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Original Research

Association between endocrine therapy and cognitive decline in older women with early breast cancer: Findings from the prospective CLIMB study

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Abstract ***Introduction:*** Studies investigating the long-term effects of breast cancer treatment on cognition in older women with breast cancer are lacking, even though preserving cognition is highly valued by the older population. Specifically, concerns have been raised regarding the

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Longitudinal

detrimental effects of endocrine therapy (ET) on cognition. Therefore, we investigated cognitive functioning over time and predictors for cognitive decline in older women treated for early breast cancer.

Methods: We prospectively enrolled Dutch women aged ≥70 years with stage I-III breast cancer in the observational CLIMB study. The Mini-Mental State Examination (MMSE) was performed before ET initiation and after 9, 15 and 27 months. Longitudinal MMSE scores were analysed and stratified for ET. Linear mixed models were used to identify possible predictors of cognitive decline.

Results: Among the 273 participants, the mean age was 76 years (standard deviation 5), and 48% received ET. The mean baseline MMSE score was 28.2 (standard deviation 1.9). Cognition did not decline to clinically meaningful differences, irrespective of ET. MMSE scores of women with pre-treatment cognitive impairments slightly improved over time (significant interaction terms) in the entire cohort and in women receiving ET. High age, low educational level and impaired mobility were independently associated with declining MMSE scores over time, although the declines were not clinically meaningful.

Conclusion: Cognition of older women with early breast cancer did not decline in the first two years after treatment initiation, irrespective of ET. Our findings suggest that the fear of declining cognition does not justify the de-escalation of breast cancer treatment in older women.

1. Introduction

The incidence of breast cancer has substantially increased over the past 50 years. In 2020, approximately 2.3 million women were diagnosed with breast cancer worldwide, making it the most prevalent tumour type among women [1]. As more than 30% of these women were 70 years or older, studies investigating the older breast cancer population are urgently needed.

Approximately 80% of breast cancers diagnosed in women aged ≥70 years are hormone receptor-positive, and adjuvant endocrine therapy (ET) is widely prescribed to the older population [2]. Adjuvant ET strongly improves survival, reduces the risk of recurrence and is generally well tolerated [3]. Yet, as growing evidence suggests that oestrogens play an important role in brain functioning and cognition [4], concern has been raised about the detrimental effects of ET on cognition. Pre-clinical and neuropsychological studies demonstrated a neuroprotective influence of oestrogens as oestrogen deprivation in women, who underwent surgical menopause, was associated with a decreased verbal memory performance and oestrogen replacement therapy was associated with intact cognitive functioning [5–7]. However, studies investigating the effect of various endocrine treatments on cognitive functioning have yielded conflicting results [8–13]. Few studies have focused on cancer-related cognitive decline in older women with breast cancer, treated with ET, even though this population has a limited cognitive reserve and might be vulnerable to cognitive side-effects [14]. The effect of ET on cognition in older women is, therefore, largely unknown.

The aim of this study was to investigate cognitive functioning up until two years after treatment initiation in older women with non-metastatic breast cancer, stratified for ET, and to identify predictors of a cognitive decline.

2. Methods

2.1. Study design

We prospectively included women aged ≥70 years in the multicenter, observational CLIMB Every Mountain (CLIMB) study, designed to investigate patient-reported outcomes in older women with primary operable breast cancer. Details of this study were extensively described in previous publications [15–17]. In brief, we included older women diagnosed between 2013 and 2018 in nine Dutch hospitals. Eligible patients were women aged ≥70 years with stage I-III primary operable breast cancer. Women with a previous breast cancer diagnosis, advanced dementia or inability to read Dutch were excluded. The study was approved by the Medical Ethics Review Committee of the LUMC (CCMO:NL43463.058.13), and written informed consent was obtained from all participants.

2.2. Geriatric assessment and follow-up

Before systemic treatment initiation, all women underwent a geriatric assessment as part of standard care, which included the Mini-Mental State Examination (MMSE) [18] for cognitive functioning, the 'Timed Up and Go' (TUG) test for mobility [19] (cut-off >12 s [20]),

Table 1
Patient and tumour characteristics.

