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Clinic, pathologic and molecular landscapes in ultra-young women with breast cancer in the State of São Paulo: a real-world study

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ABSTRACT

Introduction: Breast cancer (BC) centers are increasingly attending "ultra-young" women (UYW) patients (≤ 30 years), who usually present aggressive tumors and face specific problems. **Objectives:** We aimed to examine a multicentric casuistic view, addressing clinicopathological and molecular characteristics of BC, as well as therapeutic measures and oncological outcomes. **Methods:** A retrospective multicentric observational study of UYW with infiltrating BC was carried out. The patients were treated between the period from January 1991 to December 2019. Clinical, epidemiological, morphological, molecular, therapeutic and outcomes data were collected from the charts. **Results:** A total of 293 patients were followed for a average period of 34.5 months. Nulliparity was referred by 204 women (75.5%), of whom 81 (37.1%) were overweight or obese. Positive family history in first-degree relatives was verified in 25 patients (10.1%). Only 30 patients underwent genetic tests, which revealed inherited pathogenic mutations in 12 of them (37.5%). Thirty-two (32) cases were classified as T_1 at diagnosis (10.9%), while "De novo" stage IV was found in 29 patients (9.8%). Mastectomy was performed in 175 women (70.2%), quadrantectomy in 46 women (18.4%), and mammary adenectomies in 28 women (11.2%), of which 149 cases were reported after neoadjuvant chemotherapy (56.0%). A total of 111 patients had at least one positive lymph node (47.4%). The rate of patients with estrogen receptor-negative was 32.7% and the rate of patients with Human Epidermal Growth Factor Receptor 2-positive (HER2-positive) was 25%. The frequency of Luminal A neoplasias was 16.6%, Luminal B/HER2- was 35.9%, Luminal B/HER2+ was 15.1%, HER2 overexpressed was 9.3%, and Basal was 22.9%. Taking into account the outcomes, 173 patients were alive without disease (65.7%); 23 patients were alive with any form of recurrence (8.7%); and 67 patients (25.4%) evolved to BC deaths. **Conclusions:** It was concluded that UYW with BC are commonly diagnosed at advanced stages, present adverse morphological and molecular parameters, and have unfavorable prognosis.

KEYWORDS: breast neoplasms; ultra-young women; prognosis; therapeutics.

INTRODUCTION

In recent years, there has been great interest in breast cancer (BC) in young women. Current epidemiological data suggest that a substantial number of young women is affected with this neoplasia, being BC one of the leading causes of cancer related to deaths in this age range[1]. These patients share some unfavorable biological characteristics, with more aggressive tumors, that are likely to be larger in size when diagnosed, and correlated with higher

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locoregional recurrence rate and lower survival[2-4]. Young women are often less likely to seek early medical assistance.

In this context, it is necessary clarify what it means the term "ultra-young" women (UYW), since the definition for young woman in BC scenario varies according to the literature[5]. Considering a specific age related to health problems, such as future reproduction, background mutational process, emotional distress and management dilemmas, we advocate a subdivision of young women with BC into three subgroups: young (< 40 years), very young (≤35 years), and ultra-young (≤ 30 years).

Specialized centers in BC are increasingly attending UYW. Nevertheless, crucial aspects of the disease in this age range remain controversial and deserve further investigation. Managing patients of this age range, using the knowledge required for older patients, has become more and more difficult. Given these facts, it is meaningful to increase our wisdom on BC in UYW. In this article, we have considered a multicentric casuistic view that has occurred in several BC Centers located in the State of São Paulo, through a retrospective research organized by Brazilian Society of Mastology, São Paulo Region. Clinicopathological and molecular characteristics of BC in this age group, as well as therapeutic measures and oncological outcomes were addressed.

METHODS

We conducted a retrospective multicentric observational study with consecutive female ultra-young patients with BC.

Population

Only patients with infiltrating breast carcinomas aged less than or equal 30 years were included.

Only nine of 23 collaborating centers, invited to participate in this study, sent the completed worksheets to join the research project as follows: Hospital Pérola Byington, Instituto do Câncer do Estado de São Paulo, Hospital Sírio Libanês, Clínica Prof. Alfredo Barros, Hospital de Câncer de Barretos, Faculdade de Ciências Médicas de Santos, Hospital Regional de Presidente Prudente, Hospital das Clínicas de Botucatu and Instituto Arnaldo Vieira de Carvalho.

