Dear Author,

Please, note that changes made to the HTML content will be added to the article before publication, but are not reflected in this PDF.

Note also that this file should not be used for submitting corrections.

# AUTHOR QUERY FORM

ELSEVIER	Journal: EJC	Please e-mail or fax your responses and any corrections to:
	Article Number: 9212	E-mail: corrections.eseo@elsevier.sps.co.in Fax: +31 2048 52799

Dear Author,

Please check your proof carefully and mark all corrections at the appropriate place in the proof (e.g., by using on-screen annotation in the PDF file) or compile them in a separate list. Note: if you opt to annotate the file with software other than Adobe Reader then please also highlight the appropriate place in the PDF file. To ensure fast publication of your paper please return your corrections within 48 hours.

For correction or revision of any artwork, please consult <u>http://www.elsevier.com/artworkinstructions.</u>

Any queries or remarks that have arisen during the processing of your manuscript are listed below and highlighted by flags in the proof. Click on the ' $\underline{O}$ ' link to go to the location in the proof.

Location in article	Query / Remark: <u>click on the Q link to go</u> Please insert your reply or correction at the corresponding line in the proof
Q1	Please confirm that given name(s) and surname(s) have been identified correctly.
<u>Q2</u>	Please check that the affiliations link the authors with their correct departments, institutions, and locations, and correct if necessary.
<u>Q3</u>	Would you consider changing the phrase 'would be parallel but higher to that of' to 'would not just be parallel to but higher than those of' in the sentence 'While2]' ? Please check, and correct if necessary.
<u>Q4</u>	The significance symbol P, has been represented by both P and p, and needs to be consistent throughout the text. Please check and amend as necessary.
Q5	Please check the edit(s) made in the sentence 'Thepatients)', and correct if necessary.
<u>Q6</u>	One or more sponsor names may have been edited to a standard format that enables better searching and identification of your article. Please check and correct if necessary.
<u>Q7</u>	The country names of the Grant Sponsors are provided below. Please check and correct if necessary. 'Sanofi' - 'United States'.
	Please check this box if you have no corrections to make to the PDF file



- Baseline cognitive functions among elderly patients 3
- with localised breast cancer  $\overset{\bigstar, \overleftrightarrow, \overleftrightarrow}{\leftarrow}$ 4

Marie Lange<sup>a,b,c,d,e,f,1</sup>, Bénédicte Giffard<sup>a,b,c,d,2</sup>, Sabine Noal<sup>f,k,3</sup>, Olivier Rigal<sup>g,h,4</sup>, Jean-Emmanuel Kurtz<sup>1,5</sup>, Natacha Heutte<sup>e,f,j,1</sup>, Christelle Lévy<sup>k,6</sup>, Djelila Allouache<sup>k,6</sup>, Chantal Rieux<sup>f,3</sup>, Johan Le Fel<sup>g,4</sup>, Aurélie Daireaux<sup>f,3</sup>, Bénédicte Clarisse<sup>f,3</sup>, Corinne Veyret<sup>h,4</sup>, Philippe Barthélémy<sup>i,5</sup>, Nadine Longato<sup>i,5</sup>, Francis Eustache<sup>a,b,c,d,2</sup>, Florence Joly<sup>b,e,f,l,\*</sup>

- 8
- 9
- 10
- 11
- 12 02 <sup>a</sup> INSERM, U1077, Caen, France
- <sup>b</sup> Normandie Université, UMR-S1077, Caen, France 13
- 14 <sup>c</sup> Ecole Pratique des Hautes Etudes, UMR-S1077, Caen, France
- 15 <sup>d</sup> CHU de Caen, U1077, Caen, France
- 16 e INSERM, U1086, Caen, France
- <sup>f</sup> Unité de Recherche Clinique, Centre François Baclesse, Caen, France 17
- 18 <sup>g</sup> Service des soins de support, Centre Henri-Becquerel, Rouen, France
- 19 <sup>h</sup> Département d'Oncologie médicale, Centre Henri-Becquerel, Rouen, France
- <sup>i</sup> Département d'hématologie et d'oncologie, Hôpitaux universitaires de Strasbourg, Strasbourg, France 20
- <sup>j</sup> UFR des sciences pharmaceutiques, Université de Caen Basse-Normandie, Caen, France 21
- <sup>k</sup> Comité Sein, Centre François Baclesse, Caen, France 22
- 23 <sup>1</sup>CHU de Caen, Service d'Oncologie, Caen, France

\* Data in this paper were presented in part as an oral communication at the ASCO Annual Meeting (Chicago, 31st May 2013–4th June 2013), as a poster at the meeting of the Federation of the European Societies of Neuropsychology (Berlin, 12-14th September 2013), and as a poster at the conference of International Cognition and Cancer Taskforce (Seattle, 10-12th February 2014).

The registration identification number of this clinical trial is NCT01333735.

\* Corresponding author at: Service de recherche clinique, Centre François Baclesse, BP 5026, 3 Av. Général Harris, 14076 Caen Cedex 05, France. Tel.: +33 231455002; fax: +33 231455097.

