in paraffin and stained with hematoxylin-eosin, were processed according to the acceptable routine [1].

Once the diagnosis of fibroadenoma was established according to the standard acceptable classification [1] the following entities were noted, and if present, entered into a database file: apocrine metaplasia, papillomatosis, duct-ectasia, sclerosing adenosis, florid fibrocystic disease, stippled epithelial calcifications, duct carcinoma *in situ*, lobular carcinoma *in situ*, and infiltrating duct carcinoma. The two longest diameters of the tumor were recorded and their product computed. The use of fine-needle localization was also noted. The patients were arbitrarily divided into two age groups: women of 40 years and younger, and patients older than 40.

Statistical analysis and cluster analyses were applied to the whole group as well as to the two separate age groups.

Statistical analysis

The SAS statistical package (SAS institute, Carey, North Carolina) was used for correlation analysis, chi-square and *t*-tests. Cluster analysis was performed using the SPSS version for personal computers to analyze possible hierarchical structures of the various pathological entities associated with fibroadenoma. Prior to examining different clustering algorithms, a similarity coefficient, expressing the nearness of any two pathological entities, was defined as the relative prevalence of patients having any two pathological entities. Three agglomeration methods were used to form a rectangular similarity coefficient matrix: average linkage, single linkage, and complete linkage. The cluster analysis started by defining as many clusters as the number of pathological entities. In each consecutive step the two closest entities were merged to form a new cluster that replaced the previous ones. In a series of consecutive steps, all the initial pathological entities were transformed into one large cluster. The method of hierarchical cluster analysis has been reported previously and was used to study complex structures composed of numerous variables in order to detect any possible internal hierarchy of such systems [14].

Results

A total of 147 consecutive surgical excisional biopsies were performed in 147 women. In 117 patients the diagnosis was based on a clinically detectable, smooth and firm mass. Diagnosis was further confirmed by mammography and ultrasonography (in women 35 years and older) or by ultrasonography in patients younger than 35. Surgery was performed in 30 patients following a radiological non-palpable finding that was diagnosed pre-operatively as fibroadenoma. Patients' age range was 18–79 (mean 43.6 ± 15.7 years); 84 patients were older than 40 years (52.6 ± 17.2) and 63 patients were 40 years or younger (27.5 ± 8.2). The age-specific distribution of fibroadenoma is shown in Figure 1.

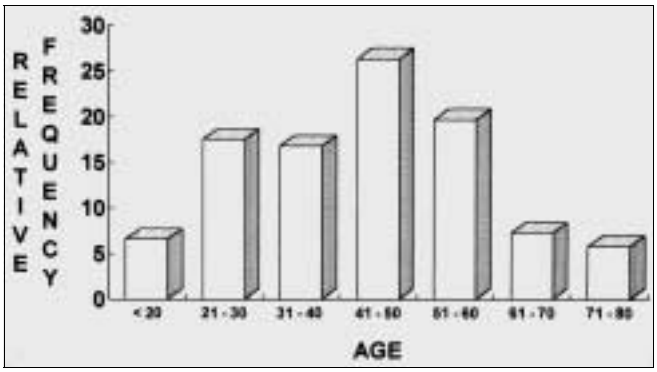

Figure 1. Age-specific distribution of fibroadenoma in 147 patients. Values are expressed in percent.

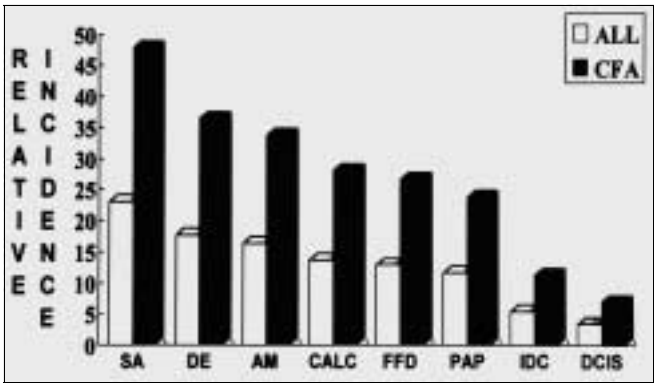

Figure 2. Relative incidence of fibroadenoma-associated pathology in the whole group (ALL) and in the complex-fibroadenoma group (CFA).
SA = sclerosing adenosis, DE = duct ectasia, AM = apocrine metaplasia, CALC = epithelial calcifications, FFD = florid fibrocystic disease, PAP = duct papillomatosis, IDC = infiltrating duct carcinoma, DCIS = duct carcinoma *in situ*. Values are expressed in percent.

