Research Article

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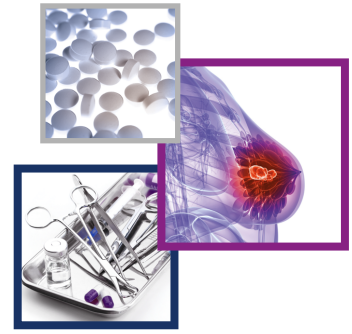
Breast Cancer Management



Main phenotypes and histological types of breast cancer in young women attended at a reference hospital in women's health in the city of São Paulo

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Summary points

- Observing the number of breast cancer (BC) cases and their types would characterize a profile of the patients we receive in the state of São Paulo/Brazil.
- Prospecting, according to the responsible Brazilian department, for new cases of BC in Brazil between the years 2020 and 2022.
- Analysis of the expression patterns of the cancer gene expands the understanding of BC as a heterogeneous group of diseases.
- Presentation of the most present histological types in the cases analyzed, as well as the verification of the highest incidence of ductal carcinomas of 81.03% (n = 45).
- The presence or absence of estrogen, progesterone and HER2 receptor expression (ER/PR/HER2) is the key to the stratification of the molecular subtype.
- Immunohistochemical techniques are widely applied to identify markers of different molecular subtypes.
- Analysis of cases distributed by age in comparison with the main BC subtypes when using the immunohistochemistry technique, with relevance for increasing cases between 36 and 40 years old, 54.50% (n = 139).
- Additions of prognostic and predictive information obtained from prospective and retrospective studies on molecular subtypes of BC, will contribute to specific treatment in terms of surgery, regional and systemic therapy and follow-up.
- Triple-negative BC remains a clinical challenge and several clinical trials are underway in an attempt to identify mechanisms to help improve results for this patient subgroup.

It is estimated that there were 198,840 new cases of breast cancer (BC) in Brazil between 2020 and 2022. Young women who are affected by invasive BC with a triple-negative phenotype generally present more aggressive tumors that are intrinsically resistant to targeted therapies. This study evaluated the phenotypic and histological profile of BC in women up to the age of 40 years. Between 2015 and 2017, we identified 255 women with positive biopsy for carcinoma and with immunohistochemical panel, 51.76% who had a profile for luminal B (n = 132); 22.74% for triple-negative (n = 58). Of the samples, 65.88% presented histology as invasive ductal carcinoma – nonspecial type (n = 168). The results are in accordance with the literature regarding the high prevalence of triple-negative BC in young women and histological type invasive ductal carcinoma – nonspecial type.

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Keywords: breast cancer • histologic type • phenotypic profile

For Brazil, it is estimated that 66,280 new cases of breast cancer (BC), for each year of the 2020–2022 triennium. This value corresponds to an estimated risk of 61.61 new cases per 100 thousand women. In 2017, there were 16,724

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deaths due to female BC, equivalent to a risk of 16.16 per 100 thousand. Without considering nonmelanoma skin tumors, female BC occupies the first most frequent position in all Brazilian regions, with an estimated risk of 81.06/100 thousand in the southeast; 71.16/100 thousand in the South region; 45.24/100 thousand in the Midwest region; 44.29/100 thousand in the northeast region; and 21.34/100 thousand in the North region [1,2]. In the world, BC is the most incident among women, the highest expected incidence rates outside of Brazil were in Australia and New Zealand, in the countries of the North Europe and Western Europe [3,4].

Based on the expression of hormone receptors (HRs): estrogen receptor (ER) and progesterone receptor (PR), the human epidermal growth factor 2 (HER2) receptor and measurement of the Ki-67 proliferation index (albeit with less analytical validity number than molecular tests), the approach to a standardized subtyping, recommended by the St Gallen consensus is presented [5].

During the 12th St. Gallen International Breast Cancer Conference Expert Panel, 2011, the classification of BC subtypes performed using immunohistochemistry (IHQ) and FISH was adopted for the deliberations on therapeutic strategies [6].

In the 13th St. Gallen International Breast Cancer Conference Expert Panel, 2013, the classification in clinical-pathological subtypes was modified, considering the semiquantitative evaluation of the expression of PR in clinical evolution and the response to treatment. Luminal A-like tumors were defined as: ER-positive, HER2-negative, Ki-67 <14% and PR-positive with expression >20%. Among the luminal B-like HER2-negative, ER-positive tumors with PR-negative or PR expressed in less than 20% of the stained nuclei were included, as well as ER-positive tumors with PR-positive and Ki-67>14%. The HER2-enriched tumors: ER and PR-negative and HER2-positive; triple-negative: absence of expression of ER, PR and HER2, have maintained their ratings since the 2011 conference [5,7].