E-mail addresses: m.lange@baclesse.fr (M. Lange), benedicte.giffard@unicaen.fr (B. Giffard), s.noal@baclesse.fr (S. Noal), olivier.rigal@chb. unicancer.fr (O. Rigal), J-Emmanuel.KURTZ@chru-strasbourg.fr (J.-E. Kurtz), n.heutte@baclesse.fr (N. Heutte), c.levy@baclesse.fr (C. Lévy), d.allouache@baclesse.fr (D. Allouache), c.rieux@baclesse.fr (C. Rieux), johan.lefel@chb.unicancer.fr (J.L. Fel), aurelie.daireaux@neuf.fr (A. Daireaux), b.clarisse@baclesse.fr (B. Clarisse), corinne.veyret@chb.unicancer.fr (C. Veyret), philippe.barthelemy@chru-strasbourg.fr (P. Barthélémy), nadine.longato@chru-strasbourg.fr (N. Longato), neuropsycho@chu-caen.fr (F. Eustache), f.joly@baclesse.fr (F. Joly).

Address: U1086 INSERM-UCBN, Centre François Baclesse, BP 5026, 3 Av. Général Harris, 14076 Caen Cedex 05, France. Tel.: +33

231455002; fax: +33 231455097.

<sup>2</sup> Address: Inserm-EPHE-UCBN U1077, CHU Côte de Nacre - CS 30001, F-14033 Caen Cedex, France. Tel.: +33 231065197; fax: +33 231065198.

<sup>3</sup> Address: Service de recherche clinique, Centre François Baclesse, BP 5026, 3 Av. Général Harris, 14076 Caen Cedex 05, France. Tel.: +33 231455002; fax: +33 231455097.

<sup>4</sup> Address: Service des soins de support, Centre Henri Becquerel, Rue d'Amiens, 76038 Rouen Cedex 1, France. Tel.: +33 232082918; fax: +33 232082936.

<sup>5</sup> Address: Hôpitaux Universitaires de Strasbourg, Departement d'hematologie et d'oncologie, Hôpital de Hautepierre, 1, Av Molière, BP 49, 67200 Strasbourg, France. Tel.: +33 3 88 12 83 14.

<sup>6</sup> Address: Comité Sein, Centre François Baclesse, BP 5026, 3 Av. Général Harris, 14076 Caen Cedex 05, France. Tel.: +33 231455050; fax: +33 231455097.

http://dx.doi.org/10.1016/j.ejca.2014.05.026

0959-8049/© 2014 Published by Elsevier Ltd.

# ARTICLE IN PRESS M. Lange et al. / European Journal of Cancer xxx (2014) xxx–xxx

Received 17 February 2014; received in revised form 22 April 2014; accepted 29 May 2014

# Abstract *Purpose:* Cognitive deficits (CD) are reported among cancer patients receiving chemotherapy, but may also be observed before treatment. Though elderly patients are expected to be more prone to present age-related CD, poor information is available regarding the impact of cancer and chemotherapy on this population. This study assessed baseline cognitive functions (before adjuvant treatment) in elderly early stage breast cancer (EBC) patients. *Methods:* Women >65 years-old with newly diagnosed EBC were included in this prospective

study. Episodic memory, working memory, executive functions and information processing speed were assessed by neuropsychological tests. Questionnaires were used to assess subjective CD, anxiety, depression, fatigue, quality of life\_and geriatric profile. Objective CD were defined using International Cognition and Cancer Task Force criteria. A group of elderly women without cancer coupled with published data related to healthy women were used for comparison (respectively to subjective and objective CD).

**Results:** Among the 123 elderly EBC patients ( $70 \pm 4$  years) included, 41% presented objective CD, which is greater than expected in healthy population norms (binomial test P < .0001). Verbal episodic memory was mainly impaired (21% of patients). No correlation was observed between objective CD and cancer stage or geriatric assessment. Subjective CD only correlated with verbal episodic memory (P = .01).

*Conclusions:* This is the first large series assessing baseline cognitive functions in elderly EBC patients. More than 40% presented objective CD before any adjuvant therapy, which is higher than what is reported among younger patients. Our results reinforce the hypothesis that age is a risk factor for CD in EBC patients.

© 2014 Published by Elsevier Ltd.

## 61 **1. Introduction**

Beyond difficulties with memory, attention and con-62 centration reported by cancer patients, it has become 63 increasingly apparent that cytotoxic drugs given for 64 non-central nervous system tumours might induce cog-65 nitive side-effects. This phenomenon - called 66 "chemobrain" - has been particularly studied among 67 young women treated with chemotherapy for breast 68 cancer. According to the literature, these cognitive trou-69 bles could affect 15-50% of chemotherapy-treated 70 71 patients and are usually moderate in severity [1]. Never-72 theless, recent longitudinal studies revealed that about 73 20-30% of breast cancer patients have cognitive impairment before starting adjuvant treatment [2]. This indi-74 cates that beside exposure to cytotoxic drugs, other 75 76 factors including postoperative dysfunctions, psychological distress related with the diagnosis, fatigue, genetic 77 factors and also the biological adverse effects of cancer 78 itself are involved, suggesting an impact of cancer as a 79 80 whole on cognitive functions [3,4].

