Comparative analysis of the histopathological and epidemiological profile of ductal and lobular breast carcinomas diagnosed at the Hospital de Clínicas da Universidade Federal do Paraná during the period 2008-2013

Análise comparativa do perfil histopatológico e epidemiológico dos carcinomas ductal e lobular da mama diagnosticados no Hospital de Clínicas da Universidade Federal do Paraná entre 2008 e 2013

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ABSTRACT

Introduction: Breast cancer is the second leading cause of cancer death among women worldwide, and epidemiological studies may help understanding its mechanisms. **Objective:** To carry out a survey of the number of breast cancer cases diagnosed in a period of six years. **Methods:** The profile of breast cancers diagnosed in a tertiary hospital in Curitiba was compared with the literature, using a retrospective analysis of ductal/special types and lobular breast carcinoma reports issued between 2008 and 2013. **Results:** Three hundred twenty-seven (91.6%) cases of ductal/special types carcinoma and 30 (8.4%) cases of lobular carcinoma were diagnosed, totaling 357 samples. From these cases, 27 (7.5%) were carcinoma *in situ* (20 ductal and seven lobular) and 330 (92.4%) were invasive carcinoma (307 invasive ductal/special types and 23 lobular). The prevalence of breast cancer among women was 99.1% and the majority of patients were older than 50 years of age (67.2%). Regarding the União Internacional de Controle do Câncer/American Joint Committee on Cancer (UICC/AJCC) staging, 49.2% of the ductal/special types tumors were diagnosed in Stages I or II, while 56.6% of lobular carcinomas were diagnosed in Stages II or III/IV. Regarding the Nottingham score, most cases were intermediate grade (43.9%). A total of 61% of the tumors were estrogen receptor positive (ER+) and 54% were progesterone receptor positive (PR+). Moreover, 36.1% presented positive human epidermal growth factor receptor 2 (HER2+), a rate higher than that indicated by the literature. **Conclusion:** The breast carcinomas evaluated in this study presented a profile similar to that reported in the literature, with some peculiarities inherent to the local pathology service. Nevertheless, the low frequency of *in situ* cases indicates failure in early diagnosis.

Key words: ductal carcinoma of the breast; lobular carcinoma; pathology; epidemiology; oncology.

RESUMO

Introdução: O câncer da mama é a segunda causa de morte por câncer entre as mulheres em todo o mundo, e estudos epidemiológicos podem auxiliar no entendimento dos seus mecanismos. Objetivos: Realizar um levantamento do número de casos dos carcinomas da mama diagnosticados em um período de seis anos. Método: Foi comparado com a literatura o perfil dos carcinomas da mama diagnosticados em um hospital terciário de Curitiba, por meio da análise retrospectiva dos laudos de carcinomas da mama ductal/ tipos especiais e lobular de pacientes atendidos entre os anos de 2008 e 2013. Resultados: Foram diagnosticados 327 (91,6%) casos de carcinoma ductal/tipos especiais e 30 (8,4%) de carcinoma lobular, totalizando 357 amostras. Desses casos, 27 (7,5%) eram de

carcinoma in situ *(20 ductal e sete lobular) e 330 (92,4%), invasores (307 ductal invasor + tipos especiais e 23 lobular). A prevalência de tumores da mama nas mulheres foi de 99,1%, tendo os pacientes, na sua maioria, mais de 50 anos (67,2%). Em relação ao estadiamento da União Internacional de Controle do Câncer/American Joint Committee on Cancer (UICC/AJCC), 49,2% dos tumores ductal + tipos especiais foram diagnosticados em estadio I ou II, enquanto 56,6% dos tumores lobular concentraram-se nos estadios II ou III/IV. Quanto à escala de Nottingham, grande parte dos casos era de grau intermediário (43,9%). Um total de 61% dos tumores eram receptor de estrogênio positivo (RE+) e 54%, receptor de progesterona positivo (RP+). Por outro lado, 36,1% apresentaram receptor 2 de fator de crescimento epidermal humano positivo (HER2+), taxa superior à indicada pela literatura.* **Conclusão:** *Os carcinomas da mama avaliados neste estudo apresentaram perfil semelhante ao exposto na literatura, com algumas peculiaridades inerentes ao serviço local. Entretanto, a baixa frequência de casos* in situ *indica falha no diagnóstico precoce.*

Unitermos: carcinoma ductal de mama; carcinoma lobular; patologia; epidemiologia; oncologia.

