Understanding the Occurrence and Characteristics of Molecular Subtypes of Breast Cancer in the Midwest Region of São Paulo

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Compreendendo a Ocorrência e as Características dos Subtipos Moleculares do Câncer de Mama no Centro-Oeste Paulista, São Paulo

Comprendiendo la Ocurrencia y las Características de los Subtipos Moleculares del Cáncer de Mama en el Centro Oeste Paulista, São Paulo

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ABSTRACT

Introduction: Breast cancer is one of the main public health challenges, highly incident with significant impact on female morbimortality. Its molecular heterogeneity reflects different clinical behaviors and prognoses, reinforcing the importance of immunophenotypic characterization for therapeutic guidance and diagnostic improvement. **Objective:** Analyze the distribution of molecular subtypes of breast cancer in patients treated at the oncology service in Ourinhos, São Paulo, between 2017 and 2023. **Method:** Retrospective, descriptive, and observational study based on the review of medical records and the identification of cellular markers for the classification of luminal A-like, luminal B-like, luminal B/HER2, HER2-positive, and triple-negative subtypes. Statistical analysis was performed using the chi-square test of independence, with a significance level of 0.05. A total of 505 cases were analyzed, with the luminal B subtype being the most prevalent (51.1%), followed by luminal A (21.4%). **Results:** A statistically significant association was observed between age groups and molecular subtypes (p=0.0235), with a higher frequency of aggressive tumors, as HER2-positive and triple-negative in younger women. **Conclusion:** The results demonstrate that different age groups in the region present predominant characteristics according to age, highlighting the importance of understanding the local epidemiological profiles of breast cancer.

Key words: Breast Neoplasms/immunology; Receptors, Cell Surface; Immunohistochemistry; Epidemiology; Oncology.

RESUMO

Introdução: O câncer de mama é um dos principais desafios de saúde pública, apresentando alta incidência e impacto significativo na morbimortalidade feminina. Sua heterogeneidade molecular reflete diferentes comportamentos clínicos e prognósticos, o que reforça a importância da caracterização imunofenotípica para o direcionamento terapêutico e para o aprimoramento do diagnóstico. **Objetivo:** Analisar a distribuição dos subtipos moleculares do câncer de mama em pacientes atendidos no serviço de oncologia da cidade de Ourinhos, São Paulo, entre os anos de 2017 e 2023. **Método:** Pesquisa retrospectiva, descritiva e observacional, baseada na revisão de prontuários médicos e na identificação de marcadores celulares para classificação dos subtipos luminal A-like, luminal B-like, luminal B/HER2, HER2 positivo e triplo-negativo. A análise estatística foi realizada por meio do teste do qui-quadrado de independência, com nível de significância de 0,05. Foram analisados 505 casos, sendo o subtipo luminal B o mais prevalente (51,1%), seguido do luminal A (21,4%). **Resultados:** Observou-se associação estatisticamente significativa entre as faixas etárias e os subtipos moleculares (p=0,0235), com maior frequência de tumores agressivos, como HER2 positivo e triplo-negativo, em mulheres mais jovens. **Conclusão:** Os resultados demonstram que diferentes faixas etárias da Região apresentam características predominantes conforme a idade, evidenciando a importância de compreender os perfis epidemiológicos locais do câncer de mama.

Palavras-chave: Neoplasias da Mama/imunologia; Receptores de Superfície Celular; Imuno-Histoquímica; Epidemiologia; Oncologia.

