Cognitive Impairment in Patients with Breast Cancer before Surgery: Results from a CANTO Cohort Subgroup

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ABSTRACT

Background: Twenty to 30% of patients with breast cancer have cognitive impairment after surgery and before adjuvant treatment, but very few studies have focused on cognition before any treatment. This study used a subgroup of women with newly diagnosed breast cancer from the French cancer and toxicities (CANTO) cohort to describe cognition before any treatment in comparison with a group of healthy controls (HC).

Methods: Cognitive assessment was performed before any breast cancer treatment (surgery or neoadjuvant treatment) on women with newly diagnosed invasive stage I–III breast cancer and HCs. Objective cognitive performance, cognitive complaints, anxiety, depression, and fatigue were assessed. Objective cognitive impairment was defined according to International Cognition and Cancer Task Force recommendations.

Results: Of the 264 included patients with breast cancer (54 ± 11 years) and 132 age-matched HCs (53 ± 9 years), overall objective cognitive impairment was observed in 28% of patients with breast cancer and 8% of HCs ($P < 0.001$). Cognitive complaints were reported by 24% of patients versus 12% of HCs ($P < 0.01$). Patients reported significantly more anxiety and emotional and cognitive fatigue than HCs ($P < 0.01$). After adjustment, significantly more patients with breast cancer had overall objective cognitive impairment than HCs [OR = 3.01; 95% confidence interval (CI): 1.31–6.88] without significant difference between groups for cognitive complaints (OR = 1.38; 95% CI: 0.65–2.92). Cognitive complaints were positively associated with fatigue (OR = 1.03; 95% CI: 1.02–1.05).

Conclusions: In this prospective study, compared with HCs, patients with localized breast cancer had more objective cognitive impairment before any treatment. Cognitive complaints were mostly related to fatigue.

Impact: Baseline assessment before treatment is important to assess the impact of each cancer treatment on cognition.

Introduction

Cognitive impairment is common among patients with breast cancer during and after chemotherapy (1), with potential negative impacts on quality of life (2). This phenomenon was initially called chemobrain, but reports of cognitive disorders before any adjuvant treatment (3, 4) have led to a change in this terminology, to cancer-related cognitive impairment (CRCI). Indeed, 20% to 30% of patients with breast cancer have CRCI before the start of adjuvant treatment (5), with anatomic or functional brain anomalies (6, 7). Psychologic factors, coping style, and reactions to cancer diagnosis and planned treatment, such as worry and cancer-related posttraumatic stress, could explain these preadjuvant treatment disorders (8–10). Other implicated factors include fatigue, comorbidities, and biological mechanisms, such as inflammation and vascular changes (11–13).

In most of the longitudinal studies on preadjuvant CRCI, cognitive assessment was performed after surgery; thus one hypothesis is that preadjuvant CRCI could be partly explained by the impact of general anesthesia of the breast cancer surgery. Indeed, studies outside the cancer field observed postoperative cognitive dysfunction in some patients, which mainly concerned memory, attention, and processing speed (14). Risk factors for postoperative cognitive dysfunction include age, duration of general anesthesia, occurrence of complications, severity of surgery, and preexisting cognitive difficulties (14).

Very few studies have focused on cognition before any cancer treatment, including surgery with general anesthesia. Among the studies that do exist, some showed lower memory scores in patients with cancer compared with healthy controls (HC), although these studies assessed few cognitive domains (13, 15, 16).

This study used a subgroup of patients with breast cancer from the French, national, multicenter, prospective cancer and toxicities (CANTO) cohort (17, 18) to describe cognition in patients with breast cancer before any treatment in comparison with a group of healthy controls.

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Materials and Methods

Participants

The CANTO cohort included women with newly diagnosed, invasive, stage I–III breast cancer (17). Exclusion criteria included prior breast cancer surgery or neoadjuvant treatment.

This study is a substudy of the CANTO cohort that investigated cognitive functioning (CANTO-Cog), composed of women recruited from eight CANTO centers (Angers, Caen, Dijon, Nantes, Lille, Paris, Rouen, Villejuif). Patient who were included into the CANTO cohort in these centers have been proposed to the CANTO-Cog substudy. Specific exclusion criteria to CANTO-Cog included neurologic and known psychiatric comorbidities that might affect capacity to participate, major cognitive disorders, and documented alcohol or drug abuse. A group of age-matched HCs from the general population, without cancer (except basal cell cancer and *in situ* cancer of the cervix) and psychotropic medications, was recruited with local advertisements with the same eligibility criteria except cancer history.