Variables		Total cohort (N = 273)	ET (N = 130)	No ET (N = 143)	p-value
		N (%)	N (%)	N (%)	
Age, years	Mean (SD)	75.8 (5.2)	75.6 (4.9)	75.9 (5.4)	
70–74		139 (50.9)	65 (50.0)	74 (51.7)	0.438
75–79		66 (24.2)	33 (25.4)	33 (23.1)	
80–84		48 (17.6)	26 (20.0)	22 (15.4)	
≥85		20 (7.2)	6 (4.6)	14 (9.8)	
Tumour stage	In situ	11 (4.0)	0 (0)	11 (7.7)	<0.001
	Stage I	141 (51.6)	53 (40.8)	88 (61.5)	
	Stage II	91 (33.3)	60 (46.2)	31 (21.7)	
	Stage III	18 (6.6)	12 (9.2)	6 (4.2)	
	Unknown	12 (4.4)	5 (3.8)	7 (4.9)	
Tumour grade	Grade I	63 (23.1)	16 (12.3)	47 (32.9)	<0.001
	Grade II	116 (42.5)	72 (55.4)	44 (30.8)	
	Grade III	77 (28.2)	37 (28.5)	40 (28.0)	
	Unknown	17 (6.2)	5 (3.8)	12 (8.4)	
Hormone receptor status	ER+/PR+	180 (65.9)	98 (75.4)	82 (57.3)	<0.001
	ER+/PR−	46 (16.8)	30 (23.1)	16 (11.2)	
	ER-/PR-	29 (10.6)	0 (0)	29 (20.3)	
	Unknown	18 (6.6)	2 (1.5)	16 (11.2)	
Most extensive surgery	No surgery	12 (4.4)	0 (0)	12 (8.4)	<0.001
	Breast conserving	155 (56.8)	65 (50.0)	90 (62.9)	
	Mastectomy	106 (38.8)	65 (50.0)	41 (28.7)	
Most extensive axillary surgery	No axillary surgery	20 (7.2)	1 (0.8)	19 (13.3)	<0.001[a]
	Sentinel node	199 (72.9)	97 (74.6)	102 (71.3)	
	Axillary lymph node dissection	54 (19.8)	32 (24.6)	22 (15.4)	
Radiotherapy	Yes	170 (62.3)	78 (60.0)	92 (64.3)	0.460
Adjuvant therapy					
Chemotherapy	Yes	20 (7.3)	11 (8.5)	9 (6.3)	0.492
Trastuzumab	Yes	11 (4.0)	6 (4.6)	5 (5.3)	0.639
Endocrine therapy	*Tamoxifen*	59 (21.6)	59 (45.3)	N/A	N/A
	Aromatase inhibitor	60 (22.0)	60 (46.2)		
	Unknown	11 (4.0)	11 (8.5)		
Charlson Comorbidity	0	156 (57.1)	79 (60.8)	77 (53.8)	0.502
Index[±]	1	66 (24.2)	31 (23.8)	35 (24.5)	
	2	28 (10.3)	12 (9.2)	16 (11.2)	
	≥3	23 (8.4)	8 (6.2)	15 (10.5)	
Polypharmacy[+]	No	160 (58.6)	88 (67.7)	72 (50.3)	0.004
	Yes	99 (36.3)	34 (26.2)	65 (45.5)	
	Unknown	14 (5.1)	8 (6.2)	6 (4.2)	
Living situation	Independent	266 (97.5)	126 (96.9)	140 (97.9)	0.503[a]
	Assisted living	7 (2.6)	4 (3.1)	3 (2.1)	
Highest education	Primary school	104 (38.1)	50 (38.5)	54 (37.8)	0.752
level	High school	99 (36.6)	50 (38.5)	49 (34.3)	
	University	35 (12.8)	14 (10.8)	21 (14.7)	
	Unknown	35 (12.8)	16 (12.3)	19 (13.3)	
Marital status	Married/living with partner	122 (44.7)	58 (44.6)	64 (44.8)	0.977
	Divorced/widowed	99 (36.3)	48 (36.9)	51 (35.7)	
	Never married	12 (4.4)	5 (3.8)	7 (4.9)	
	Unknown	40 (14.7)	19 (14.6)	21 (14.7)	
Employment	Employed for wages	127 (46.5)	60 (46.2)	67 (46.9)	0.846
	Retired/unable to work	90 (33.0)	44 (33.8)	46 (32.3)	
	Else	46 (20.8)	26 (20.0)	30 (21.0)	
Groningen Activity	Not impaired	123 (45.1)	57 (43.8)	66 (46.2)	0.669[a]
Restriction Scale	Impaired	149 (54.6)	72 (55.4)	77 (53.8)	
	Missing or incomplete	1 (0.4)	1 (0.8)	0 (0)	
Malnutrition	Low risk	235 (86.1)	116 (89.2)	119 (83.2)	0.084[a]
Universal Screening	Medium risk	14 (5.1)	5 (3.8)	9 (6.3)	
Tool	High risk	5 (1.8)	4 (3.1)	1 (0.7)	
	Missing or incomplete	19 (7.0)	5 (3.8)	14 (9.8)	
Timed Up & Go test	≤12 s	163 (59.7)	83 (63.8)	80 (55.9)	0.394
	>12 s	44 (16.1)	18 (13.8)	26 (18.2)	
	Missing	66 (24.2)	29 (22.3)	37 (25.9)	