Data collection

All patients were treated between January 1991 and December 2019. The following data were recorded: age, body mass index, parity, hormonal contraception use, history of breast/ovarian cancer in the family, pathological tumor category, clinical staging, neoadjuvant and adjuvant treatments, type of surgery, number of positive lymph nodes, multicentricity/multifocality, presence of absence of peritumoral vascular invasion (PVI), histological grade (HG), nuclear grade (NG), and stage categorized according to the American Joint Committee on Cancer (AJCC) staging system.

Immunohistochemical information on estrogen receptor (ER), progesterone receptor (PgR), HER2 and Ki-67 protein were obtained from percutaneous biopsy and/or surgical specimens of patients diagnosed with the disease. ER and PgR were considered positive when the percentage of immunoreactive cells was equal or greater than 1%. The positivity for HER2 was defined as 3+ staining pattern, or gene amplification by Fluorescence in situ hybridization (FISH). Ki-67 protein was expressed in percentage of stained cells. The assessments were made by the local pathology laboratory in accordance with American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) recommendations.

We have classified the cases into five molecular subtypes, akin to modified recommendations of St. Gallen Consensus (2013)[6]:

- Luminal A-like: ER+ (≥ 10%), PgR+ (≥ 10%), HER2-, Ki-67 ≤ 20%;
- Luminal B-like HER2-: ER+ (≥ 10%), HER2-, PgR (<10%) or Ki-67 ≥ 20%;
- Luminal B-like HER2+: ER+ (≥ 10%), HER2+, any Ki-67, any PgR;
- HER2 overexpressed: HER2+ non luminal (ER < 10%);
- Triple negative: ER- (< 10%), PgR-(< 10%), HER2-.

Statistical analysis

Frequency of parameters were estimated. Statistical analyses were performed using a 0.05 P-value, calculated by the χ^2 test. The software IBM SPSS Statistics 25 was used for the analysis.

Ethical aspects

The research protocol was approved by the Ethics Committee of the Hospital Pérola Byington, which was managed by the Study Coordinator Center (number 3.001.256), and later approved by the Committees of the Collaborating Centers. An informed consent waiver was approved for all anonymous data retrospectively collected.

RESULTS

The population-based study included 293 patients up to 30 years old — that is, patients between the ages of 19 and 25 years (mean age = 27.3; median = 28). It shows the distribution of age at diagnosis in three categories as shown in Figure 1: 19–20, 21–25 and 26–30 years. They were followed by a median time of 41.5 months (1.5–207.0), with a median time of 34.5 months.

Body mass indexes are shown in Table 1. It is worth to point that 37.1% of the patients were overweight or obese.

Taking into consideration the reproductive factors, it was informed that 41.3% of the patients were current or past users of hormonal contraceptive (data available from 237 patients). Nulliparity was referred by 204 women (75.5%); parity 1–2 by 64 women (22.9%); and parity 3–4 by 28 women (10.3%) (data available from 207 patients).

We were able to collect data about family history in 246 cases. Positive family history in first-degree relatives was verified in 25 patients (10.1%), of whom 21 informed the corresponding relative's age at diagnosis: ≤30 years in two patients (9.5%); > 30 and ≤ 40 years in 10 patients (47.6%); > 40 and ≤ 50 years in 5 patients (23.8%); and > 50 years in 4 patients (19.0%). A total of 66 patients (26.8%) reported a family member with BC. Only thirty-two patients (10.9%) underwent multigene panel testing, of whom inherited pathogenic mutations were found in 12 of them (37.5%).

It is known that in most of the younger women the diagnosis is done by finding a lump. Remarkably in this casuistic view, locally advanced tumors were detected in 54.3% of cases. Detailed information about tumor sizes at diagnosis were listed as shown in Table 2. Clinical axillary lymph nodes evaluation in 283 cases revealed: N_0 in 99 cases (34.9%); N_1 in 121 cases (42.7%); N_2 in 53 cases (18.7%); and N_3 in 10 cases (3.5%). Clinical staging is showed in Figure 2, being evident high frequency of later stages. Twenty-nine patients presented systemic metastases and were classified as "De novo" stage IV (9.8%). The metastases sites were: bone — eight cases (27.5%); lung — five cases (17.2%); liver — four cases (13.7%); and multiple — 12 cases (41.3%).

