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Review

Which type of cancer is detected in breast screening programs? Review of the literature with focus on the most frequent histological features

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Summary
Breast cancer is the most frequent type of cancer affecting female patients. The introduction of breast cancer screening programs led to a substantial reduction of mortality from breast cancer. Nevertheless, doubts are being raised on the real efficacy of breast screening programs. The aim of the present paper is to review the main pathological type of cancers detected in breast cancer screening programs. Specifically, attention will be given to: in situ carcinoma, invasive carcinoma histotypes and interval cancer.

Key words: breast cancer, in situ carcinoma, invasive carcinoma, interval cancer, screening program

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Conflict of interest
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Introduction

Breast cancer is the most frequent cancer affecting female patients, accounting for 23% of all cancers in women [1]. Since its beginning, the mammography based screening program for breast cancer (breast screening program, BSP) has been considered an effective tool to reduce mortality in female patients. Nevertheless, during the last years some authors questioned the real effectiveness of screening in preventing death from breast cancer [2]. Consideration on BSP efficacy is mainly based on epidemiological data, most of which do not consider the tumor histotype.
Pathologists know very well the great variety of breast cancer histotypes and their impact on prognosis [3].
Therefore, the aim of the present paper is to review the literature focusing on the different types of breast cancer detected in BSP.
Three different breast cancers will be considered: in situ carcinoma; invasive breast carcinoma (IBC); interval cancer (IC).

In situ carcinoma

Ductal carcinoma in situ (DCIS) represented < 5% of breast cancer in pre-screening era, while its incidence increased after BSP introduction, raising to 20% of breast cancers [4].
DCIS is a proliferation of neoplastic cells, confined within the ductal and

lobular system [3]. It is a non-obligate precursor of invasive breast carcinoma.
Indeed, DCIS can be detected as occasional finding in autopsies [5] or in reduction mammoplasties [6], thus leading the authors to consider a diagnosis of DCIS as an overdiagnosis of cancer [7,8].
On the other side, DCIS comprises a great variety of morphological patterns that can be subdivided into different grades [3] (Figs. 1, 2). DCIS grading is an important prognostic feature [4,9].
DCIS grading is related to the risk to develop IBC. Maxwell et al. [9] reviewed a series of untreated DCIS and demonstrated a correlation between DCIS grade and the development of IBC. IBC developed in 48% of patients with DCIS grade 3, in 32% of DCIS grade 2 and 18% of DCIS grade 1. Furthermore, DCIS grade was related to IBC grade, as most DCIS grade 2 and 3 give rise to high grade IBC [9].
This statement holds true despite the fact that DCIS grading is not uniformly used all over the world [10], but most high-grade cases are reproducibly classified [11]. Van Maaren et al. [11] analyzed a cohort of 12,256 patients with DCIS. The incidence of breast cancer related deaths was very low (1.5% among all the cases), but it increased with increasing grade. Specifically, breast cancer related deaths were 0.7% in DCIS grade 1, 1.3% in DCIS grade 2 and 1.6% in DCIS grade 3.
Therefore, it is important to evaluate which types of DCIS are detected in BSP.
Von Luijt et al. [12] analyzed a cohort of 4232 women with screen detected DCIS: most DCIS were intermediate (32%) and high grade (52%). Similar data were obtained by Weigel et al. [13] confirming the importance of screening in detecting high grade DCIS. Furthermore, Weigel et al. [13] demonstrated that the incidence of high-grade DCIS remained high even in the second and subsequent screening rounds.
Age at the time of diagnosis is another important point to be considered.
According to von Lujit et al. [12], the risk of high-grade DCIS overdiagnosis is lower in younger women, aged 50-70 years, while it increases after the age of 70. Van Ravesteyn et al. [14] applying different statistical models, demonstrated a lower risk of DCIS overdiagnosis in women aged less than 74 years.
On the basis of the published data, most screen detected DCIS are high grade lesions, affecting women aged 50-70 years. Nevertheless, the problem of overdiagnosis for low grade DCS cases still exists.
Screen detected low grade DCIS poses several problems, as correct diagnosis and grading.
Correct diagnosis and differentiation with intraductal proliferative lesions can be a difficult challenge in daily practice. In spite of detailed descriptions published

