original reports

Advanced Stage at Diagnosis and Worse Clinicopathologic Features in Young Women with Breast Cancer in Brazil: A Subanalysis of the AMAZONA III Study (GBECAM 0115)

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abstract

PURPOSE Breast cancer (BC) in young women is uncommon and tends to present with more aggressive characteristics. To better understand and characterize this scenario in Brazil through real-world data, we performed a subanalysis of AMAZONA III study (ClinicalTrials.gov identifier: NCT02663973).

METHODS The AMAZONA III study (GBECAM 0115) is a prospective registry that included 2,950 women newly diagnosed with invasive BC in Brazil from January 2016 until March 2018 at 22 sites. Valid data were obtained from 2,888 patients regarding age at diagnosis and complete baseline information. To compare epidemiologic and clinicopathological features at the time of diagnosis, patients with BC were divided into two groups according to age: $\leq$ 40 years and $>$ 40 years. Quantitative variables were described as means, and categorical variables were described as frequencies and percentages and compared using the Pearson's χ^2 test.

RESULTS Of 2,888 women diagnosed with BC, 486 (17%) were $\leq$ 40 years old. Young women had higher educational level, most were employed and a significant number were married ($P < .001$ for all associations). Younger patients were more symptomatic at BC diagnosis ($P < .001$), and they also presented more frequently with stage III, T3/T4, grade 3 tumors, HER-2–positive, luminal B, and triple-negative subtypes.

CONCLUSION Brazilian women younger than age 40 years have unfavorable clinicopathological features of BC at diagnosis, with more aggressive subtypes and advanced stage when compared with older women. These differences are not explained by socioeconomic or ethnic imbalances. The causes of a higher prevalence of BC among young women in Brazil deserve additional investigation.

INTRODUCTION:

Breast cancer (BC) is the most common type of cancer and the main cause of cancer-related death in women globally.[1] It has been estimated that there will be $>$ 1.97 million new diagnoses of BC in women worldwide in 2020, and it is expected that 622,000 women will die of this disease.[1,2]

Brazil is the largest country in Latin America and the fifth largest country in the world in terms of population.[3] In Brazil, the prevalence and incidence of BC has progressively increased over the last years.[4] BC is the main type of cancer among Brazilian women, according to the Instituto Nacional de Câncer. There were 59,700 new BC cases in 2018[4] and there were 16,724 BC-associated deaths in 2017,[5] with a higher mortality-to-incidence ratio when compared with developed countries.[6] Previous work from our group demonstrated that Brazilian women have a higher risk of being diagnosed with late-stage BC and at a younger age than women in high-income countries.[6-8] The 5-year overall survival (OS) rates previously reported for early-stage BC in Brazil were 96.84% for stage I and 94.16% for stage II disease. In locally advanced BC (stage III), the 5-year OS is 70.48%.[7] Triple-negative and HER-2–positive BC subtypes were associated with inferior outcomes in terms of OS in patients with stage II or III BC.[7]

According to international guidelines, BC in young women ($\leq$ 40 years) is an uncommon diagnosis, with

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CONTEXT SUMMARY

Key Objective

Previous data indicate a higher prevalence of breast cancer (BC) in young women in Latin America compared with high-income countries. The purpose of this study was to characterize BC in young women in the Brazilian population through the AMAZONA III study.

Knowledge Generated

Of the women included in this representative prospective cohort, 17% were diagnosed with BC at ≤ 40 years of age. Young patients presented unfavorable clinicopathological features of BC at diagnosis, with more aggressive subtypes and advanced stage when compared with older women.

Relevance

We evaluated BC in young women at 22 Brazilian sites, including all regions of the country (public and private practice). The causes of a higher prevalence of BC among young women in Brazil deserves additional investigation since this could generate actions and public policies to reduce advanced-stage diagnosis of BC in this population.

a 0.40% to 0.45% cumulative risk of developing BC at the age of 40 years, which represents < 7% of all BC cases diagnosed in developed countries.[9] In Latin American countries, BC is diagnosed at an earlier age when compared with patients from high-income countries, with a higher proportion of BC occurring among young women. Women younger than 40 years represent approximately 20% of the new cases of BC and 14% of the deaths resulting from BC.[10,11]

In Brazil, the median age at BC diagnosis was reported to be 53 to 55 years[6-8]; however, the characteristics and prognosis of BC in young women in the Brazilian population are poorly described.[12-15] Single-institution case series of young women with BC in Brazil have reported more advanced disease stages at the of time of diagnosis, with a higher prevalence of metastatic disease.[12,16,17]

AMAZONA III (ClinicalTrials.gov identifier: NCT02669373) is a prospective cohort study that includes patients with newly diagnosed BC from January 2016 to March 2018, involving 22 Brazilian sites and representing all five regions of the country. The main objective of this subanalysis was to characterize BC in young women in this population.