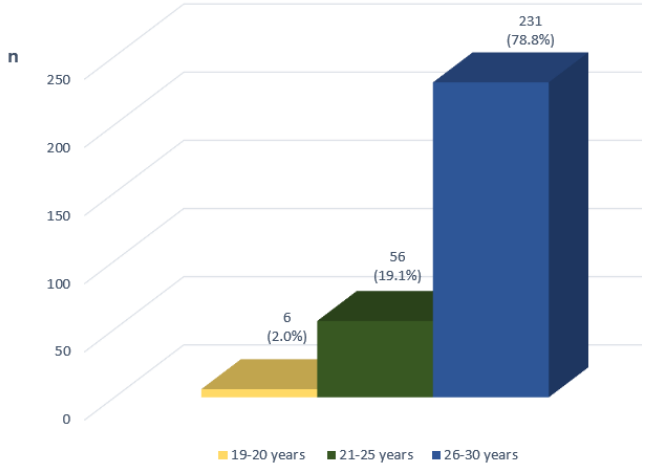


Figure 1. Age ranges of the 293 ultra young patients.

Table 1. Body mass indexes*.

Age range		n	%
< 18.5	underweight	21	9.6
18.5–< 25	normal	116	53.2
≥ 25–< 30	overweight	53	24.3
≥ 30	**obese**	**28**	**12.8**

*Without information: 75.

Table 2. Tumor size at diagnosis*.

	n	%
T_1	32	11.8
T_2	92	33.9
T_3	86	31.6
T_4	**62**	**22.7**

*Without information: 21.

Among 266 patients with attainable information, 149 of them (56.0%) received neoadjuvant chemotherapy, of whom 118 (79.1%) presented favorable clinical response (partial or total). In our study no patients underwent neoadjuvant hormone therapy.

Of all the types of local surgery performed in 249 patients with available data, mastectomy was performed in 175 patients (70.2%); breast conservative surgery was performed in 46 cases (18.4%); and unilateral or bilateral mammary adenectomies was performed in 28 patients (11.2%), as shown in Figure 3.

Sentinel node biopsy was performed in 78 patients (27.5%), and axillary dissection was made in case of involvement, and 205 were treated with up-front lymph node axillary dissection (72.4%). Information on lymph nodes involvement was obtained from 234 patients and Table 3 discriminates the results. It is worth mentioning that about half of the patients received neoadjuvant chemotherapy, likely generating interference in these findings.

Reliable information about morphologic neoplasia subtype were obtained in 260 cases. Invasive carcinoma (N_0s) was observed in 243 patients (93.4%), infiltrative lobular was extremely rare, being found in three patients (1.5%), and other subtypes were seen in 14 patients (5.3%).

Tables 4 and 5 shows, respectively, histopathological and immunohistochemical characteristics found in percutaneous biopsies before neoadjuvant chemotherapy or in the surgical specimens of the 192 patients of whom it was possible to obtain detailed information to classify the tumors in molecular immunohistochemical subtypes, as formerly systematized (Table 6).

Information about complementary radiotherapy was retrieved in 246 patients, most of them (179) received the treatment.

As previously reported, 149 women (50.8%) underwent neoadjuvant chemotherapy, 104 women (35.4%) received adjuvant chemotherapy and palliative chemotherapy was prescribed (4.4%) in 13 cases. Hormonal adjuvant, on the other hand, was prescribed in 159 women (54.2%).

Oncological outcomes are exhibited in Figure 4, unfortunately standing out the elevated contingent of BC-related deaths.

DISCUSSION

Breast Cancer in UYW represents a new challenge for physicians, who should be updated on modern biological concepts and latest recommendations for management. A more aggressive tumor behavior has been reported, and ultra-young patients are facing it with family and professional problems, as unique quality of life issues, including loss of fertility, contraception, pregnancy, sexuality, cancer during pregnancy, body image and emotional distress, all of them make the decision to do the treatment complicated[7].

A new era of classification criteria has been inaugurated and the term ultra-young come into use. We believe that it is a watershed, but not without constraints, since we consider that defining ultra-young women as those who are 30 years of age or younger would be more useful in clinical practice, as likely they share distinct biological and social particularities. For example, Cancello et al. observed more aggressive cancer phenotypes in women under 30 years, with approximately 75% of poorly differentiated lesions, compared with 55% in the group aged 30–34 years[8].

Patients under 35 years are known to have a higher rate of locoregional and distant recurrences, entailing elevated mortality.

