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Real-world, single-centre prospective data of age at breast cancer onset: focus on survival and reproductive history

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ABSTRACT

Objectives Being either young or old at the time of breast cancer diagnosis has been suggested as an indicator of a poor prognosis. We studied the effect of age at breast cancer onset in relation to survival, focusing in particular on biological subtypes and reproductive anamnesis.

Design, setting and participants Patients with early breast cancer (n=594) treated in a Finnish University Hospital during 2003–2013 were prospectively collected and followed in median 102 months.

Results Patients with luminal A-like breast cancer were older than the patients with luminal B-like (HER2-positive) (p=0.045) or patients with the HER2-positive (non-luminal) subtype (p=0.029). Patients ≥70 years received substantially less adjuvant chemotherapy (p=1.5×10^{-9}) and radiotherapy (p=5.9×10^{-7}) than younger women. Nevertheless, the estimated 10-year breast cancer-specific rates of survival were 84.2%, 92.9% and 87.0% in age groups <41 years, 41–69 years and ≥70 years, respectively, with no statistical difference (p=0.115). Survival rates were also comparable between the three age groups when assessed separately in different biological subtypes, and for patients with metastatic breast cancer there was similarly no difference between the age groups. Later menarche (p=5.7×10^{-8}) and high parity (p=0.000078) correlated with increased age at breast cancer diagnosis, but, according to the patients' oestrogen receptor (ER) status, only among ER-positive patients.

Conclusions Despite the suggested undertreatment of older patients, we report excellent long-term outcomes in all age groups in this prospective cohort. Later endogenous endocrine exposure may cause delay in breast cancer onset, but the exact biology behind this phenomenon is so far unclear.

INTRODUCTION

Age is a very strong risk factor for breast cancer.[1] Prolonged endogenous oestrogen exposure, such as early menarche, late menopause or a low number of deliveries, leads to increased breast mitotic activity and a higher probability of tumorigenic somatic events, which are subsequently also important breast cancer risk factors.[2 3] Young patients with breast cancer (<35 years) have biologically more aggressive breast cancers, with a higher proportion of oestrogen receptor (ER)-negative, high-grade cancers. These

Strengths and limitations of this study

► This was a study of contemporary, prospective breast cancer cohort in a university hospital with a relatively long follow-up.
► The material did not include patients with de novo metastatic breast cancer.
► The number of patients with the certain breast cancer subtypes could have been larger to make more detailed subgroup analyses possible.

women may, consequently, have poorer outcomes than older patients, and this difference remains even after the adjustment of prognostic factors.[4 5] On the other hand, there are convincing data that patients with breast cancer >65 years old have a shortened survival because the cancer is at a later stage at diagnosis and less intensive treatments are offered.[6]

In 2000, Perou *et al*[7] classified breast carcinomas into four 'intrinsic' subtypes with gene expression profiling. Although still a largely simplified version of the real heterogeneity, invasive breast cancer is nowadays most commonly categorised into five subtypes: luminal A-like, luminal B-like (HER2-negative), luminal B-like (HER2-positive), triple-negative or HER2-positive (non-luminal), which differ in terms of both their molecular constitutions and patient outcomes. These subtypes can be classed rather reliably using immunohistochemical (IHC) surrogates, according to the European Society for Medical Oncology (ESMO) 2015 Early Breast Cancer Clinical Practice Guidelines.[8] There is some evidence that age as a prognostic factor in breast cancer is dependent on biological subtype,[9 10] as, for example, young age has been associated with a poorer outcome, especially in luminal subtypes.[9]

Since most previous studies assessing age as a prognostic factor have used cohorts from the 20th century, we wanted to evaluate the age at breast cancer onset and its relation to

biological subtypes, traditional prognostic factors and survival in a modern, prospective cohort from a university hospital. Special emphasis was given to the possible relationship between reproductive factors, such as age at menarche, number of deliveries and age at menopause, and the age at breast cancer onset.

METHODS

Patient data for this study were prospectively collected at Oulu University Hospital in 2003–2013. All women (n=594) had been diagnosed with early, invasive breast cancer and they at least began to receive treatment at Oulu University Hospital (table 1). Patients with previous breast cancer diagnoses or distant metastases at the time of diagnosis were excluded from the study to avoid the possibility of local recurrences misdiagnosed as new breast cancers.