The mean patients' age in the previous studies addressing the impact of cancer on cognitive function was less than 65 years. Yet, because cancer increasingly appears among seniors, the impact of ageing on cognitive impairment is a relevant issue. Ageing by itself is known to be associated with some cognitive modifications,

comorbidities and functional decline, which may all have 87 an impact on the patients' independence. While both age-88 ing and cancer are expected to have an impact on cogni-89 tion, biologic processes underlying cancer led to the 90 hypothesis that age-associated declines among cancer 91 patients would be parallel but higher to that of older 92 adults with no cancer history, and that treatment-93 induced accelerated ageing would be observed only in 94 vulnerable or frail populations [2]. Although a pretreat- Q3 95 ment cognitive evaluation is a prerequisite to define the 96 part of cognitive chemotherapy-induced impairment, 97 only one study, to our knowledge, addressed this issue 98 especially among elderly breast cancer patients [5]. 99

The aim of the present prospective study was to precisely assess cognitive functioning (objective performances and subjective complaints) among elderly EBC patients before starting adjuvant therapy, and to seek for correlations with mood, fatigue, quality of life and clinical variables.

## 2. Patients and methods

## 2.1. Participants 107

106

Newly diagnosed and consecutive elderly women 108 with EBC were recruited from three French Cancer 109

162

168

comprehensive Centers (Caen, Rouen\_and Strasbourg)from January 2009 to August 2012.

Inclusion criteria were EBC and age over 65. Exclu-112 sion criteria included prior exposure to chemotherapy 113 or radiotherapy, neurological comorbidities, known 114 115 psychiatric comorbidities which might affect capacity to participate, major cognitive disorders and docu-116 mented alcohol or drug abuse. Participants with a 117 Mini-Mental State Examination (MMSE) score less 118 119 than 25 out of 30 suggesting potential pathological ageing were not eligible [6-8] as well as those reporting a 120 121 formal education less than 5 years (end of the primary school) due to the lack of normative data for such 122 individuals. 123

Patients were assessed after surgery, but before any 124 125 adjuvant treatment initiation. They were evaluated with standardised neuropsychological tests, by a graduate 126 127 neuropsychologist, and through self-report questionnaires. Cognitive performances were compared to pub-128 lished normative data, adjusted for age and/or 129 130 education. All patients gave their written informed consent to the longitudinal study which was approved by 131 the local ethics committee. 132

## 133 2.2. Assessment

The neuropsychological battery included standardised 134 neuropsychological tests assessing four cognitive 135 domains: episodic memory (verbal and visual modali-136 137 ties), working memory, information processing speed and executive functions (Table 1) [7,9–13]. The subjective 138 139 assessment consisted of a self-report measure of cognitive complaints (Functional Assessment of Cancer Therapy 140 Cognitive Scale - FACT-Cog, version 3 [14,15] - four 141 subscales: Perceived Cognitive Impairments, Impact on 142 143 Quality of Life, Comments from Others, and Perceived 144 Cognitive Abilities), assessment of depression (Beck 145 Depression Inventory – BDI [16]), anxiety (Spielberger

Table 1

Neuropsychological tests gro	uped by main	cognitive domains.
------------------------------	--------------	--------------------

State-Trait Anxiety Inventory - STAI [17]), fatigue 146 (Functional Assessment of Chronic Illness Therapy-Fati-147 gue - FACIT-Fatigue, version 4 [18]) and quality of life 148 (FACT-Breast <sub>T</sub> FACT-B, version 4 [19] incorporates 149 FACT-General - FACT-G, version 4 [20]). Geriatric 150 assessment included the Geriatric Depression Scale 151 (GDS) [21] (4-item short form), the Instrumental Activi-152 ties of Daily Living (IADL) [22], the Activities of Daily 153 Living (ADL) [23], the Charlson comorbidity index 154 [24], the number of medications and main previous med-155 ical history. Clinical variables were Performance Status 156 (PS), medications with potential impact on cognition 157 (Level 3 on the WHO analgesic ladder, anxiolytics, anti-158 depressant treatments and hypnotics), cancer stage, time 159 since surgery, type of surgery, HER2 positive and hor-160 mone receptor status. 161

2.3. Procedure

Patients completed neuropsychological tests, geriatric163scales and some self-report questionnaires (the BDI and164the STAI) in a 2 h-session with a neuropsychologist.165The other self-report questionnaires were completed by166the patients at home.167

## 2.4. Assessment criteria

According to the recommendations of the Interna-169 tional Cognition and Cancer Task Force [25] and as 170 described previously [26], an index for each patient's 171 baseline overall cognitive function was operationally 172 defined as impaired or not impaired using a 2-part crite-173 rion: if patients performed at a z-score of  $\leq 1.5$  standard 174 deviation (SD) on two or more tests, or if they performed 175 at a z-score of  $\leq 2.0$  SDs on a single test, they were classi-176 fied as impaired. This 2-step approach was designed to 177 minimise the number of potential false-positive errors 178 resulting from multiple tests and to determine the fre-179