RESUMEN

Introducción: *El cáncer de mama es la segunda causa de muerte por cáncer entre mujeres alrededor del mundo, y estudios epidemiológicos pueden contribuir al entendimiento de sus mecanismos.* ***Objetivos:*** *Determinar el número de casos de carcinoma de mama diagnosticados en un período de seis años.* ***Método:*** *El perfil de los carcinomas de mama diagnosticados en un hospital terciario de Curitiba ha sido comparado con aquel de la literatura, a través de análisis retrospectivo de historias de carcinoma de mama ductal/tipos especiales y lobulillar de pacientes atendidos entre los años de 2008 y 2013.* ***Resultados:*** *Se han diagnosticado 327 (91,6%) casos de carcinoma ductal/tipos especiales y 30 (8,4%) de carcinoma lobulillar, totalizando 357 muestras. De estos casos, 27 (7,5%) eran de carcinoma* in situ *(20 ductal y siete lobulillar) y 330 (92,4%), invasores (307 ductal invasor + tipos especiales y 23 lobulillar). La incidencia de tumores de mama en mujeres fue de 99,1%, siendo los pacientes, en su generalidad, mayores de 50 años (67,2%). Con respecto a la estadificación de Unión Internacional Contra el Cáncer/American Joint Committee on Cancer (UICC/AJCC), 49,2% de los tumores ductales + tipos especiales fueron diagnosticados en los estadios I o II, mientras 56,6% de los tumores lobulillares se concentraron en los estadios II o III/IV. En cuanto al sistema de Nottingham, gran parte de los casos era de grado intermediario (43,9%). Un total de 61% de los tumores era receptor de estrógeno positivo (RE+) y 54%, receptor de progesterona positivo (RP+). Por otro lado, 36,1% presentaron el receptor 2 del factor de crecimiento epidérmico humano positivo (HER2+), tasa superior a la indicada en la literatura.* ***Conclusión:*** *Los carcinomas de mama evaluados en este estudio presentaron perfil semejante al expuesto en la literatura, con algunas peculiaridades inherentes al servicio local. Sin embargo, la baja frecuencia de casos* in situ *indica fracaso en el diagnóstico precoz.*

Palabras clave: carcinoma ductal de mama; carcinoma lobulillar; patología; epidemiología; oncología.

INTRODUCTION

Breast cancer is the most common and the second leading cause of cancer death among women worldwide[1, 2]. Although the statistics account for it as a single disease, it is known that it has several anatomopathological classifications and distinct carcinogenesis models, as well as specific epidemiological trends[3-6].

In this context, studies indicate that approximately 95% of mammary malignancies have epithelial origin (called carcinoma), forming *in situ* or invasive lesions. It is also known that invasive mammary carcinoma are the most frequent, and 75% of them are subclassified in invasive ductal carcinoma/not otherwise specified (IDC/NOS), 15% as lobular and 10% called special subtypes[3-7]. In addition, invasive breast carcinoma are also categorized according to the immunophenotypic profile, through the immunohistochemical study for estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2), important prognostic and predictive markers, that will define the treatment and clinical management[3-5, 7]. Anatomopathological evaluation is essential

for the definition of therapeutic approach and prognosis. The same applies to epidemiological study, which defines the at-risk populations and disease screening protocol[5, 7].

Therefore, the objective of this study was to carry out a survey of the cases of ductal, special types and lobular breast carcinomas diagnosed at the Clinical Hospital of the Federal University of Paraná [Hospital de Clínicas da Universidade Federal do Paraná (HC-UFPR)] in the 2008-2013 period and to compare them with the literature.

METHOD

Sampling

A retrospective and analytical evaluation of 357 anatomopathological reports with diagnosis of ductal, special types or lobular breast carcinoma confirmed in the HC-UFPR was performed. The reports were issued by the Department of Pathological Anatomy after the analysis of material from core-needle biopsy and/or surgical specimen. This project was approved by the Human Research Ethics Committee of the HC-UFPR under the code CAAE: 17126913.1.0000.0096.