(*continued on next page*)

Table 1 (*continued*)

Variables		Total cohort (N = 273)	ET (N = 130)	No ET (N = 143)	p-value
		N (%)	N (%)	N (%)	
MMSE	≥28	195 (71.4)	95 (73.1)	100 (69.9)	0.753
	24–27	71 (26.0)	32 (24.6)	39 (27.3)	
	<24	6 (2.2)	3 (2.3)	3 (2.1)	
	Missing	1 (0.4)	0 (0)	1 (0.7)	

Abbreviations: ET: endocrine therapy, ER; estrogen receptor, MMSE; Mini-Mental State Examination, N/A; not applicable, PR; progesterone receptor.

[a] Analyzed by using the Fisher exact test. [±]In total, 156 patients had hypertension (ET 54% versus no ET: 60%), 57 had diabetes mellitus type II (ET: 19% versus no ET:22%), 15 patients had ischaemic heart disease (ET: 3% versus no ET: 6%), 12 patients had a previous cerebrovascular accident (ET: 5% versus no ET:4%) and 0 patients had any form of dementia. These pre-existing conditions did not significantly differ between the ET groups. [+]In total, 33 patients used benzodiazepines (ET 13% versus no ET: 11%), 8 patients used antidepressants (ET 2% versus no ET:4%), 5 used anticholinergics (ET 2% versus no ET: 1%) and 1 patient without ET used antipsychotic medication. These concomitant medications did not significantly differ between the ET groups.

the Malnutrition Universal Screening Tool for nutritional status [21] and the Groningen Activity Restriction Scale questionnaire for the (instrumental) activities of daily living [22]. Trained nurses conducted the assessments and collected information about tumour characteristics, the type of treatment, polypharmacy (≥5 medicines) and Charlson Comorbidity Index [23]. During the geriatric assessment, women were asked to participate in the CLIMB study.

Participants in the CLIMB study also underwent MMSE tests at 9, 15 and 27 months after treatment initiation. Total MMSE scores range from 0 to 30, with higher scores indicating better cognitive functioning. Baseline MMSE scores of 24–27 were defined as suspected mild cognitive impairment and scores of <24 as suspected dementia [24]. Clinically meaningful changes in cognition can also be detected with the MMSE by using the minimal clinically important difference (2.32 points for a mild cognitive impairment [25]).

All women from whom at least two MMSE tests were obtained were included in the analysis. If ≤5 individual items of the MMSE score were missing (6%), we calculated raw MMSE scores [26]. If >5 items were missing, the MMSE score was defined as unknown.

