

## Cognitive Changes After Adjuvant Treatment in Older Adults with Early-Stage Breast Cancer

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**Key Words.** Cognition disorders • Breast neoplasms • Aging • Chemotherapy • Cognitive changes

### ABSTRACT

**Background.** Group-based trajectory modeling is particularly important to identify subgroups of patients with pathological cognitive changes after cancer treatment. To date, only one study has explored cognitive trajectories in older patients with cancer. The present article describes objective cognitive changes before to after adjuvant treatment in older adults with early-stage breast cancer (EBC) after adjuvant treatment compared with healthy controls.

**Patients and Methods.** Participants were patients  $\geq 65$  years of age with newly diagnosed EBC and healthy controls (age-, sex-, and education-matched). The pretreatment assessment was conducted before adjuvant therapy, and the post-treatment assessment after the end of the first adjuvant treatment. Objective cognitive changes before to after treatment were evaluated based on the Reliable Change Index for cognitive decline accounting for cognitive impairment status.

**Results.** The sample consisted of women newly diagnosed with EBC ( $n = 118$ ) and healthy controls ( $n = 62$ ). Five patterns of changes before to after treatment were identified based on the presence of cognitive decline and cognitive impairment. The distribution of these five change patterns was statistically significant ( $p = .0001$ ). Thirty-six percent of patients had phase shift changes, 31% without initial objective cognitive impairment developed impairment, 15% had a normal aging, 12% had a nonpathological decline, and 6% experienced accelerated cognitive decline.

**Conclusion.** This study described for the first time objective cognitive changes before to after treatment of older adults with EBC immediately after the end of adjuvant treatment. A longer-term remote follow-up of adjuvant treatment is needed to better understand the cognitive trajectories of older patients with EBC. *The Oncologist* 2019;24:62–68

**Implications for Practice:** After the end of adjuvant treatment, 31% of older adults with early-stage breast cancer without initial objective cognitive impairment developed impairment, and 6% experienced accelerated cognitive decline. Initial cognitive functioning should be included in the balance of benefits and harms of systemic therapy for patients who are likely to be at highest risk for cognitive decline after cancer treatments. Regular cognitive follow-up of patients who had cognitive impairment before cancer treatment should monitor symptoms suggestive of neurodegenerative disease and avert the effect of cognitive disorders on patients' autonomy.

### INTRODUCTION

Cancer and cancer treatments might accelerate the cognitive aging process because of the potential relation between aging, neurodegeneration, biologic processes underlying cancer, and the effect of cancer treatments on cognition [1–3]. Group-based trajectory modeling is particularly important to identify

subgroups of patients with pathological cognitive changes after cancer treatment. Based on longitudinal assessments, in reference to the model proposed by Ahles, it is possible to evaluate whether age-associated cognitive declines in these patients parallel those of older adults with no cancer history (the phase

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shift hypothesis) or follow a steeper slope of decline (the accelerated aging hypothesis) [2].

To date, only one study has explored cognitive trajectories in older patients with cancer. This study concerned the long-term trajectories of subjective cognitive function in older survivors of breast cancer and showed that, if the majority of survivors maintained good long-term self-reported cognition, a small subset of survivors manifested accelerated cognitive decline [4].

The aim of this article is to describe the objective cognitive changes in older adults with early-stage breast cancer (EBC) after adjuvant treatment compared with matched healthy controls. This study was based on post hoc secondary analysis of previously published data [5].

## MATERIALS AND METHODS

### Participants

Inclusion criteria were EBC and age of more than 65 years [5, 6]. Exclusion criteria included prior exposure to chemotherapy or radiotherapy, neurological comorbidities, known psychiatric comorbidities that might affect ability to participate, major cognitive disorders, and documented alcohol or drug abuse [5, 6]. Participants with a Mini-Mental State Examination (MMSE) score of less than 25 out of 30, indicative of possible pathological aging, were excluded from the study [7–9]. Similarly, participants who reported a period of formal education of less than 5 years (end of primary school) were not eligible because of the lack of normative data for these individuals.

