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ARTICLE

Elucidating Pretreatment Cognitive Impairment in Breast Cancer Patients: The Impact of Cancer-Related Post-Traumatic Stress

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Abstract

Background: Pretreatment cognitive impairment in cancer patients is well established but unexplained. Similar cognitive compromise has been observed in post-traumatic stress disorder (PTSD) patients, and PTSD symptoms are a frequent concomitant of cancer diagnosis. We tested the hypothesis that pretreatment cognitive impairment is attributable to cancer-related post-traumatic stress.

Methods: Women aged 65 years or younger who were diagnosed with breast cancer (case patients) or had undergone negative routine breast imaging (control patients) at one of six participating breast centers underwent traditional and computerized neuropsychological testing, clinician-administered diagnostic assessment of stress disorders, and self-report assessments of cognitive function and depression. To minimize confounding, case patients were evaluated prior to any local or systemic treatment. Cognitive indices of case patients, control patients, and normative samples were compared. The patients' risk of overall cognitive impairment was determined. Linear regression and a mediation model were used to test the study hypothesis. All statistical tests were two-sided.

Results: The 166 case patients and 60 well-matched control patients showed near-identical deviations from population norms. Case patients scored worse than control patients on two of 20 cognitive indices (Go/Nogo commission errors, Go/Nogo omission errors). Self-reported cognitive problems were associated with Go/Nogo omission errors and more pronounced in case patients. Only PTSD symptoms (Beta = 0.27, $P = .004$) and age (Beta = 0.22, $P = .04$) statistically significantly predicted Go/Nogo errors. The effect of having cancer on Go/Nogo errors was mediated by PTSD symptoms. Case patients did not have an increased risk of overall cognitive impairment.

Conclusion: Prior to any treatment, breast cancer patients may show limited cognitive impairment that is apparently largely caused by cancer-related post-traumatic stress.

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There is no doubt that problems of cognitive functioning can considerably afflict patients with breast cancer (1,2) or other noncentral nervous system cancers (3). When neuropsychological studies started to demonstrate cognitive impairment in subgroups of cancer patients, the deficits were initially almost entirely attributed to neurotoxic effects of chemotherapy (4). This view was questioned when an increasing number of studies found evidence of pretreatment cognitive impairment. Already before adjuvant treatment, and even before surgery (5–7) or definite diagnosis (8), breast cancer patients were observed to perform poorly on neuropsychological tests in comparison with published normative data (6,9–12) or healthy control patients (7,9,13,14). In recent years, neuroimaging studies detected abnormalities of brain activation patterns during cognitive tasks in chemotherapy-naïve patients with breast cancer (15–19).

Although not all studies have found evidence of cognitive deficits in cancer patients before chemotherapy (20–22), pretreatment cognitive impairment is now widely accepted and has changed thinking (23–26) about the phenomenon once named chemobrain. Clearly, other factors than only chemotherapy neurotoxicity may cause cognitive dysfunction in cancer patients, and part of them seem to exert their influence before the start of treatment. Hypotheses regarding cancer-associated cognitive deficits include shared vulnerability for cancer and cognitive impairment, and biological effects of the cancer itself (27–31). While psychological factors have usually been taken into account as confounders, a causative role of these factors for cognitive impairment in cancer patients has rarely been examined in hypothesis-driven investigations (32,33).

The Cognition in Breast Cancer Patients: The Impact of Cancer-Related Stress (Cognicares) study was designed to test the hypothesis that cognitive impairment in breast cancer patients is mediated by cancer-related post-traumatic stress that is manifest in symptoms of post-traumatic stress disorder (PTSD). There is substantial evidence that PTSD is associated with cognitive impairment (34–42). Functional and structural brain abnormalities in patients with PTSD are well established (43, 44), among them aberrant activation patterns during a cognitive task (45,46), decreased volumes of the hippocampus (47–50) or other brain regions (51), white matter atrophy (52), and pronounced effects of aging on the brain (52). PTSD predicts cognitive impairment and brain abnormalities independently of depression or other psychological morbidity (35,37,40,52). In animal models, stress had extensive effects on the brain, most prominently suppression of adult hippocampal neurogenesis (53–55).

The prevalence of clinician-diagnosed full PTSD is low in breast cancer patients, with rates ranging from 2.4% to 6% (56–60) and only sporadically higher rates of up to 16% (61). Nevertheless, PTSD symptoms that do not meet the criteria of a full diagnosis are a frequent consequence of breast cancer (62,63), especially shortly after diagnosis (64).

In the prospective, longitudinal, multisite Cognicares study, PTSD symptoms are assessed with the Structured Clinical Interview for DSM-IV (SCID) (65). Cognitive functioning is measured with traditional and computerized neuropsychological tests in breast cancer patients and in matched cancer-free control patients. Here, we report the findings of the initial assessment conducted prior to any local or systemic cancer treatment.

Methods

Participants

Women newly diagnosed with stage 0 to IIIc breast cancer (66) at six breast centers in the area of Munich, Germany, from January 2011 to August 2013 were eligible for participation if they met the following criteria: age 18 to 65 years, fluent in German, free of substance abuse, without a history of neurological or psychotic disorder, and no prior systemic treatment for cancer. To assure that case patients and control patients did not differ in any systematic way except for the presence of cancer, only women who had had breast imaging at one of the participating breast centers were eligible for the control group. The same criteria as for case patients were applied to control patients, with the addition that control patients must neither have suffered from any malignant disease nor require further imaging, biopsy, or treatment for any breast disease.

Written informed consent was obtained from all participants. Cognicares was approved by the ethics committee of the Ludwig Maximilian University of Munich and is registered at ClinicalTrials.gov, registration number NCT01264562 (67).

Enrollment and Assessment Proceedings

Physicians at participating breast centers informed potentially eligible women briefly about the study. Patients who agreed to their contact information being forwarded to Cognicares staff were then contacted, fully informed, and asked to participate if eligibility criteria were met. Enrollment proceedings were the same for case patients and control patients.