2.3. Statistical analysis

Descriptive statistics using chi-square tests were used to compare the baseline characteristics of patients receiving ET and those who did not. We also compared the characteristics of included participants with eligible women who did not consent to the CLIMB and those who did not complete two MMSE tests.

We calculated unadjusted means and 95% confidence intervals (CIs) of MMSE scores per timepoint, stratified for ET. Absolute changes from the baseline, analysed with Wilcoxon signed-rank tests, were evaluated for the minimal clinically important difference.

Linear mixed models were used to compare MMSE scores of women with mild or severe cognitive impairments (MMSE≤27) with scores of women without impairments (MMSE 28–30), as we hypothesised that cognitively impaired women have an increased risk of cognitive decline. Associations between time, cognition at baseline, their interaction and MMSE scores were estimated, with predefined variables such as age, education, job status, comorbidities, functional status, mobility and living situation as fixed covariates. The individual was included as a random intercept. The predictors of cognitive decline were also identified with linear mixed models . We calculated the beta-coefficients (β) with 95% CI and p-values.

To investigate if MMSE scores of women who dropped out were lower than those who did not, we compared scores of women with cognitive impairments at baseline who did not complete the 2-year assessment and those who did. Moreover, we studied the MMSE scores of women who discontinued ET within two years, as early discontinuation might have been caused by cognitive problems [27]. Analyses were performed in SPSS v.25.

3. Results

Among the 379 participants, 273 women underwent ≥1 MMSE tests. Response rates were 99%, 96% and 95% at 9, 15 and 27 months, respectively (Fig. S1).

The mean age was 76 years (standard deviation (SD) 5.2) (Table 1). Of all women, 43% had at least one comorbidity and 36% used ≥5 medications. Most common comorbidities were hypertension (57%), diabetes mellitus type II (21%) and ischaemic heart disease (5%), and 12% used benzodiazepines. 55% had mild or severe functional limitations, and 16% had an impaired TUG. Only 7% received chemotherapy.

Almost half (48%) received adjuvant ET, of which 45% started with tamoxifen and 46% with aromatase inhibitors. Early discontinuation of ET during the study period occurred in 34%. Tumor characteristics, type of

surgery and polypharmacy differed between women using ET and those not using ET.

The baseline mean MMSE of all participants was 28.2 (SD 1.9), and mild or severe cognitive impairments were seen in 26% and 2%, respectively. Among women treated with ET, mean MMSE was 28.1 (SD 2.0), and mild or severe cognitive impairments were observed in 25% and 2%, respectively. Baseline mean MMSE of women not treated with ET was 28.2 (SD 1.9), with 27% having mild cognitive impairments and 2% having severe cognitive impairments.

Compared to women who only completed one (or no) MMSE test, participants who were included in this analysis were younger, had a better Groningen Activity Restriction Scale , Malnutrition Universal Screening Tool and TUG, less comorbidities and more often underwent any kind of breast cancer treatment (Table S1).

3.1. Longitudinal MMSE scores

Unadjusted mean MMSE scores of women who received ET increased but not to clinically meaningful values (change from baseline +0.3 (95%CI -0.1–0.7, p = 0.082) points after 9 months, +0.4 (95%CI 0.0–0.9, p = 0.013) points after 15 months and +0.5 (95%CI 0.1–0.9, p = 0.018) points after 27 months; Fig. 1, Table S3). MMSE scores remained unchanged both in women using an aromatase inhibitor and in those using tamoxifen (Fig. S2). Similarly, the unadjusted mean MMSE scores of women not receiving ET did not show any clinically meaningful changes (change +0.2 (95%CI −0.2–0.5, p = 0.536) points after 9 months, +0.6 (95% CI 0.3–0.9, p < 0.001) points after 15 months and +0.04 (95%CI −0.3–0.4, p = 0.871) points after 27 months).