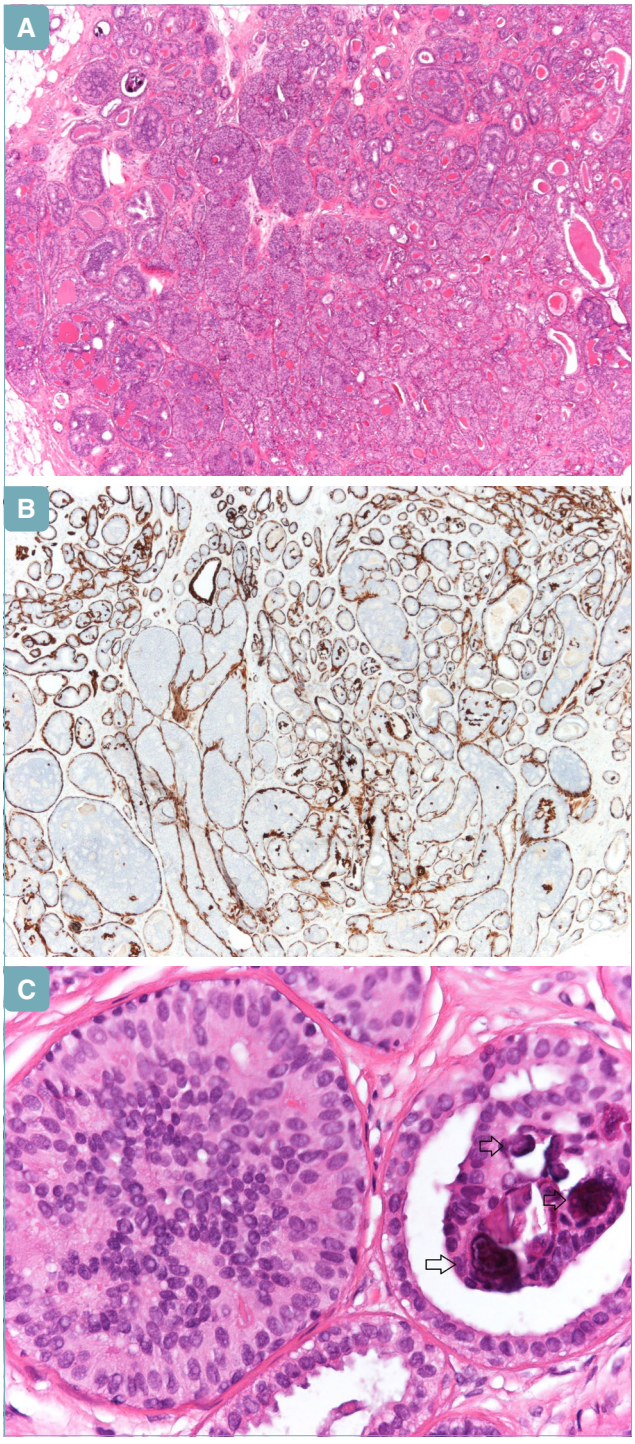

Figure 1. Low grade DCIS arising in sclerosing adenosis. (A): low power view showing closely packed glands. (B): cytokeratin 14 evidences the presence of a myoepithelial layer. (C): at higher power ducts are filled with monotonous neoplastic cells forming glandular lumina, psammomatous microcalcifications are present (arrow).

