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Breast cancer care for the aging population: a focus on age-related disparities in breast cancer treatment

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Abstract

Objective Breast cancer is a significant health issue for women worldwide and poses unique challenges for all ages. Older women face many concerns about breast cancer treatment and outcomes. This study aims to compare breast cancer management and outcomes across various age groups within a single-center experience in a region with an aging population, focusing specifically on women aged 70 and older to identify potential disparities in treatment and prognosis.

Methods We conducted a retrospective analysis of all female patients diagnosed with breast cancer at our local reference Breast Unit in northeastern Italy between January 2002 and July 2023. The primary outcome measures in this study were overall survival (OS), disease-free survival (DFS), cumulative loco-regional recurrences, and cumulative distant recurrences.

Results The study included 2478 women over 70 (31.12%), 4690 women aged between 45 and 69 (58.90%), and 795 women under 45 (9.98%). According to the study, older women were more likely to have advanced-stage cancer, whereas they received less aggressive treatment, including fewer adjuvant therapies and surgical interventions. We also observed worse prognoses in this group of patients if compared with women aged 45 to 69 years. Moreover, data showed that the incidence of breast cancer among older women has increased over time.

Conclusions Our findings highlight the need for tailored treatment strategies for older breast cancer patients to balance treatment efficacy with quality-of-life considerations. These findings call for a strategic reevaluation of treatment protocols and emphasize the importance of personalized care, particularly for older women, to improve outcomes without sacrificing the quality of life while maintaining maximum survival potential.

Highlights

· Our analysis identifies significant treatment disparities between women over 70 and younger age groups in breast cancer management.

· Our study documents the rising incidence of breast cancer in women aged 70 and older, emphasizing the urgency of addressing this demographic issue.

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· Our study emphasizes the need for tailored treatment strategies that balance cancer control with quality of life for the elderly.

· Our results advocate including older women in clinical trials to ensure that findings are representative and applicable to this growing patient population.

Keywords Breast neoplasmsm, Aged, Age factors, Geriatrics, Personalized medicine, Survival analysis

Introduction

Female breast cancer (BC) is a considerable health concern worldwide and presents unique challenges across all age groups [1–3]. Women diagnosed with breast cancer at an older age exhibit unique tumor characteristics in contrast to their younger counterparts. Older women exhibit a higher likelihood of developing estrogen receptor (ER) and progesterone receptor (PR) positive tumors characterized by lower tumor grades [4–7]. Women under 40 are more likely to exhibit aggressive subtypes, such as triple-negative BC, which are marked by poorer differentiation and increased rates of vascular invasion [8, 9]. Additionally, older women often exhibit larger tumors and increased nodal involvement [5, 10], which may lead to a higher breast cancer-specific mortality rate [2, 3, 10].

Women over 70 are underrepresented in clinical trials, leading to limited evidence for optimal treatment and posing challenges for future research in adjuvant therapies [4, 11–13]. Emerging evidence suggests that adjuvant chemotherapy may benefit healthy older women, with comparable advantages noted in both older and younger cohorts undergoing aggressive chemotherapy regimens [4, 14, 15]. Chemotherapy decreases mortality in older women with node-positive, ER-negative disease; however, its effectiveness in ER-positive disease remains uncertain [14, 16]. Endocrine therapy could be as effective as chemo-endocrine therapy in older women with midrange recurrence risk [17]. Adjuvant chemotherapy can enhance survival in specific high-risk, aggressive disease subgroups while proving ineffective in others, highlighting the necessity for risk-based treatment [14–18]. Furthermore, older BC patients are more likely to die from other causes than younger women, emphasizing the need for tailored treatments [19, 20]. Specialists must evaluate each case within a multidisciplinary approach, including breast care nurses (BCNs), who are critical spokespersons for the patients' expectations and desires [21].

Despite increasing women's life expectancy, disparities in age-specific treatment, particularly among older women, continue to be insufficiently explored [4, 11–13, 22]. The AJCC 8th edition breast cancer staging system integrates biomarkers with anatomical staging to improve prognostic accuracy and inform personalized treatment, as validated through various datasets. Kerlikowske et al. [23] analyzed mammographic screening data for women aged 40–79 across all cancer stages, revealing that staging performance is independent of age. Wu et al. [24] analyzed SEER cancer registry data for women aged 65 and older, with additional stratification for those aged 70 and 80 + in early-stage cancers (up to stage IIA). Their findings indicated that staging was age-independent; however, they noted that age over 70, particularly over 80, significantly elevated cancer-specific mortality [24].

Age-related disparities must be addressed to develop guidelines and interventions that improve older BC care, quality of life, and survival. This study aims to compare BC management and outcomes across age groups within a single-center experience in a region with an aging population, focusing on women aged ≥ 70, to identify potential disparities in treatment and prognosis.

Materials and methods

We collected data on 7963 women who had BC surgery between Jan 2002 and Jul 2023 in our local reference Breast Unit in northeastern Italy. This retrospective chart review study, which the Internal Review Board (IRB) approved, adhered to the Helsinki Declaration and followed patient consent and data processing guidelines.

Eligibility for inclusion required female patients to have a confirmed diagnosis of invasive breast cancer or ductal carcinoma in situ, complete data on age, comprehensive records of both surgical and non-surgical management, and a minimum of 6 months of follow-up. Patients with incomplete clinical records or absent follow-up information were excluded from the analysis. Patient selection and data collection were conducted using information from outpatient, hospitalization, and operative theater registers. Data extraction was carried out by breast cancer specialists, breast nurses, and a trained data manager through a systematic retrospective review of clinical files.

The following characteristics of patients were collected: age at diagnosis, family history of breast or ovarian cancer, body mass index (BMI), previous use of estrogen-containing therapies, fertility status, previous tumor diagnosis, and comorbidities. The following tumor characteristics were also considered: tumor grading, TNM classification and stage, histological type, Mib1/Ki-67 proliferation index, hormone receptors status (ER and PR positivity), Her2/neu expression, and other microscopic

pathological features such as perivascular invasion (PVI), extensive intraductal component (EIC) and multifocality/multicentricity. Oncological surgical management was evaluated by noting the type of breast surgery (breast conservative surgery (BCS) or mastectomy) and the type of axillary surgery (sentinel lymph node biopsy (SLNB) or complete axillary lymph node dissection (CALND)). A thorough examination of non-surgical treatments was conducted, encompassing neoadjuvant, adjuvant, and endocrine therapies. Furthermore, we evaluated primary non-surgical treatment, which is generally restricted to patients with metastatic disease or older, frail women who are ineligible for surgery.

We classified tumor stage using the VII edition of the TNM classification (AJCC/UICC), tumor histology using World Health Organization criteria, and tumor grade using Elston and Ellis' recommendations, as previously described [25]. As previously stated, ER, PR, Her-2/neu, the tumor proliferative fraction (Mib1/Ki-67), and PVI (using Rosen and Oberman criteria) were investigated [25, 26]. Fertility status was defined according to the STRAW (Stages of Reproductive Aging Workshop) criteria [27, 28]. BMI was collected retrospectively from patients' clinical records at the time of breast cancer diagnosis, calculated using the standard formula: weight in kilograms divided by height in meters squared (kg/m2). Comorbidities, including diabetes, hypertension, cardiovascular, pulmonary, and other chronic diseases, were coded as: none, one, two, or three or more.