RESUMEN

Introducción: El cáncer de mama constituye uno de los principales desafíos de salud pública, con alta incidencia e impacto significativo en la morbilidad y mortalidad femenina. Su heterogeneidad molecular refleja diferentes comportamientos clínicos y pronósticos, lo que refuerza la importancia de la caracterización inmunofenotípica para orientar el tratamiento y mejorar el diagnóstico. **Objetivo:** Analizar la distribución de los subtipos moleculares del cáncer de mama en pacientes atendidas en el servicio de oncología de la ciudad de Ourinhos, São Paulo, entre los años 2017 y 2023. **Método:** Investigación retrospectiva, descriptiva y observacional, basada en la revisión de historias clínicas y en la identificación de marcadores celulares para la clasificación de los subtipos luminal A-like, luminal B-like, luminal B/HER2, HER2 positivo y triple negativo. El análisis estadístico se realizó mediante la prueba de ji al cuadrado de independencia, con un nivel de significación de 0,05. Se analizaron 505 casos, siendo el subtipo luminal B el más prevalente (51,1%), seguido de luminal A (21,4%). **Resultados:** Se observó una asociación estadísticamente significativa entre los grupos etarios y los subtipos moleculares (p=0,0235), con mayor frecuencia de tumores agresivos, como HER2 positivo y triple negativo, en mujeres más jóvenes. **Conclusión:** Los resultados demuestran que diferentes grupos etarios de la región presentan características predominantes según la edad, lo que resalta la importancia de comprender los perfiles epidemiológicos locales del cáncer de mama.

Palabras clave: Neoplasias de la Mama/inmunología; Receptores de Superficie Celular; Inmunohistoquímica; Epidemiología; Oncología.

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INTRODUCTION

Breast cancer is one of the most urgent health conditions in contemporary society, especially among women due to its high incidence and significant impact on their lives. The epidemiologic scenario in Brazil reveals regional variations, the South and Southeast regions exhibit the highest rates although the disease is not bound by socio-economy or geography. Breast cancer affects women of all ages and origins and estimates indicate continuous growth of new cases in the next years[1].

Contributive factors for the development of breast cancer are wide and interrelated, involving genetic, hormone and environmental factors. Understanding these elements leads to more specific prevention and treatment strategies where healthy life habits as balanced nourishment and regular practice of physical exercises help homeostasis and reduce the risks from the disease[2,3]. Early detection and identification of mutation of the genes BRCA1 and BRCA2 associated with different factors involved in the development of breast cancer contribute to effective preventive interventions. The genetic and molecular characterization of the tumor guides individualized conducts, defining the best therapeutic course as prophylactic surgery, radiotherapy, hormone therapy or chemotherapy and reinforces the importance of a personalized approach of prevention and treatment[3-5].

The epidemiology of breast cancer subtypes reveals variations of frequency of identification of these profiles. Luminal subtypes appear more predominantly while HER2 and triple-negative are least frequent in the different contexts evaluated. The distribution of these subtypes also modifies according to the demographic characteristics, especially age, which directly influences the assistance profile and the organization of health services. In that sense, understanding how these subtypes present in distinct populational segments is essential to interpret local patterns of the disease, guide therapeutic conducts and support oncology planning strategies[1,3].

Therefore, breast cancer is a spectrum of subtypes with distinct characteristics not being a homogeneous entity. There are four subtypes: luminal A, luminal B, HER2 and basal-like[6]. These groups represent defined molecular profiles based on differences of expression of hormone human receptors, proteins involved in pathways of cellular signaling and indexes of tumor proliferation. Although this classification facilitates the clinical and therapeutic approach, it does not exhaust the biological complexity of the disease. In addition, the classification evolved to five subtypes that include, further to the already mentioned, the luminal subtype B/HER2, forming the set of profiles adopted in immunohistochemistry practice since the levels of expression of the estrogen and progesterone receptors are among the main classificatory determinants that distinguishes the groups[3]. The deep approach allows to steer the treatment, optimize diagnostic strategies and monitoring, support informed clinical decisions and improve therapeutic results[7].

The immunohistochemistry analysis predominates in Brazil due to its cost-effectiveness assuming a central role in pathological anatomy[8,9]. In situ immunolabeling technique allows to identify specific markers as estrogen and progesterone receptors, HER2 and Ki-67 immune proliferation index. This biomarker measures the rate of proliferation and chemosensitivity, although there is no consensus on cutoff values. Values below 14% represent low proliferation, 15% to 50%, intermediate proliferation and above 50%, high proliferation associated with higher tumor aggressiveness[3,9].