Tumours were classed into five intrinsic subtypes according to the ESMO Early Breast Cancer Clinical Practice Guidelines.[8] Luminal A-like carcinomas expressed both ER and progesterone receptors (PR), but HER2 was not overexpressed and Ki-67 was expressed in <15% of their cells. Luminal B-like (HER2-negative) carcinomas were also ER-positive and HER2-negative, but they either showed Ki-67 expression in >15% of their cells or were PR-negative. Luminal B-like (HER2-positive) carcinomas still expressed ER, but they also overexpressed HER2. Triple-negative breast cancers (TNBCs) were defined as tumours with no expression of ER, PR and HER2. HER2-positive (non-luminal) cases overexpressed HER2 but did not express either ER or PR.

Histopathology was assessed according to current WHO classifications, and the tumour stage was evaluated according to the TNM Classification of Malignant Tumours.[11] The expressions of ER, PR and Ki-67 were assessed using the IHC methods previously described.[12] HER2 expression was then assessed using IHC and chromogenic in situ hybridisation (CISH) to confirm any positive results. Any sample with a positive result of six or more gene copies according to CISH was considered to be HER2-positive.[13]

Statistical analyses

Statistical analyses were performed using SPSS Statistics software V.25.0 for Mac (IBM Corporation). In the analyses, age was assessed mainly using three age classes as parameters: <41 years, 41–69 years and ≥70 years. In addition, age was correlated as a continuous variable with other continuous variables of reproductive history (parity, age at menarche and menopausal age). Survival was analysed using Kaplan-Meier curves and the log-rank test. Breast cancer-specific survival (BCSS) was calculated from the date of surgical tumour removal to the time of breast cancer-related death or the end of follow-up. Relapse-free survival (RFS) was calculated from the date of the operation to the date of the first confirmed local relapse in ipsilateral or contralateral axilla, scar or breast.

Distant disease-free survival (DDFS) was calculated from the date of the operation to the date of the first confirmed distant relapse. Survival with metastatic breast cancer was calculated from the time of distant metastases diagnosis to the time of breast cancer-related death or the end of follow-up. Prognostic factors were reformatted as two-class variables for the analyses. Multivariate analyses were conducted using Cox multivariate regression analyses, where the covariates were tumour size and nodal status; tumour sizes were assessed as either T1 or T2–4 and nodal status was categorised as either N0 or N1–3. Cross-tabulation was used to compare the groups and two-sided Pearson's X^2 test or Fisher's exact test was used, as applicable, to determine significance. Continuous variables were assessed using Pearson correlation, the Mann-Whitney U test or the Kruskal-Wallis test. P values <0.05 were considered significant.

Data accessibility

The data that support the findings of this study are available from the corresponding author on reasonable request.

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination of this study.

RESULTS

The median age at breast cancer onset was 58 years (range 28–87 years) and median follow-up time was 102.0 months (mean 103.9 months). The median survival with metastatic breast cancer was 18.0 months (mean 30.2 months). The median age at menarche was 13.0 years (range 10.0–17.0 years) and median menopause age 50.0 years (range 37.0–60.0 years). The median number of deliveries at the time of breast cancer diagnosis was 2 (range 0–10).

Among the women <41 years, median menopause age was 12.0 years and the median number of deliveries was 2. There were no menopauses at time of time of breast cancer diagnosis in this age group. Among women aged 41–69 years, the median age at menarche was 13.0 years, median menopause age was 50.0 years and the median number of deliveries was 2. These figures for women ≥70 years were 14.0 years, 52.0 years and 2 deliveries, respectively.

There were 35 (5.9%) local recurrences, 61 (10.3%) distant metastases and 50 (8.4%) breast cancer-related deaths during the follow-up. The majority of patients received adjuvant chemotherapy, endocrine therapy and radiotherapy (table 1). All 61 HER2-positive patients received trastuzumab in adjuvant setting. Of those receiving adjuvant endocrine therapy, 166 (42.1%) received tamoxifen and 222 (56.3%) aromatase inhibitor, and in 6 (1.5%) patients the exact adjuvant endocrine therapy was uncertain. Age at breast cancer onset was not associated with the first site of distant recurrence.