Cognitive domain	Test	Outcome measure	Range
Episodic memory			
Verbal episodic memory	Grober and Buschke procedure [20]	4 free recalls	(4×) 0–16
Visual episodic memory	Rey Complex Figure [19]	Recall score	0-36
Working memory	WAIS-III [21]: Arithmetic	Number of resolved problems	0-22
	WAIS-III: Digit-span	Correct trials, forward	0–16
		Correct trials, backward	0–14
	WAIS-III: Letter-number sequencing	Total correct trials	0-21
Information processing speed	TMT A [18]	Time to complete and errors	$\geqslant 0$
Executive function			
Flexibility	TMT B [18]	Time to complete and number of perseverative	$\geq 0$
		errors	
Information generation	Verbal fluency [17]: Category (animal) and Letter P	Total score over 2 min	$\geqslant 0$

WAIS, Wechsler adult intelligence scale; TMT, trail making test.

quency of impairment rather than low performance. By 180 181 using curves based on the binomial probability distribution [27], we determined that in a battery of eight inde-182 pendent tests approximately 17% of the population 183 184 would perform two SDs below the mean on a single test, 185 making 17% considered as the significant threshold. Like for overall cognitive function, using the classification 186 criteria described above, a cognitive domain was consid-187 188 ered as impaired if it included one impaired score.

189 As a reference of self-report cognitive complaints in 190 the general population, a group of 71 healthy women 191 matched on age and education to the EBC patients included (recruited through local advertisements and 192 among associations) completed the FACT-Cog. Clini-193 cally significant symptoms of mood disorders and 194 195 fatigue were operationally defined as ratings on the 196 BDI  $\ge$  8 [16], STAI  $\ge$  56 [17] and FACIT-Fatigue < 37 197 [28]. Geriatric profile was established using GDS (0-4, high score = more depression), IADL (0-8, low scor-198 e = no functional status problem) and ADL (0-6, high 199 200 score = no functional status problem) scores; patients were considered as having a frailty profile if they had 201 at least one alteration of these scores (GDS > 0). 202 IADL > 0, ADL < 6). 203

## 204 2.5. Statistical analysis

Published normative data, adjusted for age and/or 205 education, were used to convert patients' raw neuropsy-206 chological test scores into standardised scores (z scores; 207 mean, 0; SD, 1). Descriptive statistics were generated for 208 the socio-demographic and clinical variables. Compari-209 sons were made by chi square, Student's, and Wilco-210 xon's tests. The correlations between cognitive 211 complaints and objective cognitive scores and other 212 self-report measures were assessed with Spearman's 213 rank correlation coefficient. Given the large number of 214 correlations performed, a *p*-value < 0.01 was considered 215 Q4 in order to minimise type I error. All analyses were con-216 ducted using SAS version 9.3. 217

## 218 **3. Results**

## 219 3.1. Sample characteristics

Of 221 elderly patients with EBC screened, 11 were 220 221 ineligible, and 82 were not enrolled in the trial for the following reasons: lack of interest (n = 17), too much 222 burden (n = 9), travel limitations (n = 17), duration of 223 the assessment (n = 10), or other reason (n = 29). This 224 yielded a 61% participation rate. Moreover, five patients 225 were excluded from analysis because of a score above 226 227 the threshold of dementia [8]. Hence, the final sample consisted of 123 patients, whose major characteristics 228 are presented in Table 2. The majority of elderly patients 229

Demographic and clinical characteristics of all patients (n = 123).

Demographic	
Age (years) (mean, SD, range)	70 (4.10) [65–
	83]
Education level (low/middle/high) (%)	66/15/18
(mean, SD)	11 (2.77)
Clinical	
PS (WHO = 0) (%)	91
Co-morbidities (%) Charlson index (0/1–2)	78/22
>3 co-medications	27
Medications with potential impact on cognition*	24
(%)	
Cancer stage I-II (%)	87
Time since surgery (days) (median, range)	36 [19–141]
Lumpectomy/mastectomy (%)	72/28
Lymph node dissection (%)	80
HER2 positive (%)	17
Hormone receptors positive (%)	88

SD, standard deviation; PS, performance status; WHO, World Health Organisation.

\* Level 3 on the WHO analgesic ladder, anxiolytics, antidepressant treatments and hypnotics.

did not exhibit geriatric comorbidities, was healthy (PS	230
0 = 91%) and two thirds had a low level of education.	23

## 3.2. Neuropsychological outcomes

Using the classification criteria described above, 41% 233 of patients (51/123, binomial test P < .0001) had 234 impaired overall cognitive function which is significantly 235 more frequent than what would be expected in the gen-236 eral population. Twenty-nine percent (36/123) exhibited 237 impairment on 1 test, whereas 12% (15/123) exhibited 238 impairment on two or more tests. Main impairment 239 was related to visual episodic memory and executive 240 functions (21 and 16% of patients, respectively - cf. 241 Fig. 1). Raw neuropsychological test scores, z-scores 242 or standard scores are shown in Table 3. 243



Fig. 1. Distribution of patients according to impaired cognitive domain. The percent of patients with cognitive impairment in each cognitive domain assessed and for at least one impaired cognitive domain.

