Original article

The comparison between the two most common histological subtypes of breast cancer – invasive ductal and invasive lobular breast carcinoma

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ABSTRACT

Introduction: Invasive lobular carcinoma (ILC) occurs in 5–15% of all cases of breast cancer. In most studies, it is found to be more common among older patients, form larger tumours and present with ill-defined margins, in comparison to invasive ductal carcinoma (IDC).

Material and methods: Histological preparations were obtained from 651 patients suffering from breast cancer. Preparations stained with hematoxylin and eosin were used to identify tumour type and grading. Samples underwent a basic molecular profile evaluation encompassing ER (oestrogen receptor), PR (progesterone receptor) and human epidermal growth factor receptor 2 (HER2) expression.

Results: 592 cases of IDC and 59 cases of ILC were detected. The median age was 60 in both groups. While there were no statistically significant differences between IDC and ILC in nodal status and tumour size for all age groups, IDC was more frequently diagnosed at higher grading (G3). G3 accounted for 32% of all IDC specimens compared to only 13% of ILC specimens. In both groups, the most prevalent combination of hormone receptors was ER+/PR+/HER2-. The differences in ER and PR expression were statistically significant; both were assessed as positive in most ILC cases and just over half of IDC. No HER2 amplification was noted in most cases in both cancer subtypes.

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Conclusions: In our study, IDC and ILC showed no difference with respect to patients' median age at the diagnosis and local disease advancement defined by TNM. ILC cases were hormone-dependent and HER2-negative more frequently than IDC. Grade 3 tumours accounted for a higher proportion of IDC cases. This was in line with several other clinicopathological analyses of breast cancer. However, there are also several papers indicating ILC's association with favourable prognostic features, not only in terms of hormone receptors and HER2 expression but also tumour size and nodal involvement. This underlines the fact that clear differences between IDC and ILC prognosis still cannot be established.

Key words: immunohistochemistry, invasive lobular carcinoma, invasive ductal carcinoma

INTRODUCTION

Breast cancer (BC) is the most common malignancy among women and one of the leading causes of female deaths [1]. It accounts for 15.2% of all new cancer cases and 7.1% of all cancer deaths [2]. Carcinoma of the breast is a heterogeneous group of tumours with variable morphology resulting in diverse behaviour and responses to therapy. The main histological variants of BC include invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC). IDC accounts for approximately 70–80% of all invasive cases of BC, while ILC occurs in 5–15% of patients, which makes it the second most common histologic type of invasive BC [3–6].

In comparison to IDC, ILC demonstrates significant pathological and clinical differences. Several distinct variants have been defined, based on their cytological (pleomorphic, apocrine, histiocytoid and signet ring); or architectural (alveolar, solid and trabecular) features [6–8]. Regarding histologic traits, the lack of E-cadherin expression accounts for its characteristic spindle-shaped or round non-cohesive cells arranged in a single-file pattern without inducing the intense desmoplastic response [6–10]. Due to the aforementioned features, ILC often fails to form distinct masses, leading to more subtle clinical and radiographic findings. The ability of ILC to evade early detection poses a great challenge for screening tests, such as mammography, which may result in a more advanced presentation stage than IDC [7, 11, 12]. In many clinicopathological studies, compared to patients with IDC, those with ILC were older, had larger tumours, higher tumour stages, lower tumour grades, more nodal metastases, higher oestrogen receptor(+), and lower HER2(-) expression [13–16]. ILC is reported to have a substantial proclivity for multicentricity, multifocality and higher incidence of bilaterality [5, 7, 11, 14, 15, 17, 18] as well as to present a unique pattern of metastatic spread with involvement of gastrointestinal sites, peritoneum, ovarian tissues and bones [7, 9, 10, 19–21]. ILC is also less likely to affect the lungs and liver [22]. Nevertheless, due to limited and contradicting data, the comparison between ILC and IDC regarding prognostic value is still undetermined [21–29].

AIM OF THE STUDY

The study's main aim was to compare clinicopathological features encompassing patients' age, histological grade, tumour size, nodal and receptors' status between the invasive ductal and lobular breast cancer cases.

