Retrospective analysis of breast cancer prognosis among young and older women in a Brazilian cohort of 738 patients, 1985-2002

FABIANA DE LIMA VAZQUEZ[1], THIAGO BUOSI SILVA[1],
RENÉ ALOÍSIO DA COSTA VIEIRA[1,2], ALLINI MAFRA DA COSTA[1], CRISTOVAM SCAPULATEMPO[1],
JOSÉ HUMBERTO TAVARES GUERREIRO FREGNANI[1], EDMUNDO CARVALHO MAUAD[1],
ADHEMAR LONGATTO[3-5] and KARI JUHANI SYRJÄNEN[1,6]

[1]Department of Prevention, Barretos Cancer Hospital, Pio XII Foundation, Barretos, São Paulo 14784-400;
[2]Department of Prevention, Faculty of Public Health, University of São Paulo, São Paulo 01246-904; [3]Laboratory of Medical Investigation 14, Department of Pathology, Medical School of São Paulo University, São Paulo 01246-903, Brazil;
[4]3B's-PT Government Associate Laboratory, Life and Health Sciences Research Institute (ICVS), School of Health Sciences, University of Minho, Guimarães, 4710-057 Braga, Portugal; [5]Molecular Oncology Research Center, Barretos Cancer Hospital, Pio XII Foundation, Barretos, São Paulo 14784-400, Brazil;
[6]Department of Clinical Research, Biohit HealthCare Ltd., 00880 Helsinki, Finland

Abstract. Invasive breast cancer (BC) is infrequent among women aged ≤40 years, however, the disease outlook in these younger patients is generally worse than among older women. The present study aimed to compare socio-demographic, clinical and pathological characteristics, and their association with long-term survival, between two random cohorts of young (≤40 years) and older (50-69 years) Brazilian patients with BC. The cohort comprised of 738 randomly selected women who were diagnosed with BC at Barretos Cancer Hospital, Pio XII Foundation (Barretos, Brazil) between January 1985 and December 2002; the patients included young women (n=376) and older women (n=362). The current analysis suggested that BC in young women is associated with numerous pathological features of aggressiveness. Second cancer and bilateral BC were independent predictors of a poor outcome in the younger group. Furthermore, C-erB-2 was positively correlated with poor outcome in the older group, whereas estrogen receptor status and TNM stage were associated with disease prognosis in both groups. The overall survival rates of the two age groups were similar except when analyzed according the treatment period (1997-2002). Although patients aged ≤40 years harbored tumors with more aggressive clinicopathological characteristics, these characteristics were not independent predictors of overall survival. The present study indicates that medical advances associated with prevention of breast cancer may improve screening programs, which may therefore increase early diagnosis and subsequently lower mortality rates.

Introduction

Breast cancer (BC) is the most frequent malignancy among women worldwide, with an estimated 14 million new cases and 8 million mortalities in 2012, which is projected to rise by at least 70% by 2030 (1). It is most common in women aged >50 years (>75% of all cases), in contrast to those aged ≤40 years, who represent only 5-25% of all BC cases. Notably, BC in these younger women is generally considered to bear a more unfavorable disease outcome, with a substantially shorter overall survival as compared with older women (2,3).

Indeed, several multivariate analyses have shown that young age is an independent predictor of unfavorable disease outcome (4), and it has been suggested to be associated with a more aggressive tumor biology that potentially reduces the survival expectancy (5,6). This increased aggressiveness of BC among younger women has been attributed to mutations in the BC susceptibility proteins, breast cancer (BRCA)1 and 2 (5,6). In addition, BC in younger women is often diagnosed at more advanced stages than in older women. In addition, BC tumors in younger women are: i) More frequently negative for estrogen receptor (ER); ii) show extensive lymphovascular invasion (LVI); iii) exhibit increased cell proliferation (assessed by the Ki-67 marker); and v) demonstrate overexpression of p53 oncogene (6).

Molecular profiling has suggested that race and ethnicity may be other important factors associated with the development of BC, particularly with its poor prognosis among

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Correspondence to: Dr Fabiana de Lima Vazquez, Department of Prevention, Barretos Cancer Hospital, Pio XII Foundation, 1331 Rua Antenor Duarte Villela, Barretos, São Paulo 14784-400, Brazil
E-mail: fabilivazquez@gmail.com

Table I. Demographics of patients with breast cancer stratified by age group.

Variable	≤40 years (n=376)		50-69 years (n=362)		P-value
	n	%	n	%	
Period of treatment					
1985-1990	59	15.7	65	18.0	0.078
1991-1996	108	28.7	78	21.5	
1997-2002	208	55.3	217	59.9	
N/A	1	0.3	2	0.6	
Schooling, years					
0-8	210	55.9	279	77.1	<0.001
9-11	106	28.2	32	8.8	
≥12	57	15.2	34	9.4	
N/A	3	0.8	17	4.7	
Overweight					
No	284	75.5	219	60.5	<0.001
Yes	44	11.7	90	24.9	
N/A	48	12.8	53	14.6	
Ethnicity					
White	297	79.0	288	79.6	0.360
Non-white	76	20.2	70	19.3	
N/A	3	0.8	4	1.1	
Marital status					
Married	254	67.6	214	59.1	<0.001
Single/divorced	110	29.3	134	37.0	
N/A	12	3.2	14	3.9	

N/A, not available.

younger women, with those of African American origin being at the highest risk of increased mortality (7). All of the aforementioned evidence indicates that BC in younger women bears a worse disease outcome compared with older women. This difference is only partially explained by the fact that mammography screening and clinical breast examinations are targeted to women aged >40 years (8).