Participants underwent a two- to two and a half–hour assessment session that was scheduled a minimum of one week after a negative mammogram for control patients and before any local or systemic intervention (except biopsy of the tumor or sentinel lymph nodes) for case patients. Participants were compensated with 15 Euro.

All assessments were conducted by master's-level psychologists who had received expert training on neuropsychological testing and PTSD diagnostics.

Measures

Assessments comprised a one-hour neuropsychological test battery, PTSD diagnostics, self-report measures of cognitive functioning and psychological morbidity, a test of premorbid intelligence, and demographic and medical data (Table 1) that were additionally extracted from medical records.

The neuropsychological battery consisted of the tests recommended by the International Cognition and Cancer Task Force (ICCTF) (26,68) or their validated German counterparts (69,70) and additional paper-and-pencil (71) and computerized tests (72) found to be sensitive for cancer-related cognitive impairment (73). Twenty indices of cognitive functioning were chosen from the tests (Table 2). The selection of indices was premeditated prior to any analyses and guided by the aim to obtain fine-grained information but to avoid redundancy.

The validated German version of the Structured Clinical Interview for DSM-IV (SCID) (65) was used for diagnosis of stress disorder and stress symptoms. If control patients endorsed more than one potentially traumatic event, the event rated as the worst by the participant was inquired. If cancer patients

Table 1. Demographic and clinical characteristics

Characteristic*	Control patients (n = 60)	Individually matched case patients (n = 60)	*P* vs control patients*	All case patients (n = 166)	*P* vs control patients*
Age, y			.97		.13
Mean (SD)	52.6 (7.8)	52.6 (7.7)		50.4 (9.1)	
Range	27.3 to 64.9	25.2 to 65.4		21.8 to 65.7	
Educational achievement†			1.00		.20
Low	7 (11.7%)	7 (11.7%)		29 (17.5%)	
Medium	30 (50.0%)	30 (50.0%)		59 (35.5%)	
High	9 (15.0%)	9 (15.0%)		23 (13.9%)	
University degree	14 (23.3%)	14 (23.3%)		55 (33.1%)	
Estimated premorbid IQ			.78		.19
Mean (SD)	115.4 (13.4)	115.8 (13.1)		112.6 (13.7)	
Partnership status			.01		.01
Living with a partner	50 (83.3%)	38 (63.3%)		110 (66.3%)	
Not living with a partner	10 (16.7%)	22 (36.7%)		56 (33.7%)	
Occupational status			.84		.27
Working	44 (73.3%)	45 (75.0%)		133 (80.1%)	
Nonworking	16 (26.7%)	15 (25.0%)		33 (19.9%)	
Native speaker of German		.	.14		.08
Yes	58 (96.7%)	54 (90.0%)		148 (89.2%)	
No	2 (3.3%)	6 (10.0%)		18 (10.8%)	
AJCC tumor stage	-				
0	-	4 (6.7%)		14 (8.4%)	
I	-	30 (50.0%)		66 (39.8%)	
II	-	21 (35.0%)		69 (41.6%)	
III	-	5 (8.3%)		17 (10.2%)	
Days since diagnosis‡					
Mean (SD)	35.7 (26.6)	17.7 (11.2)		17.0 (11.0)	
Missing	-	8		15	
Menopausal status			.67		.21
Premenopausal	23 (38.3%)	22 (36.7%)		83 (50.0%)	
Peri- or postmenopausal	31 (51.7%)	35 (58.3%)		75 (45.2%)	
Undetermined	6 (10.0%)	3 (5.0%)		8 (4.8%)	
Hormone replacement therapy ever			1.00		.29
No	47 (78.3%)	47 (78.3%)		140 (84.3%)	
Yes	13 (21.7%)	13 (21.7%)		26 (15.7%)	
Current medication potentially affecting brain function§			.53		.52
No	43 (71.7%)	46 (76.7%)		126 (75.9%)	
Yes	17 (28.3%)	14 (23.3%)		40 (24.1%)	
History of PTSD			.30		.77
No	57 (95.0%)	54 (90.0%)		156 (94.0%)	
Yes	3 (5.0%)	6 (10.0%)		10 (6.0%)	
Diagnosis of current PTSD or ASD‖			.08		.14
No	60 (100%)	57 (95.0%)		160 (96.4%)	
Yes	0 (0%)	3 (5.0%)		6 (3.6%)	
No. of current PTSD symptoms			<.001		<.001
Mean (SD)	0.4 (1.1)	4.2 (4.0)		3.7 (3.2)	
Screened positive for major depression, other depressive disorder, panic disorder, or other anxiety disorder ¶			.06		.002
No	55 (91.7%)	47 (78.3%)		119 (71.7%)	
Yes	5 (8.3%)	12 (20.0%)		46 (27.7%)	
Missing	0 (0%)	1 (1.7%)		1 (0.6%)	
Depression score#			<.001		<.001
Mean (SD)	2.9 (2.7)	5.7 (4.1)		6.2 (3.9)	
EORTC-QLQ-CF**			<.001		<.001
Mean (SD)	87.2 (20.0)	70.0 (26.2)		67.7 (27.9)	

Table 1. Continued

Characteristic*	Control patients (n = 60)	Individually matched case patients (n = 60)	P vs control patients*	All case patients (n = 166)	P vs control patients*
FEDA††			.29		.04
Mean (SD)	45.6 (12.4)	49.8 (16.9)		51.7 (17.7)	
Missing	0	2		4	

*Please note that none of the characteristics are normally distributed; therefore, Mann-Whitney U Test and Chi-Square Test were used for comparisons. All statistical tests were two-sided. AJCC = American Joint Committee on Cancer; ASD = acute stress disorder; IQ = intelligence quotient; EORTC-QLQ-CF = Cognitive Function Scale of the European Organization for Research and Treatment of Cancer Quality-of-life-Questionnaire C30; FEDA = Questionnaire of Experienced Deficits of Attention; PTSD = post-traumatic stress disorder.