A sample of healthy controls who met the same inclusion (except cancer diagnosis) and exclusion criteria were recruited by community advertisements. Healthy controls were age-, sex-, and education-matched to patients.

The pretreatment assessment (T1) was conducted after surgery and before adjuvant therapy. The post-treatment assessment (T2) was conducted after the end of the first adjuvant treatment. Adjuvant treatment was chemotherapy (CT+ group:  $n = 58$ ; median 178 days) or radiotherapy (CT– group:  $n = 61$ ; median 71 days). The interval for healthy controls was about the mean of that of the two patient groups (Table 1).

All participants provided written informed consent for the study, which was approved by the local ethics committee and registered at ClinicalTrials.gov (NCT01333735).

### Measures

Objective cognitive functioning (episodic memory, working memory, processing speed, and executive functions) was assessed with standardized and recommended neuropsychological tests [5]: the Grober and Buschke procedure; the Rey complex figure test; arithmetic, digit-span and letter-number sequencing of the Wechsler Adult Intelligence Scale-III; the trail making test, (parts A and B); and the verbal fluency test [8, 10–14].

### Sample Characteristics: Data Previously Published

A summary of sample characteristics and main previous results [5] is presented here to place the methods and results of the present study in context. Newly diagnosed women with EBC ( $n = 119$ ) aged more than 65 years and a sample of healthy controls ( $n = 62$ ) were included. As described in Figure 1, the final sample for T1–T2 analysis was 58 CT+ patients, 61 CT– patients, and 62 healthy controls. Participants' demographic and medical information is summarized in Table 1. No significant

difference in age and education was observed between the three groups at baseline [5]. No significant difference between the patient groups was observed at baseline regarding objective cognitive scores, subjective cognitive complaints, anxiety, depression, fatigue, and geriatric and biological measures [5].

Raw neuropsychological scores, cognitive complaints, and anxiety and depression scores for T1 and T2 are presented in Table 2.

According to the T1 results, 41% of patients had objective cognitive impairment (46% in the CT+ group, 26/57; 38% in the CT– group, 23/61) [5].

Based on Reliable Change Index (RCI) analysis (T1 and T2 data), overall, no significant difference was observed between the two patient groups on objective change in at least one domain or in any cognitive domain [5]. According to the mixed model analysis (groups  $\times$  time analysis), there was no significant effect of group and time on any of the objective or subjective cognitive scores [5].

### Statistical Analysis

This study was a post hoc secondary analysis of previously published data [5]. The primary goal of this study was to assess cognitive change before to after treatment, considering changes of each patient individually. To identify objective cognitive changes before to after treatment, the first parameter taken into account was cognitive decline, based on the RCI (as explained below). Cognitive impairment status was the second parameter taken into account, based on normative data and according to International Cognition and Cancer Task Force (ICCTF) definition [15], a two-part criterion: if patients performed at a z-score of  $\leq -1.5$  on two or more tests, or if they performed  $\leq -2.0$  on a single test, they were classified as impaired.

The RCI was used to determine standardized change scores for each patient on every neuropsychological score in order to compare T2 with T1 scores [5, 16, 17]. The calculation included the practice effect based on the healthy group scores (change from T1 to T2 in the healthy group). The Iverson formula includes an adapted standard error of the difference that incorporates T2's variability. The recommended decline threshold of RCI score was  $-1.645$  [16]. RCI scores were grouped together in cognitive domains. A decline in one domain was considered significant when at least one of the domain scores declined significantly.

Based on previous published results—which overall showed there was no significant difference between patient groups receiving or not receiving chemotherapy in objective cognitive decline in any cognitive domain or in at least one domain [5]—cognitive changes before to after treatment are presented independently of received treatment (chemotherapy and/or radiotherapy) and were elaborated from a decline in at least one domain.

