Correlates of cognitive impairment in adult cancer survivors who have received chemotherapy and report cognitive problems

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Abstract

Objective: Cognitive impairment negatively affects some cancer survivors who have completed chemotherapy; however, factors underlying this cognitive impairment remain poorly understood. We aimed to investigate (1) the relative importance of demographics, medical, and psychological characteristics associated with cognitive impairment; and (2) specific variables associated with cognitive impairment in adult cancer survivors who completed adjuvant chemotherapy.

Methods: We performed post-hoc analyses of baseline data from early-stage cancer survivors with cognitive complaints who received adjuvant chemotherapy 0.5–5 years earlier and volunteered for a trial designed to improve cognition. The primary outcome of self-reported cognitive impairment was measured using a questionnaire; secondary outcome of objective cognitive impairment was measured using a computerized neuropsychological test battery.

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Hierarchical linear regression determined the relative importance of demographics, medical, and psychological characteristics in associations with both self-reported and objective cognitive impairment.

Results: The sample was 95% female and 89% breast cancer patients. The final model accounted for 33% of variation in self-reported cognitive impairment (n=212, demographics 5%, medical 3%, and psychological 25%), with fatigue and stress as significant individual correlates (*p*-values 0.0001). For the secondary analysis, the final model accounted for 19% of variation in objective cognitive impairment (n=206, demographics 10%, medical 5%, and psychological 4%), with age, smoking history, and number of chemotherapy cycles as significant individual correlates.

Conclusion: We found that psychological characteristics are more important than demographic and medical characteristics in self-reported cognitive impairment, whereas other characteristics are more important in objective cognitive impairment. This suggests clinicians should investigate possible psychological problems in cancer survivors who self-report cognitive impairment.

Introduction

Some people who have survived cancer and had chemotherapy report trouble concentrating or remembering (or both). This is colloquially called "chemobrain" and more formally termed "cancer-related cognitive impairment". With improved cancer diagnoses and treatments, patients are surviving longer [1], and cognitive impairment is reported as a common problem that can affect survivors' social and professional lives [2]. Up to 70% of women with breast cancer report cognitive impairment, with many classifying it as their most problematic symptom after cancer treatment [2]. Additionally, up to 45% of solid tumor cancer survivors have objectively detected cognitive impairment after chemotherapy, although a few studies have reported no impairment [3-6].

Cognitive function can be determined from self-report questionnaires and objective neuropsychological tests. Self-report questionnaire results are associated with patients' quality of life and have advantages including easy administration and not having practice effects; their disadvantages include potential self-report bias. Neuropsychological tests are the objective "gold standard" for measuring cognitive impairment; however, they are often more difficult to administer (the International Cognition and Cancer Task Force recommends pencil-and-paper tests administered by a neuropsychologist [7]), and they may not be sensitive enough to detect the subtle cognitive impairment present in this population [8]. There is only a weak association between self-reported and objective cognitive impairment [9, 10], but both are useful measures.

Research on cognitive impairment in cancer survivors who have completed adjuvant chemotherapy suggests that it can be caused by the cancer itself and by its treatments such as chemotherapy [11, 12]. How cancer and chemotherapy induce cognitive impairment remains poorly understood, but it is likely multifactorial. One study suggested that the stress

caused by the cancer itself may contribute to cognitive impairment [13]. Proposed biological mechanisms for how chemotherapy induces cognitive impairment include damage to DNA, neurons, or nerve cells; induced hormonal changes; oxidative stress; and the immune system inflammatory response [14-16].

To obtain insight into the causes of cognitive impairment in cancer survivors who have completed adjuvant chemotherapy and who have subsequently self-reported cognitive problems, we used both self-report and objective cognitive impairment measures to identify: (1) the relative importance of demographics, cancer and its treatments, and psychological characteristics in associations with cognitive impairment; and, (2) specific variables associated with cognitive impairment.

