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Breast cancer in young women: a rising threat: A 5-year follow-up comparative study

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Abstract

Introduction: Breast cancer in young women is usually considered as breast cancer occurring in women younger than 40 years and is the most frequent cancer-related cause of death in these patients. In the past few years, there seems to be an increasing trend in the prevalence of breast cancer in young women, which, associated with poorer prognosis, more aggressive histologic features, and more frequent recurrence rates, makes it a rising threat to young women. This study aimed to evaluate the biological behavior of breast cancer in young women in our institution.

Material and methods: A retrospective, unicentric, cohort study was conducted between 2012 and 2016. All consecutive patients with breast cancer were enrolled in the study. Cases were divided into two groups: case group, those younger than 40 years, and control group, those 40 years or older. The exclusion criterion was nonoperative treatment. Several clinical and pathologic parameters were evaluated, as well as were overall survival time and disease-free survival time.

Results: The incidence of breast cancer in young women presented a rising tendency over the study period. Significant differences were observed in the comparison of the groups according to body mass index, age at menarche, age at birth of the first child, and proliferation rate. There were no differences in overall survival and disease-free survival rates between the groups.

Conclusions: Young women had a more symptomatic presentation, a greater tumor proliferation rate, but similar outcomes compared with older patients. Greater multicentric studies are needed to confirm or refute these results.

Keywords: breast cancer, age, young women

Introduction

Breast cancer in young women (BCYW) is usually considered as breast cancer occurring in women younger than 40 years and is the most frequent cancer-related cause of death in these patients. Approximately 5% of all breast cancers diagnosed in Europe occur in this population, and it has been presenting a linear rising prevalence, particularly in Portugal.[1] Young women present a special challenge because of their premenopausal hormonal status, active workforce integration, and more frequent hereditary breast cancer context. It raises issues of future cancer risk, prophylactic risk–reducing surgeries, family risk assessment, and family planning, and all of this involves extra psychosocial distress.[2]

BCYW seems to be associated with higher tumor grade, negative hormone receptors, and human epidermal growth factor receptor 2 (HER2) overexpression compared with breast cancer in older women. Moreover, growing evidence shows higher recurrence and death rates in BCYW.[3]

A clear explanation for the less favorable outcome repeatedly reported in young women is lacking. Nonetheless, the treatment approach should not be guided by age alone. This study aims to evaluate the biologic behavior of breast cancer in young patients, to promote tailored treatment, and to avoid either under or over-treatment in these patients.

Material and methods

A retrospective, unicentric, cohort study was conducted between 2012 and 2016. All consecutive female patients with breast cancer were enrolled, and cases were divided in two groups: case group (n=39)—BCYW (<40 years), and control group (n=418)—breast cancer cases of older women. The exclusion criterion was nonoperative treatment.

This study was approved by the Ethics Committee of Centro Hospitalar de Trás-os-Montes e Alto Douro.

Several parameters were evaluated and compared between the groups: body mass index (BMI), age at menarche, age at birth of the first child, breastfeeding duration, family history of breast cancer, nature of the tumor, tumor grade, tumor histologic subtype, HER2

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This study was conducted in accordance with the Helsinki declaration.

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status, proliferation rate, tumor stage, type of surgery, and lymph node dissection.

Nature of the tumor was categorized into invasive and noninvasive. Tumor grade was classified into three groups (I, II, and III) according to the Bloom and Richardson classification system,[4] and equivocal (2+) HER2 status was evaluated by fluorescence in situ hybridization. High Ki67 proliferation rate was defined as greater than 15%. Subtypes of breast cancers (luminal vs. other) were defined according to the 2015 St Gallen Consensus Conference.[5] Tumor stage was cataloged by the seventh edition of the American Joint Committee on Cancer Tumour, Node, and Metastasis classification. A stage equal to or higher than IIb was considered an advanced one. Patients underwent breast-conserving surgery or mastectomy and lymph node dissection or sentinel lymph node biopsy.

In this study, primary end points were to compare overall survival and disease-free survival between groups. Secondary end points were to assess which variables were associated with higher stages and higher recurrence and mortality rates.

Statistical analysis was performed using SPSS 26 (International Business Machines Corporation). Continuous variables were compared by Mann–Whitney tests, and chi-square or Fisher exact tests were used to compare categorical variables. Overall cumulative survival and disease-free survival were obtained by the Kaplan–Meier method and compared by the log-rank test. Significance was assumed if P values were less than 0.05.