Selection criteria

From the data available at the Department of Pathology of the HC-UFPR, the search and selection method consisted of cases with diagnosis of ductal, lobular or special types of breast carcinoma performed during the 2008-2013 period. The exclusion criteria were biopsies with results of other mammary pathologies, undetermined reports or with no the histological classification of carcinoma type. After the previous selection of the reports, the carcinomas were qualified and categorized according to the usual nomenclature of ductal carcinoma *in situ* (DCIS), lobular carcinoma *in situ* (LCIS) and invasive mammary carcinoma [invasive ductal carcinoma (IDC), special types and invasive lobular carcinoma (ILC)].

Histopathological and immunohistochemical (IHC) review

The clinicopathological variables observed in the data collection were: sex, age, tumor staging according to the international standard [União Internacional de Controle do Câncer/American Joint Committee on Cancer (UICC/AJCC)], histological grade or SBR (Scarff-Bloom-Richardson = Nottingham Histologic Score System),

presence of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) molecular markers. Results regarding the hormone receptor expression were obtained. For the identification of these receptors the IHC method was used, considering HER2 positive the cases scoring greater than or equal to 2+ and using the Allred score for the classification of ER and PR. This evaluation was performed during the period between 2008 and 2011 using the Advance TM method + DAB chromogen system with positive and negative internal controls. During the period between 2011 and 2013 the Envision method + Dual link system HRP + DAB was implemented in the IHC analysis.

Statistical analysis

The clinicopathological variables were sex, age, tumor staging (UICC/AJCC), histological grade or Nottingham Histologic Score System (SBR), presence of the ER, PR and HER2 hormonal markers. The cases with incomplete reports and/or variables not available, did not entered in the statistical analysis. The statistical relationship between the data and the histological classification was assessed using the chi-square test (χ^2) and/or Fischer's exact test using the GraphPadPrism 5.1 software.

RESULTS

In the period between 2008 and 2013, 357 cases of ductal, special types or lobular breast cancer were diagnosed in the HC-UFPR. On average, there were approximately 60 diagnoses per year, which corresponds to five new cases per month (**Figure 1**).
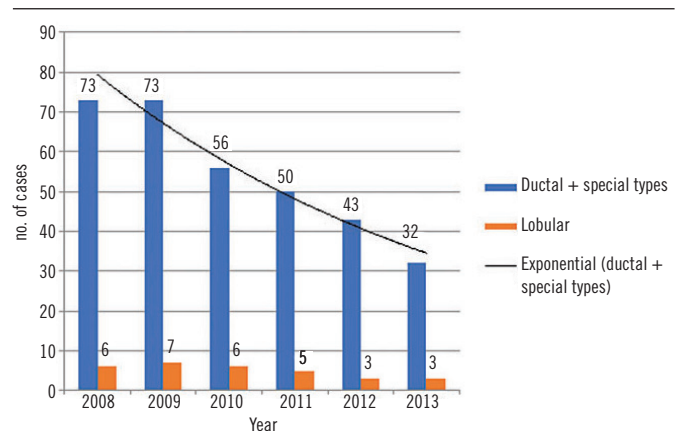

FIGURE 1 – *Distribution of the number of diagnoses of ductal/special types and lobular carcinoma per year (2008-2013)*

Distribution chart of the new cases of carcinomas per year. The trendline shows a declining line for ductal carcinomas over the years.

In the whole sample 27 (7.5%) cases of carcinoma *in situ* were found, of which 20 ductal tumors (74%) and seven (26%) lobular tumors. Whereas the invasive carcinomas totaled 330 cases (92.4%), of which 221 (66.9%) were IDC/NOS, 29 (8.7%) belonging to the special types, 23 (6.9%) lobular and 57 (17.2%) with no classification available in the report (**Table 1**).

Among the ductal carcinomas *in situ*, the comedocarcinoma subtype represented 45% of the cases, while the mixed subtype (comedo + noncomedocarcinoma) was the second most prevalent, totaling 35% and increasing the presence of comedonecrosis to 80% of the samples. Regarding the analysis of invasive mammary carcinomas of the IDC + special types group, 71.9% belonged to the invasive ductal group (IDC/NOS), followed by the mixed subtype (IDC/NOS + special type association) with 4.2% of samples. From the 13 mixed cases, 12 are IDC + mucinous and 1IDC + medullary, which raises the isolated frequency of mucinous to 17 cases (5.5%) and medullary to 3 cases (0.9%). It is also worth noting that almost 19% of the samples of this group could not have the histological classification accurately evaluated, mainly due to the absence of a surgical specimen for the complete evaluation of the lesion.