In the same meeting of specialists where most of the relevant studies on BC are presented and discussed, held in 2015, there was a revision of the proliferation index (Ki-67), being now considered low index <20% and high index>20% [8,9].

Each of these subtypes is characterized by a distinct profile of gene expression and is associated with a different profile of prognosis and metastasis. Although these subgroups have unquestionable clinical values, their etiological and prognostic significance is weighed against the verification of other factors (e.g., age, race or socioeconomic status), which are also associated with clinical results [10].

In a large population-based study involving 247,719 patients, remarkable ethnic-social and social disparities were identified, and that the prevalence of advanced cancer diagnosis is higher in women who identified themselves as black and brown, who had little or no formal education, and it was lower in women who had access to university education and who, in this research, identified themselves as white [11].

Young women (aged up to 40 years), who are affected by invasive BC, usually present tumors with clinical and pathological features associated with a more aggressive stage, with a greater chance of regional locus relapse and death than tumors in postmenopausal women (with more 50 years) [12].

Among the BC subtypes, triple-negative breast cancer (TNBC) is associated with the worst clinical outcome in patients facing excess mortality. The poor prognosis of TNBC results from its inherent aggressive nature and the lack of specific therapeutic options for these patients. There are no proven effective target therapies for this type, making it the largest clinical challenge for the management indicated by the patient [13]. It has been increasingly recognized as a heterogeneous group that exhibits substantial differences, pathological characteristics and a distinctly aggressive nature with higher rates of relapse and lower overall survival, seen the higher metastatic scenario, compared with other BC subtypes [14–18].

Despite a complete pathological response in 30% of patients, survival after metastatic recurrence is lower. This can be understood from the predilection for visceral and pulmonary metastases. Women with TNBC are more likely to develop brain metastasis, however, the median survival after brain metastasis is shorter compared with patients developing brain metastasis from other types of BC [19].

In sporadic cases, BC can be detected by self-examination, and clinical evaluation is always necessary together with mammography and/or ultrasonography. Suspected cases should be confirmed via tissue biopsy [20]. Although the exams are able to define smooth contours of the carcinomas, specifically the TNBC will not always reveal images of intratumoral characteristics, such as necrosis and fibrosis, present in the majority of this phenotype. Therefore, it is of great importance for the diagnosis of these tumors to perform biopsies and complementary techniques of IHQ [21].

Table 1. Anatomopathological factors found in patients with breast cancer up to 40 years (n = 255).

Anatomopathological factors	Patients (n)	%
Nuclear grade:		
– 1	10	3.9
– 2	127	49.8
– 3	83	32.5
Modified SBR grade (Nottingham):		
– Grade I	27	10.5
– Grade II	137	53.7
– Grade III	49	19.2
Ki-67 >14	223	87.4
Presence of perineural invasion	13	5.0
Presence of vascular invasion	6	2.3
Presence of necrosis	155	60.7
Presence of skin invasion	4	1.56
Presence of angiolymphatic invasion	16	6.2
Phenotype:		
– Luminal A	13	5.09
– Luminal B	132	51.76
– HER2-enriched	52	20.39
Triple-negative	58	22.74

In this scenario, in view of the severity and poor prognosis, especially of the TNBC, the authors of this study proposed to evaluate the incidence of different BC phenotypes and histological types among young women, even using a sampling for convenience of a large women's reference hospital located in São Paulo.

Methodology

The present study consisted of an analytical and retrospective review of 714 patients, who underwent breast biopsy between the years 2015 and 2017, considering as inclusion criterion: patients with a cut age up to 40 years at the time of the test, a positive result for BC on biopsy and IHQ panel results for ER, PR, HER2 and Ki-67. Exclusion criteria were: diagnosis for carcinoma *in situ*, other markers in IHQ panel and biopsies that did not perform this complementary exam. Patients with more than 40 years old were not considered in this study, due the intention to just analyze this range of age.

Subtype definitions were as follows: luminal A (ER+ and/or PR+, HER2- [Ki-67 <14%]), luminal B (ER+ and/or PR+, HER2+/- [Ki-67 >14%]), HER2-enriched (ER-, PR- and HER2+) and TNBC (ER-, PR-, HER2-). In the years that the biopsies considered in this study were released, there was no obligation to quantify the progesterone, and it was used the proposed classification in the consensus at the 13th St. Gallen International Breast Cancer Conference Expert Panel, 2013.