The mean size of the fibroadenoma, expressed by the product of the largest two diameters, was 3.1 ± 1.9 cm^2 for the whole group. There was no significant difference in size between the older and younger age groups (3.5 ± 2.1 vs. 2.9±1.8 cm^2 respectively, P = NS). In 52% of the cases, fibroadenoma was the only pathological entity found. In the rest of the patients (n=71), associated pathologies were observed and were considered as the complex fibroadenoma group according to previously reported criteria [15,16]. The mean age of patients with fibroadenoma only was 35.6 ± 16.5 years (range 17–72), while the mean age of patients with complex fibroadenoma was 46.8 ± 12.2 (range 21–77) (P = 0.001). The relative incidence of these entities is shown in Figure 2. The pathological entity most commonly associated with fibroadenoma was sclerosing adenosis (34/147, 23% of the whole group, and 47.9% of the complex fibroadenoma. group). Following in

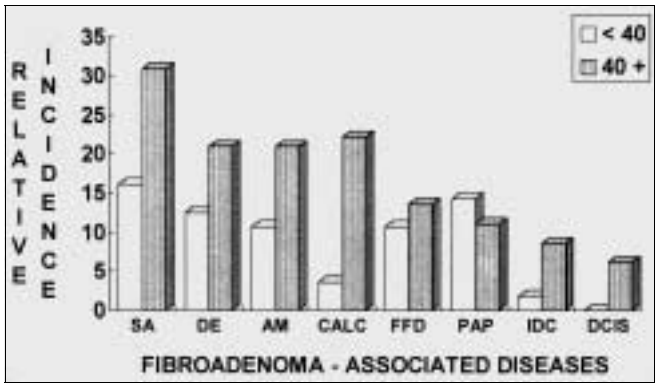

Figure 3. Relative incidence of fibroadenoma-associated pathology in women younger and older than 40 years of age. Values are expressed in percent.

descending order of frequency were duct ectasia (26/147, 17.7% of all patients; and 26/71, 36.6% of the CFA group); epithelial apocrine metaplasia (24/147, 16.3% of all patients; and 24/71, 33.8% of the CFA group), florid fibrocystic disease (19/147, 12.9% of all; and 19/71, 26.7% of the CFA group); and papillomatosis (17/147, 11.6% of all patients; and 17/71, 23.9% of the CFA group). The incidence of fibroadenoma associated with infiltrating duct carcinoma in this series was 5.4% (8/147). Of the 8 cases of infiltrating duct carcinoma, 7 occurred in women older than 40 years of age ($P = 0.001$). Duct carcinoma *in situ* was evident in 5/147 women (3.4%), all of them older than 40. Lobular carcinoma *in situ* appeared to be the rarest entity associated with fibroadenoma and occurred in only 1 of the 147 patients (0.6%).

Of the various pathological entities, several conditions appeared to be correlated with age [Figure 3]. The presence of micro-calcification correlated significantly with age: only 3.6% of patients in the younger group had stippled epithelial calcifications as compared to 22.2% of the women over 40 ($P = 0.002$). Sclerosing adenosis also correlated with age: only 16.1% of the younger age group showed this lesion compared to 30.9% in the older age group ($P = 0.005$). There were no differences between the groups with regard to duct papillomatosis and apocrine metaplasia (P = NS). Florid fibrocystic disease was more common in the older age group (13.6% vs. 10.7, $P = 0.05$). Duct ectasia was also more prevalent in the older age group: 12.9% vs. 4.7% in the younger age group ($P = 0.05$). Invasive cancer was significantly more prevalent in the older age group: 8.6% vs. 1.8% ($P = 0.001$). Correlation analysis of all pathological entities failed to reveal any significant association between their presence and the finding of infiltrating duct carcinoma, with the exception of duct carcinoma *in situ*. The presence of duct carcinoma *in situ* was accompanied by the presence of infiltrating duct carcinoma in 4/5 cases (80%). All five cases of duct carcinoma *in situ* were observed in women older than 40 years of age.

Cluster analysis

In the three agglomeration algorithms used for the similarity coefficient computation, the same results were obtained. Three significant clusters emerged: the first cluster was composed of apocrine metaplasia, duct-ectasia, and sclerosing adenosis (nearness coefficients of 16.0, 11.0 and 8.0 respectively). Papillomatosis (coefficient 6.0), florid fibrocystic disease (coefficient 4.0) and calcifications (coefficient 2.0) constituted the second cluster. Infiltrating duct carcinoma and duct carcinoma *in situ* formed the third cluster (similarity coefficients of 1 and 0.5), and lobular carcinoma *in situ* formed a cluster of its own.

Discussion

Fibroadenoma of the breast is a frequent underlying cause for both palpable and radiologically detected breast masses [1,2]. It is considered a benign lesion and constitutes a defined entity of an aberration in normal breast development rather than a true neoplasm [17]. Although encountered most commonly in women in their late teens and early twenties [6,18], fibroadenoma may occur, albeit infrequently, in older women [6,19]. In a significant number of cases, fibroadenoma is associated with additional benign pathological entities of the same group. Dupont et al. [15] assigned the term complex fibroadenoma to those fibroadenomas associated with sclerosing adenosis, epithelial calcifications, cyst formation and apocrine changes. Patients with such an association bear a higher risk of developing an invasive breast cancer [20].