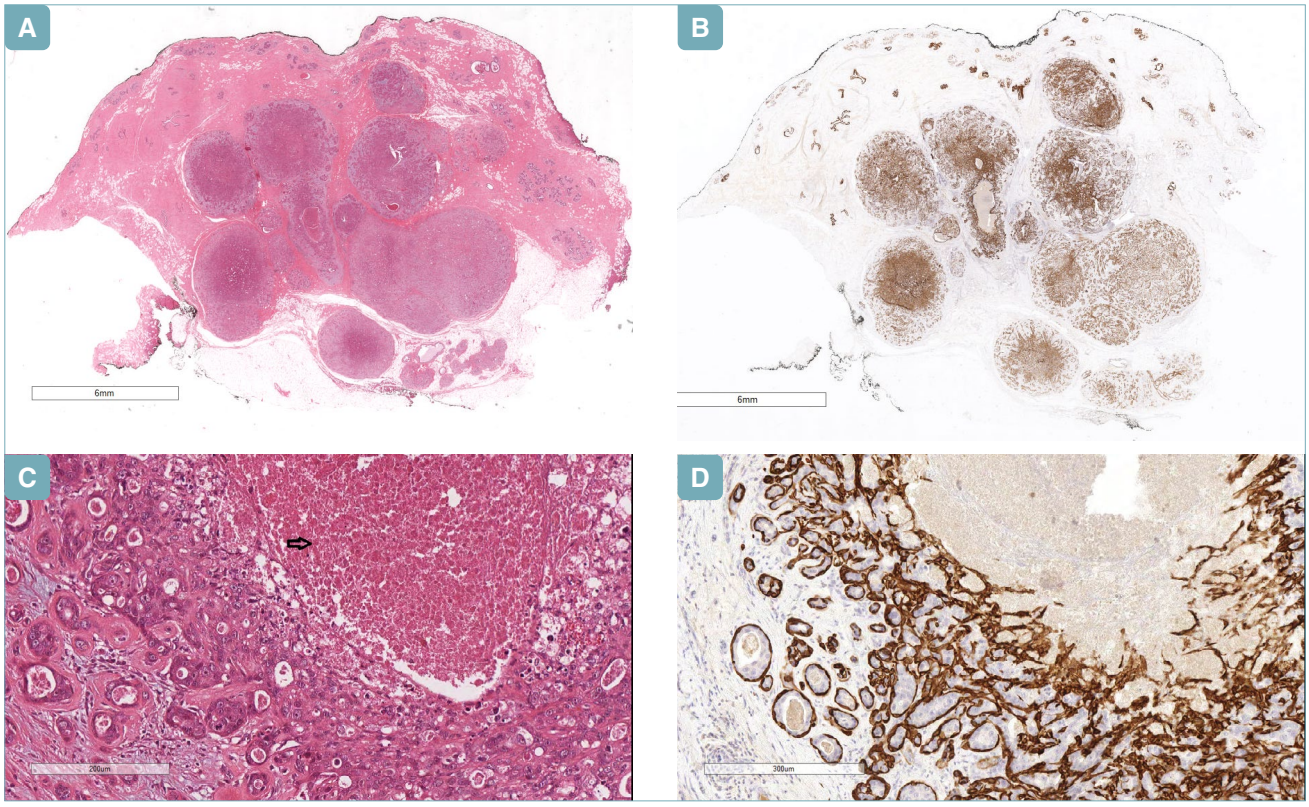

Figure 2. High grade DCIS arising in sclerosing adenosis. (A): low power view, the lesion presents a multinodular growth. (B): same lesion, stained with Cytokeratin 14 that evidences the myoepithelial layer. (C): at higher power ducts are lined by markedly atypical neoplastic cells, necrosis is present (arrow). D: cytokeratin 14 is helpful to avoid overdiagnosis of invasive carcinoma.

from a long time [15] and recently reviewed [16,17], differential diagnosis between epitheliosis (usual duct hyperplasia) and low grade DCIS, can still be a difficult task on pre-operative core biopsies. Accurate histological analysis, searching for the typical intraductal glandular structures, lined by polarized epithelial cells is fundamental for the diagnosis of low-grade DCIS. In doubtful cases, high molecular weight cytokeratins (as cytokeratin 14 or 5/6) negativity associated with strong estrogen receptor (ER) positivity in the neoplastic cells, can help to reach the correct diagnosis (Fig. 3).

DCIS grading can be difficult and still presents a high degree of variation among the different laboratories [10,18,19]. Grading variability depends on many factors, the most important being the lack of uniform criteria. Several grading systems have been proposed for DCIS, none of which is universally accepted [10,18]. On the other hand, DCIS grading is of outmost prognostic value as it can help to choose the correct treatment (surgery *vs* active surveillance). In the Sagara et al. [20] series, 1169 DCIS cases were managed without surgery, while 56,053 cases received surgical excision. After a median follow-up of 72 months, in the low-grade DCIS group breast cancer-specific survival was almost similar for both non-surgery and surgery cases (98.8% without surgery compared to 98.6% with surgery P = 0.95), thus demonstrating that a minor proportion of low-grade DCIS progress to invasion.

When low-grade DCIS is diagnosed on pre-operative core biopsies, only a minority of cases are upstaged to IBC on surgical samples. Upstaging rates vary from 0% [21] to 21% [22]. All IBC detected are well or moderately differentiated.

Evaluating data presently available in the literature, care should be taken as most of the studies consider relatively short follow-up intervals. Data retrieved from the Great Britain Breast Screening Programme [24] evidenced that women with screen detected DCIS present a long-term risks of invasive breast cancer higher than women in the general population. It is noteworthy to underline that the risk period spans for at least two