Patients were divided into five groups for better age stratification and identification of which age group in women up to 40 years of age BC were more present. The data were obtained from the system of a large laboratory, which provides services to the public health system (including the reference hospital used in this study to extract data), which covers 70% of health units in the State of São Paulo.

Results

The data collection revealed 714 biopsies that entered the period from 2015 to 2017, but only 255 (35.71%) met the inclusion criteria as a BC on biopsy. The difference of 459 (64.29%) patients were due to benign biopsies, which were not considered in analyses, as cited on exclusion criterion. For the malignant biopsies considered, ages ranged from 19 to 40 years (mean: 35.14 ± 4.01 years). The younger patient had an HER2-enriched phenotype. There was appointment for women at the maximum age, 10% being luminal A (n = 3), 60% Luminal B (n = 18), 20% HER2-enriched (n = 6) and 10% TNBC (n = 3).

It can be seen that when comparing the number of patients by age with the phenotype (Figure 1 & Table 1),

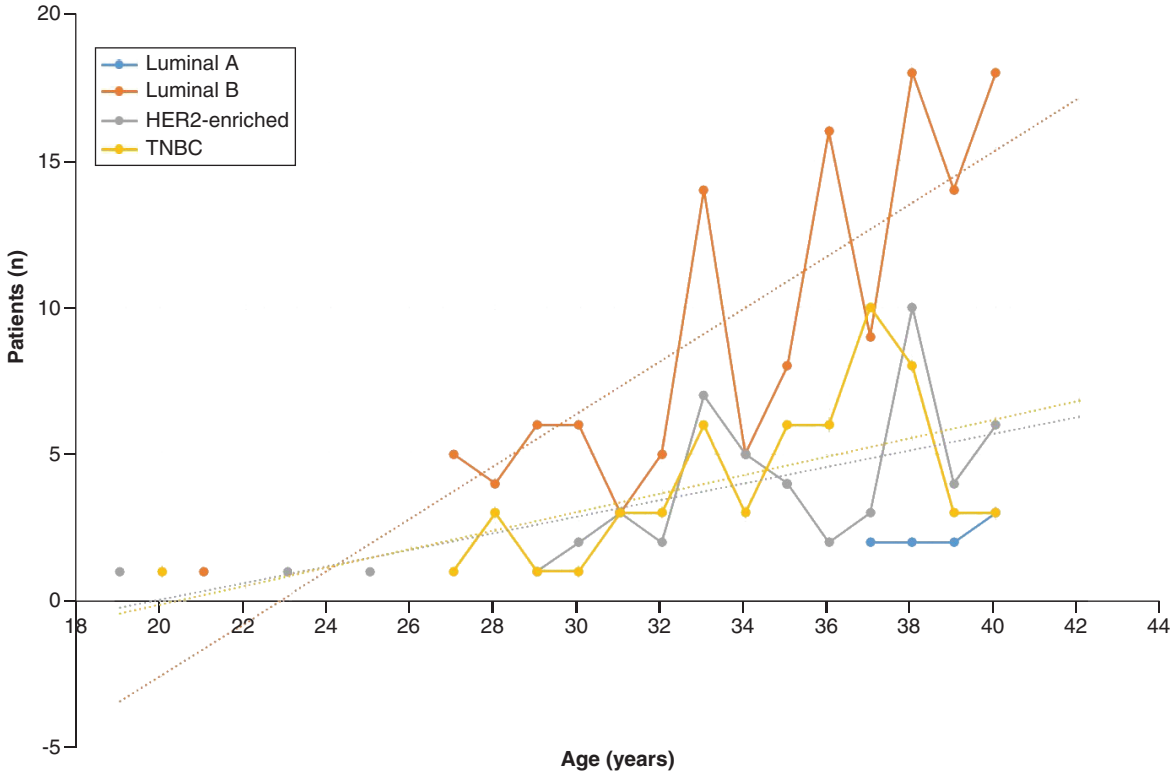

Figure 1. Proportion of patients in age (in years) and phenotype.
TNBC: Triple negative breast cancer.

luminal B presents a greater amount, in all ages of the spectrum above 27 years; except at 37 years, the largest number of patients refers to the TNBC (n = 10).

In Figure 1, as the age increases, the number of cases with the luminal B phenotype tends to increase slightly higher than the tendency to increase the HER2-enriched and TNBC phenotypes. The line referring to luminal phenotype A was not plotted due to small data sampling.