Methods

Participants

Participants were 242 Australian adult (18 years old) early-stage cancer survivors (excluding central nervous system tumors) with no evidence of a cancer recurrence, whose treatment for a solid primary tumor included at least three cycles of adjuvant chemotherapy completed in the past 0.5–5 years. Primary tumor types included breast, colorectal, gynecologic, lymphoma, lung, upper gastrointestinal, and head and neck. To be eligible, participants had to report that their cognitive impairment was "quite a bit" or more in one or both of the domains of concentration and memory on the European Organization for Research and Treatment of Cancer QLQ-C30 Cognitive Functioning scale [17]. Patients were ineligible if they had a current major cognitive disorder or an unstable psychiatric condition. All participants volunteered for and took part in a randomized controlled trial (RCT) with the purpose of evaluating the web-based Insight cognitive training program for cancer survivors with cognitive problems [18]. Patients entered the 15-week study between November 2009 and March 2014. All assessments (and the intervention) were performed independently at home. We performed unplanned cross-sectional analyses of the baseline (pre-randomization to intervention) characteristics of these patients.

Measures

Primary outcome—Patient responses to items on the Functional Assessment of Cancer Therapy Cognitive Function version 3 (FACT-COG) 37-item questionnaire were used to determine self-reported cognitive impairment. The primary outcome was the score patients received on the Perceived Cognitive Impairments (PCI) 20-item subscale of FACT-COG (range: 0–80); higher scores indicate greater cognitive impairment [19, 20]. This questionnaire and all others used in this analysis have been validated in cancer patients [21-24].

Secondary outcome—Patient responses to questions on the Cogstate computerized test battery were used to determine objectively measured cognitive impairment. The exam evaluated the following domains of cognition: visual memory, problem solving, visual learning, working memory, processing speed, and attention; participants completed it in about 18 minutes on a home computer [18, 25, 26]. The Cogstate test has been validated

against paper and pencil neuropsychological tests [27]. Additionally, a preliminary study suggested the Cogstate battery of tests may be valid in cancer patients, although this study had a small sample size [28]. The secondary outcome was an aggregate score from the Cogstate exam. To calculate this score, we first normalized the results of all assessed tasks (continuous paired associate learning task, Groton maze learning task, one card learning, one back task, two back task, detection task, and identification task) across the studied individuals, so that the normalized results for each task had mean 0 and standard deviation 1. The aggregate score for each individual patient was then the mean of their normalized results across the tasks. Higher aggregate scores indicate more impairment.

Potential correlates of self-reported cognitive impairment (PCI)—We investigated the association between PCI and pertinent demographic, medical, and psychological variables, chosen a priori and based on literature [26, 29, 30]. In particular, the following demographic variables were investigated: age (years), married/de facto relationship, education (years), smoking history (never, previous, and current), previous neurological problems (serious academic problems, severe head injury, seizures, and other problems defined in detail in Table 1 footnote), and if the patient had ever used antidepressants.

Additionally, the following medical variables related to cancer and its treatments were investigated: tumor stage (I–II, III, unknown), hormone therapy (none, Tamoxifen or Letrozole or Anastrozole, other), number of chemotherapy cycles, and time since completion of chemotherapy (months). Tumor stage was categorized with stages I and II together to avoid too few observations in a category. Hormone therapy was coded with Tamoxifen or Letrozole or Anastrozole all as one level, as all act on estrogen; however, Tamoxifen is often given to pre-menopausal women, whereas Letrozole and Anastrozole are usually only given to post-menopausal women [31]. Note that tumor type was not used as a covariate, because most (89%) were breast cancer.

The psychological variables were determined from answers to questionnaires. Specifically, fatigue was measured by the Functional Assessment of Cancer Therapy-Fatigue (FACT-F) 13-item fatigue subscale (range: 0–52); higher scores indicate less fatigue [32]. The anxiety and depression variable was assessed by the 12-item General Health Questionnaire (GHQ; range: 12–48); higher scores indicate more anxiety and depression. Stress was determined from responses to the 14-item Perceived Stress Scale (PSS; range: 14–60); higher scores indicate a higher perception of stress [23].