Subtype luminal A-like presents high levels of estrogen and progesterone receptors, Ki-67 below 14% and low degree of differentiation. Luminal B-like exhibits Ki-67 above 14%, high histological degree and possibly reduced hormone levels, associating with worst prognosis compared to luminal A-like. In addition, the manifestation of oncoprotein HER2, together with hormone receptors show the classification of subtype luminal B/HER2. On the other hand, positive HER2 has negative hormone receptors and characterizes by overexpression of receptor HER2, as shown by positive immunohistochemistry or *in situ* hybridization, with high histologic grade and tumor aggressiveness. Triple-negative presents absence of hormone receptors and expression of HER2[3,7,9,10].

The continuous survey of breast cancer molecular subtypes has boosted the improvement of therapeutic strategies. Subtypes luminal A and B, characterized by distinct hormone responses and specific genetic profiles, require differentiated clinical conducts. Luminal A, sensitive to hormone therapy, presents good response to tamoxifen and aromatase inhibitors. On the other hand, luminal B, more aggressive, requires combined approach, associating hormone therapy with chemotherapy with anthracyclines and taxanes, but evaluation of stage and tumor grade is necessary. In addition, target-therapy with trastuzumab and pertuzumab, that blocks signaling of oncoprotein HER2 and induce cellular apoptosis, is beneficial for HER2 positive. On its turn, triple-negative tumors, of difficult management, are mainly treated with chemotherapy involving taxanes and platin compounds, but immunotherapics are also utilized as pembrolizumab, that promotes specific immune response against tumor cells[3,9,11,12].

The objective of this article is to contribute to the understanding of the specific reality of the characteristics of molecular subtypes and of the epidemiology of

patients with breast cancer treated at the oncology service of the city of Ourinhos, São Paulo. It is a descriptive observational study aimed to understand the subtypes and its distribution among individuals treated at the outpatient unit. The analysis of the incidences for this target-population allows to establish a more accurate epidemiological profile directly related to the personalization of the treatment for patients with breast cancer.

METHOD

Retrospective, descriptive, observational study conducted with patients treated at the outpatient unit of *Associação da Santa Casa de Misericórdia* of Ourinhos between January 2017 and December 2023. Data were collected from medical charts, consisting in sex, age and immunohistochemistry complementary test.

Immunophenotypic profiles were established through the identification of cell markers, which allowed the categorization of the patients in subtypes luminal A-like, luminal B-like, luminal B/HER2, positive HER2 and triple-negative. The objective of this classification was to characterize the clinical and epidemiological profile of the disease in the population investigated.

The data were organized in Microsoft Excel and statistically analyzed through the chi-square test of independence with level of significance of α=0.05. The analyzes were processed in the software BioEstat®[13], version 5.3. A contingency table containing the absolute values of the positive cases distributed per age range and molecular subtype was elaborated to apply the statistical test.

The ethics committee of *Fundação Educacional do Município de Assis (Fema)* approved the study, report number 7640596 (CAAE (submission for ethical review): 86416025.6.0000.8547) in compliance with the Declaration of Helsinki[14] and Directives 466/2012[15] and 510/2016[16] of the National Health Council. Names, initials or registers were not utilized in any phase of the research to ensure the privacy and anonymity of the participants.

RESULTS

Different molecular subtypes of breast cancer per age range were evaluated through a contingency table with raw values of positive cases for each group.

Table 1 shows the distribution of molecular subtypes of breast cancer per age range (<45 years, 45–65 years and >65 years) in 505 cases.

Most of the cases occurred in the age range of 45–65 years (45.1%), followed by >65 years (36.2%) and <45 years (18.6%).

The most prevalent subtype was luminal B, accounting for 51.1% of all the cases, followed by luminal A (21.4%). HER2 (5.9%) and luminal B HER2 (8.9%) were the least frequent.

