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RESEARCH

Biological and psychological predictors of cognitive function in breast cancer patients before surgery

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Abstract

Purpose Research suggests that cancer-related cognitive impairment (CRCI) can occur before breast cancer (BC) treatment. The limited extant evidence suggests the underlying mechanisms could be stress-related. Potential psychological and biological predictors of CRCI prior to any BC treatment were examined.

Methods 112 treatment-naïve women with BC and 67 healthy controls (HC) completed a neuropsychological test battery to assess cognitive impairment and a self-report battery to assess cognitive complaints, cancer-related stress, depressive and anxiety symptoms. Morning and evening cortisol and α-amylase were collected from saliva. Multilinear regressions were conducted.

Results Treatment-naïve BC patients were more frequently impaired in verbal memory and processing speed and reported more cognitive complaints (all $p < .001$) than HC. BC patients and HC did not differ in overall cognitive impairment ($p = .21$). Steeper α-amylase, lower cancer-related stress and younger age was associated with better overall cognitive function in treatment-naïve BC patients. Higher depressive symptoms predicted higher levels of cognitive complaints in BC patients.

Conclusion Overall, these findings suggest that stress plays a role in CRCI. This study is the first to associate α-amylase with cognitive function in cancer patients, informing future research. The findings on impairment in processing speed and verbal memory among treatment-naïve BC highlight the need to screen for such impairments among BC patients and indicate that future studies on CRCI should include baseline assessments prior to BC treatment. If replicated, these findings could inform the development and testing of appropriate interventions to decrease CRCI among cancer patients.

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Keywords Breast cancer · Treatment-naïve · Cancer-related cognitive impairment · Cognitive complaints · Cortisol · A-amylase · Internalizing symptoms

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Cancer-related cognitive impairment (CRCI) is one of the most common side-effects of BC [1]. CRCI generally includes impairment of attention, executive functioning, processing speed, long-term and working memory [2]. CRCI has been reported to be as high as 75% during treatment [3] and to last up to 20 years after treatment [4]. The etiology of CRCI remains unclear and could be directly due to the cancer itself or indirectly induced by psychological or biological factors.

Most research on CRCI has been conducted in BC patients who have undergone chemotherapy [5]. However, recent evidence found CRCI in 28% of treatment-naïve BC patients compared to 8% of age-matched healthy controls (HC) [6]. Additionally, brain alterations have been found in treatment-naïve BC patients [7]. Yet, many studies assess CRCI after BC treatment (i.e. surgery) has already begun, and therefore may not represent an appropriate baseline.

Anxiety and depressive symptoms may play a role in CRCI [8–10]. Indeed, a study on treatment-naïve BC patients found that cancer-related stress was associated with CRCI [10]. This is likely due to acute or chronic stress causing overactivity and dysregulation of the stress reactivity systems, the hypothalamic pituitary adrenal (HPA) axis and the sympathetic nervous system (SNS) [11, 12]. Cortisol is a glucocorticoid hormone regulated by the HPA axis. Disrupted cortisol is common in BC patients and may be due to stress [13]. The frontal cortex and hippocampus have many cortisol receptors and play a role in regulating the HPA axis. Thus, dysregulation of the HPA axis (and heightened cortisol levels) can lead to impaired cognition that can damage the aforementioned brain areas and impair their associated cognitive functions [14], i.e. memory, executive function and processing speed. In support of this link between stress, cortisol and CRCI, one study found that an association between childhood trauma and cognitive complaints was mediated by cortisol dysregulation among BC survivors [15]. Another study on testicular cancer patients found that higher cortisol levels independently predicted neuropsychological performance [16]. Finally, a large population-based study found an association between elevated cortisol levels and cognitive impairment [17].

Alpha (α)-amylase is another biological stress marker [18], indicating SNS activity [19]. A-amylase can be elevated in BC patients [20]. A steeper α-amylase response has been associated with poorer memory performance among healthy adults [21] and elevated α-amylase linked to mild cognitive impairment in older adults [22]. While cortisol dysregulation (i.e., cortisol slope) has been found to be associated with cognitive impairment no study, that we are aware of, has examined if α-amylase slope is related to neuropsychological performance among cancer patients.

