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.

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 pre-operative 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 ± 17.7 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.

The mean size of the fibroadenoma, expressed by the product of the largest two diameters, was 3.1 ± 1.9 cm² 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 cm² 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
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 (nearlyness 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
previous 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 combi-
nation 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 pathol-
ygy 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 [7,6]. Hindle and
Alonso [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 fibroadeno-
mas – 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 sig-
nificantly 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 accept-
able 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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**Capsule**

**CD8 killer cells and multiple sclerosis**

Multiple sclerosis (MS) is an immune-mediated demyelinating disease affecting nerves of the central nervous system (CNS). Animal models of MS have illuminated how helper-type CD4+ T cells could influence the human form of the disease. Because CD8+ killer T cells are involved in cell-mediated autoimmunity and can be detected in the lesions of some MS patients, it is possible that they too might contribute to the pathology observed in MS.

To test this, Huseby et al. generated CD8+ cytotoxic T cell clones from mice immunized with a protein component of nerve myelin sheath. Transferring these cells into normal mice caused loss of coordination, spastic reflexes, and paralysis. The CNS lesions responsible for these effects were generally restricted to small blood vessels of the brain and proximal regions of white matter, a pathology that is distinct from other forms of CD4-mediated demyelinating disease. This type of perivascular lesion in the upper CNS suggests that CD8+ T cells might induce distinct forms of MS or mediate particular stages of the disease.


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**Capsule**

**Hepatitis C virus replication in mice with chimeric human livers**

Lack of a small animal model of the human hepatitis C virus (HCV) has impeded development of antiviral therapies against this epidemic infection. By transplanting normal human hepatocytes into SCID mice carrying a plasmogen activator transgene (Alb-uPA), Mercer and colleagues generated mice with chimeric human livers. Homozygosity of Alb-uPA was associated with significantly higher levels of human hepatocyte engraftment, and these mice developed prolonged HCV infections with high viral titers after inoculation with infected human serum. Initial increases in total viral load were up to 1,950-fold, with replication confirmed by detection of negative-strand viral RNA in transplanted livers. HCV viral proteins were localized to human hepatocyte nodules, and infection was serially passed through three generations of mice confirming both synthesis and release of infectious viral particles. These chimeric mice represent the first murine model suitable for studying the human hepatitis C virus *in vivo*.

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