Potential correlates of objective cognitive impairment (Cogstate)—We investigated the association between Cogstate results and the same demographic, medical, and psychological variables discussed above for PCI. We also investigated additional psychological variables from the FACT-COG subscales. The perceived cognitive abilities variable was determined from responses to the 9-item FACT-COG PCA subscale (range: 0–36); higher scores indicate greater cognitive abilities. The variable of comments from others was calculated from the 4-item FACT-COG comments subscale (range: 0–16); higher scores indicate others have noticed greater cognitive problems in the patient. Cognitive quality of life was measured by the 4-item FACT-COG QOL subscale (range: 0–16); higher scores indicate greater impact of cognitive problems on quality of life.

Statistical Methods

All statistical analyses were performed in SAS (SAS Institute, Cary, NC).

Primary statistical analysis—For the primary analysis, we performed hierarchical multiple linear regression to assess the proportion of variance in self-reported cognitive impairment (PCI) explained by demographic, medical, and psychological characteristics. We used the following three nested models to predict PCI: Model 1 (demographics only), Model 2 (demographics + medical), and Model 3 (demographics + medical + psychological). We computed R^2 for each model, to assess the proportion of variation in PCI determined by the model; then we compared it to the R^2 of the previous model, to assess the proportion of variation in PCI due to the added characteristics. Additionally, we used likelihood ratio tests (LRTs) to determine if the new set of variables added in each model improved model fit compared to the previous model. Finally, we determined regression coefficients and p-values for variables in each model, to determine individual variables that were correlated with PCI at the $\alpha = 0.05$ level of significance.

For each model, we checked the usual multiple linear regression model assumptions of linearity of continuous predictors with outcome, normality of residuals, and homoscedasticity. Additionally, we checked tolerance to assess multicollinearity; tolerances above the cutoff of 0.2 were deemed acceptable.

Secondary statistical analysis—We performed hierarchical multiple linear regression to assess the proportion of variance in objective cognitive impairment (as measured by the Cogstate results) explained by demographic, medical, and psychological characteristics. We used the same three models used for the primary analysis, with the addition of the following variables to psychological characteristics: FACT-COG PCA, FACT-COG Comments, and FACT-COG QOL. We calculated model statistics and regression coefficients as well as checked model assumptions, in the same way as for the primary analysis.

Sensitivity analyses—We performed two sensitivity analyses. (1) As a more automated approach to variable selection, we performed adaptive least absolute values shrinkage and selection operator (LASSO)-penalized variable selection multiple linear regression [33] to simultaneously select variables associated with self-reported cognitive impairment (PCI) and estimate their parameters. (2) Because being married can reduce cancer patients' distress, unmet needs, and other problems [34], the 7% of data missing for the married/de facto relationship variable could affect our results. Thus, we performed multiple imputation to see if missing data significantly changed our findings. See Online Resource 1 for details.

Results

Table 1 presents characteristics of the 242 cancer patients. Most patients were female (95%) breast cancer survivors (89%) aged in their 40s and 50s (71%) who were married or in a de facto relationship (79%). They had undergone a mean of 6.5 chemotherapy cycles (SD: 3.2) and completed chemotherapy a median of 24.2 months before the study (IQR: 14.3–38.8 months). Most common chemotherapy regimens were combination anthracycline and taxane (n =143), followed by anthracycline regimens (n=54). Radiotherapy was received by 164

participants and was predominantly to the breast. Complete case analysis (which ignored missing data) resulted in data from 212 patients being used in the primary analysis and data from 206 patients in the secondary analysis.

For both the primary and secondary analyses, model assumptions were satisfied. Specifically, continuous predictors were linear with outcome, residuals were normally distributed, and variances were constant. Additionally, tolerances were all above the accepted cutoff of 0.2, indicating that multicollinearity was not a problem.