MATERIAL AND METHODS

The analysed material consisted of histological preparations obtained from patients suffering from breast cancer. Histological and immunohistochemical (IHC) studies were performed at the Department of Pathology, Military Medical Institute in Warsaw. The biological material for the study was derived from excisional biopsies and modified radical mastectomies. Analysed tumour samples were fixed in 10% phosphate-buffered formalin for 24 h. Tissues were then dehydrated in alcohol of gradually increasing concentration and embedded in paraffin. Paraffin blocks were cut into 4 µm sections. Preparations stained with haematoxylin and eosin were used to identify tumour type (WHO classification) and histological grade of malignancy.

Routinely, samples underwent a basic molecular profile evaluation encompassing ER, PR and HER2 expression. Immunohistochemical assays were performed using the En-Vision complex HRP Cytomatic (DAKO, Santa Clara, United States, En-Vision Dual Link System-HRP, DAB, Code: K4065). Monoclonal antibodies against ER (Monoclonal Mouse Anti-Human ERα, 1 : 50 dilution, Clone: 1D5, Code: IR654, DAKO, Santa Clara, United States) and against PR (Monoclonal Mouse Anti-Human PR, 1 : 400 dilution, Clone: PgR636, Code: IR068, DAKO, Santa Clara, United States) were applied to define the expression of aforementioned receptors. Nuclear staining in > 10% of tumour cells was considered positive (+) for ER and PR.

HER2 expression was specified by the usage of the Hercept Test (Code: K5204, Dako, Santa Clara, United States) and the polyclon-

al antibody against HER2 (Rb A – Hu HER2 – Rabbit Anti-Human HER2 Protein). HER2 state was defined by evaluating its expression on the cancerous cells membranes using immunohistochemistry. HER2 analysis was determined on the basis on the maximum area of staining intensity according to the instruction in the package insert and the ASCO/CAP guidelines as follows: staining > 30% of invasive carcinoma cells was graded 3+; moderate, circumferential membranous staining in ≥ 10% of invasive tumour cells or strong circumferential membranous staining in ≤ 30% of cells was scored as 2+ staining; poor and incomplete membranous staining was given 1+ score and no staining was marked 0. Samples with score 0 and 1+ were considered negative for HER2 amplification. Score 3+ was assessed as positive, whereas score 2+ was considered equivocal and FISH was applied for the confirmation [30]. Positive and negative control preparations were previously determined.

All statistical analyses were performed with Statistica software v.13.0 for Windows. The Shapiro-Wilk, $\chi 2$ and Fisher's Exact Tests were used appropriately. Differences were considered statistically significant at $p \leq 0.05$.

RESULTS

In this study, data from 651 female patients diagnosed with breast cancer were analysed, comprising 592 cases of IDC and 59 cases of ILC. The median age of the patients was 60 years, with a range of 27–91 for IDC and 42–85 for ILC. Clinicopathological characteristics and age distribution according to histologic subtype were summarised in table 1.

Table 1. Comparison of the clinicopathological features between IDC and ILC.