# ARTICLE IN PRESS

M. Lange et al. | European Journal of Cancer xxx (2014) xxx-xxx

### Table 3

Neuropsychological test and quality of life outcomes.

110.	01	ag

_
5
•
~

Cognitive scores	No.	Mean	SD	z scores or standard scores
Episodic memory				
FR1	123	8.84	1.94	0.17 (0.88)
FR2	123	10.61	1.94	0.28 (0.83)
FR3	123	11.66	1.87	0.21 (0.83)
DFR	122	11.95	2.30	0.17 (1.14)
Rey recall	123	15.24	6.24	-1.38 (1.27)
Working memory				
Arithmetic	122	10.11	4.38	8.80 (2.55)
Digit-span forward	123	7.99	2.17	
Digit-span backward	123	4.95	1.60	
Digit-span std score				8.81 (3.01)
Letter-number sequencing	123	7.62	2.44	8.75 (2.54)
Information processing speed				
TMT A time	123	45.71	17.50	-0.32 (0.78)
TMT A errors	123	0.17	0.46	0.27 (1.42)
Executive function				
Semantic fluency score	123	27.75	7.03	0.10 (0.88)
Phonemic fluency score	123	19.24	6.50	0.03 (1.03)
TMT B time	122	111.43	45.26	-0.40 (0.67)
TMT B perseverative errors	122	0.52	0.85	0.42 (1.18)
Quality of life seconds				
EACIT Entique	111	40.02	0.16	
FACT D	111	40.02	9.10	
ГАСТ-В	112	23:40	0.27	
FACT-G global score	110	81.83	10.56	
PWB	110	24.54	3.31	
SWB	111	19.97	4.15	
EWB	112	19.19	3.62	
FWB	112	17.96	4.35	
FACT-Cog				
PCI	112	60.16	9.91	
QoL	106	11.63	4.06	
Oth	110	15.55	1.11	
PCA	108	19.38	4.97	

No., number; FR, free recall; DFR, delayed free recall; TMT, trail making test; PWB, physical well-being; SWB, social/family well-being; EWB, emotional well-being; FWB, functional well-being; PCI, perceived cognitive impairment; QoL, impact on quality of life; Oth, comments from others; PCA, perceived cognitive abilities.

## 244 3.3. Cognitive complaints

Healthy subjects had significantly more complaints on *Perceived Cognitive Impairments* and *Perceived Cognitive Abilities* FACT-Cog subscales than patients (Fig. 2). However, patients had more complaints than healthy subjects on the subscale *Impact on Quality of Life* of cognitive impairment (P < .025).

3.4. Anxiety, depression, fatigue, geriatric and quality of
life scores

Anxiety, depression and severe fatigue were observed
in 6%, 10% and 29% of the patients, respectively.
Regarding geriatric scores, 89% and 87% of the patients
had normal GDS and functional status scores. Quality
of life scores are shown in Table 3.

3.5. Relation between cognitive complaints and258neuropsychological scores, anxiety, depression and fatigue259

As shown in Table 4, cognitive complaints were 260 correlated with verbal episodic memory impairment 261 (*Perceived Cognitive Impairments* subscale, P < .01) but 262 overall cognitive scores were not correlated with 263 cognitive complaints (the four subscales of the 264 FACT-Cog). 265

However, three of the four subscales of the 266 FACT-Cog (Perceived Cognitive Impairments, Perceived 267 Cognitive Abilities and Impact on Quality of Life) were 268 significantly correlated with the measures of depression, 269 anxiety and fatigue ( $P \le .001$ ; Table 4). Furthermore, 270 the same three subscales were overall significantly associ-271 ated to quality of life scores (FACT-B and FACT-G; 272 Table 4). 273

# **ARTICLE IN PRESS**

M. Lange et al. / European Journal of Cancer xxx (2014) xxx-xxx



## QoL: Quality of Life

Fig. 2. Median Functional Assessment of Cancer Therapy Cognitive Scale (FACT-Cog) scores of patients and healthy subjects. Whiskers' boxplot indicates minimum and maximum and high scores indicate low complaints. There were significant differences between patients and healthy subjects on 2 FACT-Cog subscales. The subscale *Comments from Others* was not represented because there was no difference between groups.

# 274 3.6. Neuropsychological outcomes and clinical 275 characteristics

Cognitive impairment was not significantly correlated with geriatric profile (P = 0.83). Furthermore, there was no correlation between cognitive impairment and Charlson index, PS, medications with potential impact on cognition, cancer stage, time since surgery, type of surgery, hormonal receptor and Her2 status.