In Brazil, the incidence and mortality rates of BC are relatively high (9,10). Compared with North America, where the incidence of BC among younger women has plateaued (11), Brazil continues to present with relatively high incidence rates among women aged 30-39 years (12). Considering the increased BC mortality among young women of African origin (7), it is of note that Brazil is a country with a relatively high population of African descent, increasing the importance of assessing the characteristics of BC among young women in this country.

To the best of our knowledge, the present study analyzed the largest cohort of patients with BC aged ≤40 years (n=376) at a single institution to date, by comparing an extensive set of clinicopathological characteristics and other variables with a similarly sized cohort of BC patients aged 50-69 years (n=362). The aim of the present study was to determine whether disease outcome in younger women is poorer than that in the older women and, if supported, to estimate the significant determinants of this differential outcome in multivariate models.

Patients and methods

Study design. The present retrospective analytical study was based on the hospital records of women with invasive BC (ICD-10: C50) who were admitted to Barretos Cancer Hospital, Pio XII Foundation (Barretos, Brazil) with no previous treatment between January 1985 and December 2002. During this 17-year period, a total of 4,134 women were examined. Of those, 1,735 women were eligible and initially selected into the present study, according to the inclusion and exclusion criteria. The patients were divided into two groups: A younger group (≤40 years of age) and an older group (50-69 years of age). The original cohort included 469 patients aged ≤40 years and 1,266 patients aged 50-69 years. From this original cohort, 400 women were selected from each group using a random sample generator (SPSS software, version 20.0.0.1; IBM SPSS, Armonk, NY, USA). Clinical treatment and follow-up data were obtained from the patients' medical records. Patients without follow-up information for >12 months were contacted by telephone to update this information.

Inclusion and exclusion criteria. Patients that had undergone cancer treatment prior to admission (1,290 patients), those aged 41-49 years of age (666 patients) and those aged ≥70 years (443 patients) were excluded from the cohort. Finally, 24 women were excluded from the ≤40 years age group and 38 women were

Table II. Main clinical features of patients with breast cancer stratified by age group.

Clinical feature	≤40 years (n=376)		50-69 years (n=362)		P-value
	n	%	n	%	
Palpable nodules					0.761
No	19	5.1	20	5.5	
Yes	356	94.7	338	93.4	
N/A	1	0.3	4	1.1	
Multicentric cancer					0.158
No	358	95.2	344	95.0	
Yes	11	2.9	5	1.4	
N/A	7	1.9	12	3.3	
Multifocal cancer					0.017
No	346	92.9	341	94.2	
Yes	23	6.1	9	2.5	
N/A	1	0.3	12	3.3	
Second cancer					0.327
No	371	98.7	352	97.2	
Yes	4	1.1	7	1.9	
N/A	8	2.1	3	0.8	
Bilateral breast cancer					0.037
No	331	88.0	336	92.8	
Yes	37	9.8	21	5.8	
N/A	8	2.1	5	1.4	
Familial history					0.611
No	211	56.1	181	50.0	
Yes	49	13.0	36	9.9	
Other malignancies	74	19.7	53	14.6	
N/A	42	11.2	92	25.4	
Menopause at diagnosis					<0.001
No	363	96.5	38	10.5	
Yes	7	1.9	226	62.4	
N/A	6	1.6	98	27.1	
Comorbidities					<0.001
Absent	256	68.1	145	40.1	
1 or 2 diseases	114	30.8	175	48.3	
N/A	6	1.6	42	11.6	

N/A, not available.

excluded from the 50-69 years age group due to a lack of clinical or treatment information, or due to a non-invasive disease.

Sample size estimation. To calculate the sample size, the following assumptions were made: 30-40% mortality (13,14), ±7.5% estimation error, 5% type I error and 90% power. These conditions indicated that between 360 and 400 patients in both groups would be required for an adequately powered study. Accordingly, the final analysis included 376 women aged ≤40 years and 362 women aged 50-69 years.

Definitions of BC characteristics. BC was defined as multi-centric or multi-focal disease. Multi-centric was defined as a disease present in >1 quadrant of the breast, whereas multi-focal disease was defined as a second tumor located at a distance of at least 5 cm from the primary tumor. The tumors were also classified as synchronous or metachronous. The criteria recommended by the National Cancer Institute were used to assess comorbidities (15).