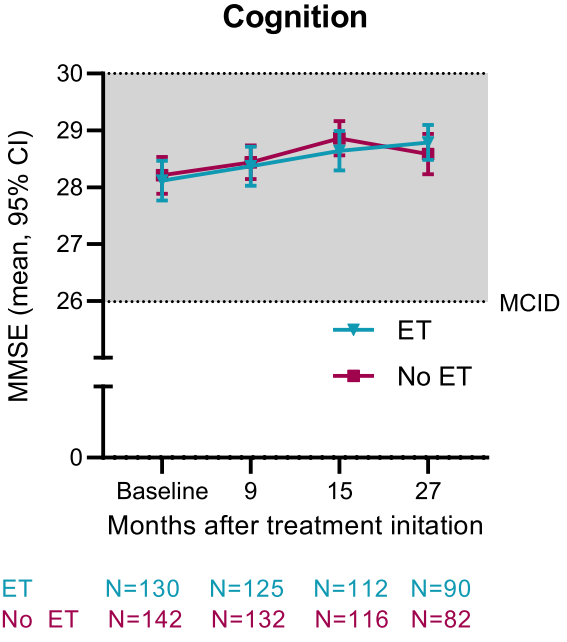

Fig. 1. Longitudinal unadjusted means and 95% confidence intervals of the MMSE scores of women treated with and without endocrine therapy. Abbreviations: MCID; minimal clinically important difference, MMSE; Mini-Mental State Examination.

3.2. MMSE scores of women with cognitive impairments at baseline

Adjusted MMSE scores differed over time between women with cognitive impairments at baseline and those without (interaction terms p < 0.001), as cognitively impaired women had a clinically meaningful improvement in MMSE means, whereas MMSE scores of women without a cognitive impairment remained unchanged (Fig. 2, Table S4). These findings were similar for the subgroup of women using ET (Fig. 3, Table S4).

3.3. Risk factors for cognitive decline

Factors that were independently associated with declining MMSE scores in the whole cohort were high age (β −0.71; 95%CI -1.15–0.26, p = 0.002), low education level (β −1.05; 95%CI -1.53–0.58, p < 0.001) and impaired TUG (β −0.73; 95%CI -1.19–0.27, p = 0.002). Yet, none of these subgroups displayed a clinically meaningful cognitive decline (Table 2, Table S5, Fig. S2). For women receiving ET, high age (β −0.62; 95%CI −1.13–0.11, p = 0.017), low education level (β −0.81; 95%CI -1.53–0.09, p = 0.027) and impaired TUG (β −1.16; 95%CI −1.94–0.39, p = 0.004) were

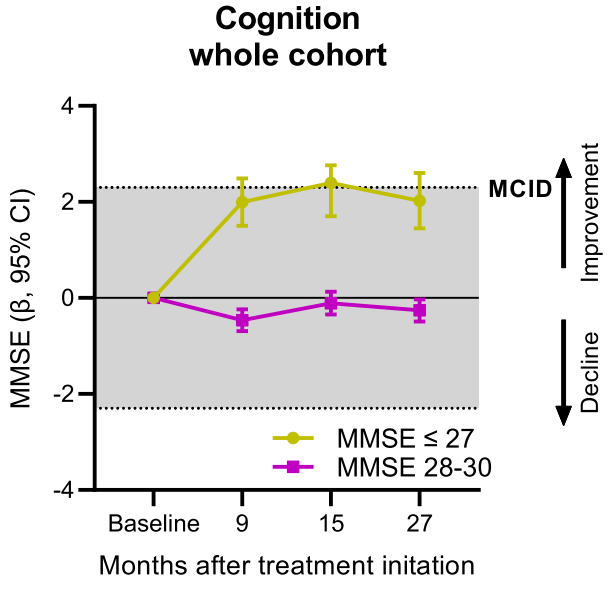

Fig. 2. Comparison of change in adjusted MMSE points compared to baseline between cognitively impaired women and women without cognitive impairment at baseline, analysed by using repeated linear mixed models, with age, education, job status, comorbidities, functional status, Timed Up and Go and living situation as covariates. Scores are presented as beta-coefficients (β) with their 95% CI. Abbreviations; MCID: minimal clinically important difference, MMSE; Mini-Mental State Examination.