## 282 4. Discussion

283 This study is the first large series assessing cognitive functions in elderly EBC patients prior to adjuvant treat-284 ment. The main result is that, compared to normative 285 data based on age and education, 41% of the patients 286 287 had cognitive impairment mainly epitomised by impaired visual episodic memory before any adjuvant treatment 288 which is significantly higher than what would be expected 289 considering healthy population norms. To avoid confus-290 ing bias from pre-treatment status to that of chemother-291 apy-induced impairment, some authors proposed the 292 293 term "chemobrain" to be replaced by "cancerbrain" [30,31]. In this way, evaluation of cognitive functions 294 295 before treatment appears essential to understand the impact of treatments on cognitive functions of cancer 296 patients especially among elderly patients. 297

In our study, the proportion of patients exhibiting 298 pre-treatment impairments was higher than the one 299 reported in studies focusing on younger breast cancer 300 patients [45-55 years-old] ranging from 20% to 30% 301 [2]. This important finding supports the hypothesis that 302 elderly patients may be more sensitive to the impact of 303 cancer on cognition, and would be consistent with the 304 link between biological processes underlying cancer, 305 ageing, neurodegeneration and a cognitive decline as 306 proposed by Ahles [32]. However, longitudinal studies 307 remain necessary to investigate whether or not cancer 308 therapies accelerate cognitive ageing [32]. 309

In a previous pilot longitudinal study exploring base-310 line cognitive functioning of elderly patients with breast 311 cancer (n = 28), 11% of the patients were found to have 312 cognitive impairment before beginning chemotherapy 313 [5]. However, 86% of the patients had an education level 314 superior to high school (against only 18% in our popu-315 lation), which may have biased the results and underes-316 timated the impact on cognition. Thus, according to the 317 concept of cognitive reserve suggesting that some sub-318 jects may cope better than others with brain damage, 319 high education level could reduce the sensitivity of 320 patients to the impact of cancer on cognition [2]. 321

# **ARTICLE IN PRESS**

M. Lange et al. | European Journal of Cancer xxx (2014) xxx-xxx

Table 4

Relations between cognitive complaints and neuropsychological, anxiety, depression, fatigue and quality of life scores.

Spearman correlation	Cognitive complaints				
	PCI	PCA	Oth	QoL	
Neuropsychological scores					
At least 1 domain impaired (t test)	-0.48	0.93	0.65	0.67	
Verbal episodic memory impairment	-0.31*	-0.10	-0.24	-0.20	
FR1	0.23	0.23	0.16	0.24	
FR2	0.23	0.18	0.16	0.17	
FR3	0.10	0.10	0.003	-0.02	
DFR	0.19	0.04	0.17	0.24	
Visual episodic memory impairment (Rey recall)	-0.05	0.009	-0.03	-0.20	
Working memory impairment	< 0.001	-0.07	-0.01	-0.05	
Arithmetic	-0.03	0.12	0.07	0.12	
Digit-span	0.09	0.12	0.10	0.10	
Letter-number sequencing	0.06	0.09	0.06	0.17	
Information processing speed impairment	0.04	-0.13	-0.11	0.20	
TMT A time	-0.06	-0.10	0.05	0.01	
TMT A errors	-0.04	-0.08	-0.10	0.21	
Executive function impairment	-0.03	-0.16	0.02	-0.12	
Semantic fluency score	0.05	0.18	-0.09	0.03	
Phonemic fluency score	-0.06	0.06	-0.10	0.20	
TMT B time	-0.06	-0.18	0.03	-0.09	
TMT B perseverative errors	-0.18	-0.08	-0.17	-0.12	
Demographic scores					
Age (years)	-0.06	0.02	-0.02	-0.15	
Education (years)	0.05	0.13	0.23	0.20	
Anxiety, depression scores					
BDI – depression	-0.38***	-0.32**	-0.20	-0.32**	
STAI State – anxiety	-0.32**	-0.35**	-0.19	-0.34**	
Quality of life scores					
FACIT-Fatigue	0.47**	0.44**	0.23	0.50**	
FACT-B	0.26*	0.25*	0.19	$0.47^{**}$	
FACT-G	0.33**	$0.47^{**}$	0.22	$0.40^{**}$	
PWB	0.25	0.34**	0.15	0.39**	
SWB	0.13	$0.27^{*}$	0.19	-0.02	
EWB	0.32**	0.36**	0.16	0.44**	
FWB	0.31**	0.39**	0.13	0.42**	

FR, free recall; DFR, delayed free recall; FACT-G subscales, PWB, physical well-being; SWB, social/family well-being; EWB, emotional wellbeing; FWB, functional well-being; PCI, perceived cognitive impairment; PCA, perceived cognitive abilities; QoL, impact on quality of life; Oth, comments from others.

 $p^* < 0.01.$ 

p < 0.001.

