

# Online Resource 1: Primary analysis results only including the breast cancer survivors and sensitivity analyses for “Correlates of cognitive impairment in adult cancer survivors who have received chemotherapy and report cognitive problems”

## Supportive Care in Cancer

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### Primary analysis results only including the breast cancer survivors

**Table A1.** Including only breast cancer survivors ( $n=216$ , 89% of original sample), 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 <sup>a</sup>		Model 2 <sup>b</sup>		Model 3 <sup>c</sup>	
R <sup>2</sup>	0.05		0.09		0.34	
R <sup>2</sup> change from previous model	-		0.04		0.25	
$p$ -value of LRT compared to previous model	-		0.26		<0.0001	
Model variables	Coeff. (95% CI)	$p$ -value	Coeff. (95% CI)	$p$ -value	Coeff. (95% CI)	$p$ -value
Intercept	38.62 (18.14, 59.11)	0.0003	43.24 (21.05, 65.43)	0.0002	9.91 (-16.88, 36.70)	0.47
<b>Demographics</b>						
Age (years)	-0.16 (-0.41, 0.09)	0.22	-0.12 (-0.37, 0.14)	0.36	-0.11 (-0.33, 0.11)	0.32
Married/de facto relationship	1.30 (-5.17, 7.77)	0.69	1.99 (-4.60, 8.59)	0.55	5.04 (-0.74, 10.81)	0.09
Education (years)	0.37 (-0.48, 1.21)	0.39	0.26 (-0.60, 1.11)	0.56	0.21 (-0.53, 0.95)	0.57
Smoking history						
Never (reference)	-	-	-	-	-	-
Previous	2.31 (-2.05, 6.67)	0.30	2.36 (-2.05, 6.77)	0.29	1.26 (-2.60, 5.11)	0.52
Current	6.43 (-4.24, 17.11)	0.24	5.83 (-4.86, 16.53)	0.28	1.72 (-7.61, 11.05)	0.72
Previous neurological problems	2.91 (-2.65, 8.47)	0.30	3.66 (-1.92, 9.25)	0.20	-0.01 (-4.90, 4.89)	0.998
Ever used antidepressants	4.25 (0.01, 8.50)	0.05	4.13 (-0.13, 8.39)	0.06	0.25 (-3.54, 4.04)	0.90
<b>Medical characteristics</b>						
Tumor stage						
I or II (reference)			-	-	-	-
III			4.65 (-1.66, 10.96)	0.15	4.06 (-1.37, 9.49)	0.14
Unknown			1.80 (-3.08, 6.69)	0.47	-0.86 (-5.12, 3.40)	0.69
Hormone therapy						
None (reference)			-	-	-	-
Tamoxifen, Letrozole, or Anastrozole			-1.64 (-6.76, 3.48)	0.53	-2.79 (-7.23, 1.64)	0.22
Other			1.69 (-8.60, 11.98)	0.75	3.55 (-5.37, 12.46)	0.43
# of chemotherapy cycles			-0.35 (-1.07, 0.37)	0.34	-0.11 (-0.73, 0.51)	0.72
Time since completion of chemotherapy (months)			<b>-0.17 (-0.31, -0.02)</b>	<b>0.03</b>	<b>-0.15 (-0.27, -0.02)</b>	<b>0.03</b>
<b>Psychological characteristics</b>						
Fatigue (FACT-F)					<b>-0.35 (-0.55, -0.15)</b>	<b>0.0007</b>
Anxiety and depression (GHQ)					0.39 (-0.03, 0.82)	0.07
Stress (PSS)					<b>1.08 (0.53, 1.62)</b>	<b>0.0001</b>

<sup>a</sup>Model 1: demographics only

<sup>b</sup>Model 2: demographics + medical

<sup>c</sup>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 190 observations, where PCI and all covariates for the fullest model (Model 3) were not missing.

## Sensitivity analysis 1: adaptive LASSO

### Methods

We performed adaptive least absolute values shrinkage and selection operator (LASSO)-penalized variable selection multiple linear regression to simultaneously select variables associated with self-reported cognitive impairment (PCI) and estimate their parameters. Adaptive LASSO shrinks the coefficients for unimportant variables to zero (thus removing them from the model) by using individual weights for each variable. These weights were determined from the coefficients resulting from ordinary least squares regression. Adaptive LASSO adds or deletes a single variable with nonzero regression coefficient during each step, and the Schwarz Bayesian Information Criterion (BIC) was used to select the final model from the results of all of these steps. Adaptive LASSO multiple linear regression was implemented in SAS using the PROC GLMSELECT procedure with level of significance  $\alpha = 0.05$ .

### Results

Table A2 presents the results of adaptive LASSO for self-reported cognitive impairment (PCI). With only five variables with non-zero coefficients, this model accounted for 30% of the variation in PCI, close to the 33% of variation explained by the full hierarchical regression model. More fatigue, anxiety and depression, and stress were associated with greater cognitive impairment. A longer time since completion of chemotherapy was associated with less cognitive impairment. Having a stage III tumor (as compared to I–II or unknown I–III) was associated with more cognitive impairment. Note that patients with a stage III tumor tended to have undergone more chemotherapy cycles (mean=8 cycles) compared to those with a stage I or II tumor (mean=6 cycles), Kruskal-Wallis p-value=0.0001.

**Table A2.** Results of *sensitivity analysis 1* that used adaptive LASSO to determine important correlates of self-reported cognitive impairment (PCI).