When comparing the quantities of cases according to the BC subtypes considered in this research, with the largest to the smallest, we have; luminal B 51.76% (n = 132), TNBC 22.74% (n = 58), HER2-enriched 20.39% (n = 52) and luminal A 5.09% (n = 13).

From the data obtained, it was highlighted that the predominant histological type among the phenotypes shown in Figure 2 was the IDC-NST, 65.88% (n = 168). It is worth mentioning that 52.97% (n = 89) of the cases with this histology refer to the luminal phenotype B 22.61% (n = 38) to the TNBC phenotype 21.42% (n = 36) to HER2-enriched and only 2.97% (n = 5) to luminal A.

Among the other histological types analyzed in this sample, the one with the highest number of cases, followed by IDC-NST was carcinoma with ductal characters, with 7.84% (n = 20) of the total sample, with the main phenotypes: 40% (n = 8) luminal B and 45% (n = 9) TNBC.

According to histological findings (Table 1), those with the highest elevation were ones with Nottingham II histological grade with 53.7% (n = 137) and nuclear grade 2 with 49.8% (n = 127). Histological grade III of Nottingham, considered the most aggressive, occurred in 19.2% (n = 49) of the analyzed samples. For the classification of the Ki-67 index following the classification of the 13th St. Gallen International Breast Cancer Conference Expert Panel, 87.4% (n = 223) of cases with a value greater than 14% were detected. Another major factor in the histological analysis performed was the high number of biopsies with the presence of necrosis, out of the 255 analyzed, 60.7% (n = 155) of these presented this finding.

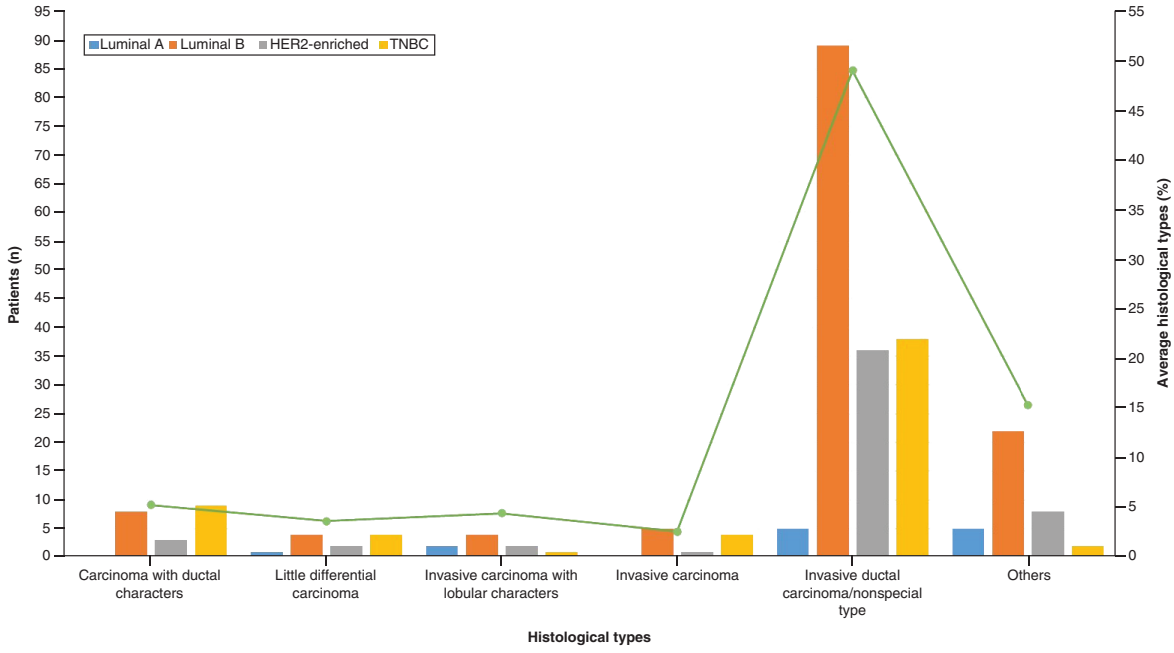

Figure 2. Proportion of patients by phenotype and histological age.
TNBC: Triple negative breast cancer.

Discussion

Detection of BC is a decisive factor in determining prognosis. Epidemiological studies in different regions of Brazil are important for the development of better prevention and screening programs.

BC is a disease that manifests itself in several clinicopathological forms, which can sometimes hinder its diagnosis in the early stages. In order to detect BC early, clinical examination of the breasts and mammography should be performed. One of the major challenges for the study and treatment of breast carcinoma is its tumor heterogeneity [22].