## RESULTS

The final sample consisted of 118 patients.

### Cognitive Changes Before to After Treatment

Five patterns of changes before to after treatment were identified based on the presence of cognitive decline and cognitive impairment (as shown in Fig. 2, where continuous lines indicate no decline and discontinuous lines indicate decline). The distribution of these five change patterns was statistically significant ( $p = .0001$ ).

**Table 1.** Demographic and clinical characteristics of patients and healthy controls

Characteristics	CT+ group n = 58 <sup>a</sup>	CT- group n = 61	Healthy group n = 62	p value
<b>Demographic</b>				
Age, yrs, mean, SD [range]	70 (3.8) [65–81]	71 (4.3) [65–83]	71 (5.4) [65–88]	.13
Age, n (%)				
65–69	32 (55)	25 (41)	31 (50)	
70–74	20 (34)	25 (41)	15 (24)	
≥75	6 (11)	11 (18)	16 (26)	
Education level, yrs, mean (SD)	11 (2.9)	11 (2.6)	11 (2.6)	.63
Education level, %				
Low	69	64	64	
Middle	17	13	13	
High	14	23	23	
Time between T1 and T2, days, median [range]	178 [93–265]	71 [31–294]	156 [99–252]	
<b>Clinical</b>				
WHO PS = 0, % <sup>b</sup>	84	98	N/A	.006
Comorbidities, %				.29
Charlson index 0	76	82	NK	
Charlson index 1–2	24	18	NK	
Comorbidities by type, %				
Pulmonary comorbidities	4	7	0	
Peripheral neurological comorbidities	2	0	1	
Thyroid comorbidities	5	5	3	
Cardiac comorbidities	0	0	2	
At least three comedications, %	21	32		.13
Medications with potential effect on cognition, % <sup>c</sup>	15	31		.0502
Cancer stage I–II, % <sup>b</sup>	74	98		<.0001
Type of surgery, % <sup>b</sup>				<.0001
Lumpectomy	52	90		
Mastectomy	48	10		
Lymph node dissection, % <sup>b</sup>	95	66		<.0001
HER2 positive, % <sup>b</sup>	28	3		.0003
Hormone receptor positive, %	84	94		.11
Protocol of adjuvant CT, %				
FEC + docetaxel	59			
FEC without docetaxel	33	N/A		N/A
Other	8			
No. of cycles of CT, mean (SD) [range]	5.5 (0.8) [3–6]			
Days after completion of first adjuvant treatment (T2), mean (SD)	67 (44.9)	26 (51.9)		<.0001
Adjuvant radiotherapy, %	89	100		.012
Adjuvant hormone therapy (% started at T2; aromatase inhibitors for all patients)	26	31		.52