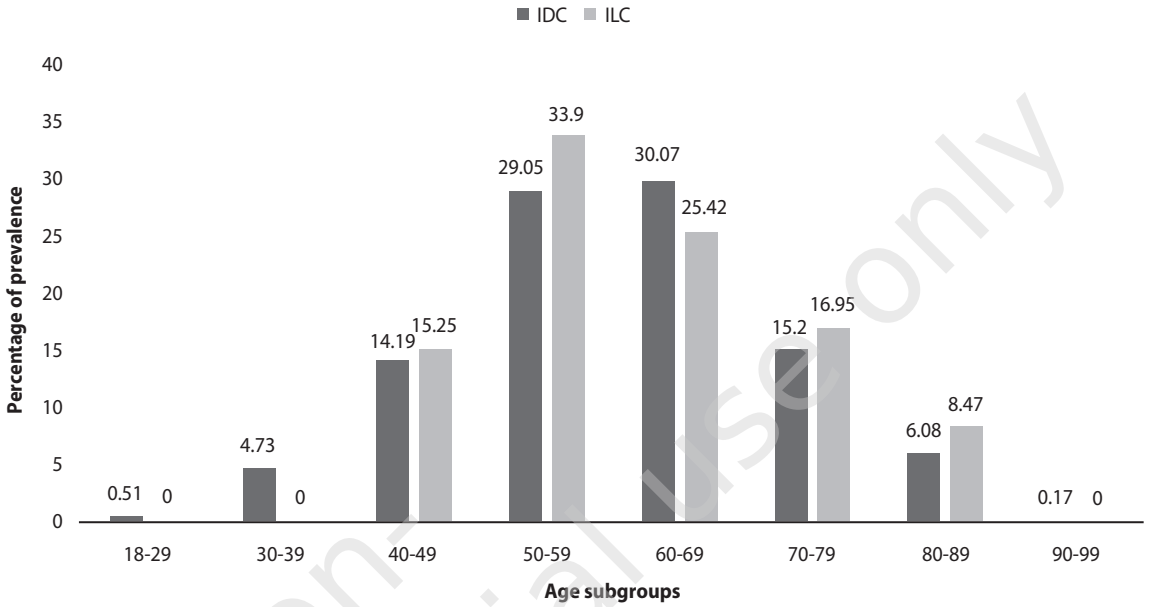
	IDC (%)	ILC (%)	p-value
No. of patients	592 (91)	59 (9)	
Age			-
Median	60	60	
Range	27–91	42–85	
≤ 29	3 (1)	0 (0)	
30–39	28 (5)	0 (0)	
40–49	84 (14)	9 (15)	
Subtotal (< 50 years)	115 (19)	9 (15)	
50–59	172 (29)	20 (34)	
60–69	178 (30)	15 (25)	
70–79	90 (15)	10 (17)	
80–89	36 (6)	5 (9)	
≥ 90	1 (0)	0 (0)	
Subtotal (≥ 50 years)	477 (81)	50 (85)	
Tumour size (T-stage)			0.919
T1a	12 (2)	1 (2)	
T1b	54 (9)	7 (12)	
T1c	232 (39)	19 (32)	
T2	244 (41)	26 (44)	
T2c	4 (1)	1 (2)	
T3	9 (2)	1 (2)	
T4	37 (6)	4 (6)	
Lymph node (N-stage)			0.271
pN0	354 (60)	39 (66)	
pN1	102 (17)	10 (17)	
pN1a	38 (6)	1 (2)	
pN1b	2 (0)	1 (2)	
pN2	41 (7)	1 (2)	
pN2a	22 (4)	2 (3)	
pN3	33 (6)	5 (8)	
Tumour grade (G)			**< 0.001**
G1	46 (8)	1 (2)	
G2	321 (54)	50 (85)	
G3	189 (32)	8 (13)	
Gx	36 (6)	0 (0)	

The median age at diagnosis for both IDC and ILC patients was found to be equal. Patients were categorized into subgroups to compare IDC and ILC distributions in groups under and above 50 years of age. Notably, no statistically significant differences were observed in the distribution of ILC and IDC before and after the age of 50. It's noteworthy that while IDC was diagnosed across all age subgroups, ILC was not diagnosed in patients below 40 years of age. The prevalence of IDC tended to increase with age, with peak rates observed in the 50–59 and 60–69 age groups. Among all IDC diagnoses, patients aged 18–29 represented a minority at only 0.51%, whereas individuals in the 50–59 and 60–69 age groups accounted for 29.05% and 30.07% of all IDC cases, respectively. ILC was diagnosed starting in the 40–49 age group, reaching its peak prevalence in the 50–59 age group, accounting for 33.90% of all ILC cases. Subsequently, the prevalence declined in the 60–69 age group to 25.42% and further decreased to 16.95% in the 70–79 age group (fig. 1).

While no statistically significant differences were found between IDC and ILC regarding lymph node involvement and tumour size across all age groups, a significant distinction was observed in grading ($p < 0.001$) (tab. 1). IDC was more frequently diagnosed at higher grading (G3) – G3 accounted for 32% of all IDC specimens compared to only 13% of ILC specimens. At the time of diagnosis, the majority of IDC and ILC cases exhibited no lymph node involvement (59.80% in the IDC group and 66.10% in the ILC group) and T1c/T2 size (80.41% for IDC and 76.27% for ILC) across most age subgroups.

The rates of immunohistochemical expression of hormone receptors and HER2 are presented in table 2. Notably, statistically significant differences were observed in ER and PR expression

Figure 1. Percentage contribution of each age group to total number of diagnoses of IDC and ILC.