METHODS

This is a subanalysis of AMAZONA III study (GBECAM 0115),[8] a prospective registry that included 2,950 women newly diagnosed with invasive BC in Brazil during the period of January 2016 to March 2018 within 22 sites, including patients covered by public and private health systems. Of these women, 2,888 had valid data regarding age at diagnosis and complete baseline information. To compare epidemiologic and clinicopathological features at the time of diagnosis of BC, patients were divided into two groups according to age: ≤ 40 years (group 1) and > 40 years (group 2). Ethnicity was defined according to the Brazilian Institute of Geography and Statistics and race of the patients was classified as white, black, brown, indigenous, and Asian.[18]

BC subtypes were classified by immunohistochemistry for estrogen receptor (ER) status, progesterone receptor (PgR) status, and HER-2 status. All tumor tissue analysis and grading were performed in local laboratories. We used data from pathology reports to classify BC into five subtypes: luminal A (grade 1-2, ER and PgR positive, HER2 negative), luminal B (grade 3, ER and/or PgR positive, HER2 negative), luminal HER2 positive, nonluminal HER2 positive and triple negative (ER and PgR negative, HER2 negative). There was no central pathological review.

Quantitative variables were described as means, and categorical variables were described as frequencies and percentages and compared using the Pearson χ^2 test and adjusted residuals, when necessary. $P < .05$ was considered statistically significant. All analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC).

The AMAZONA III study was approved by the institutional review boards of each participating center and the national ethics committee.

RESULTS

Of 2,888 women diagnosed with invasive BC, we identified 486 (17%) who were ≤ 40 years. The baseline characteristics of younger and older patients are described and compared in Tables 1 and 2.

Women aged ≤ 40 years were mostly of white ethnicity (54.2%), no statistical differences in health insurance coverage between the two age groups were found, and the majority of patients in both groups were insured by the public health system. The mean body mass index (calculated as kilograms divided by square meters) was 24.4 for patients ≤ 40 years and 24.9 for patients older than

40 years, with no statistical differences between the two groups. Also, there were no statistical differences in personal income, performance status, and family history of cancer between the two groups.

Women aged ≤ 40 years had significantly higher educational levels ($P < .001$), with group 1 versus group 2 data as follows: rates of illiteracy, 0.4% versus 5.6%; fewer than 8 years of school, 14.4% versus 30.4%; 9 to 11 years of

TABLE 1. Demographic and Socioeconomic Features by Age Groups of Brazilian Women Included in the AMAZONA III Study

Characteristic	Age at Diagnosis (years) ≤ 40	> 40	*P*
Race			
White	254 (54.2)	1,379 (58.7)	.051
Black	24 (5.1)	150 (6.4)	
Brown	183 (39.0)	803 (34.2)	
Indigenous	1 (0.2)	3 (0.1)	
Asian	7 (1.5)	14 (0.6)	
Health insurance			
Public	299 (62.0)	1,538 (64.7)	.270
Private	183 (38.0)	840 (35.3)	
Education			
Illiterate	2 (0.4)	**121 (5.6)**	< .001
< 8 years of school	64 (14.4)	**663 (30.4)**	
Completed 8 years of school	63 (14.2)	322 (14.8)	
Between 9 and 11 years of school	**168 (37.7)**	497 (22.8)	
University degree	**148 (33.3)**	574 (26.4)	
Personal income, US$			
None	82 (23.8)	350 (19.9)	.236
Less than 1 minimum wage (< 233)	38 (11.0)	207 (11.7)	
1 to 2 minimum wages (880 to 467)	134 (38.8)	788 (44.7)	
2 to 3 minimum wages (467 to 701)	37 (10.7)	153 (8.7)	
3 to 5 minimum wages (701 to 1,167)	34 (9.9)	133 (7.5)	
5 to 10 minimum wages (1,167 to 2,338)	13 (3.8)	91 (5.2)	
10 to 20 minimum wages (2,338 to 4,670)	5 (1.4)	26 (1.5)	
> 20 minimum wages (> 4,670)	2 (0.6)	15 (0.9)	
Formal working activity			
Yes	**272 (57.3)**	924 (39.8)	< .001
No	203 (42.7)	**1,398 (60.2)**	
Currently married or lives in common-law marriage			
Yes	**332 (69.2)**	1,315 (56.5)	< .001
No	148 (30.8)	**1,014 (43.5)**	
Smoking history			
Never	**352 (80.7)**	1,448 (65.8)	< .001
Former	52 (11.9)	**547 (24.9)**	
Current	32 (7.3)	205 (9.3)	
Drinks alcoholic beverages			
Yes	**127 (30.4)**	479 (22.5)	< .001
No	291 (69.6)	**1,648 (77.5)**	
BMI, mean, kg/m^2 (No.)	24.4 (486)	24.9 (2,400)	—