†Low, Hauptschulabschluss; medium, Realschulabschluss; high, Fachhochschulreife or Abitur.

‡For case patients, diagnosis of breast cancer; for control patients, negative diagnosis.

§Medications considered to potentially affect brain function: antidepressants, sedatives, benzodiazepines, neuroleptics, antihypertensives, antiphlogistics, antirheumatics, uricostatics, and glucocorticoids.

‖PTSD can only be diagnosed if symptoms have persisted for at least one month. In the first month after the onset of symptoms, ASD is diagnosed if additional symptoms are present (74).

¶Based on Patient Health Questionnaire (PHQ-D).

#Based on PHQ-D depression scale; scores range from 0 to 27, with higher scores reflecting more depression.

**Scores range from 0 to 100, with higher scores reflecting better cognitive functioning.

††Scores range from 27 to 135, with higher scores reflecting more attentional problems.

endorsed traumatic experiences other than cancer, both the cancer experience and the worst noncancer traumatic experience were inquired. All symptoms were explored, disregarding the SCID skipping rules, to allow a dimensional assessment of PTSD symptomatology.

According to DSM-IV (74), PTSD can only be diagnosed if symptoms persist for at least one month. In the first month after the onset of PTSD symptoms, patients can be diagnosed with acute stress disorder (ASD) if symptoms of derealization/dissociation are present in addition to the three symptom clusters of PTSD (ie, re-experiencing the trauma, eg, intrusive thoughts or distressing dreams; avoidance/numbing in response to trauma-reminders; and hyperarousal). Therefore, if the cancer diagnosis or another traumatic event dated back less than one month, symptoms of ASD were assessed in addition to those of PTSD.

Indices obtained from the SCID were the total number of current PTSD symptoms, diagnosis of current PTSD or ASD, and history of PTSD.

Subjective cognitive functioning was measured with the Cognitive Function Scale of the European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire C30, version 3.0 (EORTC-QLQ-CF) (75,76) and the Questionnaire of Experienced Deficits of Attention (FEDA) (77). The German version of the Patient Health Questionnaire (PHQ-D) (78,79) was used to screen for major depression or other depressive disorders, panic disorder, other anxiety disorders, alcohol abuse, and for a dimensional assessment of depression. Premorbid intelligence was estimated with a language-based test (80).

Statistical Analyses

Cognitive scores of all participants were standardized to normative data, using Z scores or percent ranks, so that performances of case patients and control patients could be compared with normative samples and with each other. Normative data were stratified for age (paper-and-pencil tests), or for age, sex, and education (computerized tests) and representative for the German population (69–72), with two exceptions: For two tests (Trail Making Tests A and B), data from a United States normative study were used (81). Of 20 cognitive indices, four could not be compared with test norms because of ceiling effects in the general population that preclude projection of the data on Z scores or percent ranks. Of these indices, only raw scores of case patients and control patients were compared.

To control for effects of age and education, a subsample of cancer patients who were individually matched to the control patients on these factors as closely as possible was included in the comparisons.

Normality was tested with the Shapiro-Wilk test. Chi-Square Test, Mann-Whitney U-Test, and Wilxocon Signed Rank Test, as appropriate, were employed. Kendall tau ($_{\tau}$) rank correlation was used to determine correlates of self-reported cognitive function.

To test the study hypothesis, multivariable linear regression models were run for all cognitive measures that showed worse performance of case patients compared with control patients. The following independent variables were selected based on theoretical considerations and forced into the model: case patient vs control patient status, number of current PTSD symptoms, depression score, age, menopausal status, dummy-coded educational achievement, premorbid intelligence, and current medication potentially affecting brain function. All negative effects of case patient status on cognitive performance were further examined for a mediation effect of cancer-related stress. Case patient vs control patient status was entered into the mediation model as independent variable, the cognitive index as dependent variable, number of PTSD symptoms as mediator, and the same variables that were included in the linear model were entered as covariates. Statistical significance was tested with a nonparametric bootstrapping procedure included in the INDIRECT macro for SPSS by Preacher and Hayes (82). To classify the overall cognitive performance of the participants as normal or impaired, we followed ICCTF recommendations (26) and determined the number of cognitive indices below the 6.68th percentile and below the 2.27th percentile of the control group, corresponding to 1.5 and 2 standard deviations below the mean in a normal distribution. We shifted the cutpoint from the most commonly used definition of cognitive impairment, two measures under 1.5 SD or one measure under 2 SD, and additionally applied three stricter definitions, increasing the number of measures below 1.5 or 2 SD by one each time (9). The relative risk (RR) of cognitive impairment in case patients and control patients according to the different definitions was tested.