On the other hand, for the lobular carcinomas *in situ*, 100% of the sampling had classic histology, while for the invasive group almost 61% had the classic pattern, followed by the ductolobular subtype with almost 22% of the total. The most striking finding, however, is that there was a significant difference between the number of early/*in situ* and more advanced/invasive cases, since these represented 92.4% of the sampling collected. Table 1 shows these data according to the type and histological subtype of each carcinoma.

Anatomopathological and epidemiological data on the diagnosed tumors were evaluated (**Table 2**). It was observed that the diagnoses of ductal + special types carcinoma were concentrated in the early invasive cases in the period evaluated,

TABLE 1 – Diagnosis of breast carcinoma in the period 2008-2013

Variable	Sampling (%)	Ductal + special (%)	Lobular (%)
DCIS histology	20 (100)		
Comedocarcinoma		9 (45)	—
Non-comedocarcinoma		4 (20)	—
Mixed		7 (35)	—
LCIS histology	7 (100)		
Classic		—	7 (100)
Pleomorphic		—	0 (0)
IDC + special types histology	307 (100)		
IDC/NOS		221 (72)	—
Mixed		13 (4.2)	—
Mucinous		5 (1.6)	—
Tubular		2 (0.6)	—
Medullary		2 (0.6)	—
Papillary		1 (0.3)	—
Micropapillary		0 (0)	—
Metaplasic		6 (1.9)	—
Not available in report		57 (18.5)	—
ILC histology	23 (100)		
Classic		—	14 (60.8)
Ductal/lobular		—	5 (21.7)
Pleomorphic		—	1 (4.3)
Not available in report		—	3 (13)

DCIS: ductal carcinoma in situ*; LCIS: lobular carcinoma* in situ*; IDC: invasive ductal carcinoma; ILC: invasive lobular carcinoma; NOS: not otherwise specified.*

TABLE 2 – Correlation between ductal + special types and lobular histologies, with anatomopathological and epidemiological variables

Variable	Total sampling (%)[1]	Ductal + special (%)[2]	Lobular (%)[3]	p[a]
Sex				
Female	354 (99.1)	324 (91.5)	30 (8.5)	$p = 1$
Male	3 (100)	3 (100)	0 (0)	
Age				
< 50 years	117 (32.7)	113 (96.6)	4 (3.4)	$p = 0.0236$*
≥ 50 years	240 (67.2)	214 (89.2)	26 (10.8)	
Staging (UICC/AJCC)				
0	27 (7.5)	20 (74)	7 (26)	
I	82 (22.9)	81 (98.8)	1 (1.2)	
II	89 (24.9)	80 (89.9)	9 (10.1)	$p = 0.0013$*
III/IV	80 (22.4)	72 (90)	8 (10)	
Not available in report[b]	79 (22.1)	74 (93.7)	5 (6.3)	
Histologic score (Nottingham)				
I	74 (20.7)	68 (91.9)	6 (8.1)	
II	157 (43.9)	143 (91.1)	14 (8.9)	$p = 0.0986$
III	73 (20.4)	72 (98.6)	1 (1.4)	
Not available in report	53 (14.8)	44 (83)	9 (17)	
RE				
Negative	91 (25.4)	91 (100)	0 (0)	
Positive	218 (61)	196 (89.9)	22 (10.1)	$p < 0.001$*
Not available in report	48 (13.4)	40 (83.3)	8 (16.7)	
PR				
Negative	114 (31.9)	111 (97.4)	3 (2.6)	
Positive	193 (54)	174 (90.1)	19 (9.9)	$p = 0.0207$*
Not available in report	50 (14)	42 (84)	8 (16)	
Receptor HER2				
Negative	170 (47.6)	155 (91.2)	15 (8.8)	
Positive	129 (36.1)	123 (95.3)	6 (4.7)	$p = 0.1787$
Not available in report	58 (16.2)	49 (84.5)	9 (15.5)	