Primary analysis

Table 2 presents the results of hierarchical regression for self-reported cognitive impairment (PCI). The results from Model 1 show that demographics accounted for 5% of the variation in PCI. The only significant individual correlate of PCI in this model was having ever used antidepressants, which was positively associated with PCI; however, antidepressant use did not remain significant when psychological characteristics were added in the final model. Model 2 shows that medical characteristics related to cancer and its treatments accounted for an additional 3% of variation in PCI; however, adding medical characteristics did not significantly improve model fit (p=0.27), and none of the individual medical characteristics were significant correlates of PCI. Model 3 shows that psychological characteristics accounted for an additional 25% of the variation in PCI; adding psychological characteristics significantly improved model fit (p<0.0001). Significant individual correlates of PCI in this model were fatigue (FACT-F) and stress (PSS); more fatigue and stress were associated with greater cognitive impairment. The negative sign for the fatigue coefficient results from higher FACT-F scores indicating less fatigue, whereas the positive sign for the stress coefficient results from higher PSS scores indicating more stress. Table A1 in Online Resource 1 presents similar primary analysis results for the 89% of our sample that is breast cancer survivors.

Secondary analysis

Table 3 presents the results of hierarchical regression for objective cognitive impairment (Cogstate results). The results from Model 1 show that demographics accounted for 10% of the variation in Cogstate results. The only significant individual correlate of Cogstate results in this model was age, which was positively associated with Cogstate results (meaning older patients had more impairment); age remained significant when medical and psychological characteristics were added in later models. Model 2 shows that medical characteristics related to cancer and its treatments accounted for an additional 5% of the variation in Cogstate results; however, adding medical characteristics did not significantly improve model fit (p-value=0.07). The additional significant individual correlates of Cogstate results in this model were smoking history (patients who were previous smokers had less impairment compared to those who had never smoked) and number of chemotherapy cycles (patients with more cycles had more impairment). Both smoking history and number of chemotherapy cycles remained significant when psychological characteristics were added in the final model. Model 3 shows that psychological characteristics accounted for an additional 4% of the variation in Cogstate results; adding psychological characteristics

did not significantly improve model fit (p-value=0.08), and no individual psychological characteristics were significantly correlated with Cogstate results.

Sensitivity analyses

Overall, the sensitivity analyses agreed with the primary results. For adaptive LASSO, fatigue and stress were the major predictors of PCI, as determined by the absolute value of their standardized coefficients (Online Resource 1 Table A2). For multiple imputation, the only notable difference was that in the final model, in addition to fatigue and stress being significant predictors of PCI, anxiety and depression (GHQ) was also a significant predictor (p-value=0.02) of PCI, which is a change from a nearly significant p-value of 0.09 in the primary analysis. See Online Resource 1 Table A3.

Discussion

Cognitive impairment negatively affects the lives of some cancer survivors who have undergone chemotherapy; however, it remains poorly understood. This study analyzed data from adult cancer survivors who completed chemotherapy and self-reported cognitive impairment to ascertain the relative importance of demographics, cancer and its treatments, and psychological characteristics in associations with both self-reported and objective cognitive impairment. We found that psychological characteristics accounted for most of the observed variation in self-reported cognitive impairment. In contrast, demographics and cancer and its treatments accounted for most of the observed variation in objectively measured cognitive impairment.

For self-reported cognitive impairment, significant individual correlates in the final hierarchical model were the psychological characteristics of fatigue and stress. These two variables were also the most important predictors of self-reported cognitive impairment in our sensitivity analysis using adaptive LASSO. As expected, more fatigue and stress were related to more self-reported cognitive impairment; this relationship is commonly seen in the literature [35].

For objective cognitive impairment, significant individual correlates in the final hierarchical model were the demographics of age and smoking history and the cancer treatment of number of chemotherapy cycles. Older age was related to more objective cognitive impairment. This agrees with prior research on normal aging [36] and in cancer patients [37, 38] that finds that older age is associated with more cognitive impairment. Previous smokers had less cognitive impairment than those who had never smoked. The cause of this relationship is unclear, because previous research suggests that smoking can temporarily increase cognitive function, but long-term smoking leads to cognitive impairment [39, 40]; it seems unlikely that quitting smoking would increase cognitive abilities above the levels of those who had never smoked. One possible explanation is that these previous smokers made a conscious decision to lead a healthier lifestyle and adopted other healthy living factors that positively affected their cognitive abilities. Alternatively, one study reported a smoking history may be protective in breast cancer survivors with the apolipoprotein E (APOE) 4 allele [41], which has been associated with greater cognitive impairment after chemotherapy in some breast cancer studies [42], but not in a larger colorectal cancer study [12]. The

proposed mechanism for a link between smoking and cognitive impairment is that smoking may provide protection by stimulating nicotinic receptors [43]. Or, perhaps this is a spurious result, because we ran multiple statistical tests, which increased our type I error to greater than 0.05. Finally, patients who underwent more chemotherapy cycles had more objective cognitive impairment, in agreement with the literature [37, 44].