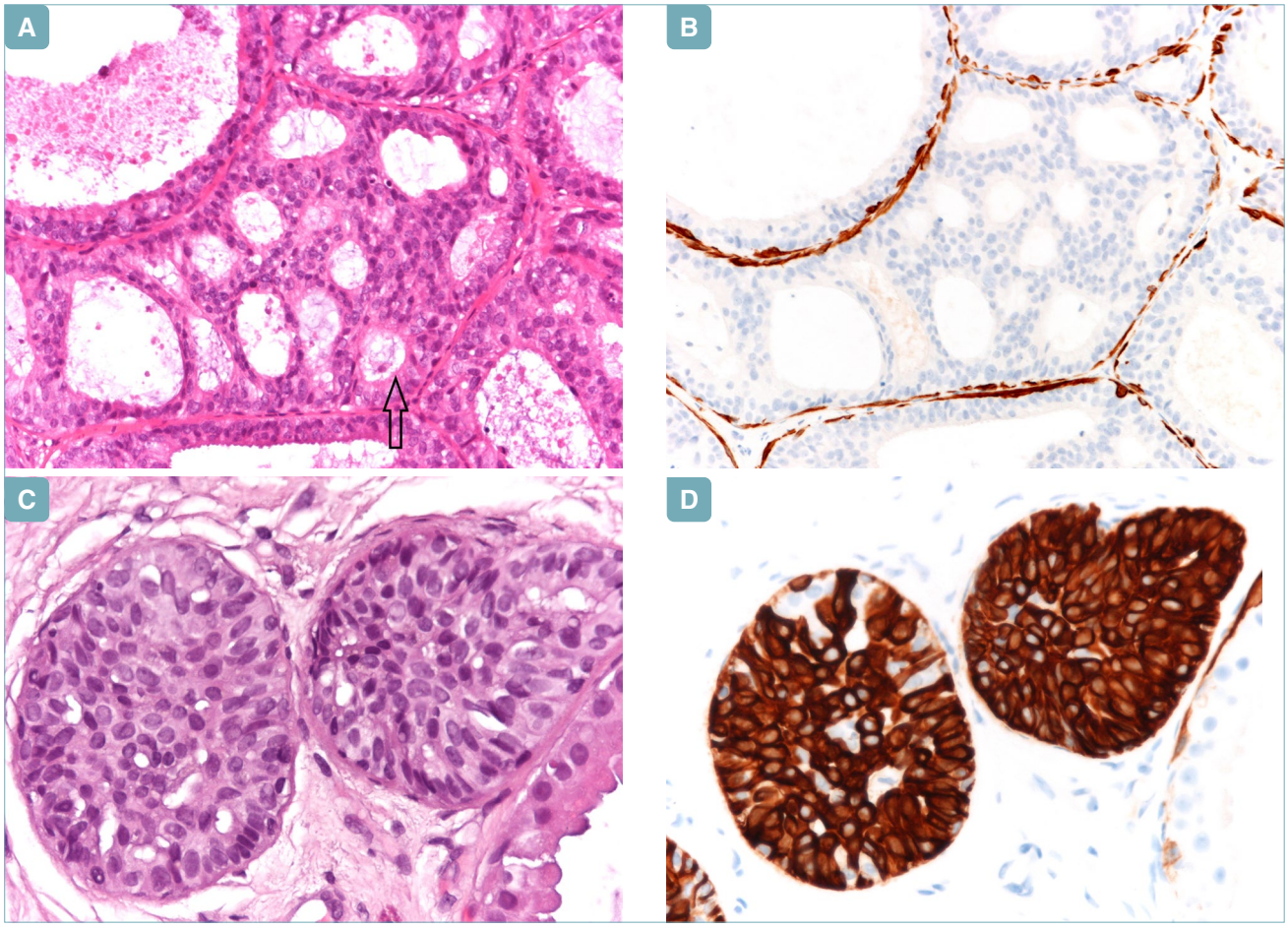

Figure 3. Low grade DCIS and differential diagnosis with florid epitheliosis. (A): low grade DCIS is characterized by a monotonous proliferation of neoplastic cells with bland nuclei. Neoplastic cells are polarized, with the secretroy pole oriented toward the lumen of the glandular strucure (arrow). (B): CK 14 stains the myoepithelial cells located at the periphery of the ducts, while the neoplastic cells are negative. (C): epitheliosis/usual duct hiperplasia is characterized by intraductal proliferation of cells devoid of atypia. Irregular spaces without any polarization are present. (D): in epithelosis CK 14 stains most of the intraductal cells.

decades after DCIS diagnosis and also comprises low and intermediate grade DCIS.

Data presently published indicate that, to exactly evaluate low-grade DCIS prognosis, further parameters should be added [25], such as correlation with clinical and mammographic findings [26] and molecular profile [27].

Lobular carcinoma in situ (LCIS) can be detected in BSP, even if less frequently than DCIS. Similarly to DCIS, LCIS covers a wide spectrum of lesions [3] each one carrying different aggressive potential. LCIS classical type can be an incidental finding, detected in association with benign calcifications [28].

Recent papers focused attention on the florid (F) and pleomorphic (P) variants of LCIS [29,30] (Fig. 4). F and P LCIS present necrosis and calcification, and therefore can be detected in BSP. F and P LCIS were considered aggressive lesions, but, due to their rarity, data were scanty and mainly based on small series. A recent study, based on 117 F and P LCIS all diagnosed on pre-operative biopsies, demonstrated that more than 60% of the F and P LCIS at presentation, can hide foci of IBC or high-grade DCIS. In addition, most invasive carcinomas were of the lobular histotype, grade 2 or 3, and thus aggressive variants of breast cancer, which are potentially lethal [30].