Immunohistochemistry (IHC) was routinely performed using paraffin sections of the tumors to classify their patterns of ER, progesterone receptor (PR) and C-erB-2 oncoprotein expression. Tumors that were negative for all of these markers were considered 'triple negative' for IHC expression. Assessment of positive reactions was performed according to the guidelines in common use for ER and PR, and the scoring system proposed by Allred *et al* was used to determine the proportion of stained nuclei and the staining intensity (16).

Table III. Histological features of patients with breast cancer stratified by age group.

Histological feature	≤40 years (n=376)		50-69 years (n=362)		P-value
	n	%	n	%	
Histological diagnosis					
Ductal carcinoma	301	80.1	289	79.8	0.867
Lobular carcinoma	59	15.7	54	14.9	
Miscellaneous	15	4.0	17	4.7	
N/A	1	0.3	2	0.6	
Tumor size (mastectomy), cm					
≤2	54	14.4	74	20.4	0.185
>2	187	49.7	195	53.9	
N/A	135	35.9	93	25.7	
T[a]					
TI/TII	196	52.1	210	58.0	0.354
TIII/TIV	84	22.3	106	29.3	
N/A	94	25.0	46	12.7	
N[a]					
Positive	147	39.1	156	43.1	0.183
Negative	197	52.4	170	47.0	
N/A	32	8.5	36	9.9	
M[a]					
No	311	82.7	311	85.9	0.740
Yes	38	10.1	35	9.7	
N/A	27	7.2	16	4.4	
Differentiation degree					
I/II	190	50.5	201	55.5	0.035
III	87	23.1	60	16.6	
N/A	99	26.3	101	27.9	
Perineural invasion					
No	241	64.1	84	23.2	
Yes	18	4.8	13	3.6	0.055
N/A	117	31.1	276	76.8	
Blood vessel invasion					
No	248	66.0	79	21.8	
Yes	4	1.1	7	1.9	0.007
N/A	124	33.0	276	76.2	
Lymphovascular invasion					
No	189	50.3	53	14.6	<0.001
Yes	80	21.3	81	22.4	
N/A	107	28.5	228	63.0	
Lymph node invasion					
N1 (1-3)	78	20.7	67	18.5	0.535
N2 (4-9)	55	14.6	49	13.5	
N3 (≥10)	42	11.2	35	9.7	
N/A	201	53.5	211	58.3	
Estrogen receptor					
Negative	89	23.7	67	18.5	0.014
Positive	126	33.5	155	42.8	
N/A	161	42.8	140	38.7	
Progesterone receptor					
Negative	90	23.9	85	23.5	0.468
Positive	124	33.0	135	37.3	
N/A	162	43.1	142	39.2	

Table III. Continued.

Histological feature	≤40 years (n=376)		50-69 years (n=362)		P-value
	n	%	n	%	
C-erB-2 oncoprotein					
Negative	117	31.3	125	34.5	0.032
Positive	58	15.4	53	14.6	
N/A	201	53.5	184	50.8	
Triple negative					
No	136	36.2	155	42.8	0.027
Yes	38	10.1	23	6.4	
N/A	202	53.7	184	50.8	
Type of breast surgery					
Without surgery	37	9.8	24	6.6	0.078
Lumpectomy	26	6.9	36	9.9	
Quadrantectomy	87	23.1	66	18.2	
Mastectomy	224	59.6	234	65.6	
N/A	2	0.5	2	0.6	
Axillary surgery					
No	58	15.4	62	17.1	0.219
Yes	316	84.0	298	82.3	
N/A	2	0.5	2	0.6	
Number of lymph nodes dissected					
1-10	61	16.2	53	14.6	0.762
11-15	76	20.2	77	21.3	
16-20	77	20.5	86	23.8	
≥2	151	40.2	144	39.8	
N/A	11	2.9	2	0.6	

[a]TNM, tumor-node-metastasis staging. N/A, not available.

Tumor staging was based on the criteria proposed by the International Union Against Cancer and the American Joint Committee on Cancer (17), and the TNM staging system was used to evaluate the BC in three aspects: Tumor size and extension (T), regional lymph node involvement (N), and the presence of distant metastasis (M). Following the determination of the T, N and M classifications, stage 0, I, II, III or IV was assigned.

Statistical analysis. Statistical analyses were run using SPSS software for Windows (version 20.0.0.1; IBM SPSS). Frequency tables used for univariate analysis of overall survival (OS; the time from diagnosis until mortality or date last seen alive) were based on the Kaplan-Meier method, where stratum-specific outcomes were compared using log-rank (Mantel-Cox) statistics. To adjust for covariates, a Cox proportional hazards regression model was used, and covariates (as listed separately) were entered in a stepwise backwards manner using the default values of entry (P=0.05) and removal (P=0.10). The variables that were significant in the univariate analysis were included in the multivariate model. All of the statistical tests were two-sided and P<0.05 indicated a statistically significant difference.