Table 1 Comparison of treatments and clinical and pathological characteristics of tumours according to age at breast cancer diagnosis

	Total	<41 years	41–69 years	≥70 years	P value
Number of patients	594	37 (6.2%)	472 (79.5%)	85 (14.3%)	
Tumour size					0.1 (T1 vs T2–4)
T1	384 (64.6%)	20 (54.1%)	315 (66.7%)	49 (57.6%)	
T2	189 (31.8%)	14 (37.8%)	144 (30.5%)	31 (36.5%)	
T3	19 (3.2%)	3 (8.1%)	12 (2.5%)	4 (4.7%)	
T4	2 (0.3%)	0 (0%)	1 (0.2%)	1 (1.2%)	
Nodal status					0.5 (N0 vs N1–3)
N0	368 (62.0%)	21 (56.8%)	298 (63.1%)	49 (57.6%)	
N1	162 (27.3%)	10 (27.0%)	125 (26.5%)	27 (31.8%)	
N2	50 (8.4%)	4 (10.8%)	40 (8.5%)	6 (7.1%)	
N3	14 (2.4%)	2 (5.4%)	9 (1.9%)	3 (3.5%)	
Histopathology					0.040
Ductal	456 (76.8%)	30 (81.1%)	368 (78.0%)	58 (68.2%)	
Lobular	91 (15.3%)	3 (8.1%)	74 (15.7%)	14 (16.5%)	
Other	47 (7.9%)	4 (10.8%)	30 (6.4%)	13 (15.3%)	
Multifocal cancer					0.57
Yes	122 (20.5%)	7 (18.9%)	101 (21.4%)	14 (16.5%)	
No	472 (79.5%)	30 (81.1%)	371 (78.6%)	71 (73.5%)	
Bilateral cancer					0.77
Yes	16 (2.7%)	1 (2.7%)	11 (2.3%)	4 (4.7%)	
No	578 (97.3%)	36 (97.3%)	461 (97.7%)	81 (95.3%)	
Histopathological grade					0.014 (grade I–II vs grade III)
Grade 1	103 (17.3%)	4 (10.8%)	82 (17.9%)	17 (21.3%)	
Grade 2	293 (49.3%)	14 (37.8%)	239 (52.2%)	40 (50.0%)	
Grade 3	179 (30.1%)	19 (51.4%)	137 (29.0%)	23 (27.1%)	
Unknown	19 (3.2%)	0 (0%)	14 (3.0%)	5 (5.9%)	
ER expression					0.000009 (negative vs positive)
Negative (0%)	92 (15.5%)	16 (43.2%)	65 (13.8%)	11 (12.9%)	
Weak (1%–9%)	18 (3.0%)	1 (2.7%)	15 (3.2%)	2 (2.4%)	
Moderate (10%–59%)	26 (4.4%)	1 (2.7%)	21 (4.4%)	4 (4.7%)	
High (>59%)	455 (76.6%)	19 (51.4%)	370 (78.4%)	66 (77.6%)	
Unknown	3 (0.5%)	0 (0%)	1 (0.2%)	2 (2.4%)	
PR expression					0.025 (negative vs positive)
Negative (0%)	146 (24.6%)	16 (43.2%)	110 (23.3%)	20 (23.5%)	
Weak (1%–9%)	81 (13.6%)	2 (5.4%)	68 (14.4%)	11 (12.9%)	
Moderate (10%–59%)	65 (10.9%)	4 (10.8%)	50 (10.6%)	11 (12.9%)	
High (>59%)	298 (50.2%)	15 (40.5%)	242 (51.3%)	41 (48.2%)	
Unknown	4 (0.7%)	0 (0%)	2 (0.4%)	2 (2.4%)	
HER2 status					0.36
HER2-negative	533 (89.7%)	33 (89.2%)	420 (89.0%)	80 (94.1%)	
HER2-positive (CISH)	61 (10.3%)	4 (10.8%)	52 (11.0%)	5 (5.9%)	
Ki-67 expression					0.0012 (0%–14% vs >14%)
Negative (<5%)	41 (6.9%)	2 (5.4%)	32 (6.8%)	7 (8.2%)	
Weak (5%–14%)	268 (45.1%)	7 (18.9%)	220 (46.6%)	41 (48.2%)	