The data presently published indicate that BSPs detect mainly high grade in situ carcinoma (both of ductal or lobular type) in younger women. These data suggest that participation to BSP can reduce the risk of IBC [31,32].

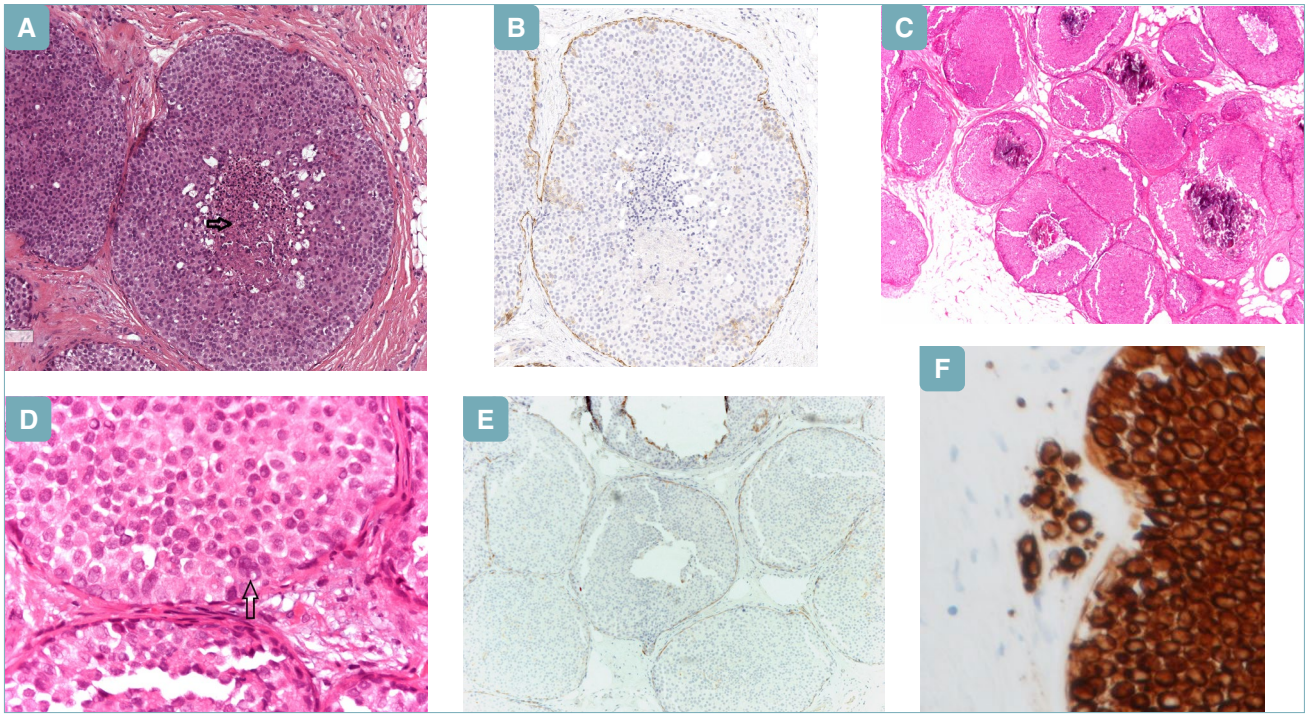

Figure 4. Lobular carcinoma in situ, florid type. (A): the acinar units are filled with a solid proliferation of neoplastic cells, with uniform nuclei, necrosis is present (arrow). (B): E-Cadherin is negative in the neoplastic cells. (C): P-LCIS is characterized by enlarged terminal ductular-lobular units, filled with neoplastic cells, resembling high grade DCIS. (D): at higher power neoplastic cells are irregular. Binucleated neoplastic cells are easily detected (arrow). (E): E-Cadherin is negative, confirming the diagnosis of P-LCIS. (F): low molecular weight cytokeratins evidence small foci of invasion.

Invasive breast carcinoma (IBC)

Most of the published data indicate that the most frequent type of screen detected IBC is luminal A type [33,34] (Fig. 5), characterized by high estrogen (ER) and progesterone receptors (PR), lack of HER2 amplification and low Ki-67 labelling index. Falck et al. [34] found that 92% of screen detected IBC were ER positive, compared to 86% of symptomatic cancers. Similarly, Ki-67 labelling index was lower than 20% in 75% of screen detected IBC, compared to 62% of symptomatic cases. On the contrary, HER2 amplification was more frequent in symptomatic cases than in screen detected IBC (24 *vs* 14%) [34].