Patients and HCs with a Mini-Mental State Examination (MMSE) score <26 out of 30 suggesting potential cognitive decline were not eligible (19, 20), nor were those reporting a formal education <5 years (end of the primary school). All study participants provided written informed consent.

Assessment

Patients were assessed before breast cancer surgery and neoadjuvant treatment. Cognitive impairment in both patients and HCs was assessed by standardized neuropsychologic tests during a 1-hour session with a graduate neuropsychologist. These tests assessed five cognitive domains: episodic memory, working memory, information processing speed, attention, and executive function (**Table 1**).

Patient reported outcomes (PRO) included measures of cognitive complaints [Functional Assessment of Cancer Therapy Cognitive Scale (FACT-Cog), version 3 (21) – four subscales: Perceived Cognitive Impairments (PCI), Impact on Quality of Life (QoL), Comments from Others (Oth), and Perceived Cognitive Abilities (PCA)], anxiety and depression (Hospital Anxiety and Depression Scale – HADS; ref. 22), and fatigue (FA12, three scores: physical, emotional, and cognitive fatigue; ref. 23). Clinical variables were Charlson index, main previous medical history, psychotropic medications (level 3 on the World Health Organization analgesic ladder, anxiolytics, antidepressant treatments, and hypnotics), cancer stage, time since diagnosis, and body mass index.

Assessment criteria

Raw neuropsychologic test results were standardized to a *z*-score using the means and SD of HCs. Cognitive domain scores were calculated on the basis of these scores (**Table 1**). According to International Cognition and Cancer Task Force (ICCTF) recommendations (24), cognitive impairment was based on a two-part criterion: *z*-score ≤ -1.5 below HCs on two or more tests, or *z*-score ≤ -2.0 below HCs on a single test. This approach was designed to minimize the number of potential false positives resulting from multiple tests and to determine the frequency of impairment rather than low performance. Overall objective cognitive impairment was defined by at least two impaired cognitive domains (11).

Clinically significant symptoms of cognitive complaints, anxiety, and depression were operationally defined as ratings ≤10th percentile on the FACT-Cog (25) and HADS score ≥11 (22).

Statistical analysis

Descriptive statistics were generated for the sociodemographic and clinical variables. Comparisons were made by χ^2, Student, and Wilcoxon tests, which were also used to estimate the associations between cognitive complaints and objective cognitive scores and other self-reported measures.

We performed multivariable logistic regression analyses to study the association between (i) overall objective cognitive impairment and (ii) cognitive complaints (PCI, FACT-Cog) and the variables most likely to

Table 1. Neuropsychologic tests grouped by main cognitive domains.

Cognitive domain	Test	Outcome measures	Range
Episodic memory			
Learning and memory	HVLT (35)	3 immediate free recalls	(3x) 0–12
		Free delayed recall	0–12
Working memory			
Verbal modality	WAIS-III (36): Digit-span	Scaled score, forward	1–19
		Scaled score, backward	1–19
	WAIS-III (36): Letter-number sequencing	Scaled score	1–19
Visual modality	WMS-III: Spatial-span (37)	Scaled score, forward	1–19
		Scaled score, backward	1–19
Processing speed	TMT A (38)	Time to complete and errors	≥0
	Stroop (37)	Time to complete color and word cards	≥0
Attention	WAIS-III (36): Symbol Search	Scaled score	1–19
	d2 test (40)	% of errors (F%)	%
		Number processed responses (GZ)	0–658
		Number of correct responses (KL)	0–299
Executive function			
Flexibility	TMT B (38)	Time to complete and number of perseverative errors	≥0
Information generation	Verbal fluency: Category (animal) and Letter P (41)	Total score over 2 minutes	≥0
Inhibition	Stroop (39)	Time to complete and number of noncorrected errors: interference card – color card	≥0

Abbreviations: GZ, quantitative performance index; HVLT, Hopkins Verbal Learning Test; KL, concentration performance index; TMT, Trail Making Test; WAIS, Wechsler Adult Intelligence Scale; WMS, Wechsler Memory Scale.

impact cognition: group (patients with breast cancer, HCs), education level (low, middle, high), age (≤49, 50–64, ≥65), neurologic/psychiatric comorbidities (yes, no), psychotropic medications (yes, no), anxiety (yes, no), depression (yes, no), and fatigue (continuous score). Subsequently, we tested for linear trend for education using the lowest category as reference. To minimize the risk of false-positive results, only associations with a $P \leq 0.01$ were considered as statistically significant. All reported P values are two-sided. All analyses were conducted using STATA version 15.0 (Stata Corp).