NOTE. Data presented as No. (%) unless otherwise indicated. Data reported in bold refers to $P < 0.05$.
Abbreviation: BMI, body mass index; US$, US dollars.

TABLE 2. Reproductive Characteristics by Age Groups of Brazilian Women Included in the AMAZONA III Study

Characteristic	Age at Diagnosis ≤ 40	Age at Diagnosis > 40	*P*
Mean age at menopause	43.5 (12)	47.8 (1,428)	NA
Mean age at menarche	12.6 (399)	13.1 (2,045)	NA
Reproductive status			
Premenopausal	**339 (76.5)**	415 (18.4)	< .001
Perimenopause	**87 (19.6)**	251 (11.1)	
Postmenopausal	17 (3.9)	**1,588 (70.5)**	
Ever used oral contraceptives			
Yes	**346 (81.8)**	1,314 (64.9)	< .001
No	77 (18.2)	**711 (35.1)**	
History of pregnancy			
Yes	383 (81.3)	**1,973 (86.5)**	.004
No	**88 (18.7)**	309 (13.5)	
Breastfeeding			
Yes	300 (87.5)	1,537 (87.0)	.809
No	43 (12.5)	230 (13.0)	
Diagnosed with breast cancer during a pregnancy			
Yes	**12 (3.2)**	9 (0.5)	< .001
No	364 (96.8)	**1,881 (99.5)**	

NOTE. Data presented as No. (%) unless otherwise indicated. Data reported in bold refers to $P < 0.05$.
Abbreviation: NA, not applicable.

school, 37.7% versus 22.8%; and university degree, 33% versus 26.4%. Also, younger women (group 1) more frequently were employed than were older patients (57.3% *v* 39.8%; $P < .001$); and more frequently were married (69.2% *v* 56.5%; $P < .001$). In relation to social habits, women in group 1 smoked less (19.2% *v* 34.2%; $P < .001$) and consumed more alcohol than women in group 2 (30.4% *v* 22.5%; $P < .001$).

There were significant differences regarding previous use of contraceptives in (81.8% v 35.1%; $P < .001$) and nulliparity (18.7% v 13.5%; $P = 0.004$) in younger and older patients. Twelve women ≤ 40 years (3.2%) had a diagnosis of BC during pregnancy, compared with nine patients (0.5%) in the older group ($P < .001$).

The mode how BC was detected differed significantly between the two groups: BC in younger women was more often detected symptomatically than in older women (73.4% *v* 64.5%; $P < .001$; Table 3). Initial tumor size was also significantly larger among younger women ($P < .001$). The prevalence of T1, T2, T3, and T4 tumors at the time of diagnosis for women in group 1 compared with those in group 2 were, respectively: 27.1% versus 36.9%, 33.6% versus 37.6%, 24.1% versus 13.9%, and 15.2% versus 11.6% (Fig 1C; Table 3). There was no statically significant difference in initial positive lymph node status between the two groups (44.1% and 39%, for group 1 and group 2, respectively; $P = .152$; Data Supplement).

Stage I disease at diagnosis occurred in 19.2% of patients aged ≤ 40 years and 27.8% in women > 40 years old ($P < .001$). In contrast, stage III disease was found in 36.8% of younger women and 25.1% of older women ($P < .001$; Fig 1A; Data Supplement). Women in group 1 had more grade 3 tumors (43.1% *v.* 30.1%; $P < .001$; Fig 1B; Data Supplement). Younger women more frequently underwent mastectomy than did older women (54.7% *v* 45.7%, $P < .001$; Data Supplement), and this difference remained statistically significant when adjusting for initial staging (Mantel-Haenszel method).