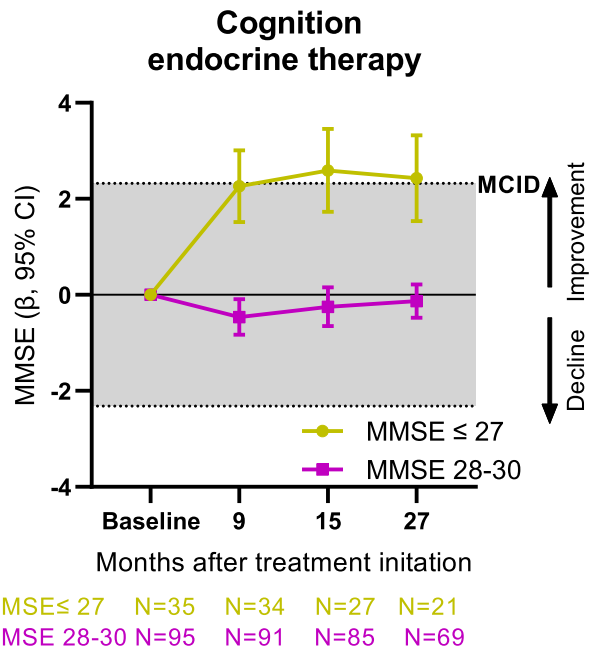

Fig. 3. Subgroup analysis of women using endocrine therapy (ET): the comparison of change in adjusted MMSE points compared to baseline between cognitively impaired women using ET and women without cognitive impairment at baseline using ET, analysed by using repeated linear mixed models, with age, education, job status, comorbidities, functional status, Timed Up and Go and living situation as covariates. Scores are presented as beta-coefficients (β) with 95% CI. Abbreviations; MCID: minimal clinically important difference, MMSE; Mini-Mental State Examination.

also independently associated with lower longitudinal MMSE scores. Again, the cognitive decline over time in these subgroups was not clinically meaningful (Table 2, Fig. S3, Table S6).

3.4. Sensitivity analyses

We compared the MMSE scores of women with cognitive impairments at baseline who dropped out before the 2-year assessment with those who did not and found that the improvement of MMSE scores was seen in both groups (Table S7, Fig. S4). Moreover, MMSE scores of the 45 women who discontinued ET within two years were similar to MMSE scores of women who did not (Fig. S5).

4. Discussion

Our results demonstrate that the cognitive functioning of women aged ≥70 years with breast cancer does not decline in the first two years after treatment initiation, irrespective of ET. Contrary to our hypothesis, women with cognitive impairments at baseline exhibited clinically meaningful improvements in MMSE scores. Although high age, low educational level and impaired mobility were independently related to decreasing MMSE scores, in none of these subgroups the decline was clinically meaningful.

A mild cognitive impairment at baseline was prevalent in 26%, which is consistent with previous studies [28]. Regarding cognitive functioning over time, no previous studies have investigated cognition in a large cohort of women aged ≥70 years with breast cancer, receiving ET or other treatment types and assessed geriatric characteristics. Mandelblatt *et al.* (N = 344) studied a younger population (mean age 68 years, SD 6) of women with breast cancer treated with ET in a prospective study and found that objectively measured cognition tended to improve in 12 and 24 months after treatment, similar to the cognition of healthy controls [29]. Furthermore, in a pilot study (N = 31), Hurria *et al.* did not find a cancer-related cognitive decline in older women (mean age 72 years, SD 7) with breast cancer receiving aromatase inhibitors compared to healthy controls, with a follow-up period of 6 months [30]. The results of the Tamoxifen and Exemestane Adjuvant Multinational trial, including 176 postmenopausal women with breast cancer, only showed significantly worse scores on verbal memory and executive functioning for tamoxifen users compared to healthy controls after 1 year of treatment [8]. However, as the mean age of the relatively fit participants was 68 years (SD 7) and they had fewer comorbidities and a higher socioeconomic status than patients in the general population [31], we cannot apply these results to most older breast cancer patients seen in daily practice. Moreover, the latter two studies only measured cognitive functioning after the first year of ET.