Results

Of the 2,308 women included from the eight CANTO centers between April 2014 and February 2017, 1,668 were invited to participate in CANTO-Cog. Eighty-one women were not eligible for inclusion due to neurologic comorbidities, known psychiatric comorbidities which might affect their capacity to participate, major cognitive disorders, and documented alcohol or drug abuse. Another 1,323 women were not enrolled due to lack of interest ($n = 370$), difficulties to organize assessment before treatment ($n = 415$), other reasons (fatigue, stress, duration of assessment, etc.; $n = 354$), or unknown reasons ($n = 184$). Therefore, 264 patients with breast cancer were included in these analyses.

Patient characteristics

Of these 264 patients (mean age: 54 ± 10.8 years), 69% ($n = 182$) had stage I–II breast cancer. Patients received their diagnosis within an average of 37 days (±70.3) of enrollment. They were compared with 132 age-matched healthy women (53 ± 9.0). Major characteristics are presented in **Table 2**.

Cognitive impairment

Overall objective cognitive impairment was observed in 28% ($n = 72$) of patients and 8% of HCs ($n = 10$; $P < 0.001$). Impaired working memory [20% of patients ($n = 52$) vs. 4% of HCs ($n = 5$)], information processing speed [36% ($n = 95$) vs. 17% ($n = 23$)], attention [16% ($n = 41$) vs. 1% ($n = 2$)], and executive function [21% ($n = 56$) vs. 8% ($n = 10$)] were more frequent in patients with breast cancer than in HCs ($P < 0.001$), except for episodic memory [19% ($n = 49$) vs. 12% ($n = 16$); **Fig. 1**; **Table 3**].

PRO results

Patients reported significantly more cognitive complaints than HCs in all FACT-Cog subscales (mean scores of PCI, PCA, QoL, and Oth; $P < 0.01$; **Table 4**). Twenty-four percent of patients ($n = 64$) reported significant cognitive complaints (PCI), compared with 12% of HCs ($n = 16$). Eight percent of patients ($n = 22$) and 2% of HCs ($n = 3$) reported a significant impact of cognitive difficulties on their quality of life (QoL).

Patients reported significantly more anxiety or depression symptoms than HCs ($P < 0.001$). Forty-one percent of patients ($n = 88$) reported anxiety and 3% depression ($n = 8$) compared with 10% ($n = 13$) and 1% ($n = 1$) of HCs.

Table 2. Demographic and clinical characteristics of patients.

	Breast cancer patients ***n*** **= 264**	**HCs** ***n*** **= 132**	***P***
Demographic			
Age, years (mean, SD, range)	54.1 (10.8) [20–83]	53.2 (9.0) [18–81]	0.55
Sample size (*n*): ≥65	43	12	
Education level[a] (%)			
Low	27 (10.2)	4 (3.0)	
Middle	116 (43.9)	54 (40.9)	0.014
High	119 (45.1)	74 (56.1)	
Missing	2 (0.8)		
Mean days since diagnosis (SD)	37 (70.3)	—	—
Clinical			
ECOG PS (=0) (%)	244 (98.0)	—	—
Comorbidities (%) Charlson index			
0	187 (70.8)	—	
1–2	57 (21.6)	—	
Missing	20 (7.6)	—	
Pulmonary comorbidities (%)	49 (19.0)	7 (5.3)	**<0.001**
Gynecologic comorbidities (%)	153 (59.3)	38 (28.8)	**<0.001**
Cardiovascular comorbidities (%)	71 (27.5)	20 (15.1)	**<0.01**
Neurologic/psychiatric comorbidities (%)	68 (26.4)	6 (4.6)	**<0.001**
Psychotropic medications[b] (%)	22 (8.3)	0	**<0.001**
Mean BMI (SD)	26.1 (5.2)	—	—
Cancer stage I–II (%)	182 (68.9)	—	—
Cancer infiltrant (%)	237 (89.7)	—	—
Grade I–II (%)	183 (80.3)	—	—
HER2-positive (%)	35 (13.3)	—	—

Note: Significant results are in bold.
Abbreviations: BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group Performance Status.
[a]Education level, number of years of school: low, <10; middle, 10–12; high, >12.
[b]Level 3 on the World Health Organization analgesic ladder, anxiolytics, antidepressant treatments, and hypnotics.