Several studies have focused on specifically BC in ultra-young patients, and almost all studies show a worse prognosis[8-14]. According to Han et al. the risk of death has increased by 5% with a 1-year age reduction for patients <35 years.[15]

The most striking result that came out from our data is that, although a relative short-interval follow-up, 25.4% of the patients evolved to death caused by BC. Xiong et al. at the MD Anderson Cancer Center, in a landmark paper of outcomes in patients diagnosed with BC before the age of 30 years, revealed 5-year overall survival rates of 87% for stage I disease; 60% for stage II, 42% for stage III, and 16% for stage IV[12]. The strength of these results is the impact of late diagnosis in patients portending a worse prognosis due to the tumor aggressiveness.

Hankey et al. highlighted that 0.6% of the BC cases were diagnosed in women aged < 30 years in the USA in the 1990s (around 1,200 new cases per year)[16]. In the recent years there has been an increase in the cases of BC in young women[17-19], leading to an excessive number of loss of lives.

Regrettably, young women tend to be diagnosed at advanced stages, reflecting decreased awareness, lack of screening and fast-growing tumors. Most young patients are diagnosed with a palpable mass. Sole 11.7% of our patients presented small T_1 lesions at the beginning of treatment. At this moment, for a reasonable conjecture, strategies of awareness, and clinical and self-examinations should be implemented in the phase of life when mammography is contraindicated. Obviously, at least for patients with family history of BC, tailored screening measures should be adopted, including echography and magnetic resonance imaging. Moreover, healthy lifestyle should be adopted for every young woman. Indeed, we found out that almost 40% of our patients presented disproportionate body max index.

Genetic testing in young woman with BC is strongly recommended regardless of the family history. It is noteworthy that the chance of carrying a germline BRCA 1/2 mutations is at least 10% in young patients with BC, which is enhanced with a positive

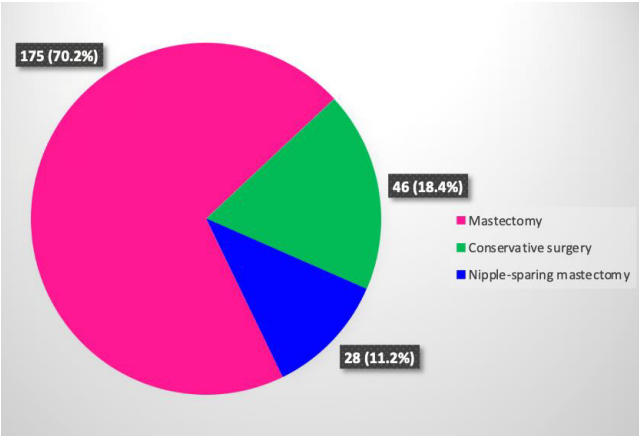


Figure 3. Types of local surgery performed in 249 patients.

Table 3. Frequency and extension of axillary lymph nodes infiltration in 234 patients with available data*.

	n	%
0	123	52.5
1–3	59	25.2
4–10	37	15.8
>10	**15**	**6.4**

*Without information: 59.

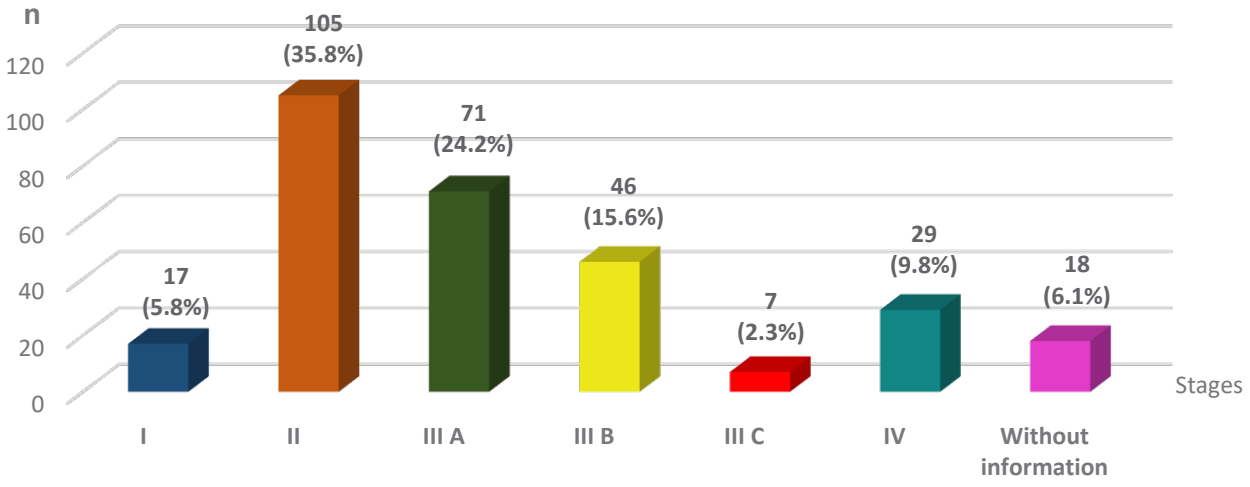


Figure 2. Clinical staging.