Previous studies on stress and CRCI have mostly been conducted during or after cancer treatment using self-report. The present study is the first, to our knowledge, to explore whether cortisol, α-amylase and stress-related psychiatric symptoms can predict CRCI in a nationwide cohort of BC patients prior to any treatment. Our hypotheses are threefold. First, we hypothesized that the treatment-naïve BC patients would have greater cognitive impairment compared to HC. Secondly, steeper cortisol and α-amylase slopes would be associated with better cognitive function. Third, greater cancer-related stress, depressive and anxiety symptoms would be positively associated with CRCI.

Materials and methods

Participants

Participants were 112 newly diagnosed treatment-naïve BC patients scheduled to receive surgery (mean age 61.8, SD: 10.7, age range: 25–81) at the National University Hospital in Iceland and 67 HC (mean age: 60.9, SD: 9.5, age range: 37–82) matched to the BC patients on age and educational level. BC patients were referred to the study shortly after their BC diagnosis by nurses involved with their BC treatment at the University Hospital of Iceland.

The HC group was selected from a large nationwide cohort study representative of the Icelandic population, called *Trauma, mental health and disclosures of sexual violence* ($N = 1{,}793$), that studied whether participants had experienced trauma. Eligibility criterion for the HCs was that they have no history of cancer. Potentially eligible HC received a letter describing the study, followed by a phone call from a research team member. The current study was a part of a larger prospective study examining the effect of Bright Light Therapy (BLT) on the psychological side effects of cancer, hence the exclusion criteria for both groups included contraindications for BLT. Exclusion criteria were: age under 18 years, current pregnancy, pre-existing anaemia, history of bipolar disorder/mania, sleep disorders (apnea, narcolepsy), shift worker, travel to another time zone during the study, no access to a phone or a computer, inability to understand or read Icelandic and history of a neurological condition (i.e. epilepsy, autism diagnosis or traumatic brain injury). Of the eligible participants, 45% of the BC patients and 78% of the HC agreed to participate in the study. In order to ensure homogeneity of the sample, four participants with BC stage 0 (TisN0M0) were removed from all data analyses.

The response rate of the BC patients was 78.5% and 100% for HC in the neuropsychological assessment, 85% for the BC patients and 97% for the HC in the self-report assessment and 50% for the BC patients in the saliva sampling (HC did not contribute saliva). All participants provided informed and written consent. The study was approved by the National Data Protection Authority, the chief medical officer at the

National University Hospital and the National Bioethics Committee (VSN-18–199) of Iceland. The study conformed to the ethical standards of the Declaration of Helsinki.

Neuropsychological assessment

The neuropsychological assessment was based on the recommendations of the International Cancer and Cognition Task Force (ICCTF) [23] and the availability of translated measures. Sustained attention and reaction time (RT) was measured with the 5-min Psychomotor Vigilance Test (PVT) [24]. Processing speed was assessed with the computerized Trail Making Test-A (TMT-A) [25, 26]. Working memory was measured with the Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV) Digit Span subtest [27]. Verbal memory and learning were assessed with the Rey Auditory Verbal Learning Fluency Test (RAVLT) [28]. Verbal fluency was measured with the Icelandic equivalent of the Controlled Oral Word Association Test (COWAT) [29]. Executive function was assessed with the computerized TMT-B [25, 26].

Psychological assessment

Cognitive complaints were measured with the Patient-Reported Outcomes Measurement Information System (PROMIS®) Cognitive Function 8a [30], with higher scores indicating fewer cognitive complaints. Depressive symptoms were measured with the Center for Epidemiological Studies Depression Scale (CES-D) [31]. Anxiety was assessed with Generalized Anxiety Disorder-7 (GAD-7) [32]. All measures were administered to both the BC patients and HC. The Impact of Events Scale-Revised (IES-R) [33] was administered only to the BC patients to assess cancer-related stress. Higher scores on all measures reflected more severe psychiatric symptoms or traits. The internal consistency (Cronbach's a) of the above measures ranged from 0.87 (GAD) to 0.96 (PROMIS Cognitive Function).