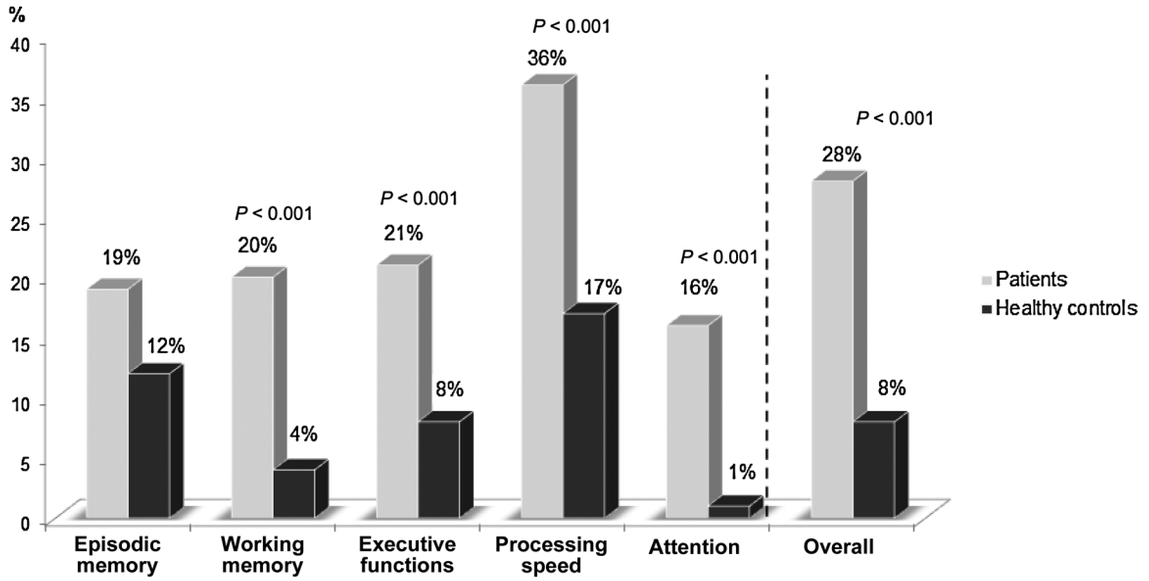

Figure 1.
Cognitive impairment in each cognitive domain and overall. Overall cognitive impairment: at least two impaired cognitive domain.

Similarly, patients reported significantly more emotional and cognitive fatigue than HCs ($P < 0.01$), although there was no significant difference in physical fatigue between the groups.

Multivariable analyses

Significantly more patients with breast cancer had overall objective cognitive impairment than HCs [OR = 3.01; 95% confidence interval (CI): 1.31–6.88; **Table 5**]. Education level ($OR_{Low\ vs.\ Middle} = 0.19$; 95% CI: 0.06–0.59), age ($OR_{\leq 49\ vs.\ \geq 65} = 3.66$; 95% CI: 1.24–10.78), and neurologic/psychiatric comorbidities ($OR_{No\ vs.\ Yes} = 3.69$; 95% CI: 1.59–8.57) were also associated with overall objective cognitive impairment.

Nevertheless, after adjustment no significantly more patients with breast cancer had cognitive complaints than HCs (OR = 1.38; 95% CI: 0.65–2.92). The significant association between group and cognitive complaints previously found was no significant after adjustment for fatigue (OR = 1.70; 95% CI: 0.91–3.18).

In addition, neither objective cognitive impairment nor cognitive complaints were associated with anxiety or depression. Overall objective cognitive impairment was not associated with fatigue, whereas cognitive complaints were associated with (cognitive fatigue, OR = 1.03; 95% CI: 1.02–1.05). Models with physical fatigue and emotional fatigue showed similar results.