Despite some selection may have occurred in our cohort due to a better response of more vital participants, the participation of women with frailty was substantial: 71% had at least one deficit in the somatic, nutritional or functional domain. Even the frailest women at baseline, such as those with an impaired MMSE, limited mobility or a low education status, did not show a clinically meaningful cognitive deterioration during the first two years of treatment. MMSE scores of women with cognitive impairments at baseline even improved during the breast cancer treatment, regardless of ET. There are several explanations for this improvement. First, pre-treatment cognitive impairments can be attributed to stress related to the recent cancer diagnosis and surgery, with the reduction of stress-inducing improvement of cognition [32]. In those who underwent surgery shortly before the administration of the baseline MMSE instead of after the administration (N = 27), cognitive functioning might have also been affected by surgery and anaesthesia, although results on the association between anaesthesia and postoperative cognitive decline are conflicting [33–35]. Second, traditional neuropsychological tests such as the MMSE are subject to practice effects, which might induce improvement [36,37]. Although practice effects are traditionally

Table 2
Association between the patient and tumour characteristics and longitudinal MMSE scores.

Variables	Whole cohort			ET group		
	β	95% CI	p-value	β	95% CI	p-value
Age						
70–74	Ref			Ref		
75–79	−0.42	−0.80, −0.04	0.032	−0.62	−1.13, −0.11	0.017
80–84	−0.71	−1.15–0.26	0.002	−0.49	−1.11, 0.14	0.125
≥85	−0.44	−1.06, 0.28	0.163	−0.14	−1.20, 0.92	0.790
Adjuvant ET	−0.09	−0.39, 0.22	0.589	N/A		
Education						
University	Ref			Ref		
Secondary school	−0.41	−0.80, 0.13	0.155	−0.00	−0.70, 0.70	0.999
Primary school	−1.05	−1.53, −0.58	<0.001	−0.81	−1.53, −0.09	0.027
Employment						
Employed	Ref			Ref		
Not employed	0.02	−0.32, 0.36	0.911	0.09	−0.38, 0.55	0.716
Unknown	−0.32	−0.90, 0.27	0.285	−0.43	−1.31, 0.46	0.341
CCI						
0	Ref			Ref		
1	−0.05	−0.42, 0.32	0.789	−0.17	−0.74, 0.39	0.551
2	−0.49	−1.00, 0.03	0.062	0.08	−0.62, 0.77	0.829
3	−0.33	−0.88, 0.22	0.242	−0.20	−1.07, 0.67	0.646
GARS						
Normal	Ref			Ref		
Impaired	0.25	−0.09, 0.59	0.154	0.22	−0.23, 0.68	0.336
Unknown	1.42	−0.73, 3.57	0.193	2.04	−0.71, 4.35	0.149
TUG						
Normal	Ref			Ref		
Impaired	−0.73	−1.19, −0.27	0.002	−1.16	−1.94, −0.39	0.004
Unknown	−0.09	−0.55, 0.37	0.699	−0.37	−1.09, 0.34	0.297
Living situation						
Independent	Ref			Ref		
Assisted living	−0.71	−1.70, 0.29	0.192	−1.35	−2.84, 0.13	0.074

The repeated measure regression of the association between patient and tumour characteristics and longitudinal adjusted MMSE scores for both the whole cohort and for women treated with ET, by using multivariate linear mixed models and calculating β and its 95% CI. Abbreviations: CCI; Charlson Comorbidity Index, ET: Endocrine therapy, GARS; Groningen Activity Restriction Scale, N/A: not applicable, TUG: Timed Up and Go, MMSE: Mini-Mental State Examination.

viewed as a source of error, they might also provide valuable information about cognition, as individuals with preserved cognition demonstrate practice effects and patients with mild cognitive problems show minor practice effects [38]. Third, the improvement might be explained by the natural course of the disease, as a previous study showed that a proportion of patients with a mild cognitive impairment shows improved cognition over time [39]. Results can also be confounded by the phenomenon of regression towards the mean, as extreme outcomes tend to be followed by more moderate ones [40].