Subtype HER2 presented the higher relative concentration in women <45 years (33.3%) above the expected, consistent with the high chi-square value of this group.

Luminal A was relatively lower in <45 years (11.1%), in contrast with high frequency in women >65 years (46.3%). This pattern reinforces the significant statistical discrepancy in age range extremities.

The hypotheses have been defined as follows: H_0 (null hypothesis) where the distribution of breast cancer subtypes is independent from the age range of the patients, without association with categorized age and subtype H_1 (alternative hypothesis), where the distribution of the subtypes varies among age ranges, indicating association between categorized age and subtype. Considering a level of significance of α=0.05, the following decision criteria was adopted: if p<005, H_0 is rejected, indicating association between age range and subtype, for $p \geq 0.05$, H_0 is not rejected, suggesting lack of evidences of association among the variables.

The test resulted in a value of p<0.05 (p=0.0235), which allows to reject H_0 and conclude there is significant difference in the distribution of subtypes among age ranges. Therefore, the major individual contributions of the total values of the test concentrate on subtypes HER2 positive and triple-negative in women younger than 45

Table 1. Distribution of the subtypes of breast cancer per age range

Subtype	<45 years	45-65 years	>65 years	Total
Luminal A	12 (11.1%)	46 (42.6%)	50 (46.3%)	108 (21.4%)
Luminal B	45 (17.4%)	116 (45.0%)	97 (37.6%)	258 (51.1%)
Luminal B/HER2	10 (22.2%)	22 (48.9%)	13 (28.9%)	45 (8.9%)
HER2	10 (33.3%)	12 (40.0%)	8 (26.7%)	30 (5.9%)
Triple-negative	17 (26.6%)	32 (50.0%)	15 (23.4%)	64 (12.7%)
Total	**94 (18.6%)**	**228 (45.1%)**	**183 (36.2%)**	**505 (100%)**

years (χ^2 = 3.49 and χ^2 = 2.17, respectively) similar to subtype luminal A in the age ranges <45 years (χ^2 = 3.27) and ≥60 years (χ^2 = 3.02), indicating discrepancies among expected and observed values in these groups. For subtypes luminal B and luminal B/HER2, low contributions for all age ranges were observed, consistent with the distribution that was kept within the expected. For other combinations, subtype and age range, the values of chi-square continued low, suggesting stable behavior among the categories analyzed (Tables 2 and 3).

DISCUSSION

Consistent with the molecular characterization presented in a former study[3], there was predominance of subtypes luminal A and B globally, defined by the expression of hormone receptors and associated with best prognosis. On the other hand, subtypes HER2 positive and triple-negative showed more aggressive biological behavior, high proliferation rate and lower global survival. The study has also highlighted the influence of age over the molecular distribution, with higher incidence of luminal tumors in post-menopause women and non-luminal subtypes in younger women, a statistically significant relation in several cohorts evaluated.

A Brazilian study[17] analyzed younger women with breast cancer and identified subtypes luminal A, luminal B, HER2 positive and triple-negative, with higher frequency of luminal tumors. The subtype triple-negative represented approximately 15% of the cases, occurring predominantly in patients younger than 40 years. Regardless of not having statistical significance among age and subtype (p>0.05), the study showed higher proportion of advanced clinical staging among younger women, which reinforces the tendency of more aggressive biological behavior in this age group.

In complementation, another Brazilian multicenter study[18] presented predominance of subtype luminal A, followed by luminal B and HER2 positive, the latter responsible for 15.7% of the cases. The mean age was 54 years with 41.1% of the patients with less than 50 years, characterizing a relatively young sample. The study reported significant differences in the prognosis of molecular subtypes with p=0.0002 for global survival, demonstrating the predictive role of the classification on the therapeutic response and clinical evolution of the disease.