A multidisciplinary team managed all patients in this study after regular multidisciplinary meetings (MDM), usually before primary treatment (surgical or neoadjuvant therapy) based on biopsy histology and before adjuvant treatment based on surgical specimen histology. The BCN helped evaluate patients during MDM, considering malignancy characteristics, age, comorbidities, expectations, and personal wishes for proposed treatments. BCN can quickly identify age-related physical and emotional weaknesses that can be measured with distress thermometers by conducting a thorough interview before the MDM. These screening tools allow BCN to refer patients to onco-geriatricians or psycho-oncologists [21, 29].

The procedures performed were mastectomy and breast-conserving surgery (BCS). We employed wire-hook or radio-guided occult lesion localization (ROLL) for non-palpable lesions [26]. Patient preference has impacted the selection of mastectomy techniques, including modified total mastectomy (MTM), skin-sparing mastectomy (SSM), and nipple-sparing mastectomy (NSM). NSM was used when BCS was ineffective for extensive or recurrent lesions. A radiolabeled human serum albumin injection was utilized for sentinel lymph node biopsy (SLNB), with completion axillary lymph node dissection (CALND) performed if necessary [30]. Radiotherapy was advised following breast-conserving surgery, except in cases where age or comorbidities were limiting factors, with advanced tumors undergoing radiotherapy to the chest wall and lymph nodes. After multidisciplinary consultations, treatment options were evaluated, including chemotherapy, endocrine therapy, and recently introduced targeted agents such as CDK4/6 inhibitors.

The study population was divided into three age groups: <45, 45–69, and ≥ 70 years [5, 9]. The resulting three groups were statistically compared. Data were analyzed using R (version 4.3.3), employing two-sided statistical tests with a significance threshold of $p<0.05$. Univariate analyses of categorical variables were conducted using the chi-square test or Fisher's exact test, the latter being utilized when expected cell counts were less than 5. The normality of continuous variables was initially evaluated using the Kolmogorov–Smirnov test, supplemented by visual representations through histograms and Q-Q plots. The Wilcoxon rank-sum test was employed for comparisons between two groups of non-parametric continuous variables, whereas the Kruskal–Wallis test was utilized for scenarios involving more than two groups. The t-test was employed to compare two groups for parametric variables, while one-way ANOVA was utilized for comparisons involving more than two groups. Survival outcomes were assessed through Kaplan–Meier curves to illustrate overall survival (OS) and disease-free survival (DFS) among various age groups, with censoring included to address patients lost to follow-up. The survival curves were compared using the log-rank test. The loco-regional and distant recurrence frequencies were compared between groups through contingency table analyses, with incidence rates calculated per person-year follow-up. Univariate and multivariate Cox proportional hazards regression models were developed to calculate hazard ratios (HRs) for overall survival (OS) and disease-free survival (DFS), accounting for potential confounding factors. Variables with a p-value below 0.05 in univariate analyses or considered clinically relevant according to existing literature were included in the multivariate models. We tested the proportional hazards assumption for our Cox regression model [31]. When this assumption was violated, we incorporated time-dependent covariates using step functions to maintain model validity. The dataset was segmented into specific time intervals, and interaction terms between time and the relevant covariate were added to represent changes in risk over time. Breast cancer incidence rates were standardized, and the cumulative percentage change over time was computed using Poisson random-walk models with Bayesian inference [32]. The local population at risk was derived from

the Italian Institute of Statistics database (http://dati.istat.it/ and https://esploradati.istat.it/databrowser/), and the World Standard Population data was obtained from Open Data Scotland (https://www.opendata.nhs.scot/). The Mann–Kendall trend test was employed to assess monotonic time trends in the data, specifically by applying it to yearly aggregated incidence figures to identify significant upward or downward trends. Results are reported as median (interquartile range—IQR) for non-normally distributed continuous variables, mean and standard deviation for normally distributed continuous variables, percentages and absolute numbers for categorical data, or reference values with corresponding 95% confidence intervals (CI.95) for estimates obtained from regression analyses.

Results

The median age of BC patients included in this study was 63 years (IQR 51–72) (Table 1). Among the women, 9.98% (795/7963) were aged < 45, 58.9% (4690/7963) were 45–69, and 31.12% (2478/7963) were ≥ 70 years. The median follow-up period was 60 months (IQR 49–60), with 60 months (IQR 59–60) for women under 45 years, 60 months (IQR 58–60) for 45–69 years, and 60 months (IQR 34–60) for those ≥ 70 years. Additionally, Fig. 1A, B, and C illustrate a significant increase in the yearly incidence of BC patients ≥ 70 years ($p < 0.001$).

Various parameters were compared among age groups; details are presented in Tables 1, 2, and 3. The results indicate that women < 45 underwent more frequent mastectomy and CALND in comparison to those aged 45–69. Moreover, younger women compared to 45–69 presented more frequently a genetic predisposition and distinct tumor profiles that showed negative prognostic patterns.

Women ≥ 70 had a higher likelihood of undergoing mastectomy and CALND compared to those aged 45–69 ($p < 0.05$). However, these women were less likely to receive adjuvant or neoadjuvant chemotherapy ($p < 0.05$). Furthermore, women aged ≥ 70 had a lower incidence of genetic predisposition and adverse prognostic factors.

Our analysis revealed significant differences in many aspects between the youngest and oldest age groups (< 45 and ≥ 70 years respectively). Younger women had a higher incidence of aggressive tumor treatment, including adjuvant and neoadjuvant chemotherapy. The younger group had a higher genetic predisposition and biomolecular markers of more aggressive tumor behavior than the older group.

Survival analysis

Figure 2A, B, C, and D show the Kaplan–Meier analysis. During the 5-year follow-up period, the study population's OS was 95.55% (CI.95 95.06–96.04%). Survival rates varied across age groups (Fig. 2A). Women < 45 years had a 5-year OS of 96.05%, those 45–69 years had a slightly higher OS of 96.51%, and those ≥ 70 had a lower OS of 93.43% (Fig. 2A). There was no significant difference in survival between the < 45 and 45–69 years groups ($p = 0.460$). However, there were substantial differences between ≥ 70 and < 45 or 45–69 years (respectively $p = 0.010$ and $p < 0.001$) (Fig. 2A). A total of 19 women aged ≥ 70 with ER-positive stage I or II tumors received primary hormonal therapy, while 729 underwent conservative breast surgery with adjuvant treatments. The groups achieved a 5-year overall survival rate respectively of 98.88% (CI.95 98–99.78%) and 100% (CI.95 100–100%) ($p = 0.868$).

The 5-year DFS for the study cohort was 92.71% (CI.95 92.08–93.35%). Significant differences in DFS were observed across age groups ($p < 0.001$) (Fig. 2B), with those < 45 having lower DFS rates. The 45–69 group showed the highest DFS at 94.07%, while those ≥ 70 had a lower DFS of 92.09% compared to the 45–69 group ($p < 0.001$). In women ≥ 70 with ER-positive stage I or II tumors, primary hormonal therapy and conservative breast surgery with adjuvant treatments achieved respectively a 5-year disease-free survival rate of 97.86% (CI.95 96.72–99.02%) and 100% (CI.95 100–100%) ($p = 0.718$).