The distribution of BC subtypes, as determined by immunohistochemistry, was distinct among young and older women (Fig 2; Data Supplement). Younger patients had a higher proportion of luminal B HER2-negative (15.8% *v* 11.4%; $P < .001$), luminal B HER2-positive (22.8% *v* 16%; $P < .001$), and triple-negative (23% *v* 14.1%; $P < .001$) tumors at diagnosis (Fig 2; Data Supplement).

DISCUSSION

BC incidence is growing in Latin America and it is considered an important health burden.[10,11,19] There is limited information about the diagnosis, treatment patterns, and outcomes of young women with BC in Latin American countries. To our knowledge, AMAZONA III is the first prospective, multicentric registry of BC in Brazil; its objective is to better describe the current scenario of BC care in the largest and most populated country in Latin

TABLE 3. Patients at Baseline: Tumor Characteristics and Type of Surgery by Age Groups of Brazilian Women Included in the AMAZONA III Study

Characteristic	Age at Diagnosis (years) ≤ 40	> 40	*P*
ECOG performance stage			
0	285 (81.0)	1,358 (74.7)	.080
1	63 (17.9)	405 (22.3)	
2	3 (0.8)	45 (2.4)	
3	1 (0.3)	7 (0.4)	
4	0 (0.0)	3 (0.2)	
Diagnostic			
Screening-detected	120 (26.6)	**807 (35.5)**	.003
Symptomatic	**331 (73.4)**	1,466 (64.5)	
TNM			
T1	114 (27.1)	**749 (36.9)**	< .001
T2	141 (33.6)	764 (37.6)	
T3	**101 (24.1)**	282 (13.9)	
T4	**64 (15.2)**	235 (11.6)	
Stage at diagnosis			
I	76 (19.2)	**541 (27.8)**	< .001
II	156 (39.4)	816 (41.9)	
III	**146 (36.8)**	489 (25.1)	
IV	18 (4.6)	101 (5.2)	
Histology			
Ductal	**392 (94.7)**	1,793 (87.6)	< .001
Lobular	15 (3.6)	**171 (8.3)**	
Mucinous	0 (0.0)	**30 (1.5)**	
Papillary	2 (0.5)	20 (1.0)	
Medullary	3 (0.7)	4 (0.2)	
Mixed	2 (0.5)	29 (1.4)	
KI-67, mean (No.)	44.7 (355)	30.3 (1,984)	—
Tumor grade			
1	46 (10.7)	**381 (17.9)**	< .001
2	198 (46.2)	**1,110 (52.0)**	
3	**185 (43.1)**	641 (30.1)	
HER-2 status			
Positive	**107 (29.6)**	438 (22.3)	.003
Negative	255 (70.4)	**1,526 (77.7)**	
Hormone receptor			
Positive	273 (71.1)	**1,646 (79.4)**	.001
Negative	**111 (28.9)**	428 (20.6)	
Breast cancer subtype			
Luminal A	106 (30.6)	**957 (51.3)**	< .001
Luminal B, HER-2 negative	**55 (15.8)**	212 (11.4)	
Luminal B, HER-2 positive	**79 (22.8)**	298 (16.0)	
HER-2 positive	27 (7.8)	135 (7.2)	
Triple negative	**80 (23.0)**	264 (14.1)	
Lymph node			
Positive	94 (44.1)	541 (39.0)	.152
Negative	119 (55.9)	847 (61.0)	
Surgery			
Breast-conserving surgery	82 (38.7)	**708 (51.3)**	
Mastectomy	**116 (54.7)**	630 (45.7)	< .001
Adenomastectomy	**8 (3.8)**	21 (1.5)	
Skin-sparing mastectomy	6 (2.8)	20 (1.5)	

NOTE. Data presented as No. (%) unless otherwise indicated. Data reported in bold refers to $P < 0.05$.