Table 2. Neuropsychological assessments and test results, raw scores

Domain/test	Cognitive index*	Control patients		Individually matched case patients			All case patients		
		n	Mean (SD)	n	Mean (SD)	P vs control patients*	n	Mean (SD)	P vs control patients*
Attention									
Alertness (TAP) (72)	RT condition 1 median, in ms (intrinsic alertness)	60	288 (62)	60	280 (51)	.69	165	279 (53)	.45
Computerized task: to press a key whenever a cross appears on the monitor. Two conditions: 1) simple reaction, 2) reaction after a signal tone that precedes the appearance of the critical stimulus	RT condition 2 median, in ms (phasic arousal)	60	295 (62)	60	279 (62)	.08	165	278 (59)	.03
	SD of RT, condition 1 (stability of intrinsic alertness)	60	46 (23)	60	50 (36)	.82	165	46 (28)	.64
	SD of RT, condition 2 (stability of phasic arousal)	60	47 (20)	60	43 (24)	.22	165	42 (20)	.07
	Index phasic alertness Higher values indicate more profit from signal	60	–0.03 (0.11)	60	0.01 (0.09)	.02	165	0.01 (0.09)	.02
Divided Attention (TAP) (72), dual task	Commission errors (divided attention, accuracy)	60	2.33 (2.73)	58	2.72 (4.29)	.86	164	2.01 (3.04)	.32
Computerized task: to press a key whenever either a visual or an acoustic critical stimulus is presented	Omission errors (divided attention, accuracy)	60	1.35 (1.23)	58	2.03 (3.29)	.86	164	1.79 (3.15)	.79
Go/Nogo (TAP) (72), task 1 of 2	RT, median, in ms (behavioral control: processing speed)	60	430 (69)	58	418 (67)	.36	164	432 (72)	.96
Computerized task: to respond to an upright cross, but not to a diagonal cross, by pressing a key	SD of RT (behavioral control: stability of performance)	60	73 (22)	58	78 (22)	.23	164	78 (24)	.09
	Commission errors (behavioral control: accuracy)	60	0.52 (0.97)	58	1.24 (1.56)	.005	164	0.94 (1.28)	.01
	Omission errors (behavioral control: accuracy)	60	0 (0)	58	0.14 (0.69)	.04	164	0.13 (0.51)	.02
Trail Making Test A (TMT-A) (68)	Completion time in seconds (visual search, psychomotor speed)	60	29.83 (8.61)	59	29.14 (9.93)	.43	165	29.65 (9.50)	.75
Task: to connect, in sequence, numbers scattered on a page									
Memory and learning									
Digit Span Forward (71)	No. of correctly repeated digit strings (short term memory)	60	7.87 (1.71)	60	7.87 (1.85)	.92	166	7.67 (1.89)	.52
Task: to repeat strings of random digits of increasing length									
Digit Span Backward (71)	No. of correct inversely repeated digit strings (working memory)	60	6.82 (1.99)	59	6.88 (1.96)	.92	165	6.70 (2.01)	.60
Task: to repeat, in reverse order, strings of random digits of increasing length									

Table 2. Continued

Domain/test	Cognitive index*	Control patients		Individually matched case patients			All case patients		
		n	Mean (SD)	n	Mean (SD)	P vs control patients*	n	Mean (SD)	P vs control patients*
Verbal Learning and Memory Test (VLMT) (70) Task: to repeat words from a 15-word list that is orally presented in 5 consecutive trials, to recall the words after a 25-minute delay	No. of correctly reported words, sum of trails 1–5 (verbal memory: learning efficiency)	60	56.50 (7.09)	58	57.17 (8.85)	.60	164	56.50 (8.84)	.96
	No. of correctly reported words after delay (verbal memory: free recall)	60	12.30 (2.98)	59	12.29 (2.94)	.90	165	12.24 (2.68)	.58
	Difference of the last trial prior to the delay and the delayed trial, ie, no. of words lost after the delay (verbal memory: consolidation)	60	1.40 (2.26)	58	1.21 (1.92)	.89	164	1.26 (1.79)	.96
Executive function									
Trail Making Test B (TMT-B) (68) Task: to alternately connect, in sequence, numbers and letters scattered on a page	Completion time in seconds (visual search, executive processing speed)	60	66.80 (20.97)	59	68.12 (22.56)	.79	164	68.30 (24.79)	.85
Regensburg Word Fluency Test (RWT), lexical search (69) Task: to orally generate words beginning with a designated letter in a 2-minute interval	No. of correctly produced words (lexical verbal fluency)	60	19.28 (5.00)	60	19.87 (5.69)	.68	165	19.41 (6.03)	.84
Regensburg Word Fluency Test (RWT), semantic search (69) Task: to orally generate words belonging to a designated semantic category in a 2-minute interval	No. of correctly produced words (semantic verbal fluency)	60	23.70 (5.33)	59	24.78 (7.56)	.67	164	24.70 (7.63)	.72

*Please note that none of the indices are normally distributed; therefore, two-sided Mann-Whitney U Test was used for all comparisons. RT = reaction time; SD = standard deviation; TAP = Tests of Attentional Performance.

All statistical tests were two-sided with a 5% significance level. To account for multiple comparisons, false discovery rate (FDA) was controlled with a Benjamini-Hochberg procedure (83). An FDA of 20% was chosen; ie, a rate of 20% false-positive findings among statistically significant results was accepted. IBM SPSS Statistics 22 (Armonk, NY: IBM Corp.) and the mediation procedure macro INDIRECT for SPSS (82) were utilized. The study was powered for post-treatment comparisons. A sensitivity analysis was performed with the statistical power analysis program G*power 3 (84).

Results

With a sample of 166 case patients and 60 control patients (Figure 1), the study was sensitive to detect small to medium effects (Cohen's d = 0.43), given a power of 0.80. The control patients were enrolled after surveillance of a benign lesion (n = 7) or routine breast imaging (n = 53), prompted in almost all cases by some family history of breast cancer. Ten control patients (16.7%) were considered at at least moderately elevated risk of breast cancer; none carried a known BRCA1 or BRCA2 mutation. The case patients were slightly younger than the control patients; however, except for partnership status, none of the demographic differences were statistically significant (Table 1). None of the control patients and six (3.6%) of the case patients had a current diagnosis of stress disorder (ASD, 4 patients; PTSD, 2 patients). In all cases, the traumatic event was cancer. In case patients, 85% of PTSD symptoms were related to cancer.

Cognitive Function: Comparisons With Normative Data

In comparison with population norms, case patients had worse scores on seven indices and better scores on three indices. Individually matched case patients and control patients showed the same deviations from normative data, ie, worse scores on five indices of attention and executive function, and better scores on two indices of verbal memory (Table 3, Figure 2).