Continued

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Table 1 Continued

	Total	<41 years	41–69 years	≥70 years	P value
Moderate (15%–30%)	141 (23.7%)	9 (24.3%)	111 (23.5%)	21 (24.7%)	
High (>30%)	136 (22.9%)	19 (51.4%)	104 (22.0%)	13 (15.3%)	
Unknown	8 (1.3%)	0 (0%)	5 (1.0%)	3 (3.5%)	
Subtype					0.00011
Luminal A-like	271 (46.2%)	9 (24.3%)	220 (46.6%)	42 (49.4%)	
Luminal B-like (HER2-negative)	192 (32.8%)	11 (29.7%)	156 (33.1%)	25 (29.4%)	
Luminal B-like (HER2-positive)	33 (5.6%)	1 (2.7%)	28 (5.9%)	4 (4.7%)	
HER2-positive (non-luminal)	27 (4.5%)	3 (8.1%)	23 (4.9%)	1 (1.2%)	
Triple-negative	63 (10.8%)	13 (35.1%)	40 (8.5%)	10 (11.8%)	
Unknown	8 (1.3%)	0 (0%)	5 (1.1%)	3 (3.5%)	
Adjuvant chemotherapy					1.5×10^{-9}
Yes	347 (58.4%)	32 (86.5%)	289 (61.2%)	26 (30.6%)	
No	247 (41.6%)	5 (13.5%)	183 (38.8%)	59 (69.4%)	
Taxane-based adjuvant chemotherapy					0.0097
Yes	190 (55.1%)	25 (78.1%)	156 (54.4%)	9 (34.6%)	
No	146 (42.3%)	7 (21.9%)	122 (42.5%)	17 (65.4%)	
Unknown	9 (2.6%)	0 (0%)	9 (3.1%)	0 (0%)	
Adjuvant radiotherapy					5.9×10^{-7}
Yes	514 (86.5%)	34 (91.9%)	472 (89.4%)	58 (68.2%)	
No	80 (13.5%)	3 (8.1%)	50 (10.6%)	27 (31.6%)	
Adjuvant endocrine therapy					0.060
Yes	391 (65.8%)	18 (48.6%)	319 (67.6%)	54 (63.5%)	
No	200 (33.7%)	18 (48.6%)	151 (32.0%)	31 (36.5%)	
Unknown	3 (0.5%)	1 (2.7%)	2 (0.4%)	0 (0%)	

CISH, chromogenic in situ hybridisation; ER, oestrogen receptor; PR, progesterone receptor.

Older age at breast cancer diagnosis correlated very closely with high parity (p=0.000078; correlation coefficient 0.17) and increased age at menarche (p=5.7×10^{-8}; correlation coefficient 0.25; figure 1). To a lesser extent, older age at diagnosis correlated with increased 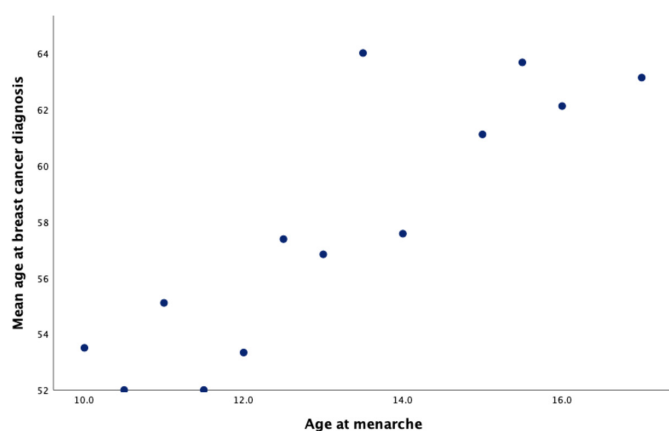menopausal age (p=0.018; correlation coefficient 0.15). When data were split according to the ER status, increased age correlated with high parity (p=0.00030; correlation coefficient 0.17), increased age at menarche (p=0.000002; correlation coefficient 0.24) and later menopause (p=0.013; correlation coefficient 0.17) among ER-positive patients only.

The median age at patients with breast cancer onset in luminal A-like was 58.0 years, luminal B-like (HER2-negative) 58.0 years, HER2-positive (non-luminal) 56.0 years, luminal B-like (HER2-positive) 53 years and 56.0 years in patients with TNBC (figure 2). When compared in pairs, the patients with luminal A-like breast cancer were older than the patients with luminal B-like (HER2-positive) (p=0.045) subtype or patients with HER2-positive (non-luminal) subtype (p=0.029). Additionally, women with luminal A-like breast cancers tended to be older than those with TNBC, but this was not a formally significant finding (p=0.081).

Figure 1 Age at menarche is strictly correlated with age at breast cancer diagnosis.