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

America. The increased proportion of BC among young women is of utmost importance, since they tend to be diagnosed in later stages and usually bear more aggressive BC subtypes that, at long run, can negatively impact their survival.[9,11,20]

We have shown that young women diagnosed with BC are more frequently employed and actively working, have a higher educational level, and most are married, highlighting the socioeconomic impact BC may have when afflicting young women. It is well known that BC and its treatment can largely affect the economy of a community, because some BC survivors experience reduced work ability.[21-23] Recently, Landeiro et al[24] reported return to work (RTW) rates of 30.3% and 60.4% at 12 and 24 months, respectively, after BC diagnosis in a cohort of 125 employed women from a single institution in Brazil. These rates are lower when compared with affected women in high-income countries. Because the cohort of young women in the AMAZONA III study represents an important productive working force from several regions of the country, additional follow-up of the RTW rates and the factors associated with the RTW decision in this population is paramount.

BC in young women is considered a somewhat rare situation, accounting for 5% to 7% of BC cases in developed countries.[9,20,25,26] In our cohort, women aged ≤ 40 years represented 17% of patients, a number significantly higher than the rates reported in the literature. In our previous work, we have reported that the median age at

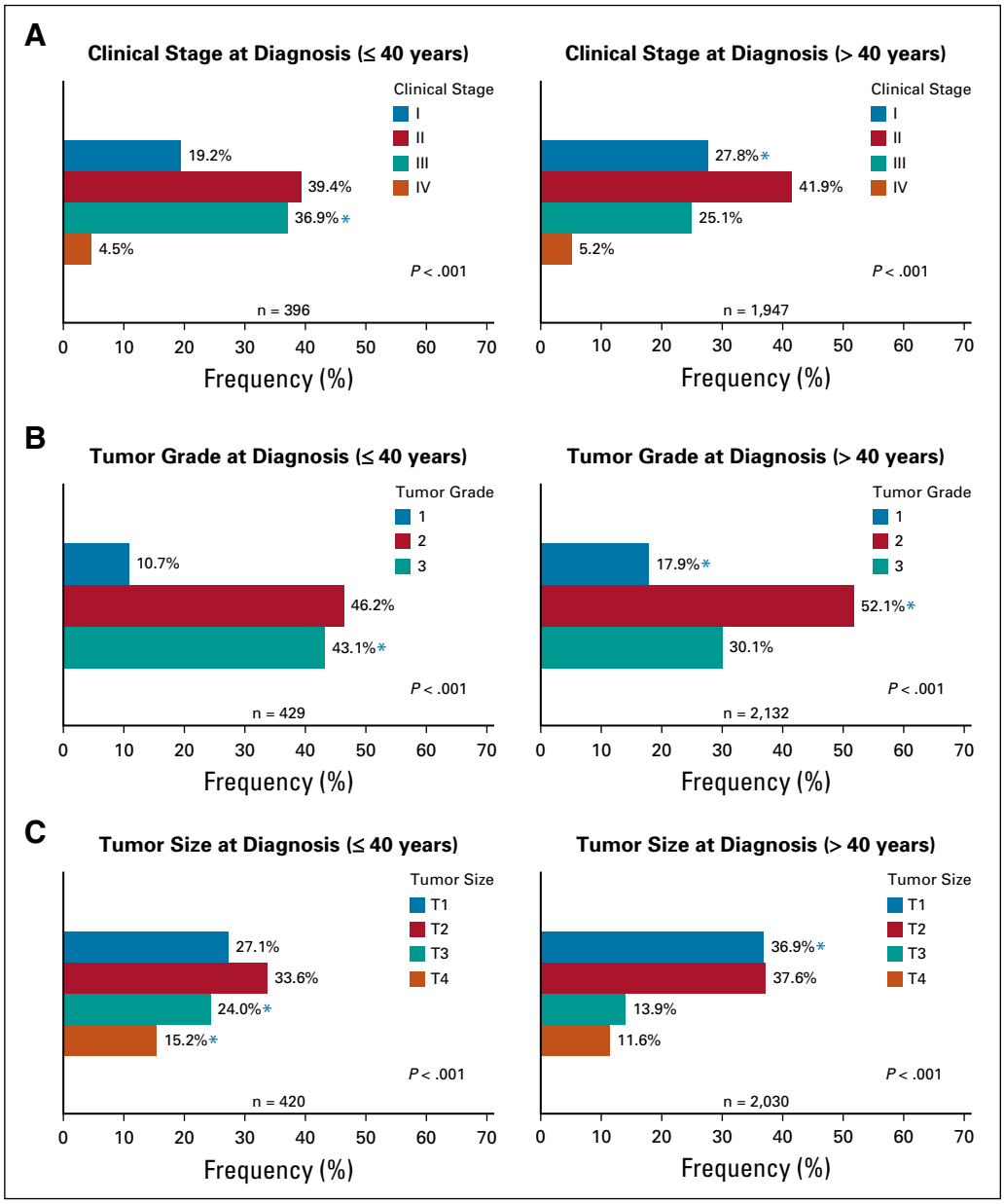

FIG 1. Bar graphs of (A) clinical stage, (B) tumor grade, and (C) tumor size at diagnosis by age groups of Brazilian women included in the AMAZONA III study. (*) $P < .001$.