Sociodemographic and clinical variables

Sociodemographic information regarding gender, age, education, relationship status, body mass index (BMI), physical activity and menopause were collected via self-report. Clinical variables were collected from the medical records of the BC patients, including cancer stage, human epidermal growth factor receptor 2 (HER2), estrogen and progesterone status.

Cortisol and α-amylase

Saliva samples were collected using Salivette tubes twice a day, upon awakening and < 30 min from bedtime, for three consecutive days. The BC patients were instructed to refrigerate the saliva samples and bring them to their next scheduled hospital appointment. Upon arrival at the hospital, the samples were refrigerated until retrieved by a research team member. At the research facility, the saliva samples were stored at -80 °C and then batched and shipped on dry ice for analysis.

The cortisol samples were frozen and stored at -20 °C. After thawing, samples were centrifuged at 3,000 rpm for 5 min. Salivary concentrations were measured using chemiluminescence immunoassay with high sensitivity (IBL International, Hamburg, Germany). The intra and inter-assay coefficients of variance were below 9%. See Rohleder et al. [34] for a description of the salivary α-amylase assays. The intra- and inter-assay coefficients for α-amylase were below 5% and 9%, respectively.

General procedure

Due to COVID-19 social restrictions and to minimize participant burden, all assessments were conducted remotely. Participants completed the psychological assessment online via REDCap [35].The Digit Span, COWAT and RAVLT were administered by trained research staff members over the phone and participants completed the TMT and PVT remotely on a computer. The BC patients completed the neuropsychological assessment on average 3 weeks after receiving the BC diagnosis. Participants were given instructions on how to extract the saliva samples at home as soon as possible within half an hour of awakening and the second sample within half an hour before bedtime for three consecutive days. The BC patients completed all measures before any BC treatment.

Statistical data analysis

T-tests and chi-square tests were used to compare the BC patients and HC on sociodemographic, clinical and psychological variables. To test the hypothesis that BC patients had cognitive impairment compared to HC, *z*-scores were calculated based on the means and standard deviations of the neuropsychological outcomes of the HC group. To assess overall cognitive performance, a global composite score (GCS) was calculated with the mean z-scores of all neuropsychological outcomes for participants with complete neuropsychological data [16]. Based on the recommendations of ICCTF [23], CRCI was categorized by having at least one neuropsychological outcome with z-scores ≤ -1.5 in two or more cognitive domains. Since the computerized neuropsychological tests were automated and undertaken at home without any supervision (because of COVID-19), time values that were 1.5 * interquartile range (IQR) away from the mean were removed (20 from PVT and 6 from the TMT-A). Welch two-sample *t*-tests, chi-square or Fisher's tests were employed to test the differences between the BC

patients and HC on neuropsychological outcomes. Listwise deletion was used in all analyses.

The diurnal cortisol and α-amylase slopes were calculated by a single regression for morning and evening over all three days. Cortisol and α-amylase values greater than four standard deviations from the mean were not included in the analyses (three values for cortisol and five for α-amylase), along with samples that were taken out of the instructed time windows (eight samples).

Multiple linear regression analyses were performed to test whether the biological variables (cortisol and α-amylase) and psychological variables (depressive symptoms, anxiety and cancer-related stress), along with age and education predicted cognitive impairment, overall cognitive function and cognitive complaints. The standardized regression coefficient was used. Welch two-sample *t*-test was employed to test whether BC patients had more cognitive complaints than the HC.

For all models, when the assumption of heteroscedasticity for linear regression was violated, the dependent variable was log-transformed. All other assumptions for the statistical analyses were met. Given that the study is a first of its kind with a small sample size, $\alpha < 0.05$ was considered significant. Effect sizes were calculated using Partial η^2. Statistical analyses were conducted in R.

Results

Table 1 shows that the BC and HC did not significantly differ on any sociodemographic variables. BC patients had significantly more anxiety ($p = 0.02$) than the HC.