Luminal A type of IBC is commonly considered a low-grade cancer, associated with good response to hormonal therapy and favourable prognosis. This statement is generally correct, but it should be remembered that luminal A type IBC comprises a wide spectrum of cancers. Invasive lobular carcinoma (ILC) usually meets the definition of luminal A cancer, showing high ER and PR expression, with Ki-67 lower than 20%. Nevertheless, ILC long term prognosis does not differ from that of IBC of no special type [35,36] depending mostly on TNM staging at presentation [35,37].

BSP can allow an early diagnosis. In Kobayashi et al.'s cases, 68.6% of screen detected IBC were staged I, compared with 38.2% only of symptomatic cases [38].

Therefore, as expected the IBC-related death rates are lower among screen detected cases, compared with symptomatic cases. Falck et al. [34] demonstrated that the mortality at 10 years was lower in patients with luminal carcinoma screen detected compared to symptomatic cases (3/92 *VS* 7/62). Moreover, worst prognosis was observed in non-luminal cases and node positive carcinomas [34].

Similar data were reported by several papers [38-43], all confirming the impact of BSP on breast cancer related mortality reduction.

Interval cancer (IC)

Interval cancer is defined as a cancer appearing between two screening examinations and after a negative mammography [44]. IC can be subdivided into three different groups [44,45]; missed cancers, radiographically occult cancers and true IC.

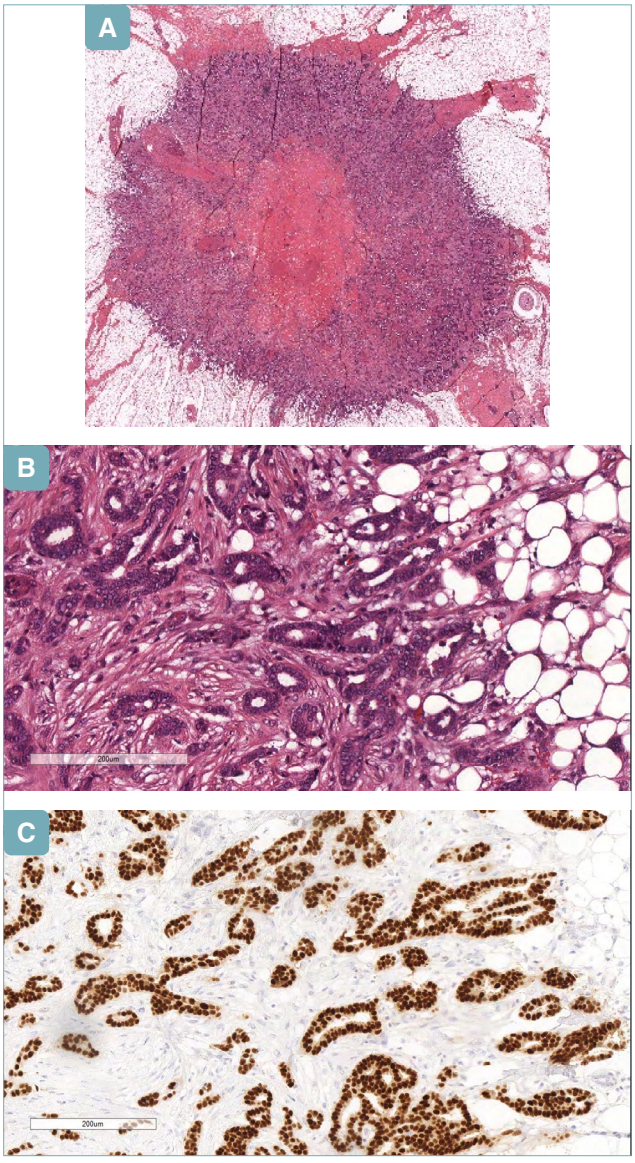

Figure 5. Tubular carcinoma (TC). (A): at low power view TC presents finely irregular margins. (B): at higher power, it is composed of angulated glands, lined by monotonous neoplastic cells. (C): almost all the neoplastic cells are strongly positive for estrogen receptor.

Missed cancers: cancers that were undetected due to technical or interpretations mistakes. This category cannot completely disappear, but can be significantly reduced with quality control programs and improved knowledge.

Radiographically occult cancers: cancers that are too small to be detected. This category comprises mainly ILC [44]. ILC is characterized by infiltrative growth (Fig. 6), leading to little architectural distortion, therefore being difficult to detect on mammography [3]. According to the data reported by Meshkat et al. [39] ILC constituted 21% of interval cancers, compared with 11% of screen detected cases. Similarly, Weber et al. [46] found lobular and ductulo-lobular carcinoma more frequent in IC.