Ethics. The present study was approved by the Research Ethics Committee of Barretos Cancer Hospital, Pio XII Foundation.
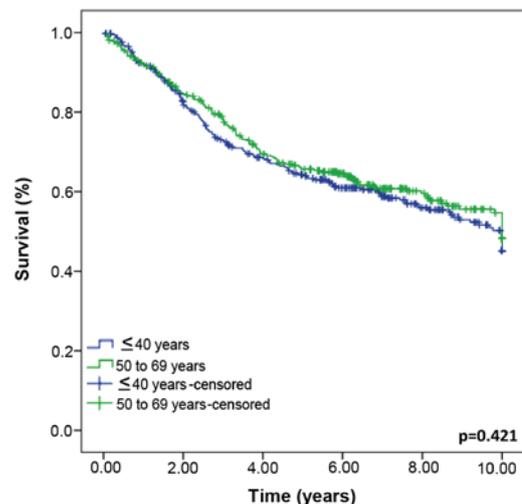

Figure 1. Overall survival rates of younger (n=376) and older (n=362) women with breast cancer.

Results

The demographic characteristics of the patients in the two series are presented in Table I. The main clinical features are

Table IV. Treatment of patients with breast cancer, stratified by age group.

Treatment	≤40 years (n=376)		50-69 years (n=362)		P-value
	n	%	n	%	
Breast reconstruction					
Without	295	78.5	346	95.6	<0.001
Immediate	35	9.3	6	1.7	
Late	43	11.4	8	2.2	
N/A	3	0.8	2	0.6	
Neoadjuvant chemotherapy					
No	312	83.0	286	79.0	0.254
Yes	62	16.5	71	19.6	
N/A	2	0.5	5	1.4	
Chemotherapy					
No	52	13.8	70	19.3	0.053
Yes (adjuvant)	201	53.5	196	54.1	
Yes (palliative)	120	31.9	92	25.4	
N/A	3	0.8	4	1.1	
Hormone therapy					
No	206	54.8	176	48.6	
Yes (adjuvant)	104	27.7	131	36.2	0.056
Yes (palliative)	59	15.7	51	14.1	
N/A	7	1.9	4	1.1	
Radiotherapy					
No	69	18.4	72	19.9	0.592
Yes	302	80.3	284	78.5	
N/A	5	1.3	6	1.7	

N/A, not available.

shown in Table II. The histopathological features and treatment characteristics are shown in Tables III and IV, respectively.

The two groups displayed significant differences in various characteristics. The older group showed a higher proportion of women with low educational level (up to 8 years of school) as compared with the younger group (77.1 vs. 55.9%, respectively; P<0.001) (Table I).

Table II shows that the groups had no differences in the presence of nodules or multicentric cancer at the first examination. The younger group had a higher proportion of multi-focal cancer and bilateral cancer as compared with the older group (6.1 vs. 2.5%, P=0.017 and 9.8 vs. 5.8%, P=0.037, respectively). Comorbidity was less frequent in the younger group than in the older group; one or two comorbidities were found in 30.3 vs. 48.3% of patients (P<0.001), respectively (Table II).

As indicated in Table III, no significant differences were identified between the groups in terms of histological types of the cancer or disease staging. The tumors in the younger group showed a greater frequency of a low degree of differentiation (23.1 vs. 16.6%; P=0.035), reduced blood vessel invasion (1.1 vs. 1.9%; P=0.003), reduced LVI (21.3 vs. 22.4%; P<0.001) and reduced perineural invasion (4.8 vs. 3.6%; P=0.055) as compared with the lesions in the older group (Table III).

The proportion of tumors that were positive for ER expression was significantly lower in the younger group than in the older group (33.5 vs. 42.8%; P=0.014). The two groups had similar negative rates of PR and C-erB-2 expression (Table III). Tumors classified as triple negative were more frequent among the younger women (10.1 vs. 6.4%; P=0.027) (Table III).

The two groups were similar in terms of the number of dissected lymph nodes. Although the younger group underwent radical mastectomy less frequently than the older group, the difference was not statistically significant (59.6 vs. 64.6%, respectively; P=0.078) (Table III). There was a higher proportion of breast reconstruction in the younger group as compared with the older group (20.7 vs. 3.9%; P<0.001) (Table IV). Furthermore, the groups had undergone similar neo-adjuvant treatments Table IV); adjuvant hormone therapy was used less frequently in the younger than in the older group, but this difference was only of borderline significance (27.7 vs. 36.2%; P=0.056) (Table IV).

The duration of follow-up ranged between 0 and 22.6 years, with a mean of 6.1 years and 8.5 months when mortality was excluded. The follow-up data were similar in the two groups (P=0.816). After 5 and 10 years, 4.9 and 10.5% of the patients, respectively, were lost to follow-up (data not shown). The

Table V. DSS according to the demographics of patients with breast cancer, stratified by age group.