Table 1 Demographic and clinical characteristics of breast cancer patients compared with the healthy control group

	Breast cancer patients ($N = 112$)	Healthy controls group ($N = 67$)	*p*
Age in years (mean, SD)	61.8 (10.7)	60.9 (9.5)	.57
Currently partnered, *N*(%)			1
Yes	74 (66.1%)	44 (65.7%)	
No	33 (29.5%)	19 (28.4%)	
Education level, *N*(%)			.55
Primary	18 (16.1%)	10 (14.9%)	
Secondary	36 (32.1%)	17 (25.4%)	
University	53 (47.3%)	37 (55.2%)	
BMI (mean, SD)	27.7 (5.0)	28.1 (4.8)	.61
Physical activity, *N*(%)			.48
None	17 (15.2%)	12 (17.9%)	
Once a week	10 (8.9%)	2 (3.0%)	
Twice a week	16 (14.3%)	10 (14.9%)	
≥ 3 times a week	64 (57.1%)	40 (59.7%)	
Menopause, yes %	88 (78.6%)	56 (83.6%)	.62
Cortisol (mean, SD)	5.1 (2.1)	-	-
Alpha-Amylase (mean, SD)	140.5 (94.8)	-	-
Depressive symptoms (mean, SD)	11.0 (8.5)	8.8 (7.3)	.08
Anxiety (mean, SD)	4.1 (3.8)	2.8 (3.3)	.02**
Cancer-related stress (mean, SD)	25.5 (14.6)	-	-
Average time since diagnosis (weeks)	3.0	-	-
Cancer stage, *N*(%)			
I	49 (73.7%)	-	-
II	36 (37.9%)	-	-
III	10 (10.5%)	-	-
HER-2 positive, *N*(%)	10 (10.8%)	-	-
Estrogen positive, *N*(%)	88 (93.6%)	-	-
Progesterone positive, *N*(%)	71 (74.0%)	-	-

BMI = Body Mass Index; HER-2 = human epidermal growth factor receptor 2; statistical significance:
* = $p < 0.05$ (two-sided)
** = $p < 0.01$ (two-sided)

Neuropsychological assessment and the prevalence of cognitive impairment

Table 2 shows the neuropsychological outcomes and impairment rates for BC patients and HC. Compared to the HC group, BC patients had significantly slower processing speed ($t[136.3] = 2.6$, $p = 0.01$, CI [0.14,0.98]). Fisher's exact test revealed they were more likely to score within the impaired range for processing speed as assessed via total time on TMT-A, $p < 0.001$. Additionally, Fisher's exact test revealed a significantly higher proportion of BC patients than HCs scored within the impaired range on verbal memory as assessed via the RAVLT total score, $p < 0.001$. The two groups did not significantly differ on the other neuropsychological test scores or impairment frequencies.

The groups did not significantly differ in their overall cognitive function assessed via the GCS. The Z-score mean of the GCS score for BC patients was -0.01 (SD: 0.5) and 0.12 for HC (SD: 0.5). Although the percentage of BC patients (8 patients: 13.8%) with cognitive impairment was greater than that of HC (3 patients, 5.7%), Fisher's exact test revealed that BC patients and HC did not significantly differ in overall cognitive impairment, $p = 0.21$.

Association of biological and psychological predictors with neuropsychological outcomes in breast cancer patients

Next, potential biological and psychological predictors were regressed on the neuropsychologically-assessed cognitive outcomes (overall cognitive function, processing speed, and verbal memory) in separate analyses.

Table 3 gives an overview of the biological (i.e. the diurnal cortisol and α-amylase slopes) and psychological (i.e. depressive symptoms, anxiety and cancer-related stress) predictors of overall cognitive function and impaired neuropsychological outcomes for BC patients, when controlling for age and education.

The model assessing the biological predictors of the BC patients' overall cognitive function was significant ($F(4,28) = 3.6$, $p = 0.02$) and accounted for 25% of the variance in overall cognitive function. Age (β=-0.44, $p = 0.02$) and a steeper diurnal α-amylase slope (β=-0.42, $p = 0.02$ significantly predicted overall cognitive function among BC patients. The model with the psychological predictors of overall cognitive function of BC patients was also significant ($F(5,41) = 3.1$, $p = 0.02$) and accounted for 19% of the variance in overall cognitive function. Age (β=-0.42, $p = 0.01$)