Cognitive Function: Comparisons With Control Patients

Case patients demonstrated better performance than control patients on two measures of alertness (phasic arousal and index phasic alertness). In the subsample of 120 individually matched case patients and control patients, only one of these differences was statistically significant (index phasic alertness) (Table 2, Figure 2). The case patients performed worse than the control patients on two indices of behavioral control (Go/Nogo commission errors and Go/Nogo omission errors) (Table 2, Figure 2). All differences between case patients and control patients retained statistical significance in a Benjamini-Hochberg procedure with a 20% FDR.

Go/Nogo commission and omission errors were aggregated into a Go/Nogo errors score, as in previous investigations (73). Multivariable linear regression did not show a statistically significant effect of case patient vs control patient status, but PTSD symptoms (Beta = 0.27, $P = .004$) and age (Beta = 0.22, $P = .04$) were statistically significant predictors of Go/Nogo errors (Table 4). Tumor stage did not statistically significantly predict Go/Nogo errors in case patients (data not shown). In a mediation model, the effect of having cancer on Go/Nogo errors (unstandardized regression coefficient B = 0.66, $P = .005$, n = 210) decreased and lost statistical significance (B = .44, $P = .07$) when the mediating effect of PTSD symptoms (bias-corrected bootstrap result for indirect effect: B = 0.21, 95% confidence interval [CI] = 0.04 to 0.46) was accounted for (Figure 3). Depression score did not statistically significantly mediate Go/Nogo errors (bias-corrected bootstrap result for indirect effect: B = 0.04, 95% CI = -0.11 to 0.21, n = 210).

Case patients had higher scores on the self-report measures of cognitive problems, EORTC-QLQ-CF and FEDA (Table 1). Both measures were associated with PTSD symptoms and depression

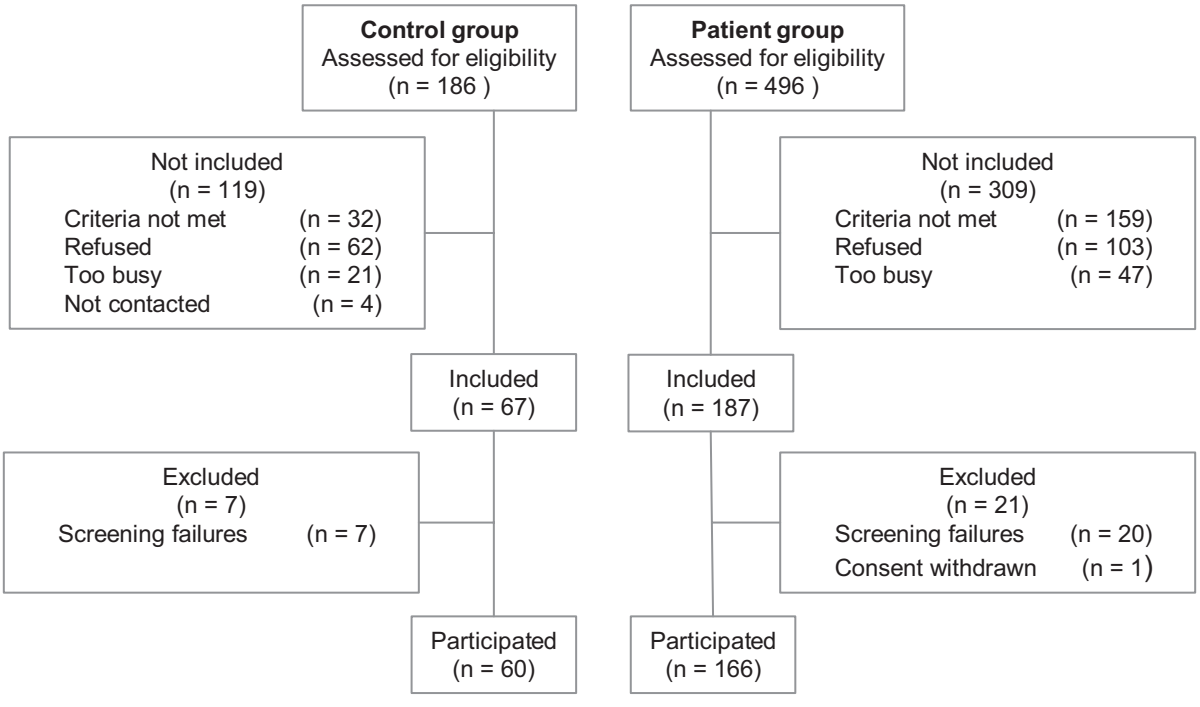

Figure 1. Flow diagram of participant enrollment.