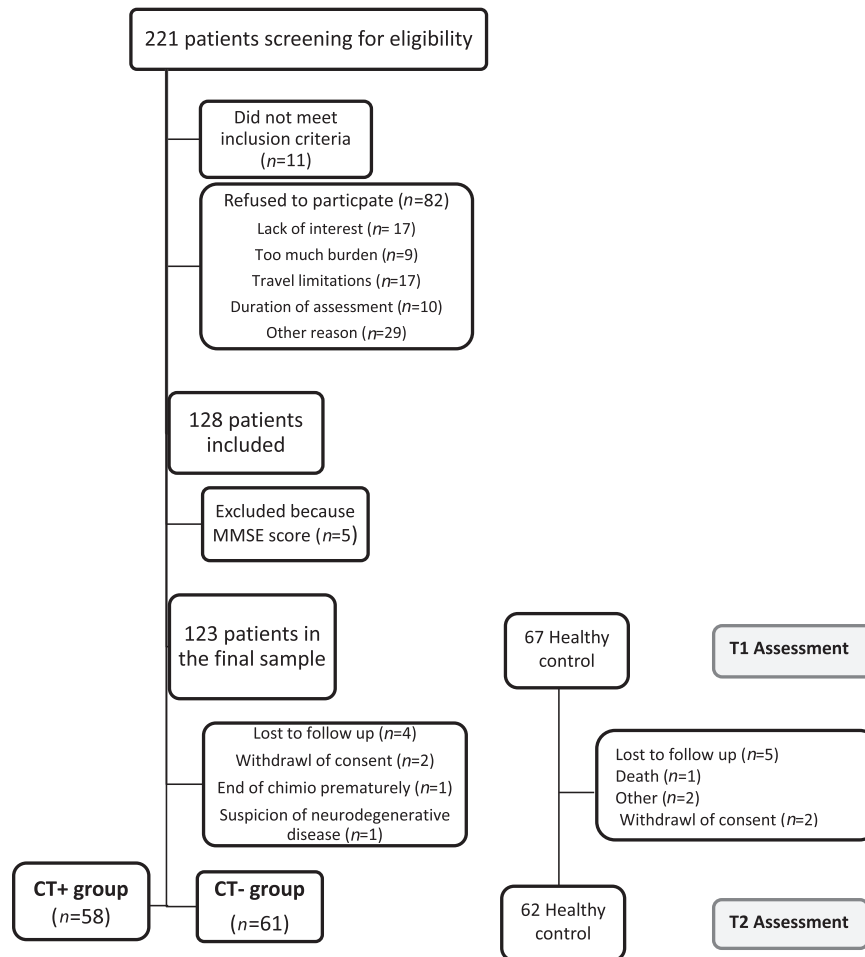
<sup>a</sup>Note for the present study result: One patient of the CT+ group had not performed all the cognitive tests, which made it not possible to calculate the Reliable Change Index grouped together in cognitive domains as for other patients. The final sample consists of 118 patients.

<sup>b</sup>p < .01.

<sup>c</sup>Level 3 on the WHO analgesic ladder: anxiolytics, antidepressant treatments, and hypnotics.

Abbreviations: CT, chemotherapy; CT+ group, group receiving chemotherapy; CT- group, group receiving radiotherapy; FEC, fluorouracil, epirubicin, and cyclophosphamide; N/A, Not applicable; NK, Not Known; PS, performance status; T1, pretreatment; T2, post-treatment; RT, radiotherapy; SD, standard deviation; WHO, World Health Organization.

Source: From [5].



**Figure 1.** Flow diagram of participant follow-up.

Abbreviations: CT+, chemotherapy; CT-, radiotherapy; MMSE, Mini-Mental State Examination; T1, pretreatment; T2, post-treatment.

### Patients Without Decline

Fifty-one percent of patients with EBC ( $n = 60/118$ ) had no cognitive decline after cancer treatment: cognitive changes of these patients were not significantly different from changes of the healthy control group. Among these patients, 30% ( $n = 18/60$ ; 15% of all patients) had *normal aging*: the same changes as healthy controls. Seventy percent of patients with no cognitive decline after treatment ( $n = 42/60$ ; 36% of all patients) had cognitive impairment before adjuvant treatment (based on normative data) but no increase in impairment after treatment: cognitive changes of these patients were not significantly different from changes of the healthy control group. For this subgroup of patients, change may correspond to the *phase shift hypothesis*, which states that patients' pretreatment cognitive functioning was below normal aging cognitive functioning (this subgroup had pretreatment impairment) and stayed below normal aging cognitive functioning after cancer treatment but without significant decline. This change parallels that of normal aging.

### Patients with Decline

Forty-nine percent of patients with EBC had a cognitive decline ( $n = 58/118$ ). Among them, 24% ( $n = 14/58$ ; 12% of all patients) had normal aging before treatment and presented a decline after treatment but did not develop impairment: although these patients had cognitive decline, their cognitive

performances remained above the threshold of impairment (*nonpathological decline*).

Furthermore, among patients with decline, 64% ( $n = 37/58$ ; 31% of all patients) had normal aging before adjuvant treatment and developed impairment after treatment (i.e., a *pathological decline*).