Variable	≤40 years (n=376)			50-69 years (n=362)		
	n	10-year DSS, %	P-value	n	10-year DSS, %	P-value
Period of treatment						
1985-1990	59	46.1	0.656	65	33.3	0.002
1991-1996	108	46.4		78	42.0	
1997-2002	208	40.7		217	60.0	
N/A	1			2		
Schooling, years						
0-8	210	42.5	0.751	279	50.0	0.551
9-11	106	48.5		32	44.6	
≥12	57	47.5		34	38.5	
N/A	3			17		
Overweight						
No	284	48.1	0.624	219	47.5	0.978
Yes	44	34.1		90	44.9	
N/A	48			53		
Ethnicity						
White	297	46.0	0.534	288	50.1	0.129
Non-white	76	42.7		70	41.0	
N/A	3			4		
Marital status						
Married	254	44.2	0.538	214	52.2	0.170
Single/divorced	110	49.5		134	42.6	
N/A	12			14		

DSS, disease-specific survival; N/A, not available.

OS rates were not significantly different between the groups (P=0.421) (Fig. 1).

Univariate analysis showed that the following characteristics were significantly associated with prognosis in the younger group: Second cancer (P=0.004), bilateral BC (P=0.100), familial history (P=0.086), menopause at diagnosis (P=0.026), associated diseases (P=0.077), tumor size (mastectomy) (P=0.075), T, N and M stage (P<0.001), degree of differentiation (P=0.127), perineural invasion (P=0.056), LVI (P=0.004), lymph node invasion (P<0.001), ER status (P=0.002), PR status (P=0.043), type of breast surgery (P<0.001), axillary surgery (P<0.001), number of lymph nodes dissected (P<0.001), breast reconstruction (P<0.001), neoadjuvant chemotherapy (P<0.028), chemotherapy (P<0.001) and hormone therapy (P<0.001) (Tables V-VIII).

In the older group, the following variables were significantly associated with prognosis: Period of treatment (P=0.002), ethnicity (P=0.129), marital status (P=0.170), palpable nodules (P=0.062), tumor size (mastectomy) (P=0.042), T, N and M stage (P<0.001), degree of differentiation (P<0.001), peri-neural invasion (P=0.095), blood vessel invasion(P<0.001), LVI (P=0.003), lymph node invasion (P<0.001), ER status (P=0.001), PR status (P=0.015), C-erB-2 expression (P=0.006), type of breast surgery (P<0.001), axillary surgery (P<0.001), number of lymph nodes dissected (P=0.005), neo-adjuvant chemotherapy (P=0.010), chemotherapy (P<0.001), hormone therapy (P<0.001), and

radiotherapy (P=0.016). None of the other variables were statistically significant predictors of survival (Tables V-VIII).

When stratified by clinical stage, no significant differences in the stage-specific survival rates between the two age groups were found (P=0.421) (Fig. 1). However, when the groups were stratified by the period of treatment, significant differences in survival rates were observed between the two groups during the treatment period between 1997 and 2002 (young vs. old group, 40.7 vs. 60.0% survival, P=0.028) (Fig. 2).

In the multivariate analysis, second cancer [hazard ratio (HR), 2.20; 95% confidence interval (CI), 1.500-29.044; P=0.013] and bilateral BC (HR, 6.60; 95% CI, 1.228-3.930; P=0.008) were independent predictors of a poor outcome, with an increased risk of mortality in the younger group. C-erB-2 (HR, 1.97; 95%; CI, 1.003-3.869; P=0.049) was a positive predictor of a poor outcome in the older group, showing an increased risk of mortality. The ER status and TNM stage were significantly associated with disease prognosis in both groups (Tables IX and X).

Discussion

The results described herein reveal important differences between the younger and older patients with BC. This is an almost unanimously accepted fact among BC investigators.

Table VI. DSS according to the clinical characteristics of patients with breast cancer, stratified by age group.

Clinical characteristic	≤40 years (n=376)			50-69 years (n=362)		
	n	10-year DSS, %	P-value	n	10-year DSS, %	P-value
Palpable nodules						
No	19	66.7	0.216	20	78.9	0.062
Yes	356	43.9		338	46.3	
N/A	1			4		
Multicentric cancer						
No	358	46.8	0.413	344	48.9	0.428
Yes	11	26.0		5	50.0	
N/A	7			12		
Multifocal cancer						
No	346	6.2	0.799	341	48.4	0.634
Yes	23	43.3		9	66.7	
N/A	1			12		
Second cancer						
No	371	45.7	0.004	352	47.8	0.545
Yes	4	25.0		7	71.4	
N/A	8			3		
Bilateral breast cancer						
No	331	48.5	0.100	336	48.8	0.575
Yes	37	30.1		21	46.2	
N/A	8			5		
Familial history						
No	211	38.8	0.086	181	54.9	0.495
Yes	49	56.7		36	61.7	
Other malignancies	74	46.6		53	36.0	
N/A	42			92		
Menopause at diagnosis						
No	363	45.4	0.026	38	28.5	0.283
Yes	7	19.0		226	45.4	
N/A	6			98		
Associated diseases						
Absent	256	40.2	0.077	145	53.1	0.925
1 or 2 diseases	114	55.7		175	42.8	
≥3 diseases	5	40.0		40	46.3	
N/A	1			2		

DSS, disease-specific survival; N/A, not available.