Table 3. Neuropsychological test results, standardized to normative data

Domain/ cognitive index	Control patients n	Control patients Z score or PR Mean (SD)	Control patients P vs test norms*	Individually matched case patients n	Individually matched case patients Z score or PR Mean (SD)	Individually matched case patients P vs test norms*	All case patients n	All case patients Z score or PR Mean (SD)	All case patients P vs test norms*
Attention									
Alertness, RT condition 1†	60	-0.65 (0.83)	<.001	60	-0.58 (0.84)	<.001	165	-0.56 (0.79)	<.001
Alertness, RT condition 2†	60	-1.03 (0.72)	<.001	60	-0.77 (0.84)	<.001	165	-0.81 (0.75)	<.001
Alertness, SD of RT, condition 1†	60	0.17 (1.13)	.46	60	0.08 (1.22)	.75	165	0.17 (1.14)	.11
Alertness, SD of RT, condition 2†	60	0.03 (0.88)	.95	60	0.27 (1.07)	.08	165	0.21 (0.94)	.02
Alertness, index phasic alertness†	60	-0.68 (0.94)	<.001	60	-0.37 (0.77)	.001	165	-0.40 (0.79)	<.001
Go/Nogo, RT†	60	-0.09 (0.95)	.49	58	0.07 (0.95)	.63	164	-0.14 (0.93)	.05
Go/Nogo, SD of RT†	60	0.07 (0.87)	.57	58	-0.12 (0.85)	.31	164	-0.15 (0.86)	.03
Trail Making Test A (TMT-A)‡	60	52.75 (28.10)	.44	59	56.95 (28.54)	.08	165	52.42 (28.83)	.31
Memory									
Digit Span Forward†	60	0.08 (0.98)	.52	60	0.08 (1.10)	.48	166	-0.04 (1.11)	.59
Digit Span Backward†	60	-0.02 (1.05)	.72	59	0.02 (1.07)	.48	165	-0.08 (1.09)	.02
VLMT learning efficiency†	60	0.76 (0.76)	<.001	58	0.84 (0.97)	<.001	164	0.74 (0.99)	<.001
VLMT free recall†	60	0.49 (1.02)	<.001	59	0.48 (1.01)	<.001	165	0.45 (0.95)	<.001
VLMT consolidation†	60	-0.01 (1.19)	.76	58	0.09 (0.99)	.51	164	0.06 (0.96)	.31
Executive function									
Trail Making Test B (TMT-B)‡	60	51.17 (29.66)	.81	59	51.61 (33.18)	.71	164	50.06 (31.85)	.88
RWT lexical search‡	60	31.70 (22.40)	<.001	60	34.50 (24.43)	<.001	165	32.42 (25.23)	<.001
RWT semantic search‡	60	34.83 (22.64)	<.001	59	39.85 (29.05)	.011	164	37.82 (30.29)	<.001

* Two-sided Wilcoxon Signed Rank Test was used for all comparisons. PR = percent rank; RT = reaction time; RWT = Regensburg Word Fluency Test; SD = standard deviation; VLMT = Verbal Learning and Memory Test.
†Z scores are given; mean = 0, SD = 1.
‡Percent ranks are given; mean = 50, range = 1 to 100.

(magnitudes of $_T$ from 0.23 to 0.44, all $P < .001$) and correlated with Go/Nogo omission errors (EORTC-QLQ-CF: $_T = -0.18$, $P = .003$, n = 224; FEDA: $_T = 0.19$, $P < .001$, n = 220). No statistically significant associations of FEDA or EORTC-QLQ-CF with any other cognitive indices or age, educational achievement, and premorbid intelligence were found.

Case patients had a relative risk of cognitive impairment between 1.03 and 1.30 (individually matched case patients: 0.76 to 1.19), depending on the definition of cognitive impairment applied (none were statistically significant) (Table 5).

Discussion

In the prospective Cognicares study, we tested the hypothesis that pretreatment cognitive impairment in breast cancer patients is attributable to cancer-related post-traumatic stress. This is the first large controlled study on this issue.

Only very limited evidence of pretreatment impairment was found. The risk of overall cognitive impairment was not increased in the case patient group. Case patients and control patients performed near identically on most cognitive tests, and both groups scored statistically significantly below or, more rarely, above the population norms on more than a third of cognitive indices.

Differences between case patients and control patients were only apparent in two subdomains of attention. Case patients outperformed control patients on two measures of alertness. Only one of these differences was observed in a subsample of individually matched patient-control pairs. Case patients showed worse performance than control patients on two indices of behavioral control, and one of these indices was reflected in both self-report measures of cognitive functioning. Consistent with the hypothesis of the study, PTSD symptoms predicted performance on these indices while the effect of case patient vs control patient status was not statistically significant when PTSD symptoms were accounted for. Mediation analysis further indicated that the observed effect of having cancer on behavioral control was mediated by PTSD symptoms.

The study design safeguarded against confounding to a large extent. Cognitive function was assessed prior to any cancer therapy to exclude potential effects of surgery. We were able to control for effects of age and education by near-perfect matching of a subsample of case patients and control patients on these factors. Great care was taken to minimize all systematic differences other than the cancer diagnosis between case patients and control patients. If control patients are nominated by the case patients or recruited through advertisements, persons who are worried about early signs of cognitive impairment or a family history of dementia may be more likely to volunteer. It has also been observed that patients tend to nominate a "relatively young and healthy friend or relative" (14). To minimize confounding by selection bias, control patients were recruited through the same enrollment procedure as cancer patients; ie, they were referred by physicians of the participating breast centers. On the downside, women at increased risk of breast cancer were overrepresented in the control group. It has been hypothesized that shared genetic risk factors might contribute to the development of cancer and cognitive decline (28). This hypothesis has not yet been empirically tested; however, our control patients' deviations from the test norms may still indicate that in association with their increased risk of breast cancer, they were also at increased risk for cognitive impairment. Alternatively, these deviations may be explained by inadequate test norms. While it has been shown that normative data are a valid means of evaluation in studies of cancer-associated cognitive impairment (85), individual sets of normative data may