Cognitive complaints were not related to education, but younger patients reported more cognitive complaints than older ones ($OR_{\leq 49\ vs.\ \geq 65} = 0.12$; 95% CI: 0.03–0.49).

Relations between cognition and other variables

Objective cognitive impairment assessed by domains was not associated with cognitive complaints. Time since diagnosis was not associated with objective cognitive impairment or cognitive complaints.

Discussion

Using a large national cohort, this study is the first to assess cognition before any breast cancer treatment. Compared with age-matched HCs, after adjustment, more patients recently diagnosed with localized breast cancer had objective cognitive impairment before any treatment, without direct link with anxiety or depression. Cognitive complaints were associated with fatigue.

According to the ICCTF, baseline cognitive assessment before treatment is important to better evaluate the role of treatment in cognitive impairment (24). Cognitive disorders were observed in 20%–30% of patients after surgery and before adjuvant treatment (5). As the use of general anesthesia may partly explain this impairment, it is essential to quantify cognitive impairment attributable to breast cancer before any adjuvant treatment. Indeed, studies on the impact of general anesthesia outside the oncology field showed postoperative cognitive dysfunction in some patients (14). Thus, baseline cognitive assessment after cancer surgery may not reflect patients' initial cognitive functioning.

We found that, after adjustment, before any cancer treatment (including breast cancer surgery), significantly more patients had objective cognitive impairment than HCs. Age, education and neurologic/psychiatric comorbidities were associated with this impairment. These results confirm those of previous studies, which showed lower memory scores prior to breast cancer surgery in patients compared with HCs (13, 16), although these studies assessed few cognitive domains.

If more patients with breast cancer seem to have cognitive complaints than HCs, after adjustment, there was no significant difference between groups. The significant association between group and cognitive complaints was no significant after adjustment for fatigue. Kesler and colleagues (13) also did not observe any difference in cognitive complaints between patients with breast cancer before surgery and HCs. Also in line with previous results, we did not show a relationship between objective cognitive impairment and cognitive complaints (26). The fact that our young patients had more cognitive complaints than older ones was observed previously (27, 28) and could be explained by the increase of cognitive complaints with normal aging independently of cancer and by their knowledge of the side-effects of cancer treatment, which may be better due to internet research, etc.

Table 3. Mean and z-score of cognitive tests and cognitive domains.