Notably, however, the present study was unable to confirm the most controversial of these issues, the suggested worse survival rate of young patients with BC, and failed to identify any difference in disease outcome between the two study groups. This finding is of major importance, asthe OS (Kaplan-Meier) did not reveal significant differences between the two groups, despite several parameters indicating that a more aggressive tumor biology is confined to the younger patients. Only when calculated for the treatment period 1997-2002 were the OS rates significantly worse among young women. We propose that there are several explanations for this finding, with insights discussed herein.

Whether there are clinicopathological differences in BC between younger and older women remains a controversial issue. Typically, the young BC age group ranges from 35 (13,18,19) to 40 (2,14,20,21), however, there is no clear consensus supporting these strict age limits for young and old. However, BC is more frequent in women aged >50 years old. In a population-derived cohort from Brazil, the prevalence of BC was found to be 14% (12), 4.5% of these patients were aged ≤35 years (3) and 26.4% were aged ≤40 years (2).

Thus, in the present study, a 40-year cut-off was used to stratify the women as younger or older. This criterion was partially supported by epidemiological data demonstrating

Table VII. OS according to the histological characteristics of patients with breast cancer, stratified by age group.

	≤40 years (n=376)			50-69 years (n=362)		
Histological characteristic	n	10-year OS, %	P-value	n	10-year OS, %	P-value
Histological diagnosis						
Ductal carcinoma	301	47.8	0.212	289	46.4	0.429
Lobular carcinoma	59	32.4		54	58.2	
Miscellaneous	15	53.0		17	58.5	
N/A	1			2		
Tumor size (mastectomy)						
≤2 cm	54	65.0	0.075	74	57.1	0.042
>2 cm	187	49.9		195	52.1	
N/A	135			93		
Stage						
I	38	90.9	<0.001	37	66.8	<0.001
II	136	66.2		135	67.6	
III	101	20.4		122	28.3	
IV	44	0.049		39	-	
N/A	57			29		
T[a]						
TI/TII	196	56.8	<0.001	210	62.8	<0.001
TIII/TIV	84	32.6		106	26.5	
N/A	94			46		
N[a]						
Negative	147	70.3	<0.001	156	70.1	<0.001
Positive	197	32.3		170	33.3	
N/A	32			36		
M[a]						
No	311	50.1	<0.001	311	50.4	<0.001
Yes	38	-		34	-	
N/A	27			17		
Differentiation degree						
I/II	190	45.1	0.127	201	58.0	<0.001
III	87	46.9		60	23.5	
N/A	99			101		
Perineural invasion						
No	241	47.3	0.056	84	65.0	0.095
Yes	18	-		13	-	
N/A	117			278		
Blood vessel invasion						
No	248	45.9	0.431	79	68.7	<0.001
Yes	4	-		7	-	
N/A	124			276		
Lymphovascular invasion						
No	189	53.8	0.004	53	76.8	0.003
Yes	80	30.5		81	29.4	
N/A	107			228		
Lymph node invasion						
N1 (1 to 3)	78	53.7	<0.001	67	52.2	<0.001
N2 (4 to 9)	55	34.8		49	13.8	
N3 (≥10)	42	14.4		35	-	
N/A	201			211		

Table VII. Continued.

Histological characteristic	≤40 years (n=376)			50-69 years (n=362)		
	n	10-year OS, %	P-value	n	10-year OS, %	P-value
Estrogen receptor						
Negative	89	16.7	0.002	67	31.2	0.001
Positive	126	47.8		155	60.4	
N/A	161			140		
Progesterone receptor						
Negative	90	16.2	0.043	85	46.3	0.015
Positive	124	49.0		135	56.4	
N/A	162			142		
C-erB-2 oncoprotein						
Negative	117	33.0	0.332	125	66.5	0.006
Positive	58	18.9		53	50	
N/A	201			184		
Triple negative						
No	136	25.2	0.711	155	69	0.236
Yes	38	26.0		23	68.8	
N/A	202			184		
Type of breast surgery						
Without surgery	37	-	<0.001	24	-	<0.001
Lumpectomy	26	0		36	35.3	
Quadrantectomy	87	61.6		66	75.7	<0.001
Mastectomy	224	47.9		234	46.6	
N/A	2			2		
Axillary surgery						
No	58	0	<0.001	62	24.1	<0.001
Yes	316	51.8		298	52.3	
N/A	2			2		
Number of lymph nodes dissected						
1 to 10	61	61.1	<0.001	53	53.3	0.005
11 to 15	76	43.9		77	42	
16 to 20	77	63.8		86	58.7	
21 and over	151	25.1		144	40.9	
N/A	11			2		

[a]TNM, tumor-node-metastasis staging; N/A, not available.

different tumor biology in different age groups (14,22). It is also important to emphasize that in Europe, regular mammography screening is a standard practice for women aged 50-69 years. This group is considered to be a biologically distinct group at high risk of developing BC with particular radiological characteristics (23). For this reason, women aged 50-69 years old were selected for comparison in the present study. As BC studies have different definitions regarding age groups, it is challenging to provide a reasonable comparison between different studies.