Strengths

A strength of this study is that it had both self-reported and objectively measured cognitive impairment data for over 200 cancer patients. Additionally, this study included data on many potential correlates of cognitive impairment. The hierarchical regression design allowed us to determine both categories of variables and individual variables significantly associated with cognitive impairment.

Limitations

The large proportion of patients who were middle-aged female breast cancer survivors limits the generalizability of our findings to other tumor types. Restricting analyses to breast cancer patients only (Table A1) did not change our conclusions; estimates and statistical significance were similar. In addition, many patients were around the age of menopause transition and received treatments that likely accelerated their transition into menopause, which can affect cognitive impairment [45]. However, because demographic and medical variables do not contribute much to the final model for self-reported cognitive impairment, the association between self-reported cognitive impairment and the other psychological variables of fatigue and stress may hold for a broader range of cancer survivors than those with our particular characteristics.

Additionally, our study did not include a control group who did not receive chemotherapy, which hinders our ability to determine the effect of chemotherapy on cognitive impairment. For example, we found that the number of chemotherapy cycles had a small but significant effect on objective cognitive impairment. However, we could not determine the overall impact of chemotherapy without such a control group.

Another limitation is that the patients in our study had to have self-reported cognitive impairment that was "quite a bit" or more and to have volunteered for an intervention trial designed to improve cognition. The results may not generalize to cancer patients who self-report milder symptoms of cognitive impairment and those who have objective cognitive impairment without reporting symptoms. Additionally, the multiple statistical tests we ran have increased our type I error to greater than 0.05; thus, our results should be interpreted cautiously. Also, our study used a relatively brief computerized neuropsychological test battery to assess objective cognitive function.

Modifications in chemotherapy regimens in recent years have seen an increase in the use of neoadjuvant chemotherapy and dose-dense regimens for early-stage breast cancer [46]. It is unknown if these changes would affect our results. There is not clear evidence regarding which chemotherapy regimens are more likely to cause impairment; however, one study found anthracyclines, which have remained a mainstay of treatment, were more likely to cause cognitive impairment than non-anthracycline regimens in breast cancer survivors [47].

Other limitations are that we could not account for all factors that might be correlated with cognitive impairment (such as pro-inflammatory cytokines, comorbidities, and sleep disturbance), and we could not infer causality from our cross-sectional study. Our study used baseline data from a longitudinal randomized controlled trial that found that participating in a cognitive training program reduced self-reported cognitive impairment and also reduced stress, and this was sustained at six month follow up [18]. Future studies could examine if interventions that reduced fatigue or stress also reduced self-reported cognitive impairment. Another direction for future studies would be to examine an intervention (like exercise) that could act on something common to all of these problems (e.g. pro-inflammatory cytokines) [48].

Conclusion

For cancer survivors who have undergone chemotherapy and self-reported high cognitive impairment, psychological characteristics (in particular, fatigue and stress) appear to play a more important role in self-reported cognitive impairment than demographic and medical characteristics do. This highlights the importance of looking for, and if appropriate treating, psychological issues in cancer survivors self-reporting cognitive impairment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding

Abbreviations

APOE	Apolipoprotein E
AJCC	American Joint Committee on Cancer
BIC	Bayesian information criterion
CI	Confidence interval
Coeff	Regression coefficient
FACT-COG	Functional Assessment of Cancer Therapy Cognitive Function questionnaire
FACT-F	Functional Assessment of Cancer Therapy – Fatigue
GHQ	General Health Questionnaire – measures anxiety and depression

IQR	Interquartile range
LASSO	Least absolute values shrinkage and selection operator
LRT	Likelihood ratio test
MI	Multiple imputation
PCA	Perceived Cognitive Abilities subscale of FACT-COG
PCI	Perceived Cognitive Impairments subscale of FACT-COG
PSS	Perceived Stress Scale
QOL	Cognitive Quality of Life subscale of FACT-COG
RCT	Randomized controlled trial
SD	Standard deviation

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Table 1.