	Breast cancer patients $n = 264$			HCs $n = 132$			
Cognitive domain/score	**Mean (SD)**	**z-scores**	**Nb of pts with impairment (%)**	**Mean (SD)**	**z-scores**	**Nb of pts with impairment (%)**	***P* = Comparison of % impairment**
Episodic memory (HVLT)		−0.2 (0.9)	49 (18.6)		0.0 (0.8)	16 (12.2)	0.11
FR1	7.4 (1.7)	−0.2 (1.0)	9 (3.4)	7.9 (1.7)	0.05 (1.0)	3 (2.3)	0.55
FR2	10.0 (1.5)	−0.1 (1.0)	18 (6.8)	10.2 (1.5)	0.02 (1.0)	9 (6.8)	1.0
FR3	10.9 (1.2)	−0.3 (1.1)	33 (12.5)	11.2 (1.1)	−0.04 (1.0)	11 (8.3)	0.21
DFR	10.3 (1.6)	−0.2 (1.1)	18 (6.8)	10.7 (1.5)	−0.002 (1.0)	6 (4.6)	0.39
Working memory		−0.5 (0.8)	52 (19.8)		0.01 (0.9)	5 (3.8)	**<0.001**
Digit-span forward	8.7 (1.9)			9.1 (1.9)			
Digit-span backward	6.0 (1.8)			7.0 (2.2)			
Digit-span[a]	9.1 (2.5)	−0.4 (1.0)	8 (3.03)	10.1 (2.6)	0.01 (1.0)	1 (0.8)	0.16
Letter-number sequencing	9.5 (2.5)	−0.5 (0.9)	11 (4.2)	11.0 (2.8)	0.008 (1.0)	0	0.02
Spatial-span forward	8.0 (1.8)			8.7 (1.5)			
Spatial-span backward	7.1 (1.7)			8.1 (1.6)			
Spatial-span[a]	10.0 (2.4)	−0.7 (1.2)	44 (16.7)	11.6 (2.1)	−0.004 (1.0)	4 (3.0)	**<0.001**
Information processing speed		0.9 (0.7)	95 (36.4)		0.003 (0.6)	23 (17.4)	**<0.001**
TMT A time	32.9 (11.6)	0.6 (1.5)	40 (15.1)	27.8 (8.1)	−0.004 (1.0)	6 (4.6)	**<0.01**
TMT A errors	0.2 (0.5)	0.5 (1.8)	50 (18.9)	0.1 (0.3)	0.003 (1.0)	12 (9.1)	0.01
Stroop time color card	62.6 (11.4)	−6.3 (0.03)	0 (0)	59.0 (9.4)	0.0 (1.0)	4 (3.0)	**<0.01**
Stroop time word card	45.8 (7.9)	0.4 (1.2)	25 (9.5)	43.5 (6.6)	−0.002 (1.0)	7 (5.3)	0.15
Symbol Search[a]	12.0 (3.0)	−0.5 (1.1)	14 (5.3)	13.3 (2.8)	0.009 (1.0)	2 (1.5)	0.07
Attention		−0.4 (0.8)	41 (15.9)		0.007 (0.6)	2 (1.5)	**<0.001**
d2 - F%	21.0 (18.3)	0.08 (1.0)	0	19.6 (18.2)	0.003 (1.0)	0	–
d2 – GZ	417.23 (83.3)	−0.6 (1.2)	18 (6.8)	457.6 (68.1)	0.009 (1.0)	2 (1.5)	0.2
d2 – KL	156.92 (35.5)	−0.6 (1.2)	31 (12.0)	174.8 (29.9)	0.01 (0.4)	0	**<0.001**
Executive function		−0.09 (0.6)	56 (21.4)		0.002 (0.7)	10 (7.6)	**<0.001**
Fluency score - Animal	30.8 (7.7)	−0.2 (1.0)	5 (1.9)	32.2 (7.4)	0.0 (1.0)	1 (0.8)	0.40
Fluency score – Letter P	21.6 (6.8)	−0.09 (1.0)	13 (4.9)	22.2 (6.5)	0.003 (1.0)	1 (0.8)	0.04
TMT B time	79.6 (35.0)	0.5 (1.5)	34 (12.9)	67.8 (22.6)	−0.002 (1.0)	6 (4.6)	**0.01**
TMT B perseverative errors	0.2 (0.4)	−0.04 (0.9)	4 (4.5)	0.2 (0.5)	−0.007 (1.0)	3 (2.3)	0.28
Stroop time – Interference[b]	49.1 (19.7)	0.08 (1.0)	12 (4.5)	47.5 (18.8)	−0.002 (1.0)	1 (0.8)	0.05
Stroop errors – Interference[b]	0.3 (1.0)	0.04 (1.2)	16 (6.1)	0.3 (0.8)	0.02 (0.8)	1 (0.8)	**0.01**

Note: Significant results are in bold.

Abbreviations: DFR, delayed free recall; FR, free recall; GZ, quantitative performance index; HVLT, Hopkins Verbal Learning Test; KL, concentration performance index; Nb of pts, number of patients; TMT, Trail Making Test.

[a]Mean score for scaled score.

[b]Time to complete and number of noncorrected errors: interference card – color card.

Several factors could be involved in cognitive difficulties before cancer treatment, including biological factors, psychologic factors, and fatigue, leading to the hypothesis that cancer itself might induce cognitive modifications (29). Furthermore, previous studies showed that anxiety and depression could be associated with biological factors including inflammatory response (30) as well as brain changes (31). We found that cognitive difficulties before breast cancer surgery were associated with fatigue, but, at the opposite of several previous results, not with anxiety or depression. Overall, this could suggest that cognitive disorders are associated not with psychologic factors, but biological factors, for example, inflammatory mechanisms that induce fatigue. Indeed, although 41% of our patients with recently diagnosed localized breast cancer reported significant anxiety, this factor was not associated with cognitive difficulties. Before treatment, women may experience anxiety that is unrelated to cognitive modifications: fear of vital outcome, treatment, body modifications, and familial and professional organization. Moreover, in comparison with HCs, our patients reported more emotional and cognitive fatigue that was related to cognitive complaints. Fatigue could be induced by the neurophysiologic effects of breast cancer itself and lead to cognitive alterations (32). Before surgery, fatigue could be induced by the tumor itself, which may be a source of proinflammatory cytokines (33). As observed in previous studies, some biological and brain modifications could play a role in cognitive disorders before treatment, especially cytokines with TNF (16). Furthermore, subtle structural and functional brain alterations have also been found before breast cancer surgery (13). Further studies that include biomarkers of inflammation are needed to better understand the biological mechanisms involved in fatigue and cognitive difficulties.