A number of reports also disagree regarding the importance of including different types of BC, for example, carcinoma *in situ* (CIS) (13,21) or metastatic disease (2,24). Other studies disagree regarding the pertinence of including patients with clinical stage I and II (25,26) or clinical stages I-III (2,20,24) cancer. The present study included TNM stage, and excluded cases of CIS due to their different histological features (27) and relatively favorable disease outcome.

The present study is based on robust parameters that were selected to reflect the true significance of the behavior of BC in young women. To the best of our knowledge, the current study includes the largest cohort of patients with BC aged ≤40 years (n=376) reported from a single institution to date. Worldwide, few institutions have studied larger samples (24,28) and the majority of large studies have been based on cancer registries (7,14,21).

Table VIII. DSS according to the treatment of patients with breast cancer, stratified by age group.

Treatment	≤40 years (n=376)			50-69 years (n=362)		
	n	10-year DSS, %	P-value	n	10-year DSS, %	P-value
Breast reconstruction						
Without	295	41.0	<0.001	346	47.7	0.263
Immediate	35	43.3		6	-	
Late	43	75.7		8	83.3	
N/A	3			2		
Neoadjuvant chemotherapy						
No	312	48.4	0.028	286	51.0	0.010
Yes	62	28.2		71	37.3	
N/A	2			5		
Chemotherapy						
No	52	65.5	<0.001	70	49.6	<0.001
Yes-adjuvant	201	60.9		196	62.5	
Yes-palliative	120	14.0		92	19.0	
N/A	3			4		
Hormone therapy						
No	206	51.8	0.001	176	52.5	<0.001
Yes-adjuvant	104	50.3		131	53.2	
Yes-palliative	59	10.8		51	11.2	
N/A	7			4		
Radiotherapy						
No	69	50.5	0.935	72	36.7	0.016
Yes	302	43.2		284	52.9	
N/A	5			6		

DSS, disease-specific survival; N/A, not available.

Table IX. Multivariate survival analysis of patients aged ≤40 years (n=178).

Variable	n	Hazard ratio	95% confidence interval	P-value
Bilateral breast cancer				
No	158	-	-	-
Yes	20	2.20	1.228-3.930	0.008
Second cancer				
No	176	-	-	-
Yes	2	6.60	1.500-29.044	0.013
Estrogen receptor				
Positive	106	-	-	-
Negative	72	2.29	1.389-3.777	0.001
T				
I/II	133	-	-	-
III/IV	45	2.14	1.258-3.640	0.005
N				
No	80	-	-	-
Yes	98	2.66	1.531-4.621	0.001
M				
No	173	-	-	-
Yes	5	5.92	2.172-16.151	0.001

Table X. Multivariate survival analysis of patients aged 50-69 years (n=151).

Variable	n	Hazard ratio	95% confidence interval	P-value
Estrogen receptor				
Positive	44	-	-	-
Negative	107	2.34	1.175-4.663	0.016
C-erB-2 oncoprotein				
Negative	108	-	-	-
Positive	43	1.97	1.003-3.869	0.049
T[a]				
I/II	110	-	-	-
III/IV	41	2.12	1.073-4.180	0.030
N[a]				
No	71	-	-	-
Yes	80	2.93	1.394-6.149	0.005
M[a]				
No	150	-	-	-
Yes	1	9.99	1.049-95.105	0.045

[a]TNM, tumor-node-metastasis staging.
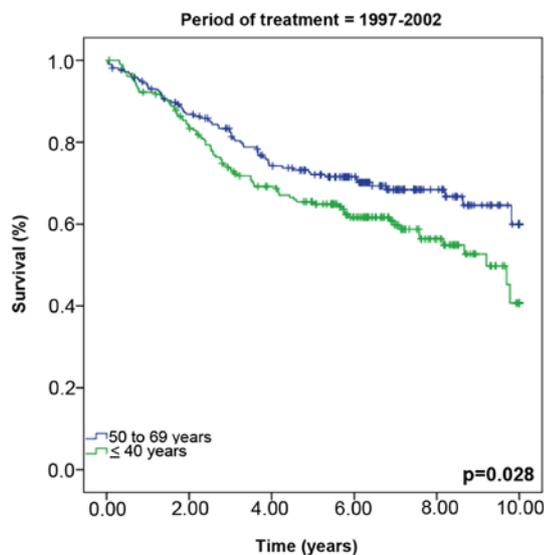
Figure 2. Overall survival rates of younger (n=208) and older (n=217) women with breast cancer in the treatment period between 1997 and 2002.