To our knowledge, the present study is unprece-322 dented in exploring differences between elderly breast 323 cancer patients and healthy controls with the FACT-324 Cog. For 2 of the 4 FACT-Cog subscales, breast cancer 325 patients reported significantly less cognitive complaints 326 327 (Perceived Cognitive Impairments and Perceived Cognitive Abilities) than healthy controls, but seemed to have 328 more complaints on Impact on Quality of life subscale. 329 One hypothesis could be that patients with breast cancer 330 are more likely to put cognitive impairment into per-331 spective due to the context of the disease, even though 332 those minor difficulties may indeed have an impact on 333 their quality of life significantly. 334

The present data also suggest that, in accordance 335 with previous studies, cognitive complaint scores were 336 correlated with anxiety, depression and fatigue scores. 337 However, no correlation was found with overall objec-338 tive cognitive scores [33], except between verbal episodic 339 memory impairment and the Perceived Cognitive 340 Impairments subscale. The latter could allow assessing 341 this cognitive domain, especially regarding memory ver-342 bal information retrieval (accounting for one third of 343 this subscale items). These results are consistent with 344 those reported by Ganz and colleagues based on cogni-345 tive complaint questionnaire assessing four subscales 346 specific to one cognitive domain, which suggested that 347

404

408

413

414

415

416

417

418

419

420

421

422

423

424

425

426

427

428

429

430

431

432 433

434

435

436

437

438

439

440

441

442

443

444 445

446

447

448

449

450

451

452

453

454

455

456

457

458

459

460

461

subjective cognitive complaints partly reflect objective 348 349 performance in domain-specific cognitive test [34].

In the present study, all patients underwent a selected 350 geriatric assessment. Interestingly, the results showed 351 that the presence of at least one impaired cognitive 352 353 domain was not significantly correlated with geriatric fragility assessed from GDS and functional status 354 (ADL and IADL). However, the definition of geriatric 355 356 fragility could be considered as relatively strict (at least 357 one score of the three scales altered), and only a few 358 number of patients were considered as having a geriatric 359 frail profile, which could represent a selection bias of our sample. Furthermore, the large majority of the patients 360 included in our study were in relatively good general 361 health as indicated by the proportion with PS 0 (91%)362 or Charlson index 0 (78%), suggesting that the propor-363 364 tion of patients with cognitive impairments (40%) could 365 have been underestimated. Indeed, nobody can exclude that the proportion of cancer patients with cognitive 366 impairment prior to adjuvant treatment could be higher 367 368 in a global and more heterogeneous population regarding geriatric conditions. 369

While the present quality of life-related data appeared 370 371 to be in the same range as those reported in the overall cancer population [29], cognitive functioning in elderly 372 373 patients remains an important issue to be taken into 374 account in the decision making of adjuvant treatment.

The lack of direct comparison with a group of 375 healthy subjects remains the main limitation of this 376 study. Furthermore, the population of patients was clin-377 ically heterogeneous regarding some characteristics 378 (cancer stage, hormonal receptor status, type of sur-379 gery...). Another possible selection bias could be the 380 low number of geriatric scores in our population or 381 the impact of patients' motivation. 382

In conclusion, this study is the first large series assessing 383 baseline cognitive functions in elderly EBC patients. The 384 main finding is that cognitive impairment prior to adjuvant 385 therapy was more frequent than what is observed or 386 reported in both comparatively healthy elderly subjects 387 and younger breast cancer patients; this reinforces the 388 389 hypothesis that age-associated decline among cancer 390 patients is pronounced (i.e. age is a risk factor for CD in breast cancer patients). Evaluation of cognition before 391 05 treatment is essential to take into account the impact of 392 393 treatments on cognitive functions, especially among elderly cancer patients. Furthermore, cancer treatments 394 could accelerate the ageing process in a vulnerable or frail 395 population. In this respect, additional research including 396 397 such baseline assessment is needed to understand, anticipate and manage the short- and long-term effects of cancer 398 therapy on the cognitive function of elderly patients. 399

#### Disclosures 400

Financial disclosures: Sanofi. **Q7 Q6** 

Conflict of interest statement

None declared. 403

## **Acknowledgements**

This work was supported by a National grant (Pro-405 gramme Hospitalier de Recherche Clinique, PHRC) 406 and Sanofi. 407