The preoperative period is stressful, and patients usually have many demands on their time, which could explain the low participation rate in our and other studies (15). Indeed, cognitive assessment before surgery was difficult to plan between breast cancer diagnosis and breast surgery ($n = 415/1{,}323$). Comparison of effect sizes for the present results and other presurgery studies is difficult due to the different tests/questionnaires used. In Sato and colleagues (34) with the Digit span backward, the only similar test, we find a similar mean accompanied with a lower SD, which reflects our larger sample size. Our presurgery results on FACT-Cog (PCI, PCA, Oth, and QoL) are relatively similar to those observed in the study of Jenkins and colleagues 2016 (15), although we observed a slightly higher PCI that

Table 4. PRO outcomes.

	Breast cancer patients $n = 264$		HCs $n = 132$		
	Mean, SD	Number of patients with pathologic scores (%)	Mean, SD	Number of patients with pathologic scores (%)	P = Comparison of mean
FACT-Cog					
PCI	57.9 (11.8)	64 (24.2)	61.7 (8.8)	16 (12.1)	=**0.001**
PCA	19.6 (5.5)	53 (20.1)	21.2 (4.5)	17 (12.9)	<**0.01**
QoL	11.8 (4.2)	22 (8.33)	14.0 (3.1)	3 (2.3)	<**0.001**
Oth	15.0 (2.1)	77 (29.2)	15.4 (1.2)	13 (9.8)	<**0.001**
HADS					
Anxiety ($n = 219$)	9.3 (3.4)	88 (41.4)	6.3 (3.2)	13 (10)	<**0.001**
Depression ($n = 239$)	4.0 (3.2)	8 (3.4)	2.7 (2.3)	1 (0.8)	<**0.001**
FA12					
Physical fatigue ($n = 238$)	25.7 (23.3)		22.5 (18.4)		0.17
Emotional fatigue ($n = 235$)	24.0 (28.7)	Not applicable	14.8 (19.9)	Not applicable	=**0.001**
Cognitive fatigue ($n = 239$)	17.8 (25.5)		10.6 (15.3)		=**0.003**

Note: Significant results are in bold.

indicated lower cognitive complaints. For the two pre–post surgery studies (13, 34), which included similar test/questionnaire with our, no significant difference was found between the two assessments. Thus, large pre–post surgery studies are needed to assess more precisely effect sizes and the cost–benefit of assessing patients prior to surgery due to low rate of recruitment of presurgery study.

Table 5. Multivariable ORs and 95% CI of overall objective cognitive impairment and cognitive complaints, and demographics, comorbidities, and QoL characteristics, based on group model.

	Overall objective cognitive impairment Multivariable[a] analysis OR (95% CI)	Cognitive complaints Multivariable[a] analysis OR (95% CI)
Groups		
HCs	1.00 (Reference)	1.00 (Reference)
Breast cancer patients	**3.01 (1.31–6.88**)	1.38 (0.65–2.92)
Education level		
Low	1.00 (Reference)	1.00 (Reference)
Middle	**0.19 (0.06–0.59)**	0.68 (0.15–3.08)
High	**0.13 (0.04–0.40)**	0.91 (0.20–4.09)
P_{trend}	<0.001	<0.01
Age (years)		
≤49	1.00 (Reference)	1.00 (Reference)
50–64	2.16 (0.94–4.96)	**0.15 (0.07–0.31)**
≥65	**3.66 (1.24–10.78)**	**0.12 (0.03–0.49)**
P_{trend}	0.04	<0.001
Neurologic/psychiatric comorbidities		
No	1.00 (Reference)	1.00 (Reference)
Yes	**3.69 (1.59–8.57)**	1.36 (0.49–3.79)
Psychotropic medications		
No	1.00 (Reference)	1.00 (Reference)
Yes	1.40 (0.38–5.13)	3.58 (0.86–14.91)
Anxiety[b]		
No	1.00 (Reference)	1.00 (Reference)
Yes	0.54 (0.26–1.13)	1.40 (0.69–2.84)
Depression[b]		
No	1.00 (Reference)	1.00 (Reference)
Yes	1.98 (0.23–16.85)	1.00 (0.15–6–71)
Cognitive fatigue [continuous score (0–100)][c]	1.01 (0.99–1.02)	**1.03 (1.02–1.05)**