Demographic, medical, and psychological characteristics of the 242 adult cancer survivors, all of whom self-reported cognitive problems after completing chemotherapy.

Characteristic	Number out of N = 242 (%)
Demographics	
Sex (Female)	230 (95.0)
Age (years), mean ± SD	53.2 ± 9.0
20–29	1 (0.4)
30–39	17 (7.0)
40–49	70 (28.9)
50–59	101 (41.7)
60–69	46 (19.0)
70–79	7 (2.9)
Married/de facto relationship	192 (79.3)
Education (years), mean ± SD	13.5 ± 2.6
Smoking history	
Never	135 (55.8)
Previous	98 (40.5)
Current	8 (3.3)
Previous neurological problems [*]	50 (20.7)
Ever used antidepressants	108 (44.6)
Medical characteristics	
Primary tumor location	
Breast	216 (89.3)
Colorectal	13 (5.4)
Gynecologic	5 (2.1)
Lymphoma	3 (1.2)
Lung	3 (1.2)
Upper gastrointestinal	1 (0.4)
Head and neck	1 (0.4)
Tumor stage [**]	
I or II	64 (26.5)
III	51 (21.1)
Unknown	127 (52.5)
Hormone therapy	
None	73 (30.2)
Tamoxifen, Letrozole, or Anastrozole	157 (64.9)
Other	12 (5.0)
Number of chemotherapy cycles, mean ± SD	6.5 ± 3.2
Time since completion of chemotherapy (months), median (IQR)	24.2 (14.3–38.8)
Psychological characteristics [***], mean ± SD	
Perceived cognitive impairments (FACT-COG PCI)	40.2 ± 14.8

Characteristic	Number out of N = 242 (%)
Perceived cognitive abilities (FACT-COG PCA)	11.9 ± 4.7
Comments from others (FACT-COG comments)	2.9 ± 3.2
Cognitive quality of life (FACT-COG QOL)	7.4 ± 4.1
Fatigue (FACT-F)	32.4 ± 10.8
Anxiety and depression (GHQ)	26.9 ± 5.9
Stress (PSS)	32.4 ± 3.9

SD: standard deviation; IQR: interquartile range.

The following variables had missing data: married/de facto relationship (17/242=7.0% missing), smoking history (1/242=0.4%), number of chemotherapy cycles (6/242=2.5% missing), FACT-COG PCA (3/242=1.2% missing), FACT-COG comments (3/242=1.2% missing), FACT-COG QOL (3/242=1.2% missing), FACT-F (2/242=0.8% missing), GHQ (1/242=0.4% missing), and PSS (4/242=1.7% missing). Tumor stage had 127/242=52.5% coded as a level "unknown" instead of missing in analysis, because these patients did not know their tumor stage; it was assumed randomly unknown stages I–III.

*
 Previous neurological problems were characterized as serious academic problems (required remedial help at school, held back a grade, or diagnosed with a learning disability), severe head injury (loss of consciousness with residual sequelae), cardiac arrest that required cardiopulmonary resuscitation, seizures, epilepsy, coma, dementia, stroke, other neurologic risk, significant alcohol abuse.

**
 Using the American Joint Committee on Cancer (AJCC) staging.

***
 Psychological characteristics were determined using the Functional Assessment of Cancer Therapy Cognitive Function (FACT-COG) questionnaire with subscales as listed above, the Functional Assessment of Cancer Therapy – Fatigue subscale (FACT-F), the General Health Questionnaire (GHQ), and the Perceived Stress Scale (PSS).

Table 2.