UICC/AJCC: União Internacional de Controle do Câncer/American Joint Committee on Cancer; ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2; 1: n = 357; 2: n = 327; 3: n = 30; [a]*p calculated from the ductal + special and lobular columns related to the respective horizontal variables, using absolute numbers and excluding the cases "not available in the report";* [b]*staging not available in report, but T ≥ 1 (invasive);* **p statistically significant (< 0.05).*

since 49.2% of these (161 samples) were Stage I or II ($p = 0.001$). Then, the advanced diagnoses represented by Stages III or IV totaled 22% of the cases (72 samples) ($p = 0.001$). On the other hand, Stage 0/*in situ*, recommended by mammographic screening, lagging behind with 6.1% (20 samples). The absence of staging in the reports was also prevalent, with the same amount on Stages III/IV, totaling 22% of the cases. On the other hand, lobular carcinoma accounted for 30% of diagnose on Stage II (nine samples), followed by 26.6% of advanced cases Stages III or IV (eight samples). Then, the lobular *in situ* with 23.3% (seven samples) and finally, Stage I had a diagnostic frequency of 3.3% (one sample) ($p = 0.001$). In all groups, statistical values were relevant ($p = 0.0013$), with emphasis on the UICC/AJCC staging data for each tumor type (**Figure 2**).
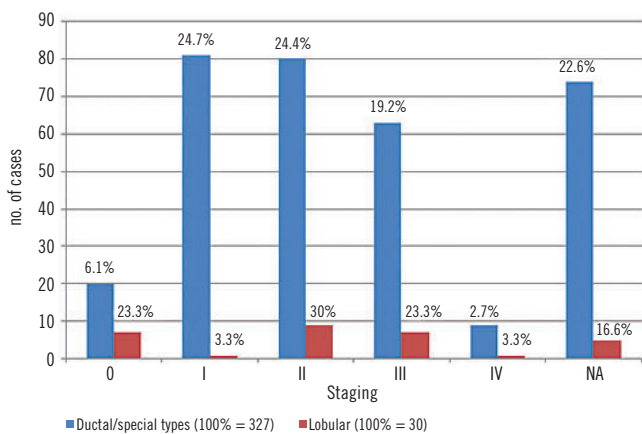

FIGURE 2 – *Staging of ductal/special types and lobular breast carcinomas diagnosed in the period between 2008-2013*

Percentage of cases diagnosed by histological type divided in stages.
NA: not available in report.

In almost all cases (354 cases), carcinomas were observed in female subjects (99.1%) aged older than 50 years (67.2%). About 45% of the cases were grade II of Nottingham, with no differences between grades I and III ($p = 0.0986$). The absence of significant values, however, may have been due to the high absence of identification in the reports, corresponding approximately to 15% of the cases. Regarding the immunohistochemical profile, it was observed that 59.9% of the ductal + special types carcinoma group (196 samples) and 73.3% (22 lobular group) of the total cases presented ER+ ($p < 0.001$). By contrast, 53.2% (174 samples) of the ductal + special types carcinoma and 63.3% (19 samples) of the lobular carcinoma were PR+, a rate of positivity lower than that one seen in ER ($p = 0.0207$). On the other hand, 37.6% (123 samples) of the ductal + special types carcinoma and 20%

(6 samples) of the lobular carcinoma were HER2+, while 47.4% (155 samples) of the ductal + special types carcinoma and 50% (15 samples) of the lobular carcinoma were HER2 negative ($p = 0.17$), indicating both groups trend not to express HER2.

Observing the prevalence of the histological subtypes found, we can note in their prognostic values and their invasive condition (invasive and pre-invasive lesions) that there is a statistically significant relationship between invasive lesions and patients aged 50 years or older, predominantly ILC ($p = 0.0356$) (**Table 3**). In addition, it is possible to observe that the histological grade for DCIS or IDC maintains a balanced distributional pattern ($p = 0.0059$). Finally, ILC showed a close relationship with staging II and III/IV tumors ($p = 0.037$), in addition to the positivity relation with ER ($p = 0.0008$) and PR ($p = 0.033$). No histology was significantly related to HER2, in spite of what was observed in the frequency (Table 2).

It should be noted that the large number of reports of carcinomas with lack of relevant anatomopathological information (IHC, tumor size, lymph node description, SBR grade or histological sub classification) can be considered a limiting factor in the results, but especially in the therapeutic approach. However, for these analyzes, these samples were taken from the statistical evaluation according to the missing variable.

