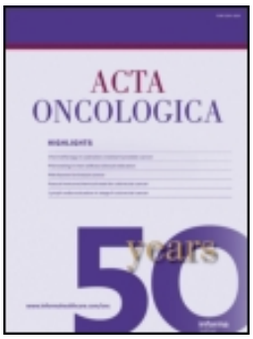

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ORIGINAL ARTICLE

Cognitive function and quality of life after surgery for early breast cancer in North Jutland, Denmark

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Abstract

Objective. The aim of this study was to assess cognitive function, quality of life, and psychological distress after surgery for early breast cancer but before initiation of adjuvant treatment. *Material and methods*. We performed a population-based study in the county of North Jutland, Denmark, including 124 women aged less than 60 years who had surgery for early breast cancer from 2004 – 2006. They were compared with an aged-matched group of 224 women without previous cancer selected randomly from the same population. The cognitive function of patients and controls was tested using a revised battery from the ISPOCD study. Data were collected on quality of life (EORTC QLQ-C30) and psychological distress (POMS). *Result.* The neuropsychological tests did not reveal significant differences between patients and controls. Compared to the control group, breast cancer patients had a significantly 3 – 4 fold increased risk of experiencing cognitive impairment. Quality of life and psychological distress were also significantly poorer among patients. *Conclusion.* This study demonstrated that women diagnosed with breast cancer experience a significant deterioration of their perceived cognitive functioning, quality of life and of psychological well being.

Breast cancer (BC) is the most common malignant disease among women in Denmark with about 4 000 new cases per year. According to present guidelines around 80% receive adjuvant treatment such as chemotherapy, radiotherapy and anti-hormonal therapy [1]. Cognitive impairment as a side effect of adjuvant chemotherapy has been reported to vary between 75% of the patients being impaired to very few patients showing a reliable decline on neuropsychological tests depending on study design and statistics used [2,3]. However, this impairment may have been present before chemotherapy since being diagnosed with BC may give rise to cognitive problems. Among women newly diagnosed with BC, symptom distress and affective distress were significant predictors of how well the patients perceived their capacity to direct attention before surgery [4]. When tested after surgery and prior to chemotherapy, studies have shown results from no differences to 35% of the BC patients having impaired cognitive function compared to population norm scores [5,6]. However, the use of norm scores may limit the ability to evaluate the influence of depression and anxiety.

The purpose of this study was to evaluate cognitive function, psychological distress, and quality of life after surgery for early BC but before the initiation of adjuvant therapy compared with an age-matched control group without prior cancer.

Material and methods

Study population

BC surgery is performed by two departments in the North Jutland County. All patients are subsequently referred to the Department of Oncology at Aalborg Hospital for treatment or control after surgery. From the referral notes we identified prospectively 196 women aged less than 60 years, who had surgery for primary BC and no evidence of metastatic disease between May 1, 2004 and July 4, 2006. By virtue of

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the unique personal ID-numbers issued to all persons at birth or immigration, we were able to select a control group of 531 women who were age-matched to the study group from the entire female population of North Jutland Country. Eligible patients were informed about the purpose of the study, the questionnaires and the psychological tests at their first visit after surgery to the Department of Oncology by a doctor or a specially trained research nurse. A letter of invitation was sent to the selected controls explaining the purpose of the study, including a questionnaire, a planned date for an interview, and a reply card to accept the invitation. We excluded from both groups women with prior cancer, diseases of the central nervous system, neurosurgery, neuropsychological testing within the last year, use of antidepressants, alcohol abuse, impairment of eye sight or hearing, illiteracy and those not having Danish as mother tongue.

Among BC patients, 124 (63%) accepted to participate (Table I). Of the remaining 72 patients, 47 (24%) refused to participate, one was excluded due to cognitive problems, eight (4.1%) had psychological problems, two had other diseases, and 14 (7.1%) declined for other reasons. Among the 531 invited controls, 224 (42%) accepted to participate, while 284 (53%) refused and 23 (5%) were excluded due to cognitive or psychological problems, previous cancer or other diseases.

Data collection

All data were collected after surgery but before initiation of any adjuvant treatment. The clinical characteristics of BC patients derived from the medical records. Data were collected regarding education, occupation, fertility, family history of BC, quality of life, and psychological distress using self-administered questionnaires filled in by the BC patients and controls at home. The questionnaires were checked for completeness by the research staff after the neuropsychological testing had been carried out.