Table 4. Histopathological tumor characteristics.

	n	%
pT		
≤ 2 cm	84	28.6
> 2–≤ 5 cm	76	26.0
> 5 cm	52	17.8
complete tumor regression	25	8.5
without information	56	19.1
Histological grade		
I	9	3.0
II	139	47.5
III	109	37.2
without information	36	12.3
Nuclear grade		
1	4	1.4
2	92	31.3
3	165	56.3
without information	32	11.0
Vascular-lymphatic invasion		
Yes	72	24.5
No	155	53.0
without information	66	22.5
Multicentricity/multifocality		
Yes	31	10.5
No	219	74.8
without information	**43**	**14.6**

Table 5. Immunohistochemical characteristics.

	n	%
ER		
+	191	65.2
-	93	31.8
without information	9	3.0
PgR		
+	168	57.3
-	115	39.2
without information	10	3.4
HER 2		
+	68	23.2
-	203	69.2
without information	22	7.5
Ki-67		
≤ 20%	70	23.9
20%	180	61.4
without information	**43**	**14.7**

family history[20]. In cases of negative ER and/or high-grade tumors, the probability reaches 30%. Nevertheless, genetic testing is not available in the Brazilian public health system and its access is also limited in the private healthcare system[21]. Apart from BRCA 1 and 2 mutations, it is important to remember that BC is one of the most common cancer diagnosed among TP53 mutation carriers (Li-Fraumeni syndrome), and its peak of incidence is under 30 years[22]. In our casuistic view, only 32 cases underwent genetic testing, but predisposing hereditary mutations were identified in 12 patients (37.5%). Despite the small number of tests, a strong relationship between hereditary background and BC in UYW was observed.

Due to large tumor size and the immunohistochemical subtyping, more than half of the cases herein described was managed by neoadjuvant treatment (chemotherapy with HER2- targeted therapy when indicated), that entails that a downsizing and a possible complete response could establish a reliable surrogate marker for disease-free survival[23]. Almost 80% of our cases presented good clinical response (partial or total).

Ideally, the objective of local surgeries in BC therapy is the complete removal of the malignant cells. In practical terms, it is not totally possible, and there are three main options to be personalized for ipsilateral operation: quadrantectomy, mammary adenectomy and mastectomy, often followed by oncoplastic manoeuvres for partial or total reconstruction.

Many case series have found out that young patients have higher locoregional recurrence rates, which could result in decreased overall survival[24-26]. For Beadle et al.[24], the best locoregional control was achieved by patients with stage II disease who underwent mastectomy with radiation. Nevertheless, Cancello et al.[8] showed that the type of surgery performed did not influence

Table 6. Molecular breast cancer subtypes frequency*.

	n	%
Luminal A-like	32	16.7
Luminal B-like/HER 2-	69	35.9
Luminal B-like/HER 2+	29	15.1
HER 2 overexpressed	18	9.4
Basal like	**44**	**22.9**

*Without information: 101.

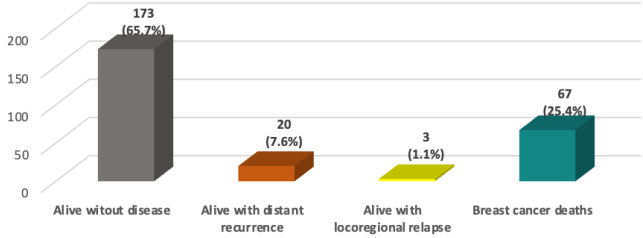


Figure 4. Oncological outcomes in 263 patients with appropriate follow-up information.

the rates of locoregional relapse. A metanalysis with more than 22,000 young patients (≤40 years) demonstrated that quadrantectomy and whole-breast radiotherapy provide overall survival control similar to mastectomy[27].