Note: Significant results are in bold.
[a]Adjusted for group (patients with breast cancer, HCs), education level (low, middle, high), age (≤49, 50–64, ≥65), neurologic/psychiatric comorbidities (yes, no), psychotropic medications (yes, no), anxiety (yes, no), depression (yes, no), and fatigue (continuous score).
[b]HADS.
[c]FA12.

If a group of HCs is a strength of the study to assess the real impact of cancer diagnosis on cognition, the selection of control group is always difficult. In the case of our study, the HCs were recruited with local advertisements in a single site and were not fully representative of all French healthy women. Limitations of this study also included that the two groups were significantly different according to education level, psychotropic medications, and neurologic/psychiatric comorbidities (e.g., head trauma without loss of consciousness, episode of hospitalization for depression; major neurologic/psychiatric comorbidities were exclusion criteria) but these variables were taken into account in multivariable analyses. Moreover, the HVLT showed the lowest sensitivity of the study tests. Despite the recommendations of the ICCTF to use it (24), with few words, semantically grouped and no measure of interference it seems to be too easy for individuals with the mild to moderate impairment that characterizes CRCI.

To our knowledge, only two studies assessed cognition in patients with breast cancer before and just after breast cancer surgery and before any adjuvant treatment. Although it should be confirmed in large studies of cognition before and after breast cancer surgery, the hypothesis that preadjuvant treatment cognitive difficulties could be partly explained by the impact of general anesthesia was not confirmed. A small study ($n = 14$) did not find cognitive impairment after breast surgery, with only one patient showing cognitive decline (15). Another study examined modifications in structural brain imaging coupled with cognitive tests, and showed that only one of the three attention scores investigated was poorer after surgery in cancer patients ($n = 32$) compared with HCs, and no significant declines in score were observed (34). This attentional dysfunction could be associated with thalamus alterations. Nevertheless, memory and executive scores were not significantly different in postoperative cancer patients compared with HCs, which suggested very subtle cognitive changes following breast cancer surgery (34).

To accurately assess the potential impact of breast surgery on cognition, further studies should include baseline cognitive assessment before breast cancer surgery and a follow-up thereafter. This will also allow researchers to account for fatigue and psychologic impacts on cognition before surgery.

Research and clinical implications

According to this study results, baseline cognitive assessment before any cancer treatment, including surgery, could better reflect patients' initial cognitive functioning and is important to assess the impact of each cancer treatment on cognition. Patients with cognitive impairment detect at this time of medical care could be beneficiate of a cognitive follow up to receive adapted supportive care. The adjuvant treatment could be also adjusted, particularly adjuvant chemotherapy (indications and type of chemotherapy) to minimize the risk to increase the cognitive impairment.

Conclusions

Using a large national cohort, this study is the first to assess cognition before any breast cancer treatment. Patients recently diagnosed with localized breast cancer had more objective cognitive impairment and cognitive complaints before surgery than healthy controls. These complaints were mostly related to fatigue. Baseline assessment before any treatment is important, especially to assess the impact of each cancer treatment on cognition, including surgery. Further understanding of the biology and correlates of cognitive dysfunction at breast cancer diagnosis are needed.

Disclosure of Potential Conflicts of Interest

B. Pistilli reports receiving commercial research grants from Puma Biotechnology, Novartis, Myriad Genetics, and Pierre Fabre and other commercial research support from AstraZeneca, MSD Oncology, and Novartis. I. Vaz-Luis reports receiving speakers bureau honoraria from Amgen, Novartis, AstraZeneca, and Kephren. No potential conflicts of interest were disclosed by the other authors.

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