Results

Patients' characteristics

Table 1 summarizes the several clinical and pathologic parameters evaluated in the electronic records of the 457 patients (39 BCYW and 418 controls) enrolled in the study. In the study period, BCYW cases increased 2% on average per year. The mean age was 36 years (±3) for the case group and 62 years (±12) for the control group. BMI was lower in the BCYW group compared with that of the control group (P=.001). BCYW patients had menarche significantly earlier (P=.022) and children significantly later (P=.004). There were no differences regarding breastfeeding time (P=.137) nor family history (5.1% vs. 1.7%, P=.175) of breast cancer in a first-degree relative. Two cases of BRCA2 and one case of PALB2 mutations were identified, all of them in the control group. BCYW had a significantly more symptomatic clinical presentation (82.1 vs. 43.5%, P=.000). The most frequent clinical presentation was a palpable lump (71.8 vs 37.3%), and the rate of diagnosis by sonography was 44.7 vs 8.5%, mammography 10.5 vs. 41.6%, and both modalities 44.7 vs. 49.9% in the BCYW and control groups, respectively. Histological type (P=.923) and grade (P=.155) were similar between groups. Immunohistochemistry revealed no differences in hormone receptor (P=.477) or HER2 status (P=.052), but BCYW showed a significantly higher rate of Ki67 proliferation marker (P=.004). Tumor size (P=.166), lymph node invasion (P=.744), and distant metastases (0.850) rates as well as early/advanced stage (P=.429) were similar between groups. There were no differences in breast-conserving surgery (P=.587) or lymph node dissection (P=.714) rates between groups. All patients were equally submitted to radiotherapy (P=.452), hormone therapy (P=.169), and anti-HER2 therapy (P=.52), regardless of the age, but BCYW was significantly more treated with chemotherapy (P=.001), particularly neoadjuvant (0.011), than patients in the control group.

Primary end points

No significant difference was observed in overall cumulative survival (Fig. 1) or disease-free survival (Fig. 2) between both groups. There were no differences in the recurrence rate (10.3 vs. 11.5%, P=.839) and mortality rate (10.3 vs. 11.2%, P=.818) between the groups, in the study period. Distant recurrences (10.3 vs. 8.6%) were more frequent than local recurrences (2.6 vs. 2.4%) in both groups.

Secondary end points

Regardless of age, advanced stage at diagnosis (≥IIb) and symptomatic presentation were indicators of worse prognosis regarding both recurrence and death. Patients with higher grade tumors had significantly higher recurrence rates. Those with older

Table 1

Patients' characteristics

Variable	BCYW Group (n=39)	Control Group (n=418)	P
Mean age (SD)	36.1 (3.1)	62 (12.2)	
Body mass index ≥25 kg/m^2	16 (41%)	239 (57.2%)	**.001***
Age at menarche (8–13 years)	31 (79.5%)	246 (58.9%)	**.022***
Age at birth of the first child (≥26 years)	16 (41%)	78 (18.7%)	**.004***
Breastfeeding time (<6 months)	10 (25.6%)	90 (21.5%)	.137*
Positive family history	2 (5.1%)	7 (1.7%)	.175†
Invasive tumor	36 (92.3%)	384 (91.9%)	.923*
Tumor grade			
1	8 (20.5%)	108 (26.7%)	
2	17 (43.6%)	206 (51%)	
3	14 (35.9%)	90 (22.3%)	.155*
Luminal tumor	37 (94.9%)	383 (91.6%)	.477*
Positive HER2 tumor	8 (20.5%)	43 (10.3%)	.052*
Ki67 proliferation rate (≥15%)	26 (68.4%)	183 (44%)	**.004***
Stage (≥IIb)	12 (30.8%)	104 (25%)	.429*
Conservative surgery	26 (66.7%)	296 (70.8%)	.587*
Lymph node dissection	17 (43.6%)	195 (46.7%)	.714*

Bold entries denote statistical significance (P<0.05).

* Pearson chi-square test.

† Fisher exact test.