The 5-year loco-regional recurrence rate was 3.22% (CI.95 2.79–3.65%). There were significant differences in recurrence rates among age groups (45–69 years vs. < 45 years and ≥ 70 years $p < 0.001$, and < 45 years vs. ≥ 70 $p = 0.022$) (Fig. 2C). Women aged ≥ 70 (3.83%) and < 45 (6.13%) had a higher rate than 45–69 (2.4%).

The 5-year cumulative distant metastasis for the entire cohort was 5.14% (CI.95 4.60–5.68%). Data analysis by age group revealed significant differences. The < 45 years had the highest rate of distant metastasis, at 9.74%, significantly higher than the rates in other age groups ($p < 0.001$) (Fig. 2D). Women aged ≥ 70 had a metastasis rate of 5.22% higher than 45–69 years (4.31%) ($p = 0.042$).

Table 4 shows univariate and multivariate Cox regression analyses of age and other tumor predictors on invasive BC OS. Patients aged ≥ 70 years had a significantly higher mortality risk within the first 36 months than those aged 45–69 years, also, after multivariate adjustment (HR 2.31, CI.95 1.63–3.27, $p < 0.001$). Different sensitivity analyses were also performed adjusting for ductal carcinoma in situ (HR 2.31, CI.95 1.63–3.27, < 0.001) and smoking (HR 2.70, CI.95 1.81–4.04, < 0.001). A further sensitivity analysis including also type of surgery showed the same results for women age and showed an increased risk for mastectomy (HR 2.17, CI.95 1.54–3.04, $p < 0.001$) and no surgery (HR 6.54, CI.95 4.03–10.61, $p < 0.001$) compared to breast conservig surgery. In contrast, younger patients

Table 1 Comparison of patient characteristics and treatment modalities based on age category

Variables	All population	< 45 years (795)	45–69 years (4690)	≥ 70 years (2478)	p(*)	p(†)
Patient characteristics						
Woman age (years)	63 (51–72)	41 (38–43)	58 (51–64)	77 (73–81)	< 0.001	1,2,3
BMI (kg/m2)	24 (22–28)	23 (21–25)	25 (22–28)	25 (22–28)	< 0.001	1,2,3
Family history	32.45% (1698/5233)	34.14% (184/539)	34.04% (1029/3023)	29.02% (485/1671)	0.001	2,3
Genetic testing					< 0.001	
Genetic testing negative	72.58% (487/671)	64.00% (112/175)	70.98% (269/379)	90.60% (106/117)		2,3
Any VUS	8.05% (54/671)	8.00% (14/175)	8.97% (34/379)	5.13% (6/117)		NS
Any positivity for genetic predisposition	19.37% (130/671)	28.00% (49/175)	20.05% (76/379)	4.27% (5/117)		1,2,3
Tobacco smoke	14.46% (905/6259)	12.78% (80/626)	16.06% (606/3773)	11.77% (219/1860)	< 0.001	1,3
Estrogen or progesterone use	30.81% (582/1889)	50.25% (101/201)	32.47% (375/1155)	19.89% (106/533)	< 0.001	1,2,3
Post-menopausal status	79.64% (6342/7963)	2.26% (18/795)	82.15% (3853/4690)	99.72% (2471/2478)	< 0.001	1,2,3
Comorbidities					< 0.001	
None	64.66% (5149/7963)	92.33% (734/795)	72.58% (3404/4690)	40.80% (1011/2478)		1,2,3
One	22.59% (1799/7963)	7.04% (56/795)	20.60% (966/4690)	31.36% (777/2478)		1,2,3
Two	9.97% (794/7963)	0.50% (4/795)	5.69% (267/4690)	21.11% (523/2478)		1,2,3
Three or more	2.78% (221/7963)	0.13% (1/795)	1.13% (53/4690)	6.74% (167/2478)		1,2,3
Previous neoplasia	8.63% (687/7963)	5.16% (41/795)	6.93% (325/4690)	12.95% (321/2478)	< 0.001	2,3
Surgical treatment						
Breast surgery					< 0.001	
Conservative	49.74% (3961/7963)	35.09% (279/795)	54.88% (2574/4690)	44.71% (1108/2478)		1,2,3
Mastectomy	48.11% (3831/7963)	62.64% (498/795)	43.97% (2062/4690)	51.29% (1271/2478)		1,2,3
No surgery	2.15% (171/7963)	2.26% (18/795)	1.15% (54/4690)	4.00% (99/2478)		1,2,3
Axilla surgery					< 0.001	
CALND	38.66% (3012/7792)	46.59% (362/777)	36.43% (1689/4636)	40.40% (961/2379)		1,2,3
SLNB	61.34% (4780/7792)	53.41% (415/777)	63.57% (2947/4636)	59.60% (1418/2379)		1,2,3
Non surgical neoadjuvant or primary treatment						
Neoadjuvant therapy	6.92% (551/7961)	12.70% (101/795)	6.87% (322/4689)	5.17% (128/2477)	< 0.001	1,2,3
Neoadjuvant radiotherapy	10.68% (77/721)	0.00% (0/101)	7.45% (24/322)	20.31% (26/128)	< 0.001	1,2,3
Neoadjuvant chemotherapy	85.16% (614/721)	99.01% (100/101)	89.44% (288/322)	74.22% (95/128)	< 0.001	1,2,3
Neoadjuvant hormonal therapy	18.03% (130/721)	0.99% (1/101)	3.11% (10/322)	7.81% (10/128)	0.016	2,3
Primary hormonal therapy	64.71% (110/170)	44.44% (8/18)	37.74% (20/53)	32.32% (32/99)	0.554	NS
Primary chemotherapy ± radiotherapy	80% (136/170)	94.44% (17/18)	94.34% (50/53)	69.70% (69/99)	< 0.001	2,3
Non surgical adjuvant treatment						
Adjuvant radiotherapy	55.1% (4199/7621)	52.06% (392/753)	60.92% (2753/4519)	44.87% (1054/2349)	< 0.001	1,2,3
Adjuvant chemotherapy	34.94% (2657/7604)	66.31% (498/751)	39.77% (1793/4508)	15.61% (366/2345)	< 0.001	1,2,3
Adjuvant hormonal therapy	75.33% (5730/7607)	69.11% (519/751)	77.38% (3490/4510)	73.36% (1721/2346)	< 0.001	1,2,3

(*)Differences among groups. (†) Group-to-group analyses that, in the case of factor variables with more than two levels, were conducted after dummifying variables. Differences statistically significant ($p < 0.05$): 1) < 45 years v.s. 45–69 years; 2) < 45 years v.s. ≥ 70 years; 3) 45–69 years v.s. ≥ 70 years. *Acronyms*: *BMI* Body Mass Index, *CALND* Complete Axillary Lymph Node Dissection, *SLNB* Sentinel Lymph Node Biopsy, *VUS* Variant of Uncertain Significance

(< 45 years) did not show a significantly increased mortality risk (Table 4). In Table 5, Patients aged ≥ 70 years had a higher risk of disease recurrence within the first 36 months than those aged 45–69 years, which remained significant after adjustment (HR 1.58, CI.95 1.21–2.08, $p < 0.001$). Patients under 45 years had a significantly higher risk of disease recurrence, which remained significant after adjustment and 36 months of follow-up (HR 1.73, CI.95 1.25–2.40, $p = 0.001$) (Table 5).