Results of *primary analysis* that used hierarchical multiple linear regression to assess the proportion of variance in self-reported cognitive impairment (PCI) explained by demographic, medical, and psychological characteristics; appropriate statistics are given for each model. Additionally, non-standardized regression coefficients and *p*-values are given for each variable (coefficients of variables with *p*-values < 0.05 are in bold).

Model statistics	Model 1[a]		Model 2[b]		Model 3[c]	
R^2	0.05		0.08		0.33	
R^2 change from previous model	-		0.03		0.25	
p-value of LRT compared to previous model	-		0.27		<0.0001	
Model variables	**Coeff. (95% CI)**	***p*-value**	**Coeff. (95% CI)**	***p*-value**	**Coeff. (95% CI)**	***p*-value**
Intercept	38.19 (19.27, 57.10)	<0.0001	41.03 (20.66, 61.41)	0.0001	9.72 (−15.64, 35.09)	0.45
Demographics						
Age (years)	−0.11 (−0.33, 0.12)	0.34	−0.10 (−0.33, 0.13)	0.40	−0.07 (−0.27, 0.13)	0.47
Married/de facto relationship	−0.08 (−6.02, 5.86)	0.98	1.18 (−4.91, 7.26)	0.70	4.43 (−0.91, 9.77)	0.10
Education (years)	0.32 (−0.48, 1.12)	0.43	0.29 (−0.51, 1.10)	0.47	0.26 (−0.44, 0.96)	0.46
Smoking history						
Never (reference)	-	-	-	-	-	-
Previous	1.55 (−2.55, 5.65)	0.46	1.65 (−2.49, 5.78)	0.43	0.84 (−2.78, 4.46)	0.65
Current	5.58 (−4.96, 16.12)	0.30	5.49 (−5.05, 16.03)	0.31	1.71 (−7.47, 10.89)	0.71
Previous neurological problems	3.80 (−1.19, 8.80)	0.13	4.13 (−0.92, 9.18)	0.11	0.80 (−3.62, 5.22)	0.72
Ever used antidepressants	**4.39 (0.39, 8.40)**	**0.03**	**4.45 (0.42, 8.49)**	**0.03**	0.52 (−3.08, 4.11)	0.78
Medical characteristics						
Tumor stage						
I or II (reference)			-	-	-	-
III			5.03 (−0.89, 10.95)	0.10	3.96 (−1.15, 9.07)	0.13
Unknown			1.45 (−3.21, 6.12)	0.54	−1.14 (−5.20, 2.92)	0.58
Hormone therapy						
None (reference)			-	-	-	-
Tamoxifen, Letrozole, or Anastrozole			−1.48 (−5.92, 2.95)	0.51	−2.09 (−5.94, 1.76)	0.29
Other			1.98 (−7.94, 11.90)	0.69	4.43 (−4.18, 13.04)	0.31
# of chemotherapy cycles			−0.27 (−0.93, 0.40)	0.43	−0.01 (−0.58, 0.57)	0.98
Time since completion of chemotherapy (months)			−0.14 (−0.28, 0.00)	0.05	−0.11 (−0.23, 0.01)	0.07
Psychological characteristics						

Fatigue (FACT-F)			**−0.38 (−0.57, −0.19)**	**<0.0001**
Anxiety and depression (GHQ)			0.34 (−0.05, 0.74)	0.09
Stress (PSS)			**1.02 (0.51, 1.53)**	**0.0001**

[a]Model 1: demographics only

[b]Model 2: demographics + medical

[c]Model 3: demographics + medical + psychological

Coeff.: regression coefficient; CI: confidence interval; LRT: likelihood ratio test; FACT-F: Functional Assessment of Cancer Therapy – Fatigue; GHQ: General Health Questionnaire; PSS: Perceived Stress Scale.

Note: all three models were run on the same 212 observations, where PCI and all covariates for the fullest model (Model 3) were not missing.

Table 3.

Results of *secondary analysis* that used hierarchical multiple linear regression to assess the proportion of variance in objective cognitive impairment (Cogstate results) explained by demographic, medical, and psychological characteristics; appropriate statistics are given for each model. Additionally, non-standardized regression coefficients and *p*-values are given for each variable (coefficients of variables with *p*-values < 0.05 are in bold).

