ABSTRACT
The precursor lesions of the ductal invasive breast carcinoma are a heterogeneous group of lesions that raise problems in defining, classifying and diagnosing them. These lesions include the usual ductal hyperplasia, flat epithelial hyperplasia (Ductal Intraepithelial Neoplasia grade 1A), atypical ductal hyperplasia (Ductal Intraepithelial Neoplasia grade 1B), and ductal carcinoma in situ (13, 16). There are three histopathological grades of the ductal carcinoma in situ: low grade (Ductal Intraepithelial Neoplasia grade 1C), intermediate grade (Ductal Intraepithelial Neoplasia grade 2) and high grade (Ductal Intraepithelial Neoplasia grade 3) of malignity (13). We focused on the distribution of the precursor lesions of the ductal invasive breast carcinoma within the pathology of mammary gland, their association with ductal invasive breast carcinoma, the shares of the age categories and sexes, as well as their histopathological study. The predominant lesion of the ductal invasive breast carcinoma was the usual ductal hyperplasia. We found the usual ductal hyperplasia as being the only precursor lesion also microscopically diagnosed at men. In the studied period, we have not found flat epithelial hyperplasia cases. The least frequent precursor lesion was the atypical hyperplasia. Comedocarcinoma was the most frequent in association with the ductal invasive carcinoma. This study aims to bring new references to those existing or to confirm the data from the pathology literature.

KEY WORDS  usual ductal hyperplasia, atypical hyperplasia, ductal carcinoma in situ

Introduction
The precursor lesions of the ductal invasive breast carcinoma are a group of architecturally and cytologically heterogeneous proliferations associated with an increased risk of subsequent development of invasive carcinoma (4). The precursor lesions of ductal invasive breast carcinoma include usual ductal hyperplasia, atypical ductal hyperplasia, flat epithelial hyperplasia and ductal carcinoma in situ.

Immunophenotypical and molecular studies proved that usual ductal hyperplasia does not have molecular characteristics that are similar to the atypical one. Atypical ductal hyperplasia has features that are similar to the low-grade ductal carcinoma in situ, and this latter is genetically different from the high-grade ductal carcinoma in situ, both of them developing different types of invasive breast carcinoma (1).

The current study follows the histopathological classification of the precursor lesions of the invasive ductal breast carcinoma, their mutual association and their association with the invasive ductal breast carcinoma.

The correct diagnosis and classification of these precursor lesions is an important matter for clinicians and histopathologists, because they are associated with the increase of the risk of developing invasive breast carcinoma.

Material and Methods
The current study is based on 605 cases of mammary lesions, spread on a three-year period, namely 2005 – 2007, having the histopathological diagnosis of: acute mastitis, fat necrosis, fibrocystic change, radial scar, adenosis, metaplasias, papillomas, myoepithelial lesions, intraductal proliferative lesions, lobular intraepithelial neoplasia, microinvasive carcinoma, infiltrating ductal carcinoma, invasive lobular carcinoma, tubular carcinoma, infiltrating cribriform carcinoma, medullary carcinoma, mucin-producing carcinomas, invasive papillary
carcinoma, invasive micropapillary carcinoma, apocrine carcinoma, metaplastic carcinomas, mesenchymal lesions, biphasic tumors (fibroadenoma, phylloides tumor), diseases of the nipple, male breast lesions.

For all these cases, we analyzed the presence of the precursor lesions of the invasive ductal carcinoma, isolated and in association, as well as their association with the invasive ductal breast carcinoma. The lesions were of the patients having undergone a surgery in the surgery clinics of the Emergency Clinical Hospital of Craiova.

The fragments of mammary tissue were fixed in 10%-concentration formaldehyde, embedded in paraffin through the usual technique and stained with hematoxilin-eosin, within the Laboratory of Pathology, in the same hospital. We made the classification of the precursor lesions in the various lesion categories according to the pathology literature.

**Results**

The current study treated 605 cases, diagnosed for female patients aged between 17 and 92 years and for male patients aged between 54 and 75 years. Histopathologically, the precursor lesions of the invasive ductal breast carcinoma had the following distribution: usual ductal hyperplasia 12% (73 cases), atypical ductal hyperplasia 2.8% (17 cases), and ductal carcinoma in situ 10.41% (63 cases).

The usual ductal hyperplasia has been found in association with benign breast lesions in 49 cases, with invasive ductal breast carcinoma in 16 cases, with atypical ductal hyperplasia in 3 cases, found isolated in 3 cases, in association with mucin-producing carcinoma and with papillary carcinoma in one case each. The usual ductal hyperplasia has been found in 88.88% from the female cases (66 cases) and in 11.11% from the male cases (7 cases).

The predominant morphological type of ductal carcinoma in situ was comedocarcinoma, with a share of 34.92% (22 cases), the rest of the shares being 9.52% (6 cases) for the cribriform type, 3.17% (2 cases) for the micropapillary type, 3.17% (2 cases) for the solid type, 1.58% (1 case) for the papillary type, and 9.52% (6 cases) for intraductal carcinomas not classified from various reasons.

The morphological types of ductal carcinoma in situ were also found in association, as follows: the comedocarcinoma with the cribriform type in 11.11% of the cases (7 cases), the solid type with the cribriform type in 7.93% of the cases (5 cases),

**Fig. 1: Usual ductal hyperplasia, Ob x200, HE stain;**

**Fig. 2: Usual ductal hyperplasia, solid pattern, Ob x200, HE stain;**

**Fig. 3: Atypical ductal hyperplasia, Ob x200, HE stain;**
comedocarcinoma with the solid type in 7.93% of the cases (5 cases).