Discussion

Key results

This study found a rise in incidence among women ≥ 70. The surgical decisions, genetic predisposition, and tumor characteristics varied significantly by age. Compared to

those aged 45–69, women < 45 had more mastectomies and faced higher genetic risks and aggressive tumors. Women aged ≥ 70 had more mastectomies than those aged 45–69 but had lower non-surgical therapy rates and genetic predispositions. Survival analysis revealed a 5-year OS highest in the 45–69 age group and lowest in the ≥ 70 age group. DFS was significantly lower in the < 45 age group. Cox regression analysis showed that women aged ≥ 70 were associated with shorter OS and DFS than the 45–69 age group.

Interpretation and comparison with the literature

The rise in annual incidence found in this study supports previous research showing an increase in BC in women over 70 [33]. Increasing female life expectancy may increase the number of older adults, while predisposing genes, lifestyle changes, and environmental pollution may increase the number of young BCs [34].

This study found that management practices, genetic predispositions, and tumor characteristics differed by age group. In our cohort, genetic predisposition was documented in only a subset of women. The criteria for genetic testing evolved over the study period but remained broadly consistent with NCCN guidelines [35], which recommend testing for women diagnosed at a younger age, those with a significant family history of breast or ovarian cancer, and in cases where pathogenic mutations are identified, either in relatives or incidentally during somatic tissue analysis, particularly with the increasing use of tumor profiling for targeted therapies. This retrospective study reflects clinical practice, where only patients who fulfilled these criteria were tested. Consequently, the reported prevalence of genetic defects may reflect a higher likelihood of testing among younger women, as well as a genuine biological propensity for earlier tumor development in individuals with germline mutations.

Our findings are consistent with existing research into the impact of age on surgical decisions and treatment outcomes in BCs. Various studies investigated surgical treatment patterns and choices, emphasizing trends toward less invasive options and variations in surgical procedures based on age and cancer characteristics [36, 37]. According to Martin et al., tumor location and patient preferences influence surgical decision-making [38]. Moreover, Kim et al. and Wen et al. investigated the impact of genetic predisposition on surgical choices and BC risk, underlining the importance of including hereditary factors in treatment planning [39, 40].

Significant variations in OS and DFS were observed among age groups. The 5-year OS rate was 95.55%, with women aged 45–69 exhibiting the highest survival and those aged ≥ 70 the lowest. Although our retrospective design limits definitive cause-and-effect conclusions, the findings suggest that a higher prevalence of advanced-stage disease, less frequent use of non-surgical treatments, and competing mortality risks in older patients contribute to these disparities. Even after adjusting for multiple factors and using breast cancer-specific survival as the primary endpoint, older age remains independently linked to poorer outcomes. These findings follow Miller et al. results that indicate that overall survival stems from a complex interplay of factors, including age, comorbidities, frailty, and treatment type, suggesting that no single component can fully account for survival outcomes [41]. In line with Miller et al., our analysis revealed that breast-conserving surgery is associated with better overall survival than mastectomy, regardless of patient age [41]. Our findings, consistent with those reported by Wyld et al. [42] and Hind et al. [43], indicate that in older, frail women with early-stage breast cancer, overall survival related to cancer mortality did not differ significantly between patients receiving primary oncological therapy and those undergoing primary surgery. Wyld et al. conducted a cluster randomized trial showing that de-escalating treatment in older populations, when following an adequately informed pathway, did not affect survival rates [42]. Nonetheless, inadequate case

(See figure on next page.)

Fig. 1 These graphs illustrate the trend in breast cancer patients' age over time (2002–2023). Panel **A** shows the proportion of breast cancer patients by age group (< 45 years, 45–69 years, ≥ 70 years) treated at the Breast Unit from 2002 to 2023. The x-axis indicates calendar years, and the y-axis indicates the proportion of patients (in %). The three stacked regions represent the age groups: < 45 years (yellow), 45–69 years (blue), and ≥ 70 years (red). These data illustrate how the age distribution of breast cancer patients has changed over time. The yearly incidence of the subgroup ≥ 70 in the age categories has significantly increased over time (Kendall $p < 0.001$ and Sen's slope 0.725). Panel **B** displays the yearly standardized incidence rate (rates per 100,000 women) of breast cancer in the local population over time from 2002 to 2023. The x-axis indicates calendar years, and the y-axis indicates the incidence rate (per 100,000). The solid black line represents the entire population, while the colored/dashed lines show incidence rates by age group (< 45 years, 45–69 years, and ≥ 70 years). A significant upward trend is observed for women ≥ 70 years ($p < 0.001$). Panel **C** shows the cumulative percentage change in local breast cancer incidence for each age group (< 45 years, 45–69 years, and ≥ 70 years) from 2002 to 2023. The x-axis indicates calendar years, and the y-axis indicates the relative percentage change compared with the baseline (2002). Each colored band represents the temporal trend and any accompanying uncertainty around the estimates. A pronounced increase is observed in the ≥ 70 years group, confirming the significant rise in incidence for older women