Table 2 A comparison of the breast cancer patients and healthy controls on their neuropsychological performance and impairment (categorized as scoring $z \leq$ -1.5) frequency in each outcome

Cognitive domain	NP test outcome measure†	Raw score, mean (SD) *N*		Z-score, mean (SD)‡	*p*–value Group Differences (*z*-scores)	Impairment frequency by test ($z <$ -1.5) *N* (%)		p-value ($\chi 2$ or Fisher's test)
		HC	BC	BC		HC	BC	
Reaction time (RT)	PVT Mean RT	424.2 (104.8) *N* = 58	417.7 (113.5) *N* = 67	.06§ (1.1)	.74	7 (12.1%)	6 (9.0%)	.46
Processing speed	TMT-A (s)	51.2 (15.2) *N* = 61	59.7 (23.1) *N* = 80	-.56 (1.5)	.01*	6 (7.5%)	20 (25.0%)	< .001**
Working memory	WAIS-IV Digit Span (correct)	17.3 (5.1) *N* = 67	17.1 (4.6) *N* = 112	-.05 (.9)	.75	1 (1.5%)	3 (2.7%)	.79
Verbal memory	RAVLT total score	46.2 (11.9) *N* = 67	43.3 (10.8) *N* = 103	-.24 (0.9)	.11	4 (6.0%)	10 (9.7%)	< .001**
	RAVLT delayed recall	9.8 (3.1) *N* = 64	9.2 (3.4) *N* = 102	-.21 (1.1)	.21	6 (9.4%)	15 (14.7%)	.95
Verbal fluency	COWAT- Letters (H,S)	13.7 (4.8) *N* = 67	13.1 (4.3) *N* = 112	-.13 (.9)	.39	4 (6.0%)	4 (3.6%)	.09
	COWAT- Category (Animals)	21.7 (5.5) *N* = 67	20.6 (6.0) *N* = 111	-.02 (.9)	.19	2 (3.0%)	4 (3.6%)	.84
Executive function	TMT-B (s)	103.3 (38.9) *N* = 61	110.1 (48.7) *N* = 80	-.17 (1.3)	.36	6 (9.8%)	10 (12.5%)	.46

†Neuropsychological test outcome measure; ‡Z-scores of BC patients compared with HC ($HC_z = 0$); BC = Breast cancer patients; HC = healthy controls; PVT = Psychomotor Vigilance Test; TMT = Trail Making Test; WAIS = Wechsler Adult Intelligence Scale; RAVLT = Rey Auditory Verbal Learning Test; COWAT = Controlled Oral Word Association Test; §Positive z-scores indicate better performance by BC patients than HC; statistical significance:

* = $p < 0.05$ (two-sided)

** = $p < 0.001$ (two-sided)

Table 3 Biological and psychological predictors of the impaired neuropsychological outcome (processing speed) and overall cognitive function in BC patients

	Processing Speed				Overall cognitive function (GCS)†			
	β	SE *β*	*p*	η^2	*β*	SE *β*	*p*	η^2
Biological	*N* = 46				*N* = 33			
Age	.64	0.00	< .001**	.32	-.44	0.01	.02*	.18
Education	.06	0.03	.69	.00	-.08	0.05	.67	.00
Cortisol Slope	.26	0.14	.05	.09	.08	0.33	.60	.01
A-Amylase Slope	.02	0.01	.85	.00	.42	0.01	.02*	.19
Psychological	*N* = 62				*N* = 47			
Age	.52	0.28	< .001**	.22	-.42	0.01	.01*	.15
Education	.04	1.74	.73	.00	-.00	0.04	.98	.00
CES-D	.20	0.48	.24	.02	.38	0.01	.12	.02
GAD	-.22	1.11	.29	.01	-.01	0.03	.97	.00
IES-R	.34	0.31	.09	.05	-.52	0.01	.049*	.09

†GCS = Global Composite Score; TMT = Trail Making Test; CES-D = Center for Epidemiological Studies Depression Scale (CES-D); GAD = Generalized Anxiety Disorder; IES-R = Impact of Events Scale-Revised; statistical significance:

* = $p < 0.05$ (two-sided)

** = $p < 0.01$ (two-sided)

and cancer-related stress (β=-0.52, $p = 0.049$) significantly predicted overall cognitive function among BC patients.