The remaining 12% ( $n = 7/58$ ; 6% of all patients) had cognitive impairment before adjuvant treatment with an increase after treatment. This change may correspond to the *accelerated aging hypothesis*, which states that the cognitive decline of patients treated for cancer is accelerated in comparison with normal aging (healthy controls).

### DISCUSSION

The results of this study suggest that in the short term after adjuvant treatment, 36% of older adults with EBC had phase shift changes, 31% without initial objective cognitive impairment developed impairment, 15% had a normal aging, 12% had a nonpathological decline, and a small subset experienced accelerated cognitive decline.

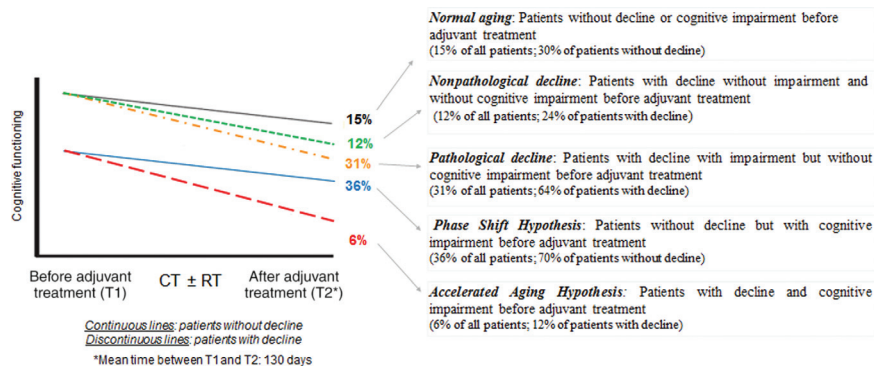
Group-based trajectory modeling is particularly important to identify subgroups of patients with pathological cognitive changes after cancer treatment, particularly in older patients, because of potential initial cognitive impairment that could be increased after treatment. Nevertheless, few studies have