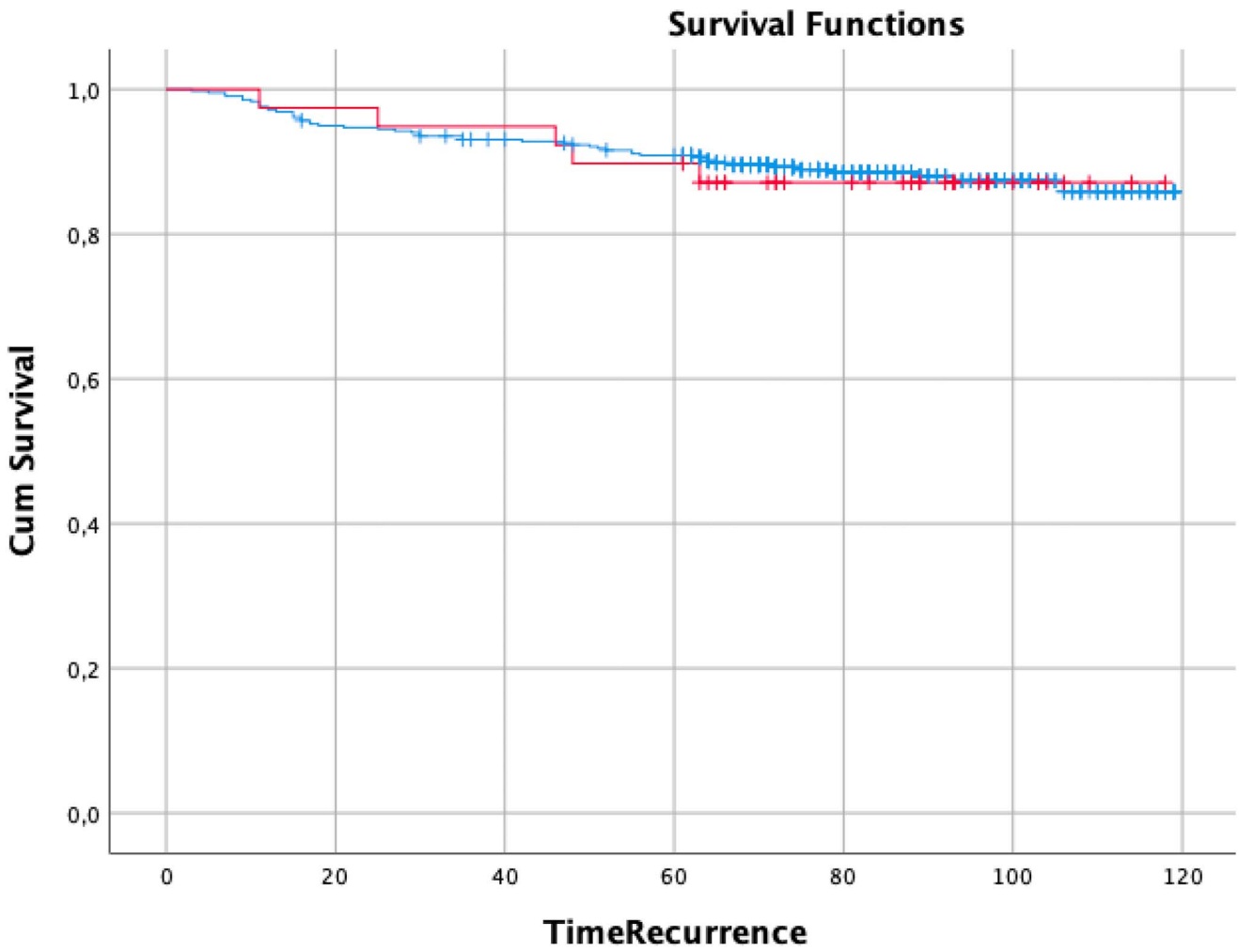

Figure 1. Kaplan-Meier curves of disease-free survival (the red line denotes <40 years; the blue line denotes 40 years and older)

age at birth of the first child and negative HER2 tumors had a significantly higher rate of mortality. Subtype of breast cancer (luminal or nonluminal), tumor proliferation score (Ki67), BMI, breastfeeding time, age at menarche, and family history did not significantly influence recurrence or mortality in this study (Table 2).

A subanalysis of prognostic risk factors in the BCYW group revealed that HER2-positive tumors presented with higher stages (P=.029) but similar recurrence and mortality rates compared with the negative ones. Moreover, patients with older age at menarche presented a significantly higher rate of recurrence (P=.049) but similar mortality. In fact, none of the remaining variables (including stage, grade, invasiveness, tumor subtype, or symptomatic presentation) were associated with higher rate of recurrence or mortality in this group.