Dense breast tissue can be an obstacle to accurate mammographic examination. On histology, dense breast is tissue characterized not only by increase in fibrous stroma, but also by lack of acinar involution and presence of cancer risk factors as atypical hyperplasia [47]. Therefore, dense breast constitutes a fertile soil for radiographically occult cancers. Introduction of more accurate screening tools such as full-field digital mammography screening (FFDM) or tomosynthesis could improve early diagnosis [48-50].

Proper BSP tailored on the different breast densities are proposed [51].

True interval cancers: IC (interval cancers) appearing clearly on the diagnostic mammogram in absence of any suspect feature on the preceding screening examination [44,45]. The morphological spectrum of true IC is wide and comprises almost all types of in situ and invasive breast cancer, the proportion of aggressive cases being higher.

DCIS presents as IC on rare occasions only [39]. Symptomatic DCIS is usually larger, of higher grade and more frequently associated with invasive foci than the screen detected [39].

True ICs usually present a higher rate of grade 2 and 3, HER2 amplified, ER negative IBC [39]. Furthermore, true ICs usually affect younger patients 46), show higher Ki-67 labelling index and present more frequently at stage II or higher [39,48-52].

Among true IC, triple negative breast cancers (TNBC) are encountered. TNBC constitute a heterogenous group of carcinomas that can be very difficult to be detected in BSP due to their specific pathological features, that can simulate benign lesions as fibroadenomas [53] (Fig. 7). According to a series published by Elfgen et al. [53], 8.6% of TNBC had a delay in diagnosis due to mammographic misclassification. Doebar et al. [54] demonstrated that the lowest frequency of a DCIS component was observed in the TNBC group (34.1%) thus suggesting that the TNBC rapidly develop the invasive component.

True IC have worst prognosis even among BRCA mutation carriers.

BRCA mutation carriers develop more frequently aggressive variants of IBC, showing a high percentage of TNBC [55]. Therefore, BSP can have an important prognostic impact among BRCA mutation carriers. Pilewskie et al. [56] studied a population of 124 BC affecting BRCA mutation carries: 92 were detected in