The present study included a large number of patients with invasive BC presenting at advanced clinical stages. These features are not unusual and are inherent to the existing healthcare system in Brazil. Brazilian women have limited access to clinics that provide mammography examinations and organized population-based screening programs do not exist; consequently, the majority of the BC cases in Brazil are detected at advanced stages. This is in contrast to the situation in developed countries, where regular mammography screening enables the detection of the majority of cases of BC at an early stage (14,19,21). Indeed, prior to 2002, there was no formal recommendation from the Brazilian Health Authorities to provide mammography examinations in asymptomatic women. Therefore, as the presence of palpable and/or ulcerated lesions were a requirement for medical care, a substantial proportion of women exhibited these signs at their first examination. These characteristics are an inherent bias of the present study design resulting in a cohort enriched by BC patients with aggressive tumors at baseline. However, the overall relative survival rate of the older women (50-69 years old) improved between 1997 and 2002, attributable to improvements in treatment, such as chemotherapy and hormone therapy (29).

Mammography is undoubtedly an important diagnostic tool for non-palpable lesions, despite sensitivity limitations among women aged ≤40 years. It is speculated that regular programs for BC prevention could minimize the number of cases of advanced stage disease in Brazil (30). Hereditary BC associated with BRCA1/2 mutations have a prevalence of ~2.3% (31) in Brazil. Furthermore, studies of Latin American women have demonstrated that a family history of BC is less prevalent in Latin America than in the North American population (32). In the present study, mutations were not investigated, however, the familial history of BC was similar between the two study groups. However, the presence of second cancer was similar in the younger and older groups; this is consistent with the results of a previous study, where it was attributed to longer exposures to pathogenic factors (33).

The prevalence of bilateral disease was higher in the younger age group and is one of the indicators of more aggressive tumors, for example tumors with T stage II/III, grade III differentiation, negative ER/PR status and positive lymph node invasion are more aggressive (33). Conversely, the older women more frequently presented with other diseases associated with their BC, which can have an adverse influence on clinical outcome and contribute to a poor prognosis (34). However, the present results identified indicators of worse prognosis to be more common among the younger women.

Accordingly, younger women presented with a higher proportion of tumors with grade III differentiation (poorly differentiated), as reported in a previous study (33). Similarly, the present study observed significant differences between the two groups in terms of perivascular blood vessel invasion and LVI, with older women showing higher proportions of both types of invasion. Notably, this result conflicts with the previously reported data (35,36).

The present study also observed that a higher proportion of older women were positive for ER compared with younger women. This finding is consistent with the results of a previous study, in which advanced age was correlated with positive ER status and vice versa (36). This observation also agrees with the disease outcome data of the current cohort, as a negative ER status is typically associated with a more unfavorable prognosis. By contrast, PR expression did not significantly differ between the two age groups, in agreement with a previous report (26). Conversely, a previous study observed that a negative PR status occurs more frequently in the BC of younger women (35). However, the prognostic value of PR was visible only as a part of an algorithm, but not on its own (37). The present findings also revealed that triple negative BC, which are considered to predict a poor prognosis, were more common in younger women, as previously reported (13).

As anticipated, more important differences in factors that usually influence the efficacy of treatment were observed between the two groups, including tumor stage at the time of diagnosis, tumor characteristics and comorbidities. Of note, the present study included patients with follow-up times of up to 22 years (mean, 6.75 years). This is another important feature of the present study, as only a small number of studies have reported long-term follow-up data of 10 (20,25,36,38) or 15 years (2,14,24,28). In addition, BC treatment strategies have undergone rapid developments in the past two decades, and this development may have contributed to the prognostic differences between the two groups included in the current study. In the younger group, fewer patients received adjuvant hormone therapy and more women received palliative chemotherapy when compared with the older group. This is a clear limitation inherent to all retrospective studies where active intervention is no longer possible. However, the current observations clearly support proposals to also initiate monitoring programs for long-term BC patients.

Finally, the present results did not show significant differences in survival rates between the two study groups (Fig. 1). By contrast, a previous study conducted in central Brazil demonstrated a significant difference in survival rates between patients aged ≤40 years and those aged 40-50 years (P=0.0002) or those aged >50 years (P=0.03). However, this study excluded clinical stage IV disease and included far fewer patients than the present study (20). A previous study reported that BC mortality remains high among young patients, with an OS of ~60% over 5 years, compared with 85% among women aged >50 years (20). The equal survival rates between young and old women observed in the present study have been reported in previous studies (38,39), however, in general, the results have been highly variable among the published literature (40-43).

In conclusion, BC among young women is generally considered to be more aggressive and associated with a worse prognosis compared with BC in older women, whereas the prognostic value of age itself remains more controversial. The results of the present study suggest that BC in young women is associated with numerous pathological features of aggressiveness, including tumor grade, hormone receptor status and degree of differentiation, having been implicated as independent determinants of BC prognosis. However, the OS rates of the two age groups proved to be very similar, except when the data were stratified by the treatment period. For women treated during 1997-2002, the 10-year survival rate of the older women was ~60% compared with 40.7% in the younger cohort. The current study concludes that this increase in 10-year survival is due largely to improvements in treatment, increased early diagnosis and certain tumor characteristics, with the patient's age itself not being an independent prognostic factor. The present study indicates that medical advances associated with prevention of breast cancer may improve screening programs, which may therefore increase early diagnosis and subsequently lower mortality rates.

Acknowledgements

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