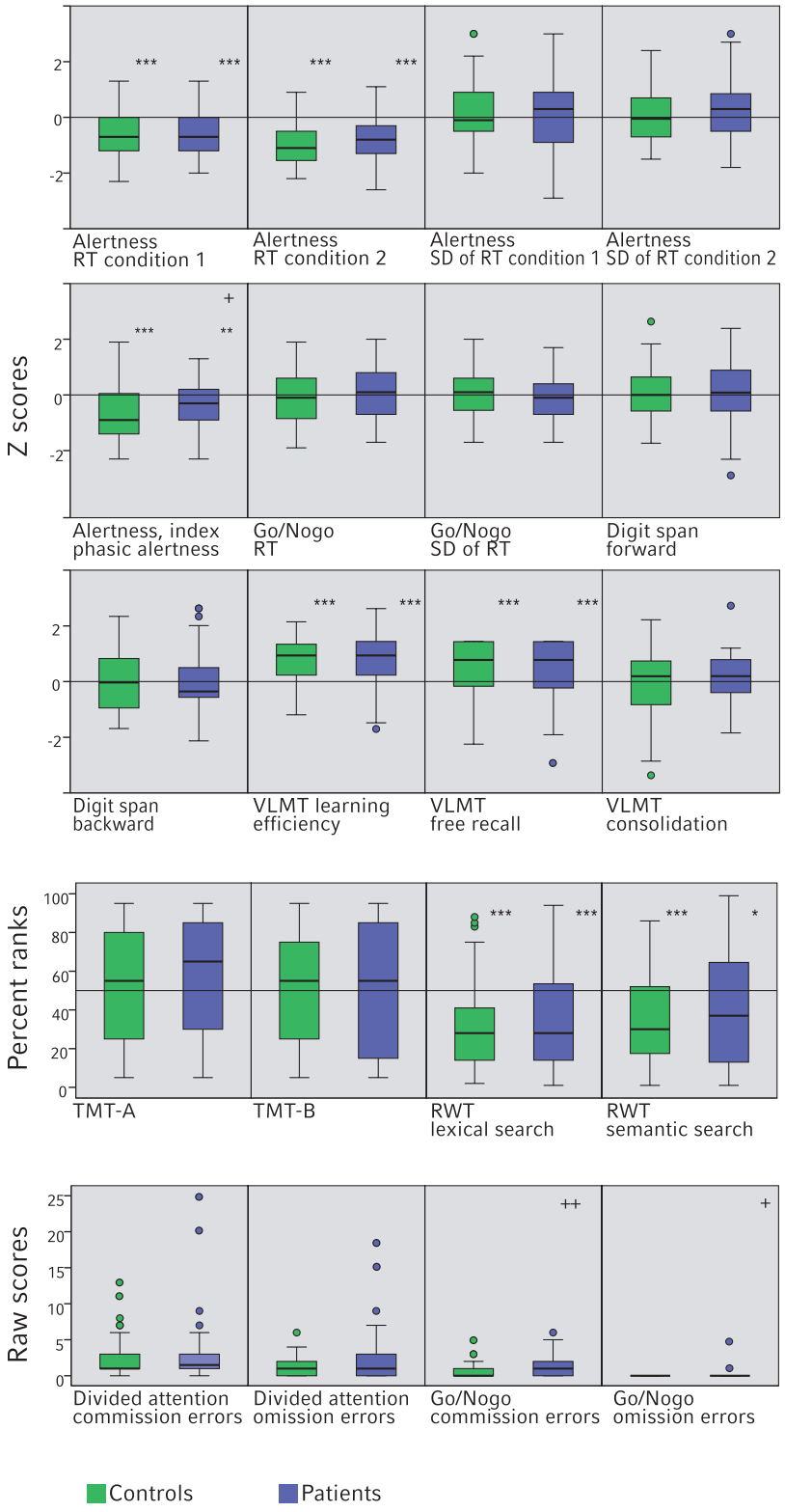

Figure 2. Cognitive indices of individually matched case patients and control patients. **Boxes** represent median and interquartile range. Please note that four measures could not be projected on Z scores or percent ranks because of ceiling effects. Raw scores are given for these measures. Wilcoxon Signed Rank Test was used for comparisons with test norms. Groups were compared with Mann-Whitney U Tests. All statistical tests were two-sided. * Different from normative data at $P < .05$. ** Different from normative data at $P < .01$. *** Different from normative data at $P < .001$. + Different between patients and controls at $P < .05$. ++ Different between patients and controls at $P < .01$. RT = reaction time; RWT = Regensburg Word Fluency Test; SD = standard deviation; TMT = Trail Making Test; VLMT = Verbal Learning and Memory Test.

Table 4. Multivariable linear regression model predicting Go/Nogo errors (n = 210)

Adjusted coefficient of determination (R^2) = 0.09			
Variable	B (95% CI)	Beta	P*
Case patient vs control patient status†	0.44 (-0.032 to 0.908)	0.14	.07
No. of current PTSD symptoms	0.12 (0.039 to 0.196)	0.27	.004
Depression score‡	-0.04 (-0.102 to 0.020)	-0.12	.19
Age	0.03 (0.001 to 0.065)	0.22	.04
Menopausal status§	-0.08 (-0.634 to 0.480)	-0.03	.79
Educational achievement: medium‖	0.05 (-0.498 to 0.603)	0.02	.85
Educational achievement: high‖	-0.03 (-0.715 to 0.662)	-0.01	.94
Educational achievement: university degree‖	-0.12 (-0.709 to 0.471)	-0.04	.69
Estimated premorbid IQ	-0.01 (-0.029 to 0.002)	-0.13	.08
Current medication potentially affecting brain function¶	0.19 (-0.272 to 0.650)	0.06	.42

* Statistical significance of the estimated regression coefficients was tested with a t statistic, controlling for all other variables in the regression model. All tests were two-sided. B = unstandardized regression coefficient; Beta = standardized regression coefficient; CI = confidence interval; IQ = intelligence quotient; PTSD = post-traumatic stress disorder.
† Coding: controls = 0, patients = .1
‡ Scores range from 0 to 27, with higher scores reflecting more depression.
§ Coding: 1 = premenopausal, 2 = peri- or postmenopausal.
‖ Educational achievement was dummy-coded with low educational achievement as reference category.
¶ Coding: 0 = no, 1 = yes.