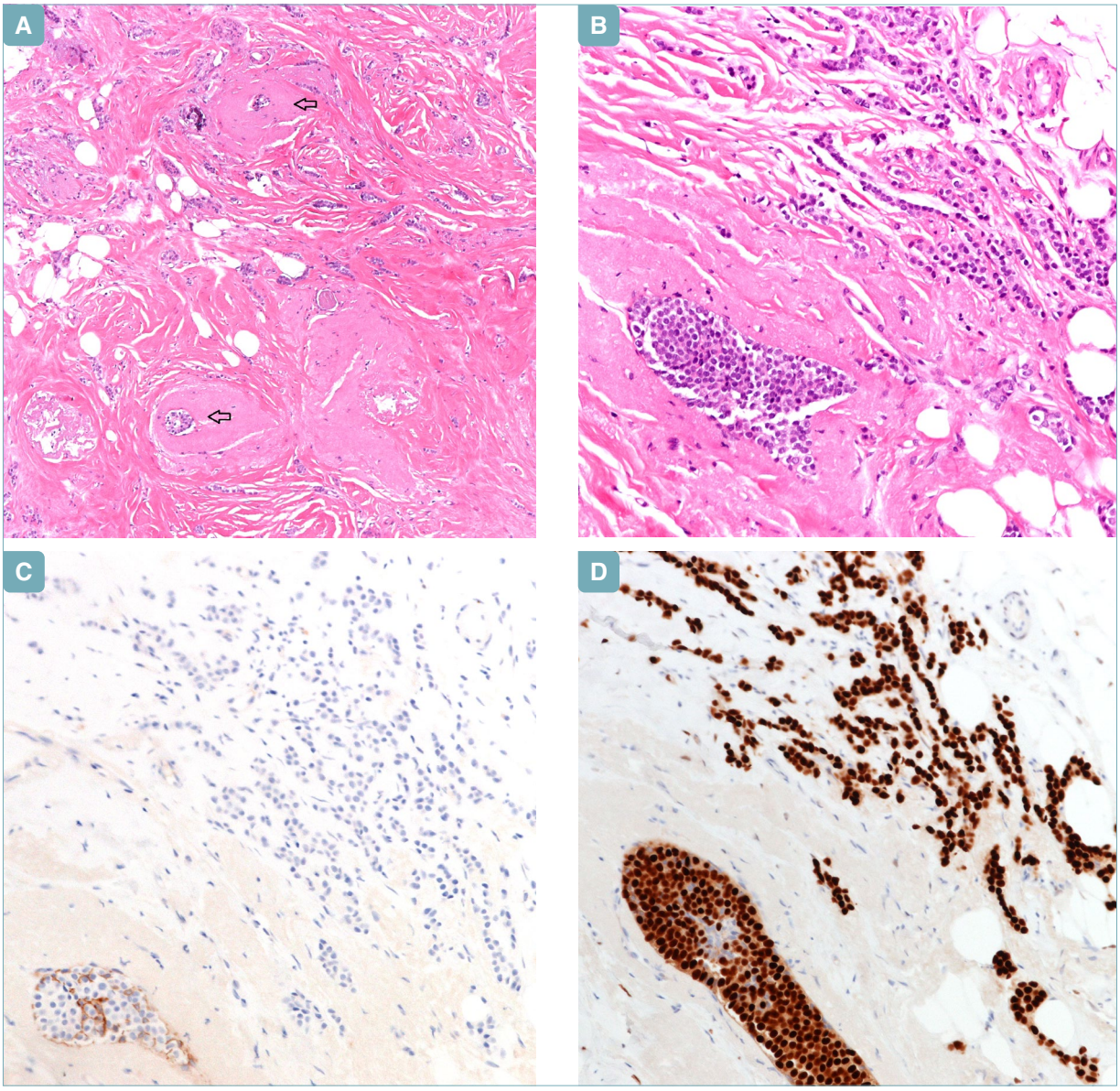

Figure 6. Invasive lobular carcinoma (ILC). (A): mammographically detected ILC associated with obliterative mastopathy. Obliterating ducts (arrow) show in situ lobular carcinoma of classical type; the surrounding tissue is infiltrated by neoplastic cells with minimal architectural distortion. (B): at higher power, neoplastic cells surround obliterating duct with in situ lobular carcinoma. (C): both in situ and invasive components are E-Cadherin negative. (D): both in situ and invasive components are strongly positive for estrogen receptor.

BSP, while 22 were spontaneous (11 of which were true IC), and 10 were occasional findings in prophylactic mastectomy. Even in the BRCA mutated population, IC affected younger women, tumours were larger and more frequently node positive than the screen detected ones [56]. These data led to the conclusion that BSP can be useful also in BRCA mutated population.

Conclusion

Data recently published confirm the BSPs efficacy in early breast cancer detection, leading to a decrease in breast cancer related mortality [57,58]. A study performed on the Italian population [59] demonstrated that organized BSPs led to a 30% reduction for stages II+ of IBC, thus leading to early diagnosis and easier cure potential.

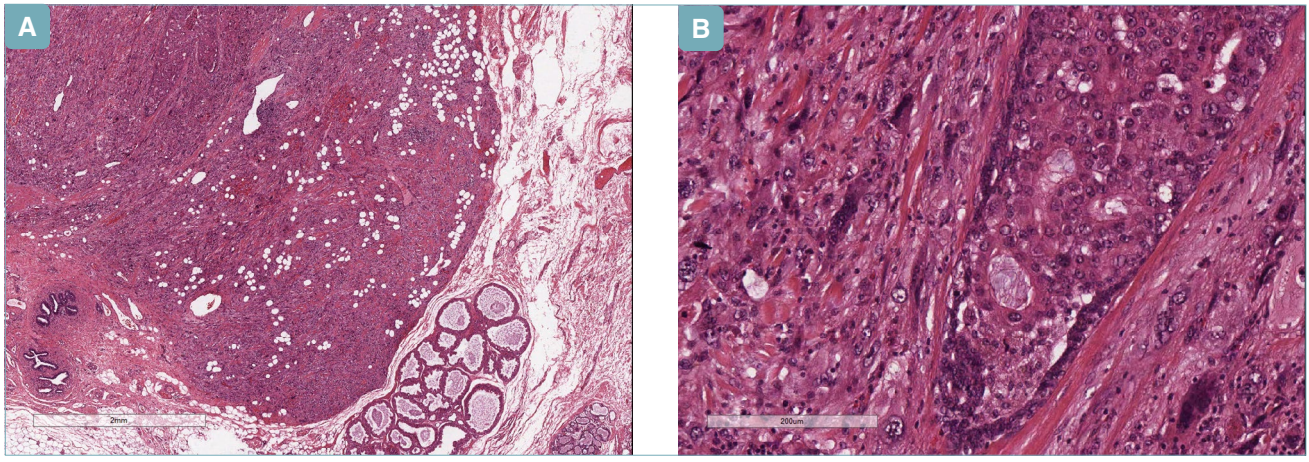

Figure 7. Metaplastic carcinoma. (A): at low power MC shows lobulated margins that can simulate a fibroadenoma. (B): at higher power MC is composed of markedly atypical cells, high nuclear grade in situ duct carcinoma is also present.

On the other hand, higher rate of DCIS detection can cause overdiagnosis and overtreatment of harmless lesions. Improving knowledge on DCIS behavior can help in the selection of truly aggressive lesions deserving treatment [60].

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