Model statistics	Model 1[a]		Model 2[b]		Model 3[c]	
R^2	0.10		0.15		0.19	
R^2 change from previous model	-		0.05		0.04	
p-value of LRT compared to previous model	-		0.07		0.08	
Model variables	**Coeff. (95% CI)**	***p*-value**	**Coeff. (95% CI)**	***p*-value**	**Coeff. (95% CI)**	***p*-value**
Intercept	−0.63 (−1.30, 0.05)	0.07	−0.78 (−1.50, −0.06)	0.03	−0.76 (−1.87, 0.35)	0.18
Demographics						
Age (years)	**0.02 (0.01, 0.02)**	**0.0001**	**0.02 (0.01, 0.02)**	**<0.0001**	**0.02 (0.01, 0.03)**	**<0.0001**
Married/de facto relationship	−0.04 (−0.25, 0.17)	0.71	−0.05 (−0.26, 0.17)	0.65	0.04 (−0.27, 0.18)	0.70
Education (years)	−0.01 (−0.04, 0.02)	0.41	−0.01 (−0.04, 0.02)	0.36	−0.01 (−0.04, 0.01)	0.34
Smoking history						
Never (reference)	-	-	-	-		
Previous	−0.13 (−0.28, 0.02)	0.09	**−0.15 (−0.30, −0.01)**	**0.04**	**−0.20 (−0.35, −0.05)**	**0.01**
Current	−0.03 (−0.43, 0.37)	0.89	−0.01 (−0.41, 0.38)	0.95	−0.07 (−0.47, 0.33)	0.73
Previous neurological problems	−0.02 (−0.20, 0.16)	0.83	−0.02 (−0.20, 0.15)	0.79	−0.05 (−0.23, 0.13)	0.59
Ever used antidepressants	0.09 (−0.05, 0.24)	0.20	0.11 (−0.03, 0.25)	0.12	0.08 (−0.08, 0.22)	0.31
Medical characteristics						
Tumor stage						
I or II (reference)			-	-	-	-
III			−0.08 (−0.29, 0.13)	0.45	−0.09 (−0.30, 0.12)	0.42
Unknown			−0.08 (−0.25, 0.08)	0.32	−0.08 (−0.24, 0.09)	0.36
Hormone therapy						
None (reference)			-	-	-	-
Tamoxifen, Letrozole, or Anastrozole			0.12 (−0.04, 0.28)	0.13	0.15 (−0.01, 0.31)	0.07
Other			−0.11 (−0.46, 0.24)	0.54	−0.05 (−0.39, 0.30)	0.80
# of chemotherapy cycles			**0.03 (0.00, 0.05)**	**0.02**	**0.03 (0.005, 0.052)**	**0.02**
Time since completion of chemotherapy (months)			−0.002 (−0.007, 0.003)	0.40	−0.001 (−0.006, 0.004)	0.80
Psychological characteristics						

Fatigue (FACT-F)			0.003 (−0.005, 0.012)	0.44
Anxiety and depression (GHQ)			0.01 (−0.003, 0.031)	0.10
Stress (PSS)			−0.02 (−0.04, 0.005)	0.12
Perceived cognitive abilities (FACT-COG PCA)			−0.01 (−0.03, 0.01)	0.17
Comments from others (FACT-COG comments)			0.01 (−0.02, 0.03)	0.53
Cognitive quality of life (FACT-COG QOL)			0.01 (−0.02, 0.04)	0.48

[a] Model 1: demographics only

[b] Model 2: demographics + medical

[c] Model 3: demographics + medical + psychological

Coeff.: regression coefficient; CI: confidence interval; LRT: likelihood ratio test; FACT-F: Functional Assessment of Cancer Therapy – Fatigue; GHQ: General Health Questionnaire; PSS: Perceived Stress Scale; FACT-COG: Functional Assessment of Cancer Therapy Cognitive Function questionnaire.

Note: all three models were run on the same 206 observations, where Cogstate results and all covariates for the fullest model (Model 3) were not missing.