Adjuvant ET is recommended in women with hormone receptor-positive breast cancer and leads to a proportional risk reduction in breast cancer recurrence and death. However, ET in older women should be administered judiciously, based on careful evaluation of its risks and benefits, also taking into account the individual life expectancy and risk of side-effects. Some older women, especially those with low risk-tumour types and multimorbidity, may be overtreated as they might not experience the intended treatment benefit of ET due to a high probability of death from other causes. Undertreatment of older women with breast cancer is also a well-documented phenomenon [41]. In addition to the increased risk of musculoskeletal symptoms or depression in (pre-)frail older women [42], fear of cognitive side-effects might play a role in this undertreatment. Our results, suggesting that concerns about declining cognition do not justify withholding ET in older women, not even in those with a low educational status, high age or impaired mobility, aid in further optimising the balance between overtreatment and undertreatment of older women with breast cancer.

To our knowledge, this is the first cohort that investigates two-year cognitive functioning in a large group of women aged ≥70 years with breast cancer, half of whom were treated with ET. The CLIMB is a unique longitudinal cohort that provides real-world evidence on treating older women with breast cancer and gathers geriatric measurements at several timepoints. Since ET is the most important systemic treatment for older women and usually prescribed for several years, our data present essential information on long-term

outcomes for older women with breast cancer. Moreover, we obtained both pre- and post-treatment assessments of cognition, which enabled us to investigate potential treatment-induced changes. Additional strengths of our analysis are the high compliance rates and large sample size.

A limitation of our study may be that women included in our analysis were generally more fit compared to women who did not participate or only underwent one MMSE test, causing participation bias. The underrepresentation of very frail older patients in studies is a well-documented phenomenon and may be caused by participation burden [43,44]. Nevertheless, as 43% of the participants had at least one comorbidity and more than half suffered from functional limitations, we still believe that our study sample represents a frail group of older breast cancer survivors, and results can be extrapolated to real-world practice. Second, we performed MMSE tests during the first two years of ET, although current guidelines recommend at least five years of ET use, with extended durations of up to 10 years becoming increasingly common. For women using ET for courses of 5–10 years, we cannot say with certainty that ET has no impact on long-term cognition. Although exploratory analyses did not show a clinically relevant cognitive decline in women treated with chemotherapy, we cannot draw firm conclusions about the effect of chemo brain on cognitive functioning since only 7% received chemotherapy. Additionally, we did not include a matched sample of older women without cancer to investigate cognition in the general population, and our study lacked information on the underlying causes of cognitive decline and previous exposure to chemotherapy. Some data were missing, as indicated in the tables and figures, and we chose not to exclude patients with missing data in order to minimise the risk of bias. Last, even though the MMSE is easy to use and has an excellent ability to detect dementia, it may be subjected to practice effects or misclassification, and evidence regarding the detection of a mild cancer-related cognitive decline is limited [45]. Future studies with a battery of neuropsychological testing may be needed to further examine the effect of breast cancer treatment on cognition, although assessments with such a battery can be burdensome to older patients with cancer. Moreover, a recent study showed that the MMSE did have a good ability to detect clinical changes in cognitively unimpaired patients compared to other cognitive tests [46], which strengthens our findings.

5. Conclusions

Breast cancer treatment has no detrimental effect on the cognition of older breast cancer survivors in the first two years after diagnosis, irrespective of ET. Even in older women with frailties at baseline, no cognitive decline over time was observed. Thus, our data suggest that the fear of declining cognition does not justify the de-escalation of breast cancer treatment in older women.

Author contributions

Conceptualization: GJL, NAdG, JEAP, Data curation; NAdG, MGMD, JCB and AAL. Formal analysis: JCB, MF and AAL, Funding acquisition: GJL, NAdG and JEAP. Investigation: JEAP, SPM, NAdG, MGMD and JCB. Methodology: JEAP, NAdG, SPM, MGMD, JCB, MF and AAL. Project administration: NAdG, GMD and AAL. Resources: JEAP. Supervision; JEAP, GJL, NAdG, SPM and MGMD. Visualization: JCB. Roles/Writing—original draft: JCB, AAL, NAdG, SPM, JEAP, MGMD and GJL. Writing—review & editing: all authors.

Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2023.02.008.

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