Table I. Overview of the study population.

	Breast cancer patients N (%)	Control group N (%)
Invited	196 (100)	531 (100)
Included	124 (63)	224 (42)
Excluded, reason:		
Declined participation	47 (24)	284 (53)
Cognitive problems	1 (0.5)	4 (0.8)
Psychological problems	8 (4.1)	2 (0.4)
Other diseases	2 (1.0)	5 (0.9)
Previous cancer	0 (0.0)	10 (2.0)
Other	14 (7.1)	2 (0.4)
Age, years among excluded		
Mean (range)	51.1 (23 – 59)	48.8 (29 – 59)

Rating scales and questionnaires

Quality of life was measured by the EORTC QLQ-C30 questionnaire validated internationally by the EORTC Study Group on QOL [7]. The Danish version used incorporates five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea or vomiting), one global health scale, and six single items (dyspnoea, sleeplessness, loss of appetite, constipation, diarrhoea, and financial difficulties [8].

The General Perceived Self-Efficacy (GPS) represents a dispositional coping factor in times of stress. We used the Danish version of the 10-item scale [9], with responses ranging from *strongly disagree* (1) to *strongly agree* (4). It has been documented to have a high validity and reliability in various populations [10]. The sum of the 10 items was used. Chronbach's: 0.9 showed fine internal consistency in this study.

To measure psychological distress we used the Profile of Mood States (POMS) 65-items questionnaire which assesses transient, fluctuating affective states in individuals and which is also sensitive in detecting mood disturbance such as anxiety and depression [11]. The present study: from 0.8 to 0.9 for all six scales demonstrated very good internal consistency with Chronbach's α: from 0.8 to 0.9 for all six scales.

To assess subjective cognitive functioning, we used four questions about memory, concentration/attention, mental fatigue, and vitality from the International study of Postoperative cognitive dysfunction ISPOCD 2 study, concerning change in subjective cognitive functioning within the last month [12]. The subjects rated themselves on a seven-point scale, ranging from 1 (major improvement) over 4 (no change) to 7 (greatest decline). In the analysis 1 – 3 was considered as improvement, 4 no change, and 5 – 7 impairment.

Neuropsychological testing

General intellectual capacity was assessed using the Danish Adult Reading Test (DART) which is translated from the National Adult Reading test and shown to provide an accurate estimate of premorbid intelligence level [13]. It consists of 50 phonetically irregular words to be read aloud. The score used is the number of words pronounced correctly according to a standardized set of criteria.

The test battery used to evaluate cognitive function was the revised version of the neuropsychological test

battery from the ISPOCD 2 study [12]. It consists of four tests giving five test scores: 1) Visual Verbal Learning Test (VLT), (a total and a delayed score), 2) Concept Shifting Test (CST), 3) Stroop Colour Word Interference Test (SCWT), 4) Letter-Digit Coding Test (LDCT). Testing was designed to encompass the following cognitive domains: episodic memory (intermediate and long-term memory), simple and complex attention, concentration, cognitive speed and flexibility, visual scanning, and executive function. The test battery has been translated into Danish and validated for sensitivity to small and moderate postoperative cognitive decline in European patients [14].

All tests were administered in a quiet room and in a fixed order at the Department of Oncology by four trained research assistants. Testing occurred at a mean of 34.5 (range 19 – 75) days after surgery or at the date of inclusion for the controls.

Ethical considerations

The study was approved by the Ethical Committee for Viborg and North Jutland Counties with journal nr: VN 2004/15 Onk. KFE-Aa 24.3.2004. Oral and written information was given about the study, and those who accepted to participate gave informed consent before the neuropsychological testing.

Statistical methods

The statistical Package for the Stata version 9.2 for Windows was used for all statistical analyses. Descriptive statistics included t-test and Pearson's χ^2 to test for group differences with respect to demographic and other variables. Data from the neuropsychological tests, psychological data, and the quality of life ratings did not follow a normal distribution and are therefore presented with medians and Interquartile Ranges (IQR). The raw tests cores were z-transformed based on the mean and standard deviation (SD) of the scores of the control group The Wilcoxon nonparametric test was used to evaluate group differences. A definition of lower than expected cognitive function (at least three tests -1.5 SD below the mean or at least two tests -2.0 SD below the mean of the control group) was applied to the test scores. Differences in rates of impaired cognitive function were examined with Fisher's exact test and relative risk (RR). In an effort to control for multiple comparisons significance was calculated with a two-sided 1% probability of error. Bivariate correlations using Spearman rank correlation were computed between the neuropsychological test scores and the subscales from EORTC-C30, POMS, and Subjective Cognitive Functioning Questionnaire. Internal consistency was evaluated using Chronbach's Alfa.