Discussion

Approximately 8.5% of all cases of breast cancer in this study were diagnosed in young women, which is higher than the proportion revealed by the Global Cancer Observatory in 2020 (32883/531086, 6.2%) in Europe. Nonetheless, we excluded patients not submitted to surgery, which may explain this difference. In this study period, BCYW cases increased 2% on average per year, which is a lower value than previously described in Portugal (2.68).[1] The mean age in younger women with breast cancer in this study was 36 years, which is in concordance with other studies.[6-12] In contrast to some American series,[13,14] family history of breast cancer was not more frequent in BCYW. In fact, only three cases of inherited breast cancer–associated gene mutations were identified, all of them in the control group, and only one of them had a family history of breast cancer. This agrees with growing evidence that shows distinct gene mutations in young women. Identification of age-specific molecular, biological, and genomic aberrations could explain clinical and pathological differences between younger and older patients with breast cancer and promote tailored treatment approaches.

In accordance with the literature,[15] almost all patients in the BCYW group were symptomatic at diagnosis, often referring to a lump, which enhances the paramount importance of self-examination, especially because in Portugal and other countries, there is no organized screening for breast cancer until later in life (50 years). On the other hand, breast density may make imaging detection difficult and low clinical suspicion may delay the diagnosis in young women.[16]

Tumor diameter, lymph node invasion, and distant metastases at presentation rates were not higher in the BCYW group as verified in some published works.[6-9,14] There were no differences regarding histologic type between groups, with the literature showing variable data regarding this topic.[8,9] In contrast to some studies, histologic grade,[6,8,9,14] hormone receptor,[6-9,14,17,18] and HER2[6-9,17,18] receptor status were not significantly different