(p < 0.001). In the case of ILC, a vast majority exhibited positive expression for both ER and PR, with percentages reaching 91.53% for ER and 88.14% for PR. In contrast, IDC cases showed a lower prevalence, with just over half displaying positive expression for ER (63.68%) and PR (59.29%). While most cases in both cancer subtypes did not show HER2 overexpression (82.43% for IDC and 93.22% for ILC), a higher occurrence was noted in IDC cases (p = 0.0173). Furthermore, upon analysing age groups, a significant difference was identified between IDC and ILC groups in PR expression in both under and above 50 years of age subgroups (p = 0.0149 and < 0.001, respectively).

DISCUSSION

ILC is the second most common histological type of BC. In our study, it accounted for 9% of specimens, which is consistent with the results of other histopathological analyses of BC, which typically report an ILC incidence ranging from 9% to 15% [15–18, 23, 24, 31, 32].

Table 2. Immunohistochemical expression of hormone receptors and HER2 by histological type.

	ER No. (%)			PR No. (%)			HER2 No. (%)			
	negative	positive	p-value	negative	positive	p-value	(0/1+)	(2+)	(3+)	p-value
IDC	215 (36)	377 (63)	**< 0.001**	241 (41)	351 (59)	**< 0.001**	488 (83)	32 (5)	72 (12)	**0.0173**
ILC	5 (8)	54 (92)		7 (12)	52 (88)		55 (93)	4 (7)	0 (0)	

The patterns of ER, PR, and HER2 expression in relation to histological subtypes were summarised in table 3. Our analysis revealed statistically significant differences in the distribution of ER, PR, and HER2 expression between the ILC and IDC groups. The most prevalent combination observed was ER+/PR+/HER2- in both IDC and ILC cases, accounting for 48.82% of IDC cases and 72.88% of ILC cases, respectively. Subsequently, in IDC cases, the second most prevalent receptor combination was identified as triple-negative, with ER-/PR-/HER2- expression observed in 25.84% of all IDC cases. Conversely, in ILC cases, the second most prevalent receptor combination was ER+/PR-/HER2-, accounting for 11.86% of all ILC cases. Additionally, ER-/PR+/HER2- expression in ILC accounted for 8.47% of all ILC cases. Notably, no cases of triple-negative ILC were observed in our study.

Table 3. Relationship between histological type of invasive BC and the basic immunohistochemical profile.

	IDC No. (%)	ILC No. (%)	p-value
ER-/PR-/HER2 (0/1+)	153 (26)	0 (0)	**< 0.001**
ER-/PR-/HER2 (2+)	9 (1)	0 (0)	
ER-/PR-/HER2 (3+)	36 (6)	0 (0)	
ER-/PR+/HER2 (0/1+)	17 (3)	5 (8)	
ER+/PR-/HER2 (0/1+)	29 (5)	7 (12)	
ER+/PR-/HER2 (2+)	2 (0)	0 (0)	
ER+/PR-/HER2 (3+)	12 (2)	0 (0)	
ER+/PR+/HER2 (0/1+)	289 (49)	43 (73)	
ER+/PR+/HER2 (2+)	21 (4)	4 (7)	
ER+/PR+/HER2 (3+)	24 (4)	0 (0)	

Analysing various papers, no consensus concerning differences in patients' age has been reached. Our study follows some conducted studies [17, 24, 32], in which no statistically significant difference in ILC and IDC incidence between two age groups – under or equal to 50 years old and above 50 years old has been found. However, in several analyses [13–15, 22, 23, 25], ILC was found to be diagnosed significantly more frequently in patients over 50 years of age. Moreover, the vast majority of studies estimate that despite only slight differences in median age at diagnosis, ILC could be characterised by a higher median age at diagnosis [8, 13, 14, 16, 22, 23]. In our study, comparably to other analyses [17, 24, 32, 33], we determined a similar median age between these groups.