Results

Study population

About two thirds of the patients had a mastectomy, while one third had breast conserving surgery, and 55% were node positive (Table II). Half of the patients had tumours less than 20 mm, 81% of the tumours were ductal and 76% hormone receptor positive (oestrogen and/or progesteronereceptor positive by >10% of the tumour cells staining positive by immunohistochemistry).

Table III shows that no significant differences were found between BC patients and the control group with respect to age, marital status, years in school, age at menarche, menopausal status, use of oral contraceptives and hormone replacement therapy, and age at any childbirth. Compared to controls, BC patients tended to have a longer education and to be more likely to have a family history of BC, but these differences did not reach statistical significance. There were no significant differences between age among included and excluded participants in the study (patients 49.6 / 51.1 $p=0.16$ and controls 48.2/48.8 $p=0.39$) (Tables I and III).

Table II. Clinical characteristics of 124 breast cancer patients included.

	N, (%)
Surgery	
Mastectomy	84 (68)
Lumpectomy	40 (32)
Tumour size, mm	
0–19	63 (51)
20+	61 (49)
Tumour histology	
Ductal	100 (81)
Lobular	12 (9.7)
Other	12 (9.7)
Removed nodes	
<10 Nodes	25 (20)
10+ Nodes	99 (80)
Nodal status	
Positive	68 (55)
Negative	55 (44)
Unknown	1 (0.8)
Hormone Receptor status	
Positive	94 (76)
Negative	29 (23)
Unknown	1 (0.8)

Table III. Characteristics of breast cancer patients and controls without cancer.

Characteristic	Breast cancer patients N = 124, (%)		Control group N = 224, (%)		P* BCvC
Age, years					
Mean	49.6		48.2		0.10
Range	29–59		28–59		
Marital status					
Married/living with a partner	109 (88)		186 (83)		0.23
Living alone	15 (12)		38 (17)		
Years in school					
< =9	22 (18)		47 (21)		0.12
>9	96 (77)		174 (78)		
Other	6 (4.8)		3 (1.3)		
Education level					
No education	10 (8.1)		29 (13)		0.20
<3 years	60 (48)		103 (46)		
3–4 years	36 (29)		74 (33)		
>4 years	11 (8.9)		8 (3.6)		
Other	7 (5.7)		10 (4.0)		
Age at menarche					
<12 years	27 (22)		62 (28)		0.07
13–14 years	66 (53)		130 (58)		
15+ years	22 (18)		25 (11)		
Unknown	9 (7.3)		7 (3.1)		
Menopausal status					
Pre/perimenopausal	72 (58)		141 (63)		0.37
Postmenopausal	52 (42)		83 (37)		
Oral contraceptive use					
Never	19 (15)		27 (12)		0.46
<5 years	35 (28)		59 (26)		
5 –	26 (21)		47 (21)		
10 –	19 (15)		33 (15)		
15+	23 (19)		53 (24)		
Unknown	2 (1.6)		5 (2.2)		
Hormone replacement therapy					
Never	102 (82)		190 (85)		0.53
Ever	21 (17)		30 (13)		
Unknown	1 (0.8)		4 (1.8)		
Family history of breast cancer					
Yes	37 (30)		47 (21)		0.09
No	85 (69)		176 (79)		
Missing	2 (1.6)		1 (0.5)		
Age at childbirth	**N**	**Mean (SD)**	**N**	**Mean (SD)**	
1. child	111	25.5 (4.8)	203	25.3 (4.7)	0.68
2. child	95	29.4 (5.1)	165	28.5 (4.5)	0.16
3. child	28	31.3 (5.1)	59	31.1 (4.4)	0.86
4. child	4	32.4 (7.2)	6	31.4 (5.2)	0.82

*P-values for breast cancer patients versus controls using t-test or χ^2.