Age at breast cancer onset and survival
BCSS, DDFS, RFS or survival with metastatic breast cancer did not differ statistically significantly between the three age groups (figure 3). Similarly, no statistically significant
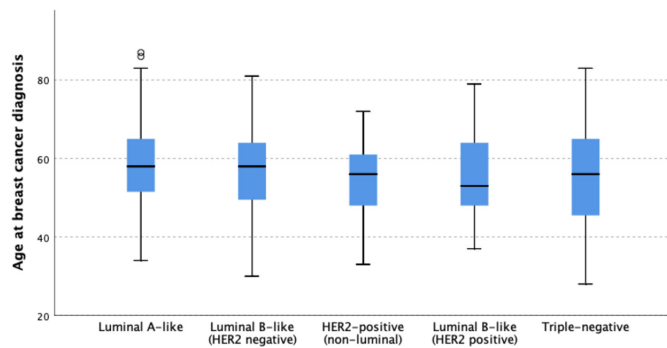
Figure 2 The distribution of breast cancer subtypes and age at diagnosis. When subtypes are compared in pairs, women with luminal A-like breast cancer are older than women with the luminal B-like (HER2-positive) (p=0.045) or those with the HER2-positive (non-luminal) subtype (p=0.029). The black line indicates median age, the blue boxes represent 25th and 75th percentiles, whiskers show variability outside the upper and lower quartiles, and circles represent outlier values.

differences were found when age groups were compared in pairs. Five-year estimated BCSS rates were 94.6%, 96.5% and 92.6%, and 10-year estimated BCSS rates were 84.2%, 92.9% and 87.0% in the age groups of <41 years, 41–69 years and ≥70 years, respectively.

Survival between the age groups was not statistically significantly different, when analysis was done separately in different biological subtypes. We also conducted a survival analysis according to ER and HER2 status, without taking Ki-67 into account. Although in the group of ER-positive and HER2-negative patients, BCSS and DDFS were shorter in <41-year-old women (p=0.042 and p=0.029, respectively), these differences were not significant in multivariate analysis.

The traditional prognostic factors, such as tumour size, nodal status, proliferation or intrinsic subtype, had a prognostic value (BCSS) of similar magnitude, when studied separately in the three age groups (data not shown). However, smaller number of patients limited the reliability of the analysis in <41-year-old women.

DISCUSSION

In this contemporary, prospective cohort of 594 women with early breast cancer, comparable survival rates between the age groups of <41 years, 41–69 years and ≥70 years are reported. Stratification by breast cancer biological subtype did not affect the survival results. Another main result from the data was that later menarche or an increased number of deliveries was very closely correlated with older age at breast cancer diagnosis.

Breast cancer onset is proportional to the median age of the underlying population at risk.[14] In this prospective study, the material median age at breast cancer diagnosis was 58.0 years, in line with most reports from Western countries with mammography screenings.[15 16] It has been reported that both young and old age at breast cancer onset indicates a poorer prognosis, compared

with 'middle-aged' women,[17 18] although this observation has not been present unanimously in all studies.[19 20] In addition, in the present work, the 'middle-aged' group of women (41–69 years old) had a statistically non-significant trend of the best BCSS and DDFS rates. Excellent BCSS rates in all age groups (10-year Kaplan-Meier estimate 91.4% in the whole cohort) may partly explain why larger differences between the groups were demonstrated in our study. Indeed, the survival rates were significantly better than reported in most previous studies assessing age and breast cancer prognosis. In a large Swedish cohort study, women either under 40 years or at least 80 years at diagnosis had the worst prognosis, while in the whole population, 10-year BCSS was slightly over 70%.[17] An Australian study, which used the same three age groups as we did, reported 10-year survival rates as low as 49% in women <40 years, while women aged 40–69 at diagnosis had a 10-year survival rate of 73%.[21]

Less frequent use of adjuvant (chemo)therapies and less optimal surgery due to comorbidities may at least partially explain the poorer prognosis of the elderly observed previously.[5 22 23] Younger women are likely to receive more intensive treatments, but they also have a tendency to develop more aggressive breast cancer subtypes.[24 25] In our cohort, almost 70% of patients ≥70 years did not receive adjuvant chemotherapy compared with fewer than 15% of women <41 years. Also, radiotherapy was considerably less frequently administered in older women. These differences may be due to frailty caused by many comorbidities and poor performance status among older women, which were not investigated in our study. The youngest patients had also more aggressive biological subtypes compared with the oldest patients, but these differences are small to explain all discrepancies in the administration of adjuvant chemotherapy. Moreover, the oldest patients experienced more mastectomies and hence received less radiotherapy. On the other hand, all HER2-positive patients received trastuzumab as an adjuvant therapy. Since prognosis did not differ between the age groups in the current study, despite significant differences in the use of adjuvant treatments, there is a possibility that younger patients were overtreated, rather than that older patients were undertreated.