There is a lack of clear differences established in the local advancement of ILC and IDC at diagnosis. Our study found no distinction in tumour size distribution and nodal involvement, as both groups predominantly comprised T2 and T1c tumours and rarely involved regional lymph nodes. This similarity in tumour size and nodal status between ILC and IDC has been noted in several papers [34–37]. However, most recent studies suggest that ILC tends to present with larger tumour sizes [13, 15–17, 23, 25, 26, 33] and involve lymph nodes more frequently than IDC [13, 15, 17, 23–26, 33]. The status of axillary lymph nodes (ALN) is considered one of the most significant prognostic factors for BC [38]. Prior research has revealed conflicting findings regarding ALN status between ILC and IDC. While most recent studies show an association between ILC and a higher incidence of positive ALN involvement [16, 17, 33], some studies report less frequent ALN positivity in ILC [39].

Similarly varied results were reported concerning differences in histological level of dedifferentiation of IDC and ILC. In our analysis, specimens in both groups were most commonly assessed as G2; however, in IDC, G3 tumours accounted for a higher proportion. Among available histopathological studies of ILC and IDC, in concordance with our results, the majority of ILC tumours are classified as Grade 2 [16, 17, 24, 33], and IDC tends to have a higher proportion of dedifferentiated Grade 3 tumours [17, 24, 26], which in some studies even represented the majority of IDC cases [40].

We determined that most IDC and ILC specimens showed positive expression of ER and PR. ER-positive and PR-positive tumours accounted for a significantly higher proportion of ILC than IDC, as commonly reported [5, 14, 17, 21, 25], with only several reports stating no difference in the frequency of ER positivity [34] and PR positivity [34]. In our material, not a single case of ILC showed simultaneous ER and PR negativity, which was rarely observed in other analyses [13, 23, 40]. This observation may be explained by the rare occurrence of triple-negative breast cancers (TNBC). Analysis of 171,881 patients from the SEER database revealed that among 144,651 cases of IDC and 16,433 cases of ILC, only 1.1% of ILC and 12.5% of IDC cases were classified as TNBC [13]. TNBCs, characterized by the absence of targets for endocrine therapy and HER2 blockade, are believed to occur more frequently in younger patients and have a poorer prognosis [41].

HER2 positive status was proved to be an independent prognostic factor associated with worse survival outcomes for ILC patients [24], yet the vast majority of papers, similarly to our results, indicate the absence of HER2 overexpression in ILC specimens or a higher proportion of HER2 negative tumours in this group in comparison to IDC [14, 15, 24, 25]. In the study regarding comparison between rarely described groups of classical-type ILC presenting overexpression of HER2 and cases with HER2 negativity, PR expression was strongly correlated with HER2 overexpression [42]. This data, being another piece of evidence of the inverse interaction between PR expression and HER2 positivity, might suggest an absence of PR expression as a predictor for HER2(+) status. Consequently, in our study, cases of ER+/PR+/HER2- made up the largest percentage (73% of all ILC material) as far as hormonal status is concerned, in concordance with similar papers' results [13–15, 24, 25].

The lack of data concerning the clinical course of patients is a limitation of this study, as it prevents any analysis of differences in prognosis between ILC and IDC, which is a widely discussed topic. IDC tends to metastasize to the lungs and liver more frequently than ILC [22], whereas ILC is associated with metastases to the gastrointestinal tract, peritoneum, ovaries and bones [7, 10, 15, 20, 21, 28]. ILC was also shown to have a higher rate of contralateral breast relapse [37, 43] and might be less responsive to neoadjuvant chemotherapy [5, 13, 22, 23, 44]. Using data from five neoadjuvant trials in the GBG meta-database, Huober et al. performed a retrospective analysis to determine the factors associated with relapse. Their research showed that the prognosis for ILC patients was poorer than that of IDC patients, even though all of the patients reached a complete pathologic response [45]. However, no clear differences in terms of disease-free and overall survival were reported, as most published studies brought conflicting results [15, 21, 23–29, 31].

CONCLUSIONS

In our study, IDC and ILC showed no difference with respect to patients' median age at the diagnosis and local disease advancement defined by TNM. ILC cases were hormone-dependent and HER2-negative more frequently than IDC. Grade 3 tumours ac-

counted for a higher proportion of IDC cases. This was in line with several other clinicopathological analyses of breast cancer. However, there are also several papers indicating ILC's association with favourable prognostic features, not only in terms of hormone receptors and HER2 expression but also tumour size and nodal involvement. This underlines the fact that clear differences between IDC and ILC prognosis still cannot be established.

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Authors' contributions:
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