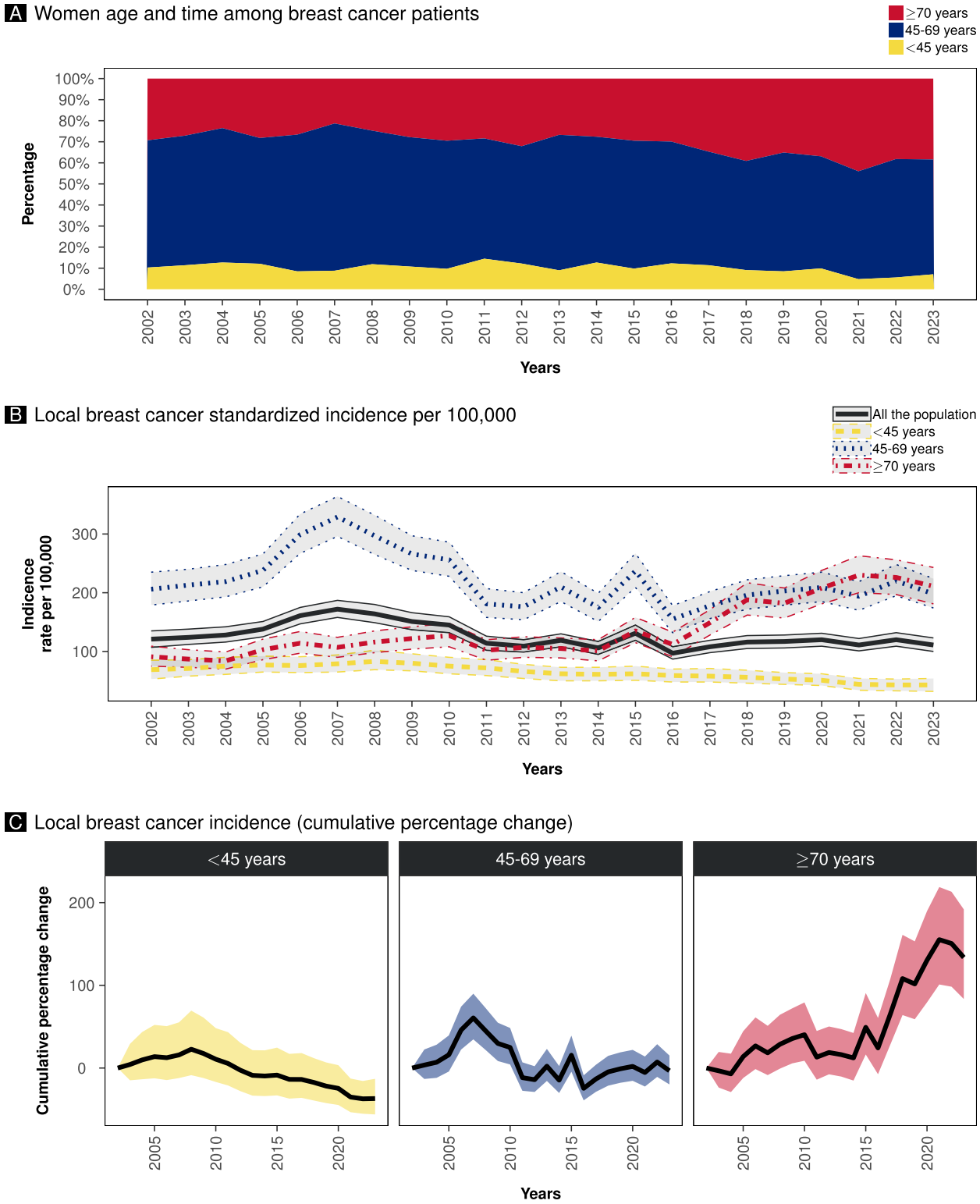

Fig. 1 (See legend on previous page.)

Table 2 Comparative analysis of tumor characteristics across age groups

Variables	All population	< 45 years (795)	45–69 years (4690)	≥ 70 years (2478)	p(*)	p(†)
Tumor characteristics						
Tumor histology					< 0.001	
Invasive carcinoma non-special type	67.84% (5402/7963)	75.97% (604/795)	66.33% (3111/4690)	68.08% (1687/2478)		1,2
Lobular invasive carcinoma	11.64% (927/7963)	6.42% (51/795)	11.19% (525/4690)	14.16% (351/2478)		1,2,3
Ductal and lobular invasive carcinoma	4.33% (345/7963)	3.52% (28/795)	4.56% (214/4690)	4.16% (103/2478)		NS
Other invasive carcinoma	3.89% (310/7963)	4.03% (32/795)	3.01% (141/4690)	5.53% (137/2478)		3
Ductal in situ carcinoma	12.29% (979/7963)	10.06% (80/795)	14.90% (699/4690)	8.07% (200/2478)		1,3
Tumor type					< 0.001	
Luminal A	30.11% (2398/7963)	20.38% (162/795)	30.09% (1411/4690)	33.29% (825/2478)		1,2,3
Luminal B	28.27% (2251/7963)	29.69% (236/795)	26.42% (1239/4690)	31.32% (776/2478)		3
Luminal Her	6.27% (499/7963)	12.20% (97/795)	5.88% (276/4690)	5.08% (126/2478)		1,2
Her enriched	4.19% (334/7963)	7.04% (56/795)	4.33% (203/4690)	3.03% (75/2478)		1,2,3
Basal-like	8.02% (639/7963)	11.19% (89/795)	7.83% (367/4690)	7.38% (183/2478)		1,2
Nondescript	23.13% (1842/7963)	19.50% (155/795)	25.46% (1194/4690)	19.90% (493/2478)		1,3
Ki-67/Mib-1 > 20%	41.45% (2529/6102)	58.51% (368/629)	40.45% (1409/3483)	37.79% (752/1990)	< 0.001	1,2
Comedo-like necrosis	12.14% (967/7963)	15.97% (127/795)	13.82% (648/4690)	7.75% (192/2478)	< 0.001	2,3
Multifocality/multicentricity	17.03% (1356/7963)	22.64% (180/795)	17.68% (829/4690)	14.00% (347/2478)	< 0.001	1,2,3
EIC	17.23% (1372/7963)	24.78% (197/795)	18.12% (850/4690)	13.12% (325/2478)	< 0.001	1,2,3
PVI	18.16% (1446/7963)	0.00% (0/795)	0.02% (1/4690)	0.00% (0/2478)	0.705	NS
Peritumoral inflammation	1.96% (156/7963)	0.00% (0/795)	0.02% (1/4690)	0.00% (0/2478)	0.705	NS
Lymph node characteristics						
Non axillary loco-regional lymph nodes	0.9% (72/7963)	0.88% (7/795)	1.19% (56/4690)	0.36% (9/2478)	0.002	3
Isolated tumor cells	1.29% (103/7963)	2.14% (17/795)	1.34% (63/4690)	0.93% (23/2478)	0.028	2
Micrometastasis	5.43% (432/7963)	6.79% (54/795)	5.69% (267/4690)	4.48% (111/2478)	0.020	2,3
Macrometastasis	24.1% (1919/7963)	29.43% (234/795)	22.71% (1065/4690)	25.02% (620/2478)	< 0.001	1,2,3
Extracapsular invasion of lymph node metastasis	5.86% (467/7963)	7.04% (56/795)	5.54% (260/4690)	6.09% (151/2478)	0.211	NS
Matted axilla lymph nodes	1.96% (156/7963)	1.13% (9/795)	1.81% (85/4690)	2.50% (62/2478)	0.028	2

(*) Differences among groups. (†) Group-to-group analyses that, in the case of factor variables with more than two levels, were conducted after dummifying variables. Differences statistically significant ($p < 0.05$): 1) < 45 years v.s. 45–69 years; 2) < 45 years v.s. ≥ 70 years; 3) 45–69 years v.s. ≥ 70 years. *Acronyms*: *EIC* Extensive intraductal component, *PVI* Perivascular invasion

selection for primary endocrine therapy in older women may result in poorer survival outcomes compared to breast-conserving surgery [44]. Additionally, in older women with early breast cancer at high risk of recurrence, chemotherapy is linked to enhanced breast cancer-specific survival [15]. Recent research by Gannon et al., utilizing the England Cancer Registry data, indicates that older women demonstrate lower adherence to NICE-recommended therapy regimens, potentially impacting treatment outcomes [45]. However, our data do not provide the granularity to confirm this result. Younger women had lower DFS, likely due to more aggressive disease. Cox regression analyses confirmed that older age at diagnosis predicts higher tumor-related mortality and shorter DFS, supporting previous literature that age is a predictor of breast cancer outcomes [2, 24, 33].

Lima et al. examined BC trends from 1990 to 2017 in various age groups, including 70-year-olds [33]. Their study found that BC incidence and mortality in this age group have increased worldwide. Even after controlling for fertility rates, the annual percent change in BC incidence in people ≥ 70 was significant [33], suggesting that other factors may influence these trends. Death rates for those ≥ 70 also rose, indicating a global trend of rising BC mortality in older populations [33]. Also, Wadasadawala et al. found age associated with reduced relapse-free and overall survival [46]. The increase in mortality may be due to a lack of access to effective screening and advanced treatments, which are more common in younger populations or high-income countries.