It has been proposed that the effect of age on survival may vary by breast cancer subtype. A large longitudinal cohort study provided evidence that women 40 years old or younger had worse BCSS, but only if they had luminal A-like tumours, determined in that study as ER-positive and/or PR-positive, HER2-negative and low/intermediate-grade tumours.[9] In a retrospective study by Liu *et al*,[10] the authors used almost the same criteria for biological subtypes as in the current study, concluding that the patients <41 years old at diagnosis had worse disease-free survival or DDFS, but only if the patients had luminal A-like breast cancer. Similarly, an age of <41 years was found to be an adverse prognostic factor in luminal A-like or luminal B-like cancers.[26] We found that luminal A-like cancers were over-represented among the oldest
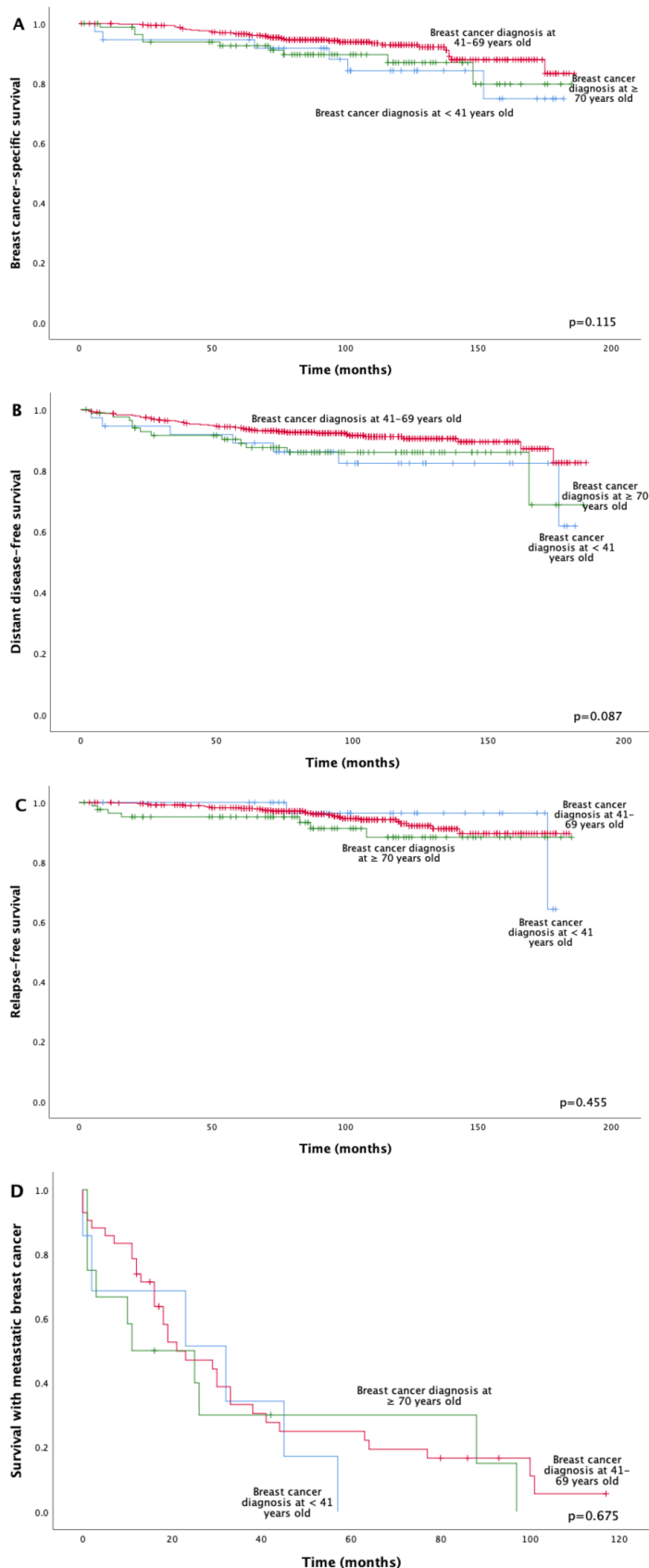
Figure 3 Kaplan-Meier plot for breast cancer-specific survival (A), distant disease-free survival (B), local relapse-free survival (C), survival with metastatic disease (D), compared between different ages at disease onset. In all figures, the blue line represents women who have been diagnosed under 41 years old, the red line women diagnosed at 41–69 years old and the green line women diagnosed at 70 years old or older.