diagnosis of BC in Brazil is 53 to 55 years,[6-8] whereas in high-income countries it is approximately 64 years.[1,27] Also, a review of the literature undertaken by Villarreal-Garza et al[11] reported a higher BC incidence and mortality rate in young women in Latin America when compared with those in developed countries (20% *v.* 12% and 14% *v.* 7%, respectively).

Another study, led by Franco-Marina et al,[19] confirmed the high incidence of BC in young women in Latin America, estimating that one in every five cases of BC is diagnosed in women younger than 45 years, almost double of the frequency observed in developed countries like the United States and Canada. This high incidence of cancer in young women remained statistically significant even after adjusting for the percentage of young women in Latin and North American populations. All these studies suggest a high prevalence of young patients with BC in Latin America, and the causes should be better investigated.

Regarding the potential modifiable risk factors for BC to develop in young women, we recognized in our cohort a significantly higher prevalence of alcohol consumption among young women. Recently, an effort has been made by public health experts and medical societies to emphasize that reducing alcohol consumption is a vital, and largely

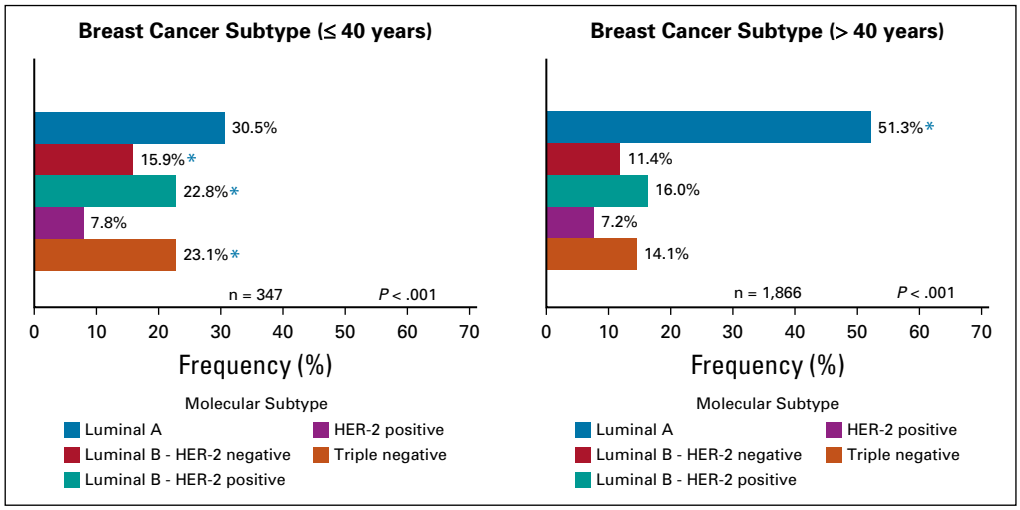

FIG 2. Breast cancer subtype by age groups of Brazilian women included in the AMAZONA III study. (*) $P < .001$.

neglected, cancer prevention strategy.[28-30] Greater attention to this matter should be given to effectively communicate the role of alcohol as a risk factor for BC and to better investigate its impact on the prevalence of BC in Latin America.