The following associations have been found in one case each (1.58%): the cribriform with the papillary type, the clinging with the papillary type, the comedocarcinoma with the clear cell, solid, apocrine and papillary types, the solid with the comedo and cribriform types, the comedo with the micropapillary type, the comedo with the solid and micropapillary types, and the papillary with the solid type.

The ductal breast carcinoma in situ was associated with the invasive ductal breast carcinoma in 79.36% of the cases (50 cases). The morphological types of ductal carcinoma in situ that have been found associated with an invasive ductal breast carcinoma were: comedocarcinoma in 31.03% of the cases (18 cases), the cribriform type in 5.17% of the cases (3 cases), the micropapillary type in 1.72% of the cases (1 case), the comedo with the solid type and the comedo with the cribriform type in 10.34% of the cases each (6 cases each), the solid type with the cribriform type in 8.62% of the cases (5 cases), the solid type with the comedo and cribriform types in 3.44% of the cases (2 cases), the comedo with the micropapillary type in 1.72% of the cases (1 case), the comedo type with the solid and micropapillary types in 1.72% of the cases (1 case), the papillary with the solid type in 1.72% of the cases (1 case), the clear-cell type with the comedo, solid, apocrine and papillary types in 1.72% of the cases (1 case).

The distribution of the age categories in the usual ductal hyperplasia cases was: the sixth decade (51-60 years) in 26.99% of the cases, the seventh decade (61-70 years) in 22.22% of the cases, the fifth decade (41-50 years) in 17.46% of the cases, the fourth decade (31-40 years) in 15.87% of the cases, the eighth decade (71-80 years) in 7.93% of the cases, the second and third decades in 4.76% of the cases each.
The distribution of the age categories in the atypical ductal hyperplasia cases was: the seventh decade in 33.34% of the cases, the sixth decade in 26.67% of the cases, the fourth decade in 20% of the cases, the fifth decade in 13.33% of the cases, and the third decade in 6.66% of the cases.

The distribution of the age categories in the ductal carcinoma in situ cases was: the seventh decade in 32.73% of the cases, the sixth decade in 25.46% of the cases, the fifth decade in 24.57% of the cases, the fourth decade in 7.27% of the cases, and the tenth decade in 1.81% of the cases.

**Discussions**

Even in the pathology literature the average age at which the usual ductal hyperplasia occurs is 45 years (11), in the current study this precursor lesion was predominant in the sixth age decade. Clinically, this lesion has a relative increased risk, of 1.5 – 2 times, of developing an invasive ductal breast carcinoma (11). Bartow SA et al. (2) state that atypical ductal hyperplasia is a rare precursor lesion, while Stomper PC et al. (12) in their studies diagnosed an atypical ductal hyperplasia in 4% of the breast biopsy samples.

In our study, the atypical ductal hyperplasia has been microscopically diagnosed in 2.8% of the breast lesion cases, being the least frequently found precursor lesion. Page DL et al. (6) found in their study the most of the atypical ductal hyperplasia cases at 46 years old women. The predominant age category in our study for the atypical ductal hyperplasia was 61-70 years. Betsil et al., Page DL et al., Pinder et al. (3, 8, and 9) suggest that more than 50% of the cases with ductal carcinoma in situ develop an invasive breast carcinoma and that the transformation to invasive is associated with the morphological type of ductal breast carcinoma in situ. Thus, the comedocarcinoma evolves into invasive lesion more frequently and quickly than the ductal breast carcinoma with low grade of malignity.

In our study the comedocarcinoma was predominant, isolated (33.33%) and in association with other morphological types of ductal carcinoma in situ, as well as with the invasive ductal breast carcinoma (31.03%). In a study by A. Kricker et al. (5) the cases that prevailed were of cribriform or solid type ductal carcinoma in situ, isolated or in association with other morphological types of ductal carcinoma in situ (65 % of the cases). In SEER Cancer Statistics (10) the ductal carcinoma in situ occurred in 35.4% of the cases. Wellings SR. Et al. (15), Alpers CE et al. (1) state that about two thirds of the invasive breast carcinomas are associated with the ductal carcinoma in situ. In our study, the ductal carcinoma in situ was associated with the invasive ductal breast carcinoma in more than two thirds of the cases (79.36%).

In a study made in 2005 on the population of Australia, 51% of the cases of ductal breast carcinoma in situ were found in the age interval 50 – 69 years (14). Within SEER Cancer Statistics, the ductal carcinoma in situ was predominant in the age interval 60 – 79 years (10).

In the current study, the ductal carcinoma in situ was predominant in the sixth and seventh age decades, confirming the data from the pathology literature. Page DL, Dupont WD state that, for the over 60 years old women diagnosed with ductal carcinoma in situ, there is a 40% absolute risk of developing an invasive breast carcinoma in the next 20 years (7).

**Conclusions**

From the total of the cases of breast pathology, the predominant precursor lesion of the invasive ductal carcinoma was the usual ductal hyperplasia. The ductal carcinoma in situ occurred with higher frequency than the usual ductal hyperplasia. In the studied period, there were no cases of flat epithelial hyperplasia. The usual ductal hyperplasia was the only precursor lesion also found at men. The usual ductal hyperplasia was predominant in the sixth age decade. The atypical hyperplasia was the least frequent precursor lesion. The atypical hyperplasia was associated with the invasive ductal carcinoma in less than half of the cases. The atypical hyperplasia was the most frequent in the age category of 61-70 years. The comedocarcinoma was predominant in association with the invasive ductal carcinoma. The ductal carcinoma in situ was predominant in the seventh age decade.

**References**


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