Performance on the neuropsychological test battery

The general intellectual capacity, as evaluated by the DART test, showed comparable results for BC patients and controls indicating no significant difference with respect to intelligence (Table IV). The raw score and the z-score results of the five cognitive tests were comparable for patients and controls, except for a borderline significant trend ($p = 0.07$) towards a better long time memory (verbal learning delayed) in the control group. Applying the definition of lower than expected cognitive function revealed a rate of impaired cognitive function of 3.8% among the control group and 7.3% among the patient group corresponding to a RR of 2.0 (95% CI: 0.8 – 5.1).

Table IV. Neuropsychological test scores of the study population.

Cognitive function	Breast cancer patients (N = 124)		Control group (N = 224)		
	Median (IQR)*	Z-score	Median (IQR)*	Z-score	P ** BC v C
Test battery:					
DART	30.0 (7.0)		30.0 (11)		0.4
Verbal learning total (45 words)	33.0 (7.0)	−0.004	34.0 (7.0)	0.000	0.8
Verbal learning delayed (15 words)	12.0 (2.5)	−0.210	13.0 (3.0)	0.000	0.07
Concept shifting test (seconds)	30.3 (10.0)	−0.070	29.6 (10.8)	0.000	0.7
Stroop colour word test (seconds)	39.2 (11.5)	−0.160	37.9 (10.3)	0.000	0.3
Letter digit coding (numbers)	36.0 (9.0)	−0.160	37.0 (8.0)	0.000	0.2

*(IQR) Interquartile Range. **P-values: breast cancer patients versus control group.

Self rated cognitive function

In contrast to the results from the formal testing of cognitive functions, Table V shows that the BC patients rated themselves as impaired with respect to cognitive abilities such as memory, concentration, mental fatigue, and vigour, after being diagnosed with BC and subsequently operated. Compared with the control group, BC patients gave significantly lower self ratings on all four measures, the relative risk (RR) with a 95% confidence interval (CI), of developing a perceived cognitive impairment being 4.2 (CI: 2.7 – 6.5) for memory, 4.5 (CI: 3.0 – 6.9) for concentration, 6.4 (CI: 4.1 – 10.0) for mental fatigue, and 3.2 (CI: 2.4 – 4.3) for vigour. Due to the discrepancy between the self-reported measures and the neuropsychological test scores, we examined the correlations between the two measurements. No significant correlations were found between any of the domains of the test battery, the subjective measures of cognitive function, or ratings of psychological distress.

Quality of life and psychological distress

Compared with the controls, BC patients had significantly lower scores in three of the EORTC QLQ-C30 functional scores (role, emotion, social), indicating a poorer function, and they scored significantly higher on the symptom scores for fatigue, pain and loss of appetite (Table VI). The global health score was also lower among the BC patients. Though the EORTC QLQ-C30 functional score for cognitive function was lower among BC patients, the difference did not reach statistical significance. The distributions of scores for several function-scores were skewed which explain why there was a significant difference between two equal medians e.g. for social function.

Evaluating psychological distress using the POMS, BC patients had a significantly higher level of tension or anxiety, they were more depressed and confused, and had a significantly lower level of vigour. No significant difference was detected for General Perceived Self-efficacy. We compared qual-

Table V. Change in perceived cognitive function during four weeks preceding the assessment.

Perceived cognitive function	Breast cancer patients N = 124 (%)	Control group N = 224 (%)	P* BC v C
Memory			
Impairment	52 (42)	22 (9.8)	<0.0001
No change	68 (55)	190 (85)	
Improvement	4 (3.3)	12 (5.4)	
Concentration			
Impairment	62 (50)	24 (11)	<0.0001
No change	59 (48)	189 (84)	
Improvement	3 (2.4)	11 (4.9)	
Mental fatigue			
Impairment	73 (60)	20 (8.9)	<0.0001
No change	47 (38)	192 (85.7)	
Improvement	4 (3.2)	12 (5.4)	
Vigour			
Impairment	76 (61)	42 (19)	<0.0001
No change	36 (29)	155 (69)	
Improvement	12 (9.7)	27 (12)	

*P-values breast cancer patients versus control group.

Table VI. Psychological characteristics measured by EORTC QLQ-C30, POMS, and General Perceived Self-efficacy.