- References
- [1] Joly F, Rigal O, Noal S, Giffard B. Cognitive dysfunction and 409 cancer: which consequences in terms of disease management? 410 Psychooncology 2011;20:1251-8. 411 412
- [2] Ahles TA. Brain vulnerability to chemotherapy toxicities. Psychooncology 2012;21:1141-8.
- [3] Scherling CS, Smith A. Opening up the window into "Chemobrain": a neuroimaging review. Sensors (Basel) 2013;13: 3169-203
- [4] Ahles TA, Saykin AJ. Candidate mechanisms for chemotherapyinduced cognitive changes. Nat Rev Cancer 2007;7:192-201.
- [5] Hurria A, Rosen C, Hudis C, et al. Cognitive function of older patients receiving adjuvant chemotherapy for breast cancer: a pilot prospective longitudinal study. J Am Geriatr Soc 2006;54:925-31.
- [6] Crum RM, Anthony JC, Bassett SS, Folstein MF. Populationbased norms for the mini-mental state examination by age and educational level. JAMA 1993;269:2386-91.
- [7] Kalafat M, Hugonot-Diener L, Poitrenaudl J. French standardization of the "Mini Mental State" (Mms) Greco version. Revue De Neuropsychologie 2003;13(2):209-36.
- [8] Folstein MF, Folstein SE, Mchugh PR. "Mini-Mental State". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-98.
- [9] Cardebat D, Doyon B, Puel M, et al. Formal and semantic lexical evocation in normal subjects. performance and dynamics of production as a function of sex, age and educational level. Acta Neurol Belg 1990;90:207-17.
- [10] Rey A. Manual of copy and memory reproduction test of complex geometric figures. Paris: Éditions Centre De Psychologie Appliauée: 1959.
- [11] Reitan R. Validity of trail making tests as an indicator of organic brain damage. Percept Motor Skills 1958;8:271-6.
- [12] Van Der Linden M, Adam S, Agniel A, Antérion-Thomas C, Baisset-Mouly C, Coyette F, et al. Assessment of memory impairment. Marseille: Solal; 2004.
- [13] Wechsler D. Wechsler adult intelligence scale-III. San Antonio: The Psychological Corporation; 1997.
- [14] Joly F, Lange M, Rigal O, et al. French version of the functional assessment of cancer therapy-cognitive function (Fact-Cog) version 3. Supp Care Cancer 2012;20:3297-305.
- [15] Wagner LI, Sweet J, Butt Z, et al. Measuring patient self-reported cognitive function: development of the functional assessment of cancer therapy-cognitive function instrument. J Support Oncol 2009;7:W32-9.
- [16] Beck AT, Beamesderfer A. Assessment of depression: the depression inventory. Mod Probl Pharmacopsychiatry 1974.7.151-69
- [17] Spielberger SD. Manual for the state-trait anxiety inventory (Stai). Palo Alto, CA: Consulting Psychologists Press; 1983.
- [18] Yellen SB, Cella DF, Webster K, et al. Measuring fatigue and other anemia-related symptoms with the functional assessment of cancer therapy (fact) measurement system. J Pain Symptom Manage 1997;13:63-74.

487

488

489

490

491

492

493

494

495

496

497

498

499

500

501 502

503

504

505

506

- [19] Brady MJ, Cella DF, Mo F, et al. Reliability and validity of the
  functional assessment of cancer therapy-breast quality-of-life
  instrument. J Clin Oncol 1997;15:974–86.
- [20] Cella DF, Tulsky DS, Gray G, et al. The functional assessment of
   cancer therapy scale: development and validation of the general
   measure. J Clin Oncol 1993;11:570–9.
- [21] Clement JP, Nassif RF, Leger JM, Marchan F. Development and
  contribution to the validation of a brief French version of the
  Yesavage geriatric depression scale. Encephale 1997;23:91–9.
- [22] Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontol-ogist 1969;9:179–86.
- [23] Katz S, Downs TD, Cash HR, Grotz RC. Progress in develop ment of the index of Adl. Gerontologist 1970;10:20–30.
- 476 [24] Charlson ME, Pompei P, Ales KL, Mackenzie CR. A new
  477 method of classifying prognostic comorbidity in longitudinal
  478 studies: development and validation. J Chronic Dis
  479 1987:40:373–83.
- 480 [25] Wefel JS, Vardy J, Ahles T, Schagen SB. International cognition
  481 and cancer task force recommendations to harmonise studies of
  482 cognitive function in patients with cancer. Lancet Oncol
  483 2011;12:703–8.
- 484 [26] Wefel JS, Vidrine DJ, Veramonti TL, et al. Cognitive impairment
   485 in men with testicular cancer prior to adjuvant therapy. Cancer
   486 2011;117:190–6.

- [27] Ingraham LG, Aiken CB. An empirical approach to determining criteria for abnormality in test batteries with multiple measures. Neuropsychology 1996;10:120–4.
- [28] Wratten C, Kilmurray J, Nash S, et al. Fatigue during breast radiotherapy and its relationship to biological factors. Int J Radiat Oncol Biol Phys 2004;59:160–7.
- [29] Brucker PS, Yost K, Cashy J, et al. General population and cancer patient norms for the functional assessment of cancer therapy-general (Fact-G). Eval Health Prof 2005;28: 192–211.
- [30] Hede K. Chemobrain is real but may need new name. J Natl Cancer Inst 2008;100, pp. 162–163, 169.
- [31] Hurria A, Somlo G, Ahles T. Renaming "Chemobrain". Cancer Invest 2007;25:373–7.
- [32] Ahles TA, Root JC, Ryan EL. Cancer- and cancer treatmentassociated cognitive change: an update on the state of the science. J Clin Oncol 2012;30:3675–86.
- [33] Pullens MJ, De Vries J, Roukema JA. Subjective cognitive dysfunction in breast cancer patients: a systematic review. Psychooncology 2010;19:1127–38.
- [34] Ganz PA, Kwan L, Castellon SA, et al. Cognitive complaints after breast cancer treatments: examining the relationship with neuropsychological test performance. J Natl Cancer Inst 2013;105: 509 791–801. 510

511