Model statistics	Adaptive LASSO model	
R <sup>2</sup>	0.30	
Model variables	Coeff.	Standardized Coeff.
Intercept	18.42	0
<b>Demographics</b>		
<b>Medical characteristics</b>		
Tumor stage III	1.34	0.04
Time since completion of chemotherapy (months)	-0.06	-0.06
<b>Psychological characteristics</b>		
Fatigue (FACT-F)	-0.40	-0.30
Anxiety and depression (GHQ)	0.19	0.07
Stress (PSS)	0.96	0.26

Coeff.: regression coefficient; FACT-F: Functional Assessment of Cancer Therapy – Fatigue; GHQ: General Health Questionnaire; PSS: Perceived Stress Scale

## Sensitivity analysis 2: multiple imputation

### Methods

The 7% of data missing for the married/de facto relationship variable is a concern. Therefore, for the second sensitivity analysis, we determined if our primary analysis results changed when we used multiple imputation (MI) to impute missing values. We implemented multiple imputation in SAS using PROC MI with fully conditional specification (FCS), which performs multivariate imputation by chained equations. We used the following auxiliary variables when they were not already in the model, because they were correlated at 0.10 or higher with either or both of the marriage variable or its missingness: fatigue (FACT-F) and anxiety and depression (GHQ). We ran 20 imputations, based on the suggestion by Graham, Olchowski, & Gilreath (2007) to run 20 imputations for 10% missing data (Prev Sci 8:206–213. <https://doi.org/10.1007/s11121-007-0070-9>).

## Results

Overall, the MI results are consistent with the primary results (Table A3). The one notable difference is that in the final model using MI, in addition to fatigue and stress being significant predictors of PCI, anxiety and depression (GHQ) is also a significant predictor ( $p$ -value=0.02) of PCI.

**Table A3.** Results of *sensitivity analysis 2* that used multiple imputation to fill in missing values for the primary analysis with the outcome of self-reported cognitive impairment (PCI). Non-standardized regression coefficients and  $p$ -values are given for each variable (coefficients of variables with  $p$ -values < 0.05 are in bold).

Model variables	Model 1 <sup>a</sup>		Model 2 <sup>b</sup>		Model 3 <sup>c</sup>	
	Coeff. (95% CI)	$p$ -value	Coeff. (95% CI)	$p$ -value	Coeff. (95% CI)	$p$ -value
Intercept	42.35 (24.82, 59.87)	<0.0001	46.69 (27.65, 65.73)	<0.0001	7.22 (-17.35, 31.80)	0.56
<b>Demographics</b>						
Age (years)	-0.15 (-0.36, 0.05)	0.14	-0.16 (-0.37, 0.05)	0.15	-0.07 (-0.26, 0.11)	0.44
Married/de facto relationship	-1.61 (-7.19, 3.96)	0.57	-1.05 (-6.65, 4.55)	0.71	2.93 (-1.99, 7.85)	0.24
Education (years)	0.33 (-0.41, 1.07)	0.38	0.36 (-0.38, 1.11)	0.34	0.40 (-0.25, 1.04)	0.23
Smoking history						
Never (reference)	-	-	-	-	-	-
Previous	-0.00 (-3.84, 3.83)	0.998	0.21 (-3.69, 4.10)	0.92	-0.17 (-3.53, 3.20)	0.92
Current	5.24 (-5.22, 15.71)	0.33	4.85 (-5.60, 15.30)	0.36	0.97 (-8.08, 10.02)	0.83
Previous neurological problems	3.61 (-1.02, 8.25)	0.13	3.86 (-0.79, 8.51)	0.10	1.35 (-2.69, 5.38)	0.51
Ever used antidepressants	<b>4.20 (0.45, 7.95)</b>	<b>0.03</b>	<b>4.09 (0.33, 7.85)</b>	<b>0.03</b>	0.29 (-3.04, 3.62)	0.87
<b>Medical characteristics</b>						
Tumor stage						
I or II (reference)			-	-	-	-
III			5.38 (-0.21, 10.97)	0.06	3.66 (-1.17, 8.49)	0.14
Unknown			1.04 (-3.39, 5.48)	0.65	-1.06 (-4.89, 2.78)	0.59
Hormone therapy						
None (reference)			-	-	-	-
Tamoxifen, Letrozole, or Anastrozole			-2.01 (-6.19, 2.17)	0.35	-1.93 (-5.57, 1.69)	0.30
Other			1.81 (-7.33, 10.95)	0.70	4.27 (-3.65, 12.18)	0.29
# of chemotherapy cycles			-0.41 (-1.03, 0.21)	0.19	-0.11 (-0.64, 0.43)	0.70
Time since completion of Chemotherapy (months)			-0.11 (-0.24, 0.02)	0.09	-0.10 (-0.21, 0.01)	0.07
<b>Psychological characteristics</b>						
Fatigue (FACT-F)					<b>-0.34 (-0.52, -0.16)</b>	<b>0.0002</b>
Anxiety and depression (GHQ)					<b>0.45 (0.07, 0.82)</b>	<b>0.02</b>
Stress (PSS)					<b>0.98 (0.49, 1.47)</b>	<b>&lt;0.0001</b>

<sup>a</sup>Model 1: demographics only

<sup>b</sup>Model 2: demographics + medical

<sup>c</sup>Model 3: demographics + medical + psychological

Coeff.: regression coefficient; CI: confidence interval; 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 242 observations after multiple imputation was used to fill in missing values.