Schonberg et al. analyzed SEER-Medicare data from 1992 to 2003, tracking women with BC until 2006 [2, 47]. They found that 80-year-old women with stage I/II BC, despite having similar tumor characteristics as younger women, received less aggressive treatment and had higher mortality rates for early-stage BC. Older

Table 3 Comparison of tumor staging by age group

Variables	All population	< 45 years (795)	45–69 years (4690)	≥ 70 years (2478)	p(*)	p(†)
Tumor staging						
Tumor size					< 0.001	
Tis	12.29% (979/7963)	10.06% (80/795)	14.90% (699/4690)	8.07% (200/2478)		1,3
T1	64.02% (5098/7963)	62.01% (493/795)	66.16% (3103/4690)	60.61% (1502/2478)		1,3
T2	19.7% (1569/7963)	23.27% (185/795)	16.48% (773/4690)	24.66% (611/2478)		1,3
T3	2.07% (165/7963)	3.77% (30/795)	1.54% (72/4690)	2.54% (63/2478)		1,3
T4	1.91% (152/7963)	0.88% (7/795)	0.92% (43/4690)	4.12% (102/2478)		2,3
Nodal status					< 0.001	
N0	67.89% (4959/7304)	61.55% (461/749)	69.38% (3014/4344)	67.12% (1484/2211)		1,2
N1	21.14% (1544/7304)	23.77% (178/749)	20.79% (903/4344)	20.94% (463/2211)		NS
N2	5.56% (406/7304)	8.28% (62/749)	4.83% (210/4344)	6.06% (134/2211)		1,2,3
N3	5.41% (395/7304)	6.41% (48/749)	5.00% (217/4344)	5.88% (130/2211)		NS
stage3					< 0.001	
0-I	60.48% (4761/7872)	50.70% (397/783)	65.08% (3030/4656)	54.83% (1334/2433)		1,2,3
II	24.05% (1893/7872)	27.46% (215/783)	22.01% (1025/4656)	26.84% (653/2433)		1,3
III	11.37% (895/7872)	17.24% (135/783)	9.84% (458/4656)	12.41% (302/2433)		1,2,3
IV	4.1% (323/7872)	4.60% (36/783)	3.07% (143/4656)	5.92% (144/2433)		1,3
Tumor grading					< 0.001	
G1	14.22% (1101/7740)	9.11% (70/768)	15.40% (703/4564)	13.62% (328/2408)		1,2,3
G2	56.02% (4336/7740)	52.08% (400/768)	53.72% (2452/4564)	61.63% (1484/2408)		2,3
G3	29.75% (2303/7740)	38.80% (298/768)	30.87% (1409/4564)	24.75% (596/2408)		1,2,3

(*) Differences among groups. (†) Group-to-group analyses that, in the case of factor variables with more than two levels, were conducted after dummifying variables. Differences statistically significant ($p < 0.05$): 1) < 45 years v.s. 45–69 years; 2) < 45 years v.s. ≥ 70 years; 3) 45–69 years v.s. ≥ 70 years. *Acronyms*: *TNM* Tumor, Node, Metastasis (classification)

women often opted for less aggressive treatments, leading to higher mortality compared to younger groups [2]. Women with ductal carcinoma in situ or stage I BC had slightly lower mortality than controls, while those with stage II or higher BC faced higher mortality, indicating poorer outcomes due to delayed diagnosis and less aggressive treatment [2, 47]. This is particularly relevant as some therapies offer greater benefits to the older population. For instance, He et al. demonstrated a significant advantage of radiotherapy after mastectomy in women over 65 years of age [48].

Vostakolaei et al. investigated the relationship between age at diagnosis and BC survival in Iran but, contrary to our findings, found that survival rates did not differ significantly across age groups once tumor stage, histological grade, and other factors were considered [49]. They also discovered that older patients typically had more advanced and poorly differentiated tumors [49]. In our setting, young women may receive newly developed treatments that justify the more aggressive therapeutic approach and partially explain our population's different outcomes from those of Vostakolaei et al.

Treatment decisions for women over 70 are complicated by their psychological, clinical traits, and prognosis [49, 50]. Age-specific disparities in treatment and survival are also highlighted [51–53]. Understanding the impact of age on disease severity, treatment choices, responses, and long-term outcomes is vital for enhancing care and survival for all ages. Young women often face more aggressive forms of BC and poorer outcomes than older women, necessitating tailored, multidisciplinary approaches to optimize health, maintain quality of life, and address specific issues like fertility and mental and sexual health [34]. Conversely, older women should receive personalized treatment strategies as well, as recent studies show that age should not restrict BC management, highlighting that inadequate treatment can reduce survival chances in this group [15, 54].

Strengths and weaknesses

The study's strengths encompass two decades of data collection, a diverse age range, multidisciplinary patient management, and comprehensive tumor characteristics. The strengths enhance the credibility and depth of the findings. Nonetheless, it is important to acknowledge several limitations. The retrospective design may introduce biases in data selection and collection, precluding the determination of causality. The analysis of non-surgical treatments is constrained by incomplete data concerning chemotherapy-related variables, such