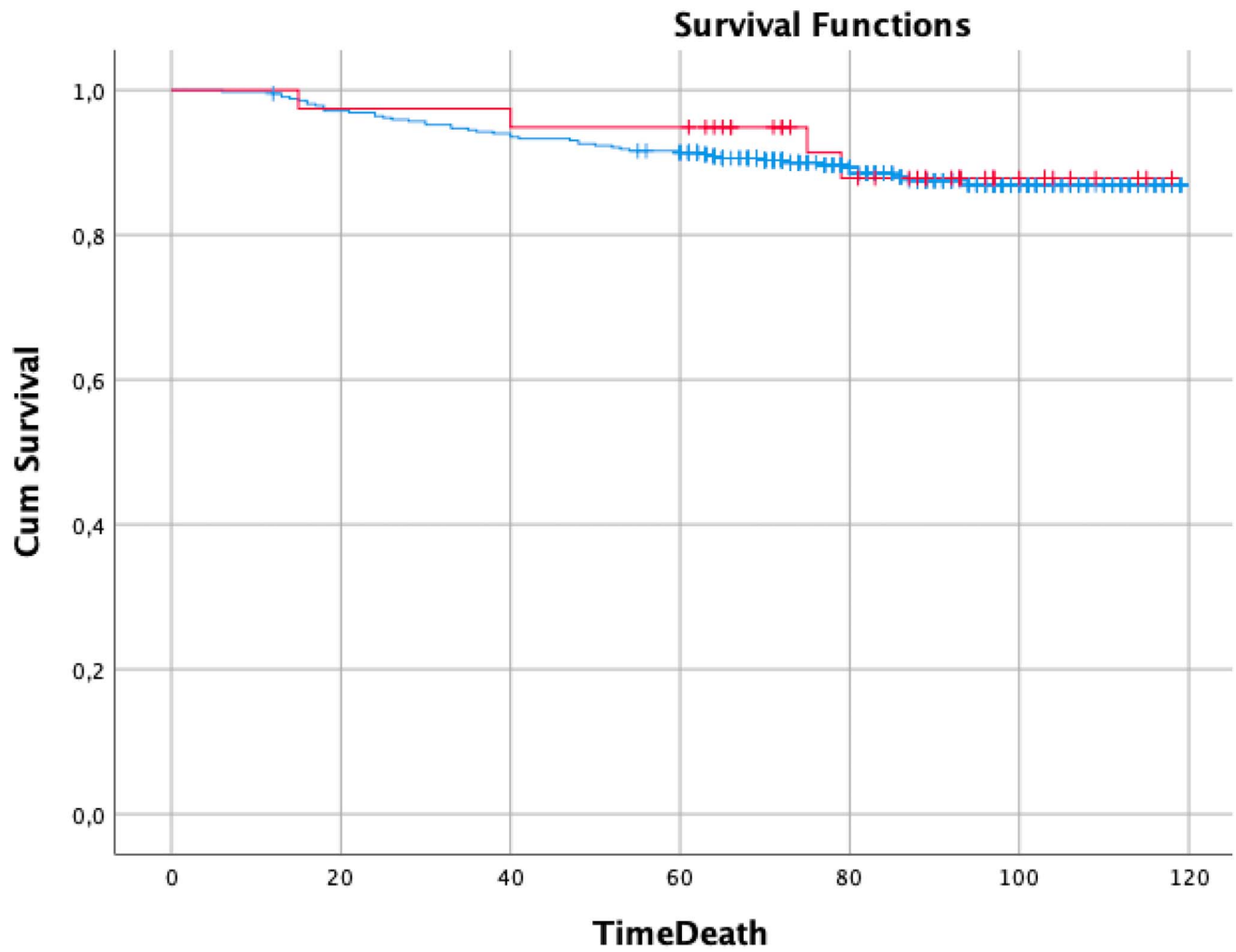

Figure 2. Kaplan-Meier curves of overall survival (the red line denote <40 years; the blue line denotes 40 years or older)

between groups. However, proliferation marker Ki67 was significantly higher in the BCYW group, which is in agreement with an Italian study.[18]

Regarding treatment modalities, the rate of breast conservation surgery did not differ between groups. In addition, hormone therapy and monoclonal antibody therapy were equivalent, as expected because of similar hormone and HER2 receptor status between groups. Nonetheless, younger patients were significantly more often submitted to chemotherapy, especially neoadjuvant, probably because of a higher proliferation rate.

Table 2

Secondary end points

Variable	Stage≥IIb *P*	Recurrence *P*	Mortality *P*
Symptomatic presentation	**0.000***	**0.000***	**0.000***
Stage		**0.000***	**0.000***
Grade	**0.032***	**0.010***	0.772*
Age at birth of the first child	0.375*	0.071*	**0.044***
Invasive tumor	**0.000***	0.466*	**0.023***
Positive HER2 tumor	0.172*	0.351*	**0.025***
Luminal tumor	**0.039***	0.208*	0.233*
Basal-like tumor	0.477*	0.640*	0.671*
Ki67 proliferation rate	0.990*	0.262*	0.053*
Breastfeeding time	0.200*	0.308*	0.128*
BMI	0.200*	0.810*	0.176*
Age at menarche	0.274*	0.915*	0.263*
Family history	0.586*	0.267*	0.301*

Bold entries denote statistical significance ($P<0.05$).
* Pearson chi-square test

Neither recurrence nor mortality rates were higher in the BCYW group, contrasting with the literature.[6,14,19,20] In this study, symptomatic presentation, higher stage, higher grade, and invasive tumors were identified as negative prognostic factors, as expected. Moreover, later parity was associated with a higher mortality rate. Previous studies have shown conflicting results regarding this issue.[21] A curious finding was that positive HER2 tumors were associated with higher stages in younger patients, but with lower mortality rates in the control group, which makes us question whether HER2 status (and anti-HER2 therapies) differently influences prognosis of breast cancer depending on the age of patients, although the benefit of adjuvant trastuzumab seems independent of age in the literature.[22] So, despite presenting more symptomatic presentation and tumors with a higher proliferation rate, BCYW patients did not present worse prognosis in this study.

This was the first Portuguese study regarding this issue.

Limitations

As negative aspects, this was an unicentric study with a small sample and, possibly, a short follow-up.

Conclusion

The incidence of breast cancer in young women has a rising tendency, and the lack of formal screening at this age makes self-examination paramount for diagnosis. Current life habits can contribute to an increasing risk of breast cancer in this population (late/low parity and use of oral contraceptives). Young women have a more symptomatic presentation, probably because of nonorganized screening until later in life. Moreover, BCYW is more frequently HER2-positive and presents with higher tumor proliferation rates. Despite these aggressive traits, BCYW presents similar outcomes as compared with older patients. We failed to identify risk factors of mortality in BCYW, which makes us wonder whether there are unknown mutations in this population that can explain the worse outcomes. Greater multicentric studies are needed to confirm or refute these results.

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