For cognitive impairment, both multilinear regression models for the potential biological ($p = 0.15$) and psychological predictors ($p = 0.18$) of verbal memory were insignificant and therefore removed from Table 3 for the sake of simplicity. The model with the biological predictors of processing speed was significant ($F(4,41) = 5.7$, $p < 0.001$), accounting for 30% of the variance. Age significantly predicted processing speed (β=0.64, $p < 0.001$), while the diurnal cortisol slope was marginally significant, β=0.26, $p = 0.05$. The model with the psychological predictors of processing speed was also significant, $F(5,56) = 4.6$, $p < 0.001$, accounting for 23% of the variance. Again, age significantly predicted processing speed, β=0.52, $p < 0.001$ while cancer-related stress was marginally significant, β=0.34, $p = 0.09$.

Cognitive complaints

BC patients had significantly more cognitive complaints than HC (t[164.3] = 3.5, p < 0.001, CI [1.59,5.71]). Table 4 gives an overview of the biological (i.e. the diurnal cortisol and α-amylase slopes) and psychological (i.e. depressive symptoms, anxiety and cancer-related stress) predictors of the BC patients' cognitive complaints.

The cognitive complaints of the BC patients were regressed on age, education, anxiety, depressive symptoms and cancer-related stress. The model accounted for 22% of the variance in overall cognitive complaints, ($F(5,78) = 5.8$, $p < 0.001$). The significant predictor of cognitive complaints were depressive symptoms (β=-0.36, $p = 0.01$), while education was marginally significant (β=-0.18, $p = 0.09$).

Table 4 Biological and psychological predictors of cognitive complaints (assessed via PROMIS-Cognitive function) in BC patients

	Cognitive complaints			
	β	SE *β*	*p*	η^2
Biological	*N* = 54			
Age	.18	0.11	.23	.02
Education	-.02	0.68	.89	.00
Cortisol slope	.09	3.62	.54	.00
A-Amylase slope	.00	0.18	1	.00
Psychological	*N* = 84			
Age	-.00	0.09	.96	.00
Education	-.18	0.50	.09	.04
CES-D	-.36	0.14	< .01**	.09
GAD	.11	0.34	.47	.00
IES-R	-.05	0.09	.73	.00

CES-D = Center for Epidemiological Studies Depression Scale (CES-D); GAD = Generalized Anxiety Disorder; IES-R = Impact of Events Scale-Revised; statistical significance:

* = $p < 0.05$ (two-sided)

** = $p < 0.01$ (two-sided)

However, the model assessing the biological predictors of cognitive complaints was insignificant ($p = 0.73$).

Discussion

This is the first national cohort study to examine biological and psychological predictors of CRCI among treatment-naïve BC patients. Additionally, this is the first study, to

our knowledge, to examine whether α-amylase is associated with cognitive function in cancer patients. In line with previous studies [6, 7, 36], we found that BC patients presented with greater cognitive impairment compared to HC in terms of processing speed and verbal memory impairments. As such, our hypothesis that BC patients would present with more cognitive impairment than HC was partially supported. However, we found no differences between the BC patients and HC in other cognitive domains or overall cognitive function. These results are in line with previous findings [10]. The current findings however contradict those of Lange et al. [6] who found group differences in overall cognitive function, which is the only other study we know of employing a nationwide cohort of treatment-naïve BC patients and comparing them with HC. This discrepancy may partly be explained by differences in recruitment strategy since Lange et al. recruited HCs via local advertisements, which may have contributed to bias in their results in that those with greater impairment may have self-selected to participate. Our findings also contradict those of Schilder and colleagues [37] who found differences in overall cognitive function when comparing treatment-naïve BC patients to HC. Again, the reason could have been differences in recruitment strategy, since the BC patients in their study chose the HC participants. This resulted in group differences in age, IQ, co-morbidities and health behaviour which may have influenced their findings.