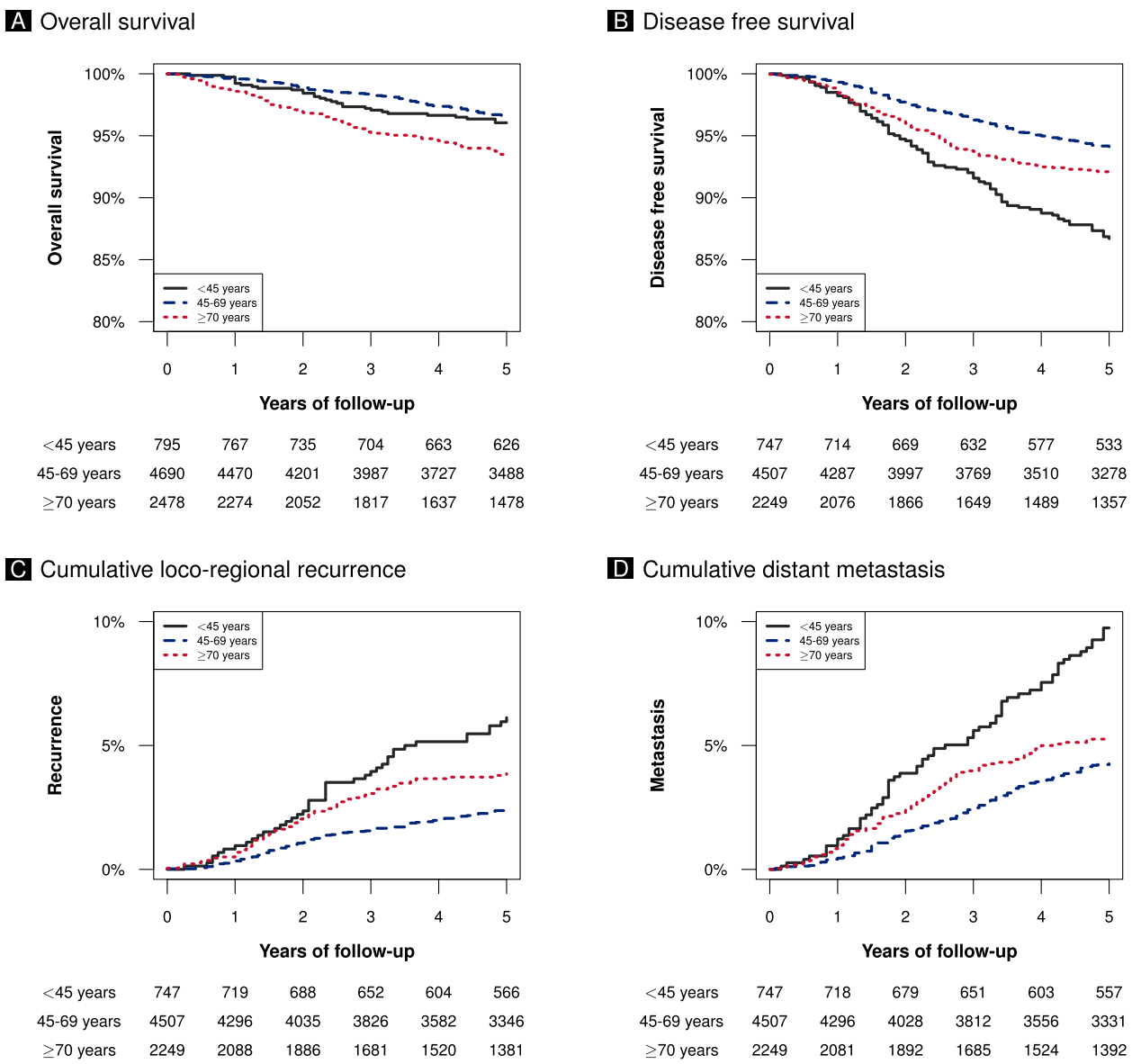

Fig. 2 These panels display the Kaplan–Meier analyses (stage IV at diagnosis and patients who did not undergo surgery were excluded from Panels **B**, **C**, and **D**). Panel **A** shows overall survival (OS) [only cancer-related mortality], with statistically significant differences between < 45 years vs. ≥ 70 years ($p = 0.010$) and 45–69 years vs. ≥ 70 years ($p < 0.001$). The 5-year OS rates were 96.05% (CI.95 94.64–97.47%) for < 45 years, 96.51% (CI.95 95.94–97.08%) for 45–69 years, and 93.43% (CI.95 92.36–94.52%) for ≥ 70 years. Panel **B** depicts disease-free survival (DFS), with all three curves significantly different from each other ($p < 0.001$). The 5-year DFS rates were 86.69% (CI.95 84.19–89.27%) for < 45 years, 94.12% (CI.95 93.39–94.85%) for 45–69 years, and 92.03% (CI.95 90.81–93.26%) for ≥ 70 years. Panel **C** shows the cumulative loco-regional recurrence rate, with significant differences between 45–69 years vs. < 45 years and ≥ 70 years ($p < 0.001$), and between < 45 years vs. ≥ 70 years ($p = 0.022$). The 5-year cumulative loco-regional recurrence rates were 6.13% (CI.95 4.31–7.91%) for < 45 years, 2.40% (CI.95 1.92–2.88%) for 45–69 years, and 3.86% (CI.95 2.99–4.73%) for ≥ 70 years. Panel **D** shows the cumulative distant metastasis rate, with statistically significant differences between < 45 years vs. 45–69 years and ≥ 70 years ($p < 0.001$), and between 45–69 years vs. ≥ 70 years ($p = 0.042$). The 5-year cumulative distant metastasis rates were 9.74% (CI.95 7.49–11.94%) for < 45 years, 4.26% (CI.95 3.63–4.89%) for 45–69 years, and 5.26% (CI.95 4.24–6.26%) for ≥ 70 years

as side effects, treatment interruptions, specific medication regimens, potential underdosing, more common in older women [45], therapies for prior malignancies, and patient performance status. Despite our efforts to address these limitations through a comprehensive review of clinical records and the inclusion of detailed data on comorbidities and prior cancer diagnoses, certain specific information remained inaccessible from historical records. Furthermore, the utilization of routinely collected clinical data may lead to measurement

Table 4 Univariate and multivariate (*) Cox regression analysis for overall survival (OS) (events 299). The table is displaying the hazard ratios (HRs), 95% confidence intervals (CIs), and *p*-values for each predictor under univariate and multivariate conditions (*). In this analysis, we excluded cases of ductal in situ carcinoma

Variables	HR (CI.95)	p	HR (CI.95)(*)	p(*)
Overall survival				
Age categories				
45–69 years	Reference	–-	Reference	–-
< 45 years (0–36 months)	1.54 (0.95—2.50)	0.079	1.16 (0.71—1.92)	0.548
≥ 70 years (0–36 months)	2.50 (1.85—3.37)	< 0.001	2.31 (1.63—3.27)	< 0.001
< 45 years (> 36 months)	0.57 (0.26—1.24)	(†)	0.31 (0.12—0.77)	(†)
≥ 70 years (> 36 months)	1.01 (0.66—1.54)	(‡)	0.96 (0.60—1.56)	(‡)
TNM stage II-III-IV	9.93 (6.95—14.2)	< 0.001	6.72 (4.45—10.15)	< 0.001
Tumor grading G2-G3	5.51 (2.93—10.35)	< 0.001	2.18 (1.01—4.68)	0.046
Tumor histology				
Invasive carcinoma non-special type	Reference	–-	–-	–-
Lobular invasive carcinoma	1.25 (0.91—1.71)	0.166	–-	–-
Ductal and lobular invasive carcinoma	0.96 (0.57—1.61)	0.865	–-	–-
Other invasive carcinoma	1.45 (0.88—2.37)	0.143	–-	–-
Non luminal A tumor type	4.66 (3.21—6.76)	< 0.001	2.36 (1.49—3.74)	< 0.001
Ki-67/Mib-1 > 20%	3.41 (2.61—4.45)	< 0.001	1.37 (0.99—1.90)	0.061
Comedo-like necrosis	0.79 (0.50—1.24)	0.308	–-	–-
Multifocality/multicentricity	1.14 (0.86—1.51)	0.366	–-	–-
EIC	0.52 (0.36—0.74)	< 0.001	0.75 (0.50—1.13)	0.169
PVI	1.47 (1.14—1.89)	0.003	0.90 (0.67—1.19)	0.450
Peritumoral inflammation	0.94 (0.78—1.12)	0.475	–-	–-
Comorbidities				
None	Reference	–-	Reference	–-
One	0.67 (0.49—0.92)	0.013	0.64 (0.46—0.91)	0.013
Two	1.13 (0.79—1.62)	0.500	0.78 (0.52—1.18)	0.248
Three or more	1.99 (1.20—3.31)	0.008	1.11 (0.63—1.96)	0.721
Previous neoplasia	1.33 (0.93—1.91)	0.122	–-	–-
No surgery	9.81 (6.84—14.07)	< 0.001	3.66 (2.46—5.44)	< 0.001

Time-dependent covariates modeled using step functions: (†) Not significantly different than 0–36 months; (‡) Significantly different than 0–36 months. *Acronyms*: *EIC* Extensive intraductal component, *PVI* Perivascular invasion, *TNM* Tumor, Node, Metastasis (classification)

errors or misclassification bias. Second, while our overall cohort is substantial, certain subgroups exhibited limited numbers, potentially leading to less precise performance estimates and heightened uncertainty within those strata. Third, while we improved our statistical approach by incorporating time-dependent covariates into the Cox proportional hazards model and conducting rigorous tests to validate the proportional hazards assumption, residual confounding factors may still be missing from our analysis. Specifically, the lack of detailed data on smoking status (divided into never, former, and current users) and alcohol consumption could influence patient outcomes and were not taken into account. However, in a sensitivity analysis, smokers without stratification in current and former users did not alter the relationship between women's age at diagnosis and survival. In contrast to women's age at diagnosis, a well-established prognostic factor, some studies suggest that while alcohol is a well-established risk factor for breast cancer development, its role in modifying prognosis post-diagnosis remains unclear [7, 55, 56]. According to these findings, we believe that additional information on alcohol consumption or tobacco habits would not have changed our results. Finally, while we expanded our assessment of comorbidities, the limited availability of certain patient data may have underestimated their impact on treatment decisions and outcomes, particularly in older women. Comorbidities, previous cancer history, and whether surgery was performed served as proxies for adjuvant treatment contraindications, but they may not capture all of the nuances that influence clinical decisions.