While comparing these results with the regional study conducted in the Midwest region of São Paulo, there was a partial convergence of the national and international trends. The chi-square test revealed statistically significant association between age and molecular subtype (p=0.023), demonstrating that the distribution of subtypes is not homogeneous among age ranges. The major contributions to the value of χ^2 were observed for subtypes HER2

Table 2. Expected values and individual contributions (χ^2) per molecular subtype and age range

Molecular subtype	<45 years (E/χ^2)	45-65 years (E/χ^2)	≥65 years (E/χ^2)	Interpretation
Luminal A	20.10/3.27	48.76/0.16	39.14/3.02	High incidence in ≥65 years
Luminal B	48.02/0.19	116.48/0.00	93.49/0.13	Predominant in all age ranges
Luminal B/HER2	10.00/0.31	22.00/0.13	13.00/0.67	Balanced distribution
HER2 positive	8.38/3.49	20.32/0.14	16.31/0.67	Higher concentration in <45 years
Triple-negative	5.58/2.17	13.54/0.18	10.87/0.76	High tendency in younger women

Table 3. Chi-square test applied to the association among subtypes and age ranges

Test applied	χ^2 calculated	χ^2 tabulated (α=0.05)	df	p	Decision
Association among subtypes and age ranges	**17.71**	—	8	**0.0235**	**Rejects H_0 — there is significant association**

Captions: df = degrees of freedom; H_0 = null hypothesis.

positive (χ^2 = 3.49), luminal A (χ^2 = 3.27) and triple-negative (χ^2 = 2.17), all of them concentrated in the age range lower than 45 years, indicating strong influence of these subtypes in the global significance of the test.

These results indicate that for the population investigated, there is statistically expressive association among younger age and more aggressively biological subtypes, mainly subtypes HER2 and triple-negative compatible with the pattern described in former studies[3,17]. In counterpart, the predominance of subtype luminal B over luminal A is different than it was observed in varied Brazilian sites[18], where luminal A was the most prevalent, possibly reflecting regional, methodological and sample differences. Therefore, the influence of regionality is necessary for the composition of breast cancer subtypes, emphasizing that populations of different Brazilian regions can present distinct patterns of molecular distribution.

In an integrative manner, the studies analyzed converge when they indicate that luminal subtypes are the majority of the cases, but diverge in relation to the proportion between luminal A and luminal B and frequency of subtypes HER2 positive and triple-negative. These quantitative variations reflect the impact of regional and populational factors on the molecular characterization and show that, although the general tendency was kept stable, the magnitude of statistical differences depends on the context analyzed.

Considering the molecular heterogeneity and statistical behavior observed, it is evident the necessity of new investigations that explore possible direct interactions among molecular subtypes, especially in regard to the coexistence of hybrid profiles and phenotype transition in the course of tumor progression. Deepening these analyzes can widen the understanding about breast cancer biology in the Midwest region of the state of São Paulo, especially in the municipality of Ourinhos, and support more specific, personalized and evidences-based therapeutic strategies.

CONCLUSION

Subtype luminal B was the most prevalent among breast cancer cases analyzed in São Paulo Midwest region followed by luminal A. There was statistically significant association among age ranges and molecular subtypes, indicating that younger women presented higher frequency of tumors of more aggressive biological behavior as subtypes HER2 positive and triple-negative. These findings reinforce the relevance of the molecular characterization in clinical practice, since they allow to understand the regional epidemiological profile, improve the diagnosis, the prognosis and steer more personalized and effective therapeutic conducts to treat breast cancer.

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CONTRIBUTIONS

All the authors contributed substantially to the conception and design of the study, acquisition, analysis and interpretation of the data, writing and critical review. They approved the final version for publication.

DECLARATION OF USE OF AI

The authors utilized generative artificial intelligence (AI) to support the writing of the article alone and are fully responsible for the analysis, interpretation or synthesis of the results without AI intervention.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interests to declare.

DATA AVAILABILITY STATEMENT

All content underlying the text is contained in the manuscript.

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