DISCUSSION

Frequency of carcinomas at the HC-UFPR according to histological type and tissue invasion

The carcinomas of the ductal (DCIS/IDC) + special types and lobular (LCIS/ILC) groups corresponded, respectively, to 91.6% and 8.4% of the total cases. In the isolated evaluation of the IDC + special types group (307 cases), 71.9% were IDC/NOS and 9.2%, special types (including the mixed type) (Table 1). It is noteworthy that, as from 2012, the World Health Organization (WHO) introduced the "no special type" (NST) classification as a synonym for IDC/NOS, so that many reports evaluated since that time have already brought such an update with no effect in the object of this evaluation[8]. In all evaluated years, the sum of ductal and special types carcinomas represented more than 90% of the cases (Figure 1). According to the literature, the average incidence of breast carcinomas among women is 75%-80% for invasive ductal, 10% for special types and 10%-15% for lobular[4, 5, 9]. Therefore the HC-UFPR cases are close to the usual statistics for IDC and special types carcinomas, but shown to be decreased in relation to the expected mean for lobular carcinomas.

TABLE 3 – Relation between breast *in situ* and invasive carcinomas with age and anatomopathological variables[a, b]

Tumor characteristics	IDC (*n* = 221) *n* (%)	ILC (*n* = 23) *n* (%)	*p*	DCIS (*n* = 20) *n* (%)	*p*	LCIS (*n* = 7) *n* (%)	*p*	Special types (*n* = 29) *n* (%)	*p*
Age									
< 50 years	78 (35.2)	3 (13)	0.0356*	4 (20)	0.2203	1 (14.2)	0.4264	11 (37.9)	0.8375
≥ 50 years	143 (64.7)	20 (86.9)		16 (80)		6 (85.7)		18 (62)	
Staging (UICC/AJCC)									
0	NA	NA		20 (100)		7 (100)		NA	
I	67 (30.3)	1 (4.3)		NA		NA		10 (34.4)	
II	69 (31.2)	9 (39.1)	0.037*	NA	NA	NA	NA	11 (37.9)	0.5862
III/IV	55 (24.8)	8 (34.7)		NA		NA		5 (17.2)	
Not available in report[c]	30 (13.5)	5 (21.7)		0 (0)		0 (0)		3 (10.3)	
Histologic score (Nottingham)									
I	52 (23.5)	6 (26)		1 (5)		0 (0)		8 (27.5)	
II	116 (52.4)	14 (60.8)	0.2187	7 (35)	0.0059*	0 (0)	-	8 (27.5)	0.1215
III	43 (19.4)	1 (4.3)		9 (45)		0 (0)		8 (27.5)	
Not available in report	10 (4.5)	2 (8.6)		3 (15)		7 (100)		5 (17.2)	
ER									
Negative	64 (28.9)	0 (0)		3 (15)		0 (0)		11 (37.9)	
Positive	145 (65.6)	22 (95.6)	0.0008*	9 (45)	> 0.9999	0 (0)	-	17 (58.6)	0.3894
Not available in report	12 (5.4)	1 (4.3)		8 (40)		7 (100)		1 (3.4)	
PR									
Negative	78 (35.2)	3 (13)		4 (20)		0 (0)		13 (44.8)	
Positive	130 (58.8)	19 (82.6)	0.033*	8 (40)	> 0.9999	0 (0)	-	15 (51.7)	0.4104
Not available in report	13 (5.8)	1 (4.3)		8 (40)		7 (100)		1 (3.4)	
Receptor HER2									
Negative	113 (51.1)	15 (65.2)		5 (25)		0 (0)		19 (65.5)	
Positive	91 (41.1)	6 (26)	0.1737	7 (35)	0.3857	0 (0)	-	8 (27.5)	0.1533
Not available in report	17 (7.6)	2 (8.6)		8 (40)		7 (100)		2 (6.8)	

UICC/AJCC: União Internacional de Controle do Câncer/American Joint Committee on Cancer; ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2; IDC: invasive ductal carcinoma; ILC: invasive lobular carcinoma; DCIS: ductal carcinoma in situ*; LCIS: lobular carcinoma* in situ*; NA: not applicable; [a]excluding the 57 samples without histologic sub classification in the report, according to Table 1; [b]p calculated from the ductal + special and lobular columns related to the respective horizontal variables, using absolute numbers and excluding the cases "not available in the report", calculated using IDC as a reference histological group; [c]staging not available in report, but T ≥ 1 (invasive); *p statistically significant (< 0.05).*

The ILC diagnoses (6.9%), for example, are far below than that described in the literature[4] and also contrary to the increase in the incidence of this type of tumor verified in the last 20 years[10, 11]. The reason for this deviation may be related to the biological characteristics of lobular carcinoma, which, in its *in situ* form, is usually an incidental finding during biopsy, and in the invasive form it produces few mammographic and clinical changes[5, 7]. Therefore, the diagnosis of this type of tumor is more difficult, which contributes to the low frequency in the HC-UFPR statistics.