**Table 2.** Neuropsychological measures, cognitive complaints, and anxiety and depression scores

Measure	CT+ group		Paired t test p	CT- group		Paired t test p	Healthy controls		Paired t test p	p value <sup>a</sup>
	Mean (SD)	Mean (SD)		Mean (SD)	Mean (SD)					
<b>Neuropsychological</b>										
Episodic memory										
Immediate recall	31.3 (5.0)	32.0 (5.7)	.249	31.0 (4.4)	32.1 (5.5)	.024	31.8 (5.4)	32.2 (5.7)	.465	.758
Rey recall	15.6 (6.3)	16.8 (6.5)	.046	15.0 (6.3)	17.6 (6.8)	.001	16.9 (5.0)	18.7 (5.5)	.004	.068
Working memory										
Arithmetic	10.3 (4.3)	9.7 (4.2)	.068	10.0 (4.5)	10.3 (7.9)	.205	10.5 (4.7)	10.3 (4.5)	.555	.801
Digit-span forward	7.2 (1.8)	7.5 (1.9)	.123	8.7 (2.3)	9.0 (2.8)	.345	7.8 (1.9)	8.1 (2.0)	.077	<.001
Digit-span backward	5.0 (1.7)	4.7 (1.5)	.226	4.9 (1.5)	5.1 (1.8)	.304	5.2 (1.6)	5.4 (1.7)	.204	.147
L-n sequencing	7.6 (2.3)	7.6 (2.3)	.646	7.7 (2.5)	8.1 (2.6)	.060	8.3 (2.6)	8.8 (2.5)	.062	.015
Processing speed										
TMT A time	46.6 (16.0)	42.7 (15.3)	.049	44.2 (18.6)	40.3 (15.6)	.044	49.6 (20.0)	50.4 (20.1)	.660	.002
TMT A errors	0.1 (0.3)	0.2 (0.5)	.252	0.2 (0.6)	0.2 (0.4)	.454	0.2 (0.5)	0.2 (0.4)	1.0	.362
<b>Executive functions</b>										
Fluency category	27.3 (6.6)	27.1 (8.4)	.711	28.5 (7.4)	28.7 (7.2)	.891	26.5 (6.9)	27.2 (6.3)	.341	.133
Fluency letter	18.9 (6.9)	19.9 (7.4)	.076	19.7 (6.2)	21.2 (6.3)	.023	20.7 (6.0)	21.5 (5.6)	.179	.135
TMT B time	110.2 (43.5)	110.5 (51.8)	.882	112.1 (48.1)	101.7 (43.3)	.024	122.3 (53.7)	116.3 (61.3)	.365	.142
TMT B pers. errors	0.5 (0.8)	0.3 (0.7)	.115	0.6 (0.9)	0.5 (0.9)	.201	0.7 (0.9)	0.7 (1.0)	1.0	.020
<b>Cognitive complaints (FACT-Cog)<sup>b</sup></b>										
PCI	61.7 (10.2)	56.4 (13.3)	.002	58.9 (9.6)	57.9 (12.0)	.382	55.4 (9.4)	54.8 (11.0)	.481	.008
QoL	11.5 (4.3)	10.5 (4.6)	.240	11.8 (3.9)	11.7 (4.0)	.682	13.2 (2.7)	12.9 (3.3)	.540	.106
Oth	15.7 (0.8)	15.3 (1.7)	.084	15.4 (1.3)	15.3 (1.4)	.530	15.2 (1.6)	15.3 (1.3)	.450	.685
PCA	20.6 (4.0)	18.4 (5.5)	.002	18.4 (5.6)	18.9 (5.1)	.467	17.6 (4.5)	17.1 (5.2)	.465	.031
<b>Anxiety, depression<sup>c</sup></b>										
Beck	3.0 (3.4)	3.5 (3.3)	.219	3.7 (3.3)	3.6 (3.7)	.846	3.7 (2.4)	3.6 (2.3)	.507	.063
STAI	39.05 (10.5)	36.37 (11.1)	.056	36.35 (11.0)	36.10 (11.0)	.887	32.16 (7.9)	33.79 (8.4)	.143	.001

<sup>a</sup>Comparison of changes between groups; analysis of variance.<sup>b</sup>For cognitive complaints measures, higher scores represent fewer complaints (i.e., a better functioning).<sup>c</sup>For anxiety and depression measures, higher scores represent more anxiety and higher of level depression.Abbreviations: CT+ group, group receiving chemotherapy; CT- group, group receiving radiotherapy; FACT-Cog, Functional Assessment of Cancer Therapy for Cognitive Scale; L-n, letter-number; Oth, comments from others; PCA, perceived cognitive abilities; PCI, perceived cognitive impairment; pers. errors, perseverative errors; QoL, quality of life; STAI, State-Trait Anxiety Inventory; T1, pretreatment; T2, post-treatment; TMT, Trail Making Test.  
Source: Published in [5].





**Figure 2.** Cognitive trajectories in older patients with early-stage breast cancer after adjuvant treatment.

Two parameters were taken into account to identify objective cognitive trajectories: cognitive decline (based on the Reliable Change Index, which takes into account the healthy group scores) and cognitive impairment (based on normative data). The first percentage indicates among all patients (without distinction of decline status) the proportion of patients identified on each trajectory. The second percentage indicates among the subgroup “patients without decline” (represented by continuous lines) or “patients with decline” (represented by discontinuous lines) the proportion of patients identified on each trajectory. Abbreviations: CT, chemotherapy; RT, radiotherapy.

assessed cognitive functioning in older patients with cancer, and few have used an individual analysis of cognitive performances to measure changes of cognitive aging before to after treatment. To the best of our knowledge, only one study has described individual cognitive change in older patients with cancer. However, this study assessed only self-reported cognitive function (based on two items of the European Organization for Research and Treatment of Cancer’s Quality of Life Questionnaire-C30) of older breast cancer survivors and showed that only 7.6% of the cohort had accelerated decline [4].