Women younger than 40 years are usually diagnosed with more aggressive disease and have worse prognosis (based on more advanced clinical stage and worse histopathological characteristics, with a high prevalence of high-grade tumors), and they have a higher risk of recurrence when compared with older women.[11,16,19,31] This is especially observed in luminal BC subtypes, for which young women have inferior outcomes compared with older women with the same initial tumor characteristics.[32] For these reasons, younger women sometimes receive more aggressive treatment than do older women.[17,20,33]

Histopathological and immunohistochemical characteristics presented in our study also corroborate the data from the literature,[11,17,33,34] with a larger number of locally advanced lesions (T3, T4) and poorly differentiated tumors among young women. Although the luminal subtype is still the most frequent among young women, we reported significant differences in the frequency of the luminal subtype between older and younger women, with more luminal B type (15.8% *v* 11.4%, group 1 *v* group 2, respectively) or luminal B/HER-2 positive (22.8% *v* 16%, group 1 *v* group 2, respectively) in the latter group. In comparison with series of young women from the United States[35,36] and Europe,[37] our population had a greater proportion of triple-negative subtype BC (23% *v* 14.1%). In a previous retrospective, single-center cohort report (N = 738), a lower proportion of ER-positive tumors were reported in younger women as compared with older women (33.5% *v* 42.8%), and higher proportion of triple-negative BC (10% *v* 6.4%) also was reported among young women (n = 376) as compared with older women.[34]

In our study, we observed striking differences regarding stage distribution between the two age groups. Stage I disease was more frequent among older women than younger women (27.8% *v* 19.2%, respectively), whereas younger women had significantly more stage III disease (36.9%) than older women (25.1%). Metastatic BC de novo was present in 4.5% of the women ≤ 40 years old and 5.2% of older women. Indeed, 41.4% of the young women in our study were initially diagnosed with stage III or IV BC. Our data are comparable to that of another large cohort of Latin American women, from Mexico, in which 15% of women with BC were ≤ 40 years old.[33] Also, young Mexican women had more aggressive disease at presentation, with tumors of higher grade and a larger proportion of luminal B and triple-negative cancers.[33] Similar to our data, fewer stage I tumors were found in young women and more stage III and IV disease than in their older counterparts.[33]

Another important issue to highlight is that in Brazil, there is a gap regarding the access to optimal therapy between patients in the public and private health systems, and this influences patient outcomes.[38,39] This disparity will also play an important role in young women diagnosed with advanced disease (stage III and IV), because access to optimal HER2 therapy, ovarian suppression, and CDK 4/6 inhibitors might be restricted to patients in the private health system.

Finally, BC was detected by screening in only 26% of patients ≤ 40 years old, as compared with 35.5% of older women. This finding is not unexpected, because the current national BC screening guideline recommends mammography starting at age 50 years.[40] However, they call attention to the low proportion of older women whose diagnosis is established through screening programs in Brazil. Better educational strategies, access to and compliance with screening programs are urgently needed in

Brazil. Organized screening of young, healthy women has been controversial, regarded as inefficient and even deleterious by some experts, and has not been recommended widely.[41] Individualized screening, targeting only some high-risk young women, may be beneficial, although no randomized trial has shown an impact on BC mortality.[42] All recommendations for this younger age group are based on experts' opinions and do not take into account the higher proportion of BC in young women found in our study and in other Latin American cohorts. In these populations, earlier screening should be a subject of additional research.

This study was of a large cohort of young women with BC in Brazil and was a prospective evaluation including patients from all regions of the country, from the private and the public health systems. Longer follow-up of this population will reveal important information regarding treatment patterns and outcomes. Our study has some limitations, especially regarding BC subtypes, because we did not perform central revision of the immunohistochemistry data.

At this time, we are not aware of any specific clinical or educational programs focused on this population in Brazil. Particular aspects of the care for young women with BC have been studied and reported in the literature. It would be interesting if at least the major reference centers of cancer care in Brazil could implement specific units for the care of young women with BC, addressing the particular needs of this growing population (eg, fertility preservation, precise psychosocial interventions, genetic evaluation, aspects related to corporal image and reconstructive surgery support, challenges related to a longer survival and follow-up period). Successful examples of this concept include centers in the United States (Young and Strong Program for Young Women with Breast Cancer),[43] Canada (Breast Cancer Program for Young Women),[44] and Mexico (Joven and Fuerte: Program for Young Women with Breast Cancer in Mexico).[45] A call to action from health policy planners, medical providers, researchers, patients with BC, their families, and the community in general is encouraged for better care of this emergent challenge.

In conclusion, in Brazil, a higher proportion of patients with BC are diagnosed at ≤ 40 years of age when compared with women in developed countries. Younger patients have unfavorable clinicopathological features, with advanced stages and more aggressive BC subtypes at diagnosis, when compared with older patients. The causes of a high prevalence of BC in young women should be investigated further, as should potential preventive and screening strategies.

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SUPPORT

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