Median (IQR)*	Breast cancer patients N = 124	Control group N = 224	P* BC v C
EORTC QLQ-C30			
Role function	66.7 (50.0)	100.0 (0.0)	**<0.0001**
Emotional function	79.2 (25.0)	91.7 (25.0)	**<0.0001**
Cognitive function	100.0 (16.7)	100.0 (16.7)	**0.07**
Social function	100.0 (16.7)	100.0 (0.0)	**<0.0001**
Global health score	75.0 (20.8)	83.3 (25.0)	**<0.0005**
Fatigue score	33.3 (19.4)	13.9 (33.3)	**<0.0001**
Pain score	33.3 (16.6)	0.0 (33.3)	**<0.0001**
Appetite loss score	0.0 (33.3)	0.0 (0.0)	**<0.001**
POMS			
Tension-anxiety	2.0 (8.0)	1.0 (−2.0)	**<0.005**
Depression	3.0 (7.0)	2.0 (4.0)	**<0.0005**
Vigour	16.0 (8.5)	19.0 (7.0)	**<0.0005**
Confusion	0.0 (0.0)	−1.0(1.0)	**<0.0001**
General Perceived Self-efficacy			
	31.5 (7.5)	30.0 (7.0)	0.11

*(IQR): Interquartile Range. **P-values: breast cancer patients versus control group.

ity of life and psychological function in women who had a mastectomy with those who had breast conserving surgery, but no significant differences were found (data not shown).

Relationship between perceived cognitive function and quality of life

We found significant correlations between scores on perceived cognitive function and the functional scores from QLQ-C30. The patients who rated themselves better on memory, concentration and vigour also had better scores on emotional-, cognitive-, social function, and quality of life. With respect to mental fatigue, the patients who were less mentally fatigued also had a better cognitive and social function as well as a better quality of life (all Spearman's rho moderate from 0.3 – 0.5, and all $p < 0.05$).Equivalent correlations were not found in the control group except for mental fatigue where controls with better scores also had higher scores on role, cognitive, social functioning, and a better quality of life (Spearmann's rho: 0.2 – 0.3 $p < 0.01$).

Relationship between perceived cognitive function and psychological distress

Among the patients the psychological distress as measured by POMS correlated significantly with perceived cognitive function. Patients with higher scores of anxiety, depression, confusion, anger, fatigue, and a lower score of vigour were significant more likely to perceive their memory, concentration, and mental vigour as impaired (Spearman's rho: −0.3 – −0.4, $p < 0.05$). Fewer correlations were found for the controls. Those who perceived their memory as impaired were less vigorous, and those who rated their mental vigour to be impaired also felt more fatigued and depressed (Spearman's rho: −0.2 – −0.3, $p < 0.05$).

Discussion

The present study shows that women diagnosed with and operated for early BC perceive their cognitive function, quality of life, and psychological stress as impaired but that their cognitive capacity as measured by neuropsychological testing was comparable to that of an aged- matched control group of women without cancer. The level of test scores was in agreement with scores from a healthy control group evaluated with the same tests in the ISPOCD study [15].

Studies not including a control group have shown that approximately one-third of the patients had cognitive impairment before treatment based on a normative assumption [5,16]. However Hermelink et al. [16] performed the tests one week after the BC diagnosis where the risk of psychological distress may be higher. In the present study we made the assessment at a mean of 34.5 (range 19 – 75) days after surgery. The delay of up to 75 days was due to complications to surgery (seromas or wound infections) which caused a delay in referral after surgery. Another study did not demonstrate this difference as test scores fell within normative values [6]. Using healthy controls Schagen et al. [17] also found no differences between BC patients and controls at the first assessment.

Ahles et al. [18] reported that although BC patients scored within the normal range for neuropsychological testing, 22% of the patients with stage 1 – 3 BC were significantly more likely to have a lower than expected overall cognitive performance. The control group in the present study had a similar rate of lower than expected cognitive function whereas we only found a lower than expected rate of 7.3% among the patients. Since the patients were slightly better educated, their cognitive function may have been better before surgery and with a decline after surgery resulting in similarity with the controls. This would explain the higher percentage of lower than expected even though the difference was not significant.

Although no impairment in objective cognitive function was detected among the patients, up to 60% of the patients perceived their memory, concentration, vigour, and mental fatigue as highly deteriorated. Our results are consistent with those of Bender et al. [19] while Ahles et al. [18] were unable to demonstrate any significant differences in perceived cognitive function between patients and healthy controls. We did not detect any association between objective neuropsychological tests and subjective reports of cognitive functioning. Our finding is consistent with other studies showing that the perception of cognitive dysfunction is not necessarily associated with a measurable cognitive dysfunction [2,20].