Our hypothesis that overall cognitive function and CRCI could be predicted by the biological stress markers, α-amylase and cortisol, was partially supported. A-amylase predicted overall cognitive function when controlling for cortisol, age and education. In line with our hypothesis, a steeper α-amylase slope was associated with better cognitive function. Previous studies on other populations have also found an association between α-amylase and cognitive function [21, 22]. Additionally, age predicted overall cognitive function and CRCI in BC patients, with higher age being associated with worse overall cognitive function and slower processing speed. Meanwhile, cortisol did not predict cognitive function, in contrast with previous findings [16, 17]. It should be noted, however, that the study by Amidi et al. [16] on testicular cancer patients in which cortisol predicted overall cognitive function, only collected cortisol once instead of diurnally (two saliva samples over three consecutive days). The models for the biological and psychological predictors of verbal memory impairment were insignificant.

In line with our hypothesis, cancer-related stress predicted overall cognitive function in BC patients when controlling for age, education, depressive and anxiety symptoms. Higher cancer-related stress was associated with worse overall cognitive function, in line with previous findings [10]. However, our hypothesis that depressive and anxiety symptoms would predict CRCI in BC patients was not supported, contrasting other findings [8].

Despite no measurable differences between the BC patients and HCs in overall cognitive function in this study, the BC patients did report more cognitive complaints than the HCs, in line with previous findings [6] and in contrast with others [7]. BC patients could experience CRCI in daily life but compensatory brain areas could sustain their neuropsychological performance [38] or CRCI could be too subtle for neuropsychological tests [2]. Depressive symptoms predicted cognitive complaints when controlling for the effects of age, education, anxiety and cancer-related stress, consistent with previous findings [39]. The more severe depressive symptoms the participants had, the more frequent their cognitive complaints. The model for the biological predictors of cognitive complaints was insignificant. Lastly, we found that the BC patients had more anxiety symptoms than HCs.

The strengths of the study include that this is a nationwide cohort study where all newly diagnosed BC patients were invited to participate. Additionally, the HCs were matched to the BC patients on age and education from a large nationwide cohort study representative of the population.

Limitations include a small sample size. Furthermore, since the HCs did not undergo the biological assessments, potential group differences in cortisol and α-amylase levels could not be explored. Since the study did not have an upper age limit, the groups might have differed in age-related health conditions that could have affected their cognitive function. However, the use of a nationwide cohort that is representative of the population and age-matching the HCs to the BC patients would minimize this potential confound. Indeed, the mean ages and standard deviations of the two groups did not differ. Lastly, this study was conducted mainly during the COVID-19 pandemic, which could have influenced the psychological and cognitive function of participants.

Conclusions

Our findings demonstrate that treatment-naïve BC patients were more frequently impaired in verbal memory and processing speed and had more frequent cognitive complaints than HC. Furthermore, they indicate that α-amylase and cancer-related stress can predict pre-treatment CRCI in BC patients. Further studies with larger samples are needed to verify these findings, to assess additional markers of inflammation and/or accelerated aging, and to better understand the relationship between CRCI and stress, especially the potential role of α-amylase. This knowledge may inform the development and testing of appropriate interventions. Lastly,

the findings highlight the need for baseline measurements before any BC treatment in future studies on CRCI.

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Authors' contributions S.G.A., H.B.V., K.R.J., H.F.D., T.H., L.M.W., A.A., and B.B. designed the study. S.G.A., G.A., H.R.S.T, K.S. and H.F.D. conducted the study. H.B.V., B.B., L.M.W., A.A., T.H., S.L., H.R.S.T and R.T. guided S.G.A. with the data analaysis. S.G.A. analyzed the data, drafted the manuscript, incorporated comments and finalized the manuscript. H.B.V., B.B., L.M.W., A.A., T.H., S.L., and K.R.J. discussed the results and commented on the manuscript. All authors read and approved the final manuscript.

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Data availability In accordance with the Icelandic data protection laws and the terms of approval for the current study that the National Bioethics Committee of Iceland accepted, these data cannot be made publicly available. Interested researchers who provide a methodologically sound proposal can access deidentified data. Notably, the execution of such a proposal requires approval by the National Bioethics Committee of Iceland. Proposals should be directed to heiddisb@ru.is.

Declarations

Competing interests The authors declare no competing interests.

Conflicts of interest The authors declare no potential conflicts of interest.

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