There is a concern if these conclusions are valid for UYW and for all molecular subtypes, but we are aware that the prognosis of young woman undergo breast-conserving surgeries have significantly improved compared with two decades ago, as seen by Botteri et al.[28]. Probably, this progress is owing to the policy that younger women do not have smaller volumes of breast tissue removed for cosmetic reasons (clear margins is mandatory), more accurate selection for breast conservation (tumor size, genetic testing and magnetic resonance imaging), and the anti-HER2 therapy implementation. Despite these facts, the most of the very young women continue to undergo any form of mastectomy worldwide. The arguments underpinning this conduct in very young patients are: higher risk of heritable abnormalities; more frequent local recurrences; greater life expectancy; higher mortality rate; and the paramount own patient's preference. In general, it seems to be a doctor-patient preference for mastectomy or mammary adenectomy.

The possibility of contralateral prophylactic adenectomy should be considered and accepted to individual practice. There is currently a widespread feeling in favor of bilateral mammary adenectomy in woman aged ≤ 35 years, reflecting a modern trend[29-31]. While its role is generally accepted in woman with mutated high-risk predisposing genes, Teoh et al. questioned the benefits in women who are just young at presentation or those who have a strong family history, but without demonstrable genetic mutation[32]. They suggest a multidisciplinary tailored approach to support individuals in a shared decision-making process.

Lymph nodal metastases are common in this age range. Ben Abdelkrim et al.[9], and Alipour et al.[33] observed involvement in 50% and 62% of women aged less than 25 years, whereas we noticed 47.5%. The extension of regional nodes excision should be elected case-by-case.

Our pathological findings were equivalent to those of other case series[9,10,34,35]. The most of our cases were represented by invasive carcinoma (no special type), and infiltrative lobular was very rare. Signals of neoplastic quiescence, such as histological grade I and nuclear grade I, were seen only in 3.5% and 1.5%. On the other hand, unfavorable immunohistochemical results were common. Negative ER status was observed in almost one third of the patients; negative PgR, in almost 40%; and Ki-67 > 20% was impressively common, being identified in more than 60% of the tumors. A Brazilian study, conducted by Bocchi et al., showed Ki-67 > 30% in 45.5% of the patients < 44 years and in 27.6% of women ≥ 44 years, and HER2 overexpression in 23.3% and 16.8%, respectively, in the same age rangers[34]. For us, HER2 positivity was detected in 25.0% of the cases with available information.

Breast Cancer is a heterogeneous disease, with several molecular intrinsic subtypes[36]. Basal-like (triple-negative) is more common in young patients, being more likely to be high-grade, and presenting also in this age a worse prognosis[37]. HER2-enriched subtypes, formerly showed poorer outcomes, currently, with HER2 directed therapy, are often associated to better recurrence-free survival. Our case series evidenced high frequency of luminal B and basal-like tumors, and low frequency of luminal A tumors.

An unfavorable landscape was observed in UYW with BC. We found high rate of advanced disease, with adverse pathological and molecular prognostic factors, a few genetic testing and high mortality. BC in young women is an important public health problem, more frequent in Latin American countries than in the USA, with dramatic consequences, as stated by Fidler et al.[38].

This research has raised many questions which need of further investigation. For changing the present-day scenario, we first need to educate the population, enhancing BC awareness and self-body attention since adolescence, and stimulating the adoption of a healthy life style[39]. In the study of Ogawa et al., about a breast self-examination in Japan, the average size of tumor was 2.5 cm at diagnosis for who performed it monthly, compared to 3.5 cm for those who did not[40]. A shift of this size is expected to result in a survival difference of at least 15%[39]. Self-examination practice in young women who did not undergo mammographic screening merits deeper consideration. On the other hand, appropriate and more efficient therapy is needed, taking into consideration modern strategies of precision therapy to improve outcomes. Tailored treatments offered by committed and skilled multidisciplinary teams are crucial to achieve the best holistic results when caring for the youngest women with BC.

AUTHORS' CONTRIBUTIONS

A.M.: Formal Analysis, Project administration, Software.
A.Y.: Formal Analysis, Project administration, Software.
C.F.: Investigation, Data curation.
E.P.: Investigation, Data curation.
F.A.: Investigation, Data curation.
G.T.: Investigation, Data curation.
H.V.: Investigation, Data curation.
K.C.: Investigation, Data curation.
I.Jr.: Investigation, Data curation.
J.B.: Investigation, Data curation.
J.F.: Investigation, Data curation.
L.G.: Investigation, Data curation.
M.P.: Investigation, Data curation.
R.V.: Investigation, Data curation.
T.D.: Investigation, Data curation.
V.Jr.: Investigation, Data curation.
A.B.: Conceptualization, Supervision, Writing — first draft.

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