The frequency of anxiety, depression and confusion measured by POMS was higher and vigour lower among patients compared with controls in our study. Similar data have been reported in other studies finding increased levels of depression or anxiety or both in the first year after a diagnosis of early BC [21], and up to 80% of the patients feeling anxious and depressed after primary surgery and before adjuvant chemotherapy [19]. All scores on POMS except vigour from patients and controls were lower than scores from a standardized sample of American women [22]. This may be due to cultural differences in the expression of psychological states or to different interpretations of the target words in the POMS questionnaire.

The ability to cope with life-situations was as expected similar among patients and controls, when measured by general perceived self-efficacy [10]. Despite this, patients reported significantly more psychological problems than the controls. The positive association between perceived cognitive dysfunction and higher level of depression and anxiety among patients indicate that although the tested cognitive capacity was similar to controls, psychological distress of patients may enhance the experience of impairment of perceived cognitive function. Like most others, we did not find an association between objective testing of cognitive functions and mood state [5].

The present data showed that a diagnosis of and surgery for BC have an impact on patients' health related quality of life (HRQoL). They experienced a significantly lower level of quality of life compared to controls. Furthermore, the diagnosis and surgery for BC may cause a decrease in role, emotional, and social function. Surprisingly, the EORTC C-30 cognitive-function did not differ between patients and controls though most patients experienced a negative change in cognitive function within the last month. Again this may relate to the patients functioning better than controls before surgery and with a negative change after surgery rating similarly to the controls on EORTC cognitive function. Most of our results are consistent with the findings of Scandinavian studies of HRQoL [23,24]. Patients who had better HrQoL and functional scores, e.g. emotional and social, also perceived their cognitive function as less impaired. Van Dam et al. [20] also found a significant relationship between the perceived cognitive function and the cognitive function scale from EORTC QLQ-C30.

The strength of the present study is that it is based on the entire population of North Jutland country in Denmark. The relatively large number of patients and controls ensured a sufficient statistical power to detect differences we thought would be clinically meaningful. Also the control group from the same population enabled a direct comparison with the patients thus avoiding the use of other external "normal populations". The patients and controls appeared well matched on all important factors such as IQ, age, years in school, fertility, and family history of BC though slightly more patients had used hormones in the menopause and had longer education than the control group. The higher educational level in BC patients is well known as well as the increased risk for BC with the use of hormones [25,26]. Both observations support that the two groups can be considered representative for the Danish population in general.

A weakness of our study is the low inclusion rate with the consequent risk of selection bias. Women who refused participation did not differ with respect to age and reasons for refusing compared to those included in the study. Despite this we cannot rule out that those who chose to participate had better resources in terms of education and psychological well-being than those who did not participate. However, this potential selection bias seems to be similar for BC patients and controls since they ended up being similar with respect to demographic factors (Table III). Therefore, we do not think selection bias

has exerted any great influence on the comparison between patients and controls.

Another weakness of our study may lie in the neuropsychological test battery used since it did not pick up the perceived cognitive impairment. The same tests have been demonstrated to detect changes in large groups of post surgery patients [15] but we cannot rule out entirely that the neuropsychological testing was not sufficiently sensitive to the slight but noticeable cognitive changes following a BC diagnosis and surgery. In addition, the lack of association between objective measurement and subjective assessment may reflect that the two methods tap different aspects of cognitive functioning. Self ratings of cognitive functions may be considered to be a judgment based on the memory of experiences while test results are actual measurements that are independent of subjective judgments. Daily life demands intertwined cognitive functions and is perceived more overwhelmingly than the relatively short test performed in this study. Though present in daily life, a cognitive impairment may not be detected in a short test situation with a considerate research assistant with focus on each test. Another possibility is that cognitive complaints should be seen in the context of a general feeling of psychological distress which is expressed in the association between psychological distress (depression, anxiety, anger, confusion and fatigue) and self-reported problems with memory and concentration. Our study supports this hypothesis.

In conclusion, though similar to other women without cancer with respect to intelligence and cognitive capacity, patients perceive themselves as cognitively more impaired and psychologically more distressed after a diagnosis and surgery for early BC. In addition, the reduced HrQoL may cause further distress and thereby increase the perception of cognitive difficulties.

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