Triple-negative tumors are those that, together with macroscopic, microscopic and molecular characteristics, are negative for estrogen, progesterone and HER2 receptors. TNBC tumors occur in about 10–20% of invasive BC, and this sub-type carries a poorer prognosis than the luminal tumors [15].

The appearance of the invasive component should be determined from the subtypes of invasive ductal carcinomas (IDC) rather than from the types of invasive ductal carcinomas *in situ* (DCIS) or its grade. IDC is classified into many histological subtypes according to a wide range of criteria, including cell type (as in apocrine carcinoma), amount, type and location of secretion (as in mucinous carcinoma), architectural features (as in papillary, tubular and micropapillary carcinoma) and immunohistochemical profile (as in neuroendocrine carcinoma) [23].

These tumors are known to have poor outcome with the use of hormone therapy, with high recurrence rates and lower survival, as well as unfavorable histological characteristics, such as poor differentiation and increased histological grade [24].

In developing countries, the planning of health actions is extremely important for the rational management of costs. In Brazil, the Unified Health System (SUS, in Portuguese) recommends the IHQ panel with ER, PR, HER2 and Ki-67 to assess the adjuvant treatment of breast carcinomas. The new classification of St. Gallen 2013 increased the amount of luminous B breast carcinomas [25].

Cirqueira and collegues [26] have shown that IDC-NST is the largest and most common group of invasive breast carcinomas, which corresponds to a heterogeneous group of tumors without significant histological classification.

Based upon histological findings, the majority of the TNBCs are of ductal origin; which corroborates with our findings that 47 (81.03%) of TNBC cases present histological findings compatible with ductal origin, of which, 80.85% (n = 38), invasive ductal carcinoma [27].

According to publications by Boyle [15] and Brouckaert *et al.* [19], TN tumors usually also present the histological type IDC-NST, but, different from the other phenotypes, they evolve rapidly, exhibit a high risk of early recurrence

(1 to 3 years after diagnosis), metastases rarely preceded by locoregional recurrence and a higher prevalence of visceral metastases (lung and brain) than in bones; and present high rates of premature death (3 to 5 years of disease) and rapid progression from the onset of metastases to death.

The results showed a high prevalence of BC with luminal B and TNBC phenotypes in the studied sample, totaling 51.76 and 22.74%, respectively, of the total positive samples, higher than that observed in the literature that reveals a prevalence of TNBC which can range from 10 to 15% in the general population, and kind of 10–20% of the TNBC among young women as compared with older women [28,29].

It is known that the factors race, ethnicity, origin and other characteristics are fundamental for a survey on tumor types. Our study has some limitations, like: it was not possible to access such information for laboratory quantification because, in Brazil, it is common for public health services (such as basic units and hospitals) to allocate outsourced laboratories for laboratory and imaging exams. These laboratories hold only the data from the samples received and basic data for patient identification, such as name and date of birth. Evaluation of lymph nodes, tumor size and anatomic-pathological staging were not included in the study because only biopsies were considered, sampling was not indicated for this type of evaluation.

Conclusion

In this study, the results agree with the literature regarding the high prevalence of TNBC in women under 40 years of age and that the histological type invasive ductal carcinoma/nonspecial type is presented with higher prevalence.

The number of patients diagnosed with luminal B BC remains high, but the triple-negative phenotype profile is the second most prevalent. There are still many patients who go through this disease and many times can not have a high survival rate because of the conditions of this type of cancer.

The current results illustrate the need to develop new studies to amplify the knowledge about this type of tumor, aiming to propose new diagnostic and therapeutic methods that are more effective, thus giving a greater and better quality of life to these young women.

Author contributions

GMRd Souza conceived the idea, designed and conducted the research strategy, analysis of results and preparation of the manuscript. AF Carvalho supervised the project, analysis of results and preparation of the manuscript. SF Santiago conceived the idea, authorized and made the research strategy used. MAMR Pinho performed a secondary screening of abstracts, analysis of results and preparation of the manuscript. DR Ramadan and S Tufik authorized and enabled the research strategy used. MC Feres supervised the project, performed a secondary screening of abstracts, analysis of results and preparation of the manuscript.

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No writing assistance was utilized in the production of this manuscript

Ethical conduct of research

The authors declare that there was no human participation of patients in the study. All data were collected from the laboratory's computerized system, not exceeding any limit for the control and disclosure of personal data.

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