Although generally regarded as a benign lesion, fibroadenoma has been reported to be associated with breast cancer and, in fact, has been viewed as a long-term risk factor for breast cancer [9,15,21]. In view of the unacceptably high rate of misdiagnosis of fibroadenoma [11] and the numerous reports of invasive and non-invasive cancer arising in fibroadenomas [22], physicians should be alert and cautious when evaluating the risk of a given patient within a specific age group [23].

The present study was aimed at exploring a possible orderly and hierarchical internal structure of additional pathological entities associated with fibroadenoma, and assessing the possible value of these disease entities as risk markers for synchronous breast cancer. The eligibility criteria for inclusion in this series required that both the pre- and postoperative diagnosis be fibroadenoma, which might have caused a certain bias by excluding all other indeterminate masses. Moreover, since the indication for excisional biopsy was a mass suspected of malignancy, ill-defined fibrocystic masses or mammographic asymmetry or calcifications were excluded. Thus, there may have been an even higher proportion of disease entities associated with fibroadenoma. Nonetheless, patient selection criteria in this study were specifically targeted at identifying those patients in whom the pre-operative diagnosis of fibroadenoma was not erroneous. Thus, the distribution of fibroadenoma-associated disease entities can be evaluated when certainty exists regarding the nature of the breast mass.

The use of cluster analysis of various diagnoses has been

previously described [14]. This method allows us to detect an organized intra-structure as well as an inter-relationship among various disease entities that is otherwise masked by the multitude of parameters. It can, alternately, prove that they occur at random. The results of this study highlight the orderly hierarchy that exists among the various pathological entities associated with fibroadenoma. Apparently, the specific combination of such entities does not occur at random; rather, it obeys a clear mathematical rule. The precise identity of the factor that has the most significant impact on such order is not yet determined. Although certain benign breast diseases are associated with a higher risk of developing invasive breast malignancy [16,21], correlation analysis of the data in this series failed to show any significant association of any condition, excluding fibroadenoma, with synchronous breast cancer. Nevertheless, it appears that fibroadenoma-associated pathology has a particular age group distribution: calcifications, sclerosing adenosis, duct ectasia and florid fibrocystic disease were significantly more common in the older age group. Although no significant correlation was found between these types of benign breast pathologies and cancer, the fact that seven of the eight cases of invasive cancer occurred in older women – in whom such pathologies are more frequent – deserves consideration. The lack of statistical significance may be attributed to the small number of cases of cancer in this series. It is also of interest that no correlation was observed between size of fibroadenoma, age group and, therefore, the risk of concomitant invasive cancer.

The specific clusters that emerged indicate that the proliferative breast disorders clump together with significant affinity, as shown by the similarity coefficients. The fact that all agglomeration algorithms led to the same results strongly supports the notion of orderly hierarchy. Further study investigating a larger number of patients is still required to unmask specific clusters as significant risk indicators for breast cancer.

The most significant finding in the present series was the significantly higher association between fibroadenoma and infiltrating duct carcinoma in women older than 40. The overall incidence of fibroadenoma is 32.8 per 100,000 woman-years with a peak incidence between 20 and 29 [5,6]. Hindle and Alonzo [8] found the peak incidence to be at age 21–25 years. The alarmingly high rate of erroneous clinical diagnosis of fibroadenoma (50%) and the 5% incidence of associated invasive cancer [11], together with various reports of breast cancer arising within fibroadenomas [23] call for caution. However, their disparate behavior in terms of association with invasive cancer suggests that the management of fibroadenomas – whether diagnosed clinically or radiographically – may differ in the younger and older age groups. The higher incidence of invasive cancer associated with fibroadenoma at an older age can be explained by the overall higher prevalence of breast cancer in this age group. Given the increased relative risk associated with complex fibroadenoma [15,16] and the significantly higher incidence of this condition in this age group, one would also expect an increased rate of invasive cancer. It would appear that while conservative management is acceptable for younger women [24], a more aggressive approach is advised for women above the age of 40. A serial, close follow-up, preferably with fine-needle aspiration of the mass [25], is recommended for younger patients.

In summary, our results indicate that additional types of fibrocystic disease entities accompany fibroadenoma in 50% of cases, and that such pathologies occur in an orderly hierarchical manner. The incidence of concomitant invasive breast cancer is around 5%, in agreement with previously reported data. The difference in cancer distribution by age dictates a different approach to each age group. Surgical removal seems the safest choice in women older than 35–40, while conservative management is suitable, under specific conditions, for younger women.

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