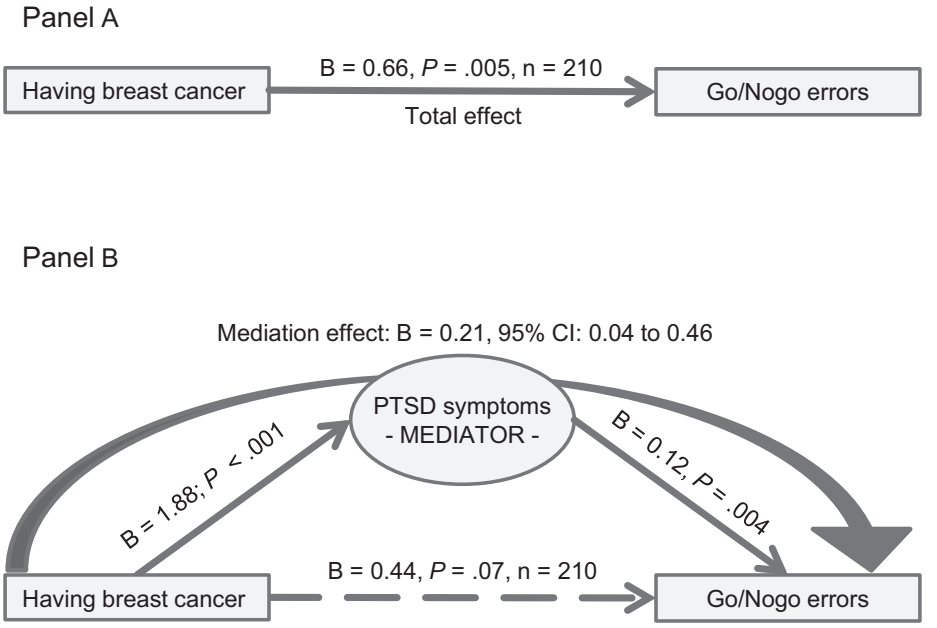

Figure 3. Mediation model. B = unstandardized regression coefficient. **A)** Having cancer increases Go/Nogo errors by a mean of 0.66 errors (total effect). **B)** Post-traumatic stress disorder (PTSD) symptoms increase Go/Nogo errors by a mean of 0.21 errors (bootstrapped mediation effect); having cancer increases PTSD symptoms by a mean of 1.88 symptoms; each PTSD symptom increases Go/Nogo errors by a mean of 0.12 errors. If mediation is accounted for, the remaining effect of having cancer on Go/Nogo errors is not statistically significant. Statistical significance of the estimated regression coefficients was tested with a t statistic, controlling for all other variables in the model. The mediation effect was tested with a nonparametric bootstrap procedure. All statistical tests were two-sided. The following covariates were included in the model: Depression score (B = -0.04, P = .19); age (B = 0.03, P = .04); menopausal status (B = -0.08, P = .79); dummy-coded educational achievement with low achievement as reference category (medium: B = 0.05, P = .85; high: B = -0.03, P = .94; university degree: B = -0.12, P = .69); premorbid intelligence (B = -0.01, P = .08); medication potentially affecting brain function (B = 0.19, P = .42)

nevertheless lack quality or validity for a particular study for a number of reasons (86).

In line with a recently published meta-analysis (87), less substantial pretreatment cognitive impairment than reported from many previous well-controlled and methodologically sound studies was found in the Cognicares study. This discrepancy may be because of elimination of additional confounding factors, especially effects of surgery, in the present study. However, again we cannot fully exclude that an increased risk of cognitive impairment in our control group has attenuated differences of cognitive functioning between the case patients and the control patients.

In addition to overrepresentation of women at increased risk of breast cancer in the control group, further limitations need to be acknowledged. To the best of our knowledge, prechemotherapy cognitive function has never before been investigated in an equally large sample of young and middle-aged breast cancer patients; however, our study was still not powered to detect

Table 5. Participants showing cognitive impairment according to definitions of increasing stringency

Definition of cognitive impairment	Control patients (n = 60)	Individually matched case patients (n = 53)*		All case patients (n = 155)*	
	No. (%)	No. (%)	RR vs controls (95% CI)	No. (%)	RR vs controls (95% CI)
Definition 1†	19 (31.7)	20 (37.7)	1.19 (0.71 to 1.98)	64 (41.3)	1.30 (0.86 to 1.98)
Definition 2‡	11 (18.3)	10 (18.9)	1.03 (0.48 to 2.23)	32 (20.6)	1.13 (0.61 to 2.09)
Definition 3§	8 (13.3)	8 (15.1)	1.13 (0.46 to 2.81)	22 (14.2)	1.07 (0.50 to 2.26)
Definition 4‖	3 (5.0)	2 (3.8)	0.76 (0.13 to 4.35)	8 (5.2)	1.03 (0.28 to 3.76)

* Please note that relative risk was not calculated if one or more cognitive indices were missing. CI = confidence interval; RR = relative risk.
† Two or more cognitive indices < 6.68th percentile (equivalent to -1,5 SD) or ≥ 1 cognitive indices < 2.27th percentile (equivalent to -2 SD) of the control group.
‡ Three or more cognitive indices < 6.68th percentile (equivalent to -1,5 SD) or ≥ 2 cognitive indices < 2.27th percentile (equivalent to -2 SD) of the control group.
§ Four or more cognitive indices < 6.68th percentile (equivalent to -1,5 SD) or ≥ 3 cognitive indices < 2.27th percentile (equivalent to -2 SD) of the control group.
‖ Five or more cognitive indices < 6.68th percentile (equivalent to -1,5 SD) or ≥ 4 cognitive indices < 2.27th percentile (equivalent to -2 SD) of the control group.

small effects. We can also not exclude that part of the observed differences of cognitive functioning between case patients and control patients are chance findings because the procedure that was used to control for multiple comparisons permitted one in five statistically significant results to be false-positive. Further, our results apply to patients who have access to excellent medical care and who enjoy relatively high standards of social security. Under different circumstances, cancer patients may show more cognitive impairment.

The Cognicares study indicates that limited cognitive impairment that may occur in breast cancer patients already before treatment is most probably largely caused by traumatic stress in the wake of a cancer diagnosis. This study focused on narrowly defined (74) post-traumatic stress. Cancer patients, however, are exposed to a multitude of stressors, many of which do not qualify as traumata but may still affect cognitive function, especially in conjunction with chronic stress (88). Future research that comprehensively investigates the consequences of stress may even more fully explain the particular vulnerability of cognitive function in pretreatment cancer patients.

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