On the other hand, 7.5% of the cases were pre-invasive (Table 1). The literature highlights that DCIS cases alone represent about 20%-30% of all new cases of breast cancer diagnosed in populations with easy access to mammography facilities[6, 9]. However, the HC-UFPR showed that the pre-invasive diagnoses did not even come close to representing the

internationally recommended value for new cases of breast malignancy. Strengthening this finding, it was verified that the invasive lesions showed a significant relation with patients older than or equal to 50 years of age, which should have the guarantee of early mammography findings (Table 3).

The data point to the inefficiency of the breast cancer screening system in Curitiba, whether for the diagnosis or the referral of early cases, mainly DCIS. Alternatively, they may also suggest that minorities of suspected cases of malignancy are referred to the HC-UFPR. Regarding the first hypothesis, the screening of breast cancer in the city may not be inadequate, conversely, its organized screening configuration is a model for the country through the Curitibana Woman Program, implemented in primary care[12]. One of the possibilities is patient's non-compliance to the Program or even the existence of difficulties to implement it correctly. The second hypothesis

raised would also be reasonable, since the Erasto Gaertner Hospital is the municipal reference for cancer treatment, and it is obvious that it receives more cases than the HC-UFPR. However, the number of referrals issue only seems to be insufficient to justify such a low pre-invasive carcinoma index.

Frequency of carcinomas in HC-UFPR according to the histological grade

It is known that the histological grade of the tumor is directly related to the number of aberrant molecular alterations of the cell, the frequency of lymph node metastases, the recurrence of the disease and death, being, therefore, an important prognostic factor. Grouping breast tumors into low-grade types (lobular neoplasia and DCIS non comedocarcinoma/IDC grade 1) and high grade (comedocarcinoma and grade 3IDC) is also proposed, since, genetically, these groups are very different. Therefore, the histological grade is very relevant for breast cancer[3, 4, 6].

In the HC-UFPR was observed that ductal or special-types carcinomas presented cases in all Nottingham grades, with comparable frequencies at the extremes of the scale, and concentrated the majority of the diagnoses in the intermediate/grade 2 interval (43.7% of the cases) (Table 2). It can be inferred that IDC are responsible for the predominance of cases in grade 2, since the special types tend to be more homogeneous, with the exception of the medullary, which are usually high degree. This finding strengthens the data in the literature, which demonstrate that ductal carcinomas present great heterogeneity[3, 4, 6]. On the other hand, the cases of lobular neoplasia of the breast demonstrated that the LCIS/ILC are essentially low grade and not aggressive, since the rate of grade 3 LCIS/ILC cases (3.3% of lobular samples) was not significant when compared to number of grade 1 and 2 cases, representing 20% and 46.6% of lobular samples, respectively[3, 4].

Despite these observations and trends, the histological-grade SBR/Nottingham relationship was not statistically significant ($p = 0.0986$), and only the degree correlation between DCIS and IDC had a significant p ($p = 0.0059$) (Tables 2 and 3).

Staging of breast carcinomas diagnosed in the HC-UFPR

Regarding the evaluated cases, the staging found (Table 2) disagrees with the recent literature. The number of diagnoses of carcinomas in Stage 0/*in situ* is lower than the expected[6, 9],

which was last in the frequency of ductal diagnoses and in second-to-last place for lobular carcinomas. Regarding LCIS case, this is expected[5], but for DCIS, it is far from the ideal[6, 9]. Although the screening system have failed to diagnose DCIS, it certainly had the merit of increasing the number of early IDC or special-type carcinomas diagnoses, which may have a relatively good prognosis[7]. This is clear when we observed that the ductal + special types cases in Stages I or II were the most frequent in the HC-UFPR (49.2% of the DCIS/IDC + special sample). However, we are still short of what is seen in developed countries, where diagnoses of DCIS are more common and the incidence of IDC tends to drop and stabilization[5, 10, 11].