Table 5 Univariate and multivariate (*) Cox regression analysis for disease-free survival (DFS) (events 480). The table is displaying the hazard ratios (HRs), 95% confidence intervals (CIs), and *p*-values for each predictor under univariate and multivariate conditions (*). In this analysis, we excluded cases that were stage IV at diagnosis and did not receive surgical treatment

Variables	HR (CI.95)	p	HR (CI.95)(*)	p(*)
Age categories				
45–69 years	Reference	–-	Reference	–-
< 45 years (0–36 months)	2.32 (1.72—3.13)	< 0.001	1.73 (1.25—2.40)	0.001
≥ 70 years (0–36 months)	1.72 (1.36—2.17)	< 0.001	1.58 (1.21—2.08)	< 0.001
< 45 years (> 36 months)	2.42 (1.60—3.64)	(†)	1.91 (1.23—2.97)	(†)
≥ 70 years (> 36 months)	0.82 (0.53—1.26)	(‡)	0.70 (0.43—1.14)	(‡)
TNM stage II-III	4.15 (3.41—5.04)	< 0.001	2.44 (1.94—3.07)	< 0.001
Tumor grading G2-G3	3.66 (2.47—5.44)	< 0.001	1.96 (1.17—3.28)	0.011
Tumor histology				
Invasive carcinoma non-special type	Reference	–-	Reference	–-
Lobular invasive carcinoma	1.04 (0.80—1.36)	0.765	1.17 (0.86—1.59)	0.317
Ductal and lobular invasive carcinoma	0.92 (0.61—1.40)	0.705	0.95 (0.59—1.54)	0.847
Other invasive carcinoma	0.80 (0.47—1.33)	0.387	0.87 (0.50—1.52)	0.622
Ductal in situ carcinoma	0.23 (0.14—0.38)	< 0.001	1.48 (0.55—4.04)	0.439
Non luminal A tumor type	3.39 (2.58—4.46)	< 0.001	2.25 (1.59—3.20)	< 0.001
Ki-67/Mib-1 > 20%	3.39 (2.75—4.17)	< 0.001	1.59 (1.22—2.07)	< 0.001
Comedo-like necrosis	1.09 (0.83—1.44)	0.531	–-	–-
Multifocality/multicentricity	1.31 (1.05—1.62)	0.016	1.13 (0.89—1.43)	0.308
EIC	1.03 (0.82—1.30)	0.812	–-	–-
PVI	2.18 (1.80—2.64)	< 0.001	1.14 (0.92—1.41)	0.226
Peritumoral inflammation	1.01 (0.99—1.04)	0.219	–-	–-
Comorbidities				
None	Reference	–-	Reference	–-
One	0.83 (0.66—1.05)	0.126	0.86 (0.66—1.13)	0.274
Two	1.42 (1.09—1.86)	0.01	1.41 (1.03—1.93)	0.033
Three or more	1.06 (0.59—1.88)	0.85	0.85 (0.44—1.62)	0.612
Previous neoplasia	1.46 (1.10—1.93)	0.008	1.37 (1.00—1.88)	0.048

Time-dependent covariates modeled using step functions: (†) Not significantly different than 0–36 months; (‡) Significantly different than 0–36 months. *Acronyms*: *EIC* Extensive intraductal component, *PVI* Perivascular invasion, *TNM* Tumor, Node, Metastasis (classification)

Relevance of the findings, generalizability, unanswered questions, and future research

Our findings emphasize the need to customize treatment protocols for different age groups, especially older women, to balance effective cancer management with quality of life. We agree with Chadha et al. [57] that improving outcomes for older women requires prospective trials to determine optimal, age-adjusted, risk-tailored non-surgical and surgical therapies, with systematic geriatric assessments as a key component. Although these insights may influence global clinical practices as the population ages, regional healthcare systems and demographic variations could limit their universal applicability. Further research is needed to translate these findings into clinical practice and public health policy, focusing on identifying patient and tumor characteristics that optimize targeted treatment and developing adaptable strategies to reduce cancer control and prevention disparities.

Conclusions

Our study found a significant increase in BC cases in women ≥ 70. This age group has different management patterns and outcomes than the 45–69 group, indicating different treatment approaches and prognoses. Despite older women's advanced cancer diagnosis, they tend to receive less aggressive treatment, including less adjuvant hormone therapy or chemotherapy. Our findings suggest that more research on this demographic is needed to refine and personalize treatment protocols. This approach has to balance efficacy and quality of life. Future clinical trials should include older women to ensure treatment decisions represent this growing patient population. We hope this approach will

improve patient management and outcomes through targeted research and clinical focus, bringing survival rates closer to younger cohorts.

Abbreviations

AJCC	American Joint Committee on Cancer
BC	Breast Cancer
BCN	Breast Care Nurse
BCS	Breast-Conserving Surgery
BMI	Body Mass Index
CALND	Complete Axillary Lymph Node Dissection
CI.95	95% Confidence Interval
DFS	Disease-Free Survival
EIC	Extensive intraductal component
ER	Estrogen Receptor
HR	Hazard Ratio
IQR	Interquartile Range
IRB	Internal Review Board
MDM	Multidisciplinary Meetings
MTM	Modified Total Mastectomy
NSM	Nipple-Sparing Mastectomy
OS	Overall Survival
OSNA	One-Step Nucleic Acid Amplification
PR	Progesterone Receptor
PVI	Perivascular invasion
ROLL	Radio-Guided Occult Lesion Localization
SLNB	Sentinel Lymph Node Biopsy
SSM	Skin-Sparing Mastectomy
TNM	Tumor, Node, Metastasis (classification)
UICC	Union for International Cancer Control
VUS	Variant of Uncertain Significance

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Condensation
Our findings emphasize the need for tailored treatment strategies for older breast cancer patients to balance efficacy and quality of life. These findings suggest reevaluating treatment protocols and emphasizing the importance of personalized care, especially for the elderly, to improve outcomes without sacrificing quality of life and maximize survival.

Authors' contributions
Substantial contributions to conception and design or acquisition of data or to analysis and interpretation of data (SB, APL, JADN, RD, BB, LL, SP, LS, LM, CC). Drafting the article or revising it critically for important intellectual content (SB, APL, JADN, RD, BB, LL, SP, LS, LM, CC). All authors have read and approved the final manuscript.

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Data availability
The data that support the findings of this study are available. However, restrictions apply to the availability of these data, which were used under license for the current study and are not publicly available. Data are, however, available from the authors upon reasonable request and with permission of the Internal Review Board.

Declarations

Ethics approval and consent to participate
The present study was approved by the internal review board of the Department of Medical Area (University of Udine). It was conducted per the Helsinki Declaration and followed the dictates of the general authorization to process personal data for scientific research purposes by the Italian Data Protection Authority. According to national legislation, the need for informed consent was waived by the IRB listed above because this was a retrospective cohort study.

Consent to publication
Not applicable.

Competing interests
The authors declare no competing interests.

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