Individual cognitive change analyses complement mixed model analysis and add meaningful clinical information. Further investigations are needed to characterize subgroups of patients who are particularly at risk of developing cognitive impairment after adjuvant treatment and who could have accelerated aging, so that therapeutic management can be adapted. This article presents cognitive changes before to after adjuvant treatment in reference to the model proposed by Ahles [2]. We observed a subgroup of patients (6%) who experienced accelerated cognitive decline. Furthermore, 31% of patients developed cognitive impairment after treatment, and 36% of older adults with EBC had phase shift changes according to the definition of Ahles [2]. This last subgroup of patients had initial cognitive impairment, but their cognitive changes paralleled those of normal aging with no cognitive decline. Overall, these results suggest that it is important not only to detect cognitive impairment before treatment but also to initiate regular cognitive follow-up, particularly in patients who had cognitive impairment before cancer treatment, to monitor the occurrence of symptoms suggestive of a neurodegenerative disease and to avert the effect of cognitive disorder on patients’ autonomy. For the majority of young patients, cognitive impairment abates within 6–12 months after treatment [18, 19]. In older patients, the recovery of cognitive impairment can be longer. Cognitive changes in the current study were obtained just after the end of adjuvant treatment and suggested acute treatment effects. A longer follow-up is necessary to confirm the results and follow patients who developed cognitive impairment after treatment or who had an accelerated decline.

Compared with the sample in this study, in real life, older patients constitute a more heterogeneous population (with

altered general state altered, geriatric frailties, or neurodegenerative disease). Our results have probably underestimated cognitive decline because recruited patients had little comorbidity or geriatric frailty and were not shown to be impaired by a cognitive screening test [6].

Insofar as cognitive impairment can interfere with care and influence prognosis, a diagnosis of cognitive impairment may influence clinical decision making [20]. Geriatric assessment at the initiation of adjuvant treatment is therefore crucial to identify patients at risk of cognitive vulnerability and to propose appropriate therapeutic follow-up and management. For subgroups of patients who are likely to be at highest risk of cognitive decline after cancer treatments, initial cognitive functioning should be included in the balance of benefits and harms of systemic therapy [3]. The comprehensive geriatric assessment often includes only a cognitive screening test, mainly the MMSE [9]. However, the mild cognitive impairments that patients with cancer may experience may not be measured by this test. Several studies have shown with various patient populations that the Montreal Cognitive Assessment (MoCA) [21] is more sensitive in detecting these subtle disorders [22–24]. In the absence of neuropsychological testing prior to starting adjuvant treatment, which may not be achievable in clinical practice, MoCA could be recommended as screening tool [1].

Cognitive deficits could be related to adherence difficulties and treatment discontinuation [25, 26]. Indeed, a relationship has been observed between cognition (prospective memory, executive functioning, working memory, and attention) and adherence, particularly in older patients [27, 28]. Cognitive assessment and follow-up are very important to avert potential effect on adherence to hormone therapy for breast cancer.

The definition of cognitive decline, inclusion of a healthy control group, RCI formula (taking into account the practice effect based on the healthy group scores, or not) and cognitive tools could influence the construction of cognitive trajectories. Hence it is important to develop a study that uses the tests and cognitive impairment criteria recommended by the ICCTF [15], uses the recommended threshold of RCI [16], and has a healthy control group to facilitate cross-study comparison.

## CONCLUSION

This study described for the first time objective cognitive changes of older adults with EBC before to after treatment and showed that immediately after the end of adjuvant treatment, 36% had phase shift changes, 31% without initial cognitive impairment developed impairment, and a small subset experienced accelerated cognitive decline. A longer-term remote follow-up of adjuvant treatment is needed to better understand the cognitive trajectories of older patients with EBC.

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## DISCLOSURES

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