However, for lobular carcinoma it is easy to understand why, despite mammography, it still appears in the HC-UFPR as more advanced cases, that is 30% Stage II and 26.6% Stage III or IV (Figure 2). Despite the lower histological aggressiveness of this tumor, its unique biological characteristics make diagnosis difficult[5]. Stage I was less frequent among lobular (3.3%) than incidental cases of LCIS (23.3%). ILC also showed a significant relationship with staging II and III/IV tumors ($p = 0.037$) (Table 3). The literature itself confirms this profile, indicating that lobular and ductal-lobular carcinomas tend to be diagnosed in more advanced Stages (III and IV), with tumor size greater than 5 centimeters and positive lymph node[5]. In the case of metastases, this tumor also contrasts with the IDC, since it has a higher frequency in the gastrointestinal tract, peritoneum, retroperitoneum, ovaries and meninges[3, 4, 7].

Therefore, in the histology-staging analysis, there was statistical relevance ($p = 0.001$), which demonstrates the inherent differences at the time of diagnosis of both types of tumor (Table 2), strengthening this finding for lobular neoplasia (Table 3).

Immunohistochemical profile of breast carcinomas diagnosed in the HC-UFPR

Lobular carcinomas tend to have a low degree of aggressiveness and high rates of hormone receptor positivity (~ 70%-80%), regardless of staging[3-5, 7]. In contrast, ductal carcinomas are more heterogeneous in both immunohistochemical profiles and aggressiveness, with general positivity for ER and PR, which are somewhat lower in this group, with greater variation in expression intervals (~ 60%-70% are ER+ and 33%-70%, PR+)[5, 13, 14]. Moreover, among all breast carcinomas, about 15% to 30% present HER2 protein overexpression, a factor that indicates a high histological grade

and a worse prognosis[3, 4, 7, 15], and cases of lobular neoplasia with HER2+ are rare[13]. Therefore, the increasing availability of hormonal therapies and the prognostic value of the receptors emphasizes the importance of knowing IHC of breast tumors[16].

Regarding the cases of ductal + special types carcinomas, the percentage of hormone receptor expression is close to the expected (59.9% ER+ and 53.2% PR+), if it is noticed that the IDC are the majority and the special types do not interfere in the frequency found (Table 2). The expression of HER2 appears high (37.6% HER2+), although most of the IDC are intermediate grade (Tables 2 and 3). This fact can: 1. be explained by the high number of cases without an available report for HER2 (49 samples), which may have covered several cases of HER2-negative tumors; 2. be justified by the inclusion of IHC 2+ as positive in HER2; 3. be explained by the prevalence of more cases of ductal carcinoma with aggressive biology in the HC-UFPR.

Regarding the lobular carcinomas, the expression of hormone receptors corresponded to that provided by the literature (73.3% ER+, 63.3% PR+), strengthening the low histological grade of this type of tumor and its high ratio with hormonal receptors. However, 20% of the cases (six samples) were HER2+, which is striking because this marker is rare in this histology[13]. Once again, this can be justified by the IHC criterion or may represent aggressive trends for the cases described. Despite this finding, there was no significant relationship of HER2 with any histology (Table 3).

Finally, ER and PR presented statistical relevance when related to histology ($p < 0.001$ and $p = 0.0207$, respectively) (Table 3), demonstrating that lobular carcinomas tend to maintain them more frequently throughout tumor progression. However, the HER2 expression, when related to histology, was not statistically relevant, although the literature expected the lobular carcinomas trend not to express it (Tables 2 and 3).

CONCLUSION

This epidemiological survey found that ductal and lobular breast carcinomas diagnosed in the HC-UFPR between 2008 and 2013, in general, presented a profile similar to that presented in the literature, with some peculiarities inherent to the local service.

Among the data that contrasted with the literature, there is a low percentage of diagnoses in Stage 0 and invasive lobular carcinoma, as well as a high percentage of ductal + special carcinomas and lobular HER2 positives.

Findings consistent with other studies included a greater number of Nottingham grade 2 cases in the evaluated histology and rare grade 3 cases in the lobular neoplasia. The predominance of Stage II (UICC/AJCC) diagnosis in both groups and the significant trend of lobular neoplasia to maintain ER and PR receptors throughout the carcinogenesis process are also highlighted.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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