women compared with HER2-positive (luminal or non-luminal) subtypes, independently of whether age was handled in analysis as a three-class factor or as a continuous factor. This over-representation of HER2-positive subtypes and under-representation of luminal A-like cancers among the youngest patients with breast cancer has been known for some time.[27 28] Young age was not an adverse prognostic factor in our study either, if assessed separately in different biological subtypes. Nevertheless, our data consisted of only nine women <41 years old with luminal A breast cancer and thus no definite conclusions from this group can be drawn. Although the prevalence of TNBC was three times more frequent among the women <41 years old compared with older age groups, this observation was not formally significant according to our statistical plan, in which we assessed age as a continuous factor. Given that more than 20% of women with a triple-negative phenotype carry a BRCA1 mutation, it would have been interesting to know the BRCA status of our patients, which unfortunately was not available.[29]

Regarding the whole cohort, without analysing different age subgroups, we have recently published the long-term survival results according to the intrinsic subgroups and traditional prognostic factors.[30] These results were well in line with the published literature, which supports the representativeness of the current material in comparison with previous studies.

Sixty-one of our patients had distant recurrence during follow-up. Survival with metastatic breast cancer was similar in all three age groups, although the low number of events, especially in the youngest and oldest subgroups, may decrease the reliability of this analysis. Previous larger studies with only patients with metastatic breast cancer have reported conflicting results regarding the association between age and survival.[31 32]

Classifying a continuous variable such as age as a class variable always somewhat distorts biological phenomena. We used three age classes, <41 years, 41–69 years and ≥70 years, based on previous studies and also because we considered this classification as the most clinically relevant. This was also a practical issue in this material, since if the cut-off for being young would have been 35 years old and the cut-off of being old would have been 75 years old, the sample sizes in these cohorts would have been only 14 and 38 patients, respectively. BRCA1/2 mutations have been found to be much more common if the breast cancer was diagnosed in the 30–35 year-age group compared with 40 years of age at disease onset.[33] Also, the oldest of the elderly patients with breast cancer had different clinicopathological profiles from those of the patients aged 70–79 years old, including a more advanced stage, lower grade and increased oestrogen sensitivity.[34 35] In our data, there were no significant differences in tumour size or nodal status between the three age groups.

Early menarche is a well-known risk factor especially for ER-positive breast cancers, although its effect is relatively small, approximately 5% for every year younger at menarche.[2] Parity first increases breast cancer risk for 5–10 years after pregnancy, but then offers a lifelong protective effect.[36] We observed that late menopause and increased parity, together with increased age at menarche, correlated with breast cancer diagnosis in older age. It is plausible that the breast cancer risk is postponed in these women, along with their delayed oestrogen exposure, but the strength of these correlations was still unexpected. Underlining the endocrine effect behind these correlations, they were observed only within ER-positive patients. To the best of our knowledge, this topic has been previously assessed only to a limited extent and our report is the first prospective study to find evidence for this correlation. Similarly to our study, among BRCA1/2 mutation carriers, nulliparity was associated with earlier breast cancer onset.[37] Feng et al,[38] using a large Chinese database, found that postmenopausal patients with breast cancer experienced menarche later than premenopausal patients with breast cancer, although the exact age at breast cancer onset was unknown in this study. As a pitfall of the current study design, we did not have access to some important lifestyle-related factors, such as weight, physical activity or diet. These potential confounding factors are known as risk factors for poorer breast cancer outcomes, but they also associate with reproductive factors.

In conclusion, we report excellent long-term outcomes for women with early breast cancer in all age groups in this prospective real-world cohort, despite the fact that older patients received less intensive adjuvant treatments. Our data also indicate that postponed endogenous endocrine exposure may cause delay in the onset of first breast cancer, although proving causality requires further confirmatory studies and the exact biology behind this phenomenon is still uncertain.

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