

Low serum carotenoids are associated with inflammatory markers and subjective cognitive impairments in breast cancer survivors

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Abstract

Cancer related cognitive impairment (CRCI) can have significant and persistent impacts on quality of life in cancer survivors. Recent evidence has reported cognitive impairments are associated with inflammation due to cancer and its treatment. Modifiable factors, such as diet, may reduce the risk or severity of CRCI. Carotenoids, primarily found in fruits and vegetables (F&Vs), have shown promise in reducing the risk of age-related cognitive decline, potentially via anti-inflammatory activities. In this cross-sectional study, sixty-seven women (29 BCS; 38 controls) were recruited from the Central Texas area. BCS had to have been diagnosed with breast cancer and completed primary treatment (either chemotherapy, radiotherapy or both) within the past 5 years, and healthy controls must have had no previous cancer diagnosis. Dietary intake was assessed with a food frequency questionnaire. Cognitive function was assessed with the NIH Toolbox Cognition Battery. The Functional Assessment of Cancer Therapy-Cognitive Function Questionnaire assessed perceived cognitive impairment. Serum levels of carotenoids were measured by HPLC-PDA, and serum soluble TNF receptor type II (sTNF-RII), interleukin-6 (IL-6), and interleukin-1 receptor agonist (IL-1ra) were measured by immunoassay. BCS were split into two groups: (1) BCS with serum carotenoid levels lower than, and including, the median; and (2) BCS with serum carotenoid levels above the median. A median split analysis was also conducted for the non-cancer controls. Univariate ANCOVA, including age as a covariate, was conducted to compare cognitive function as a function of group. Serum carotenoids and F&V intake were not significantly different between BCS and controls. Reported F&V intake was positively correlated with serum carotenoid levels ($r = .407, p = 0.001$). BCS performed similarly to controls on objective cognitive measures. Both high and low carotenoid BCS had significantly more cognitive complaints than high and low carotenoid controls ($p < 0.05$); however, high carotenoid BCS had significantly fewer cognitive complaints than low carotenoid BCS ($p = 0.036$). Partial correlations, controlling for age and BMI, demonstrated that higher serum carotenoid levels were associated with lower sTNF-RII and IL-6 levels ($p = 0.002$), but not IL-1ra. Higher serum carotenoid levels may have cognitive and anti-inflammatory benefits in BCS. Future research should continue to identify dietary patterns that can reduce memory complaints and support cognitive health in cancer survivors.

Background

- Cancer related cognitive impairment (CRCI) can have significant and persistent impacts on quality of life in cancer survivors.
- Recent evidence has reported cognitive impairments are associated with inflammation due to cancer and its treatment.
- Modifiable factors, such as diet, may reduce the risk or severity of CRCI.
- Carotenoids, primarily found in fruits and vegetables, have shown promise in reducing the risk of age-related cognitive decline, potentially via anti-inflammatory activities.

Objective

- Determine if serum carotenoids, an objective marker of fruit and vegetable intakes, predict cognitive function in breast cancer survivors.
- Examine inflammation as a potential mechanism by which carotenoids modulate cognitive function.

Methods

Sample: Breast cancer survivors (n=29) within 5 years of being diagnosed and completing chemotherapy, radiotherapy or both, and age-matched healthy controls (n=38) with no previous cancer diagnosis were recruited from the Central Texas area.

Cognitive Domains and Specific Tests

WORKING MEMORY
Ability to temporarily store and manipulate information.

EPISODIC MEMORY
Ability to learn and retain new context-dependent information.

- List Sorting Test

- Picture Sequence Memory Test
- Memory Test

LANGUAGE

Ability to translate thought and experience into words to facilitate communication. Correlates with overall intellectual ability and work achievement.

- Picture Vocabulary Test
- Oral Reading Recognition Test

Objective Cognitive Function: National Institutes of Health Toolbox for the Assessment of Neurological and Behavioral Function Cognition Battery (NIH-TB). Fully-adjusted scores that compare the score of the participant to those in the NIH-TB nationally representative normative sample within the same age, gender, race, ethnicity, and education were used to interpret participant scores.

Subjective Cognitive Function: The Functional Assessment of Cancer Therapy Cognitive Scale (FACT-Cog) assessed perceived cognitive impairments experienced within the past week as well as the impact the perceived impairments have had on quality of life.

Statistical Analysis: Differences between BCS and controls were assessed using independent t-tests or univariate ANCOVAs. Partial correlations were conducted to assess the relationship between serum carotenoids and inflammatory markers. BCS were split into two groups: (1) BCS with serum carotenoid levels lower than, and including, the median; and (2) BCS with serum carotenoid levels above the median. A median split analysis was also conducted for the non-cancer controls. Univariate ANCOVA, including age as covariate, was conducted to compare cognitive function as a function of group.

Sample Characteristics

	Breast Cancer Survivors n = 29	Controls N = 38
Age (Mean, SD)	50.1 (10.1)	50.8 (10.0)
Income (n, %) ≥ \$60,000	16 (55.1)	29 (76.4)
Race n (%)		
White	20 (69.0)	33 (86.8)
Ethnicity n (%)		
Hispanic or Latino	6 (20.7)	9 (23.7)
Education n (%)		
≥ 4 year college degree	20 (69.0)	32 (84.1)
BMI kg/m ² (Mean, SD)	29.7 (6.3)	27.6 (7.6)
Stage at Diagnosis n (%)		
DCIS	3 (10.3)	-
Stage I	8 (27.6)	-
Stage II	11 (37.9)	-
Stage III	6 (20.7)	-
Unknown	1 (3.4)	-
Treatment n (%)		
Chemotherapy Only	10 (34.5)	-
Radiation Only	8 (27.6)	-
Chemotherapy + radiation	11 (37.9)	-
Hormone Therapy	19 (65.5)	-
Surgery	29 (100)	-
Time since treatment – months (Mean, SD)	18.6 (16.3)	-
Tumor Characteristics n (%)		
ER Positive	17 (58.6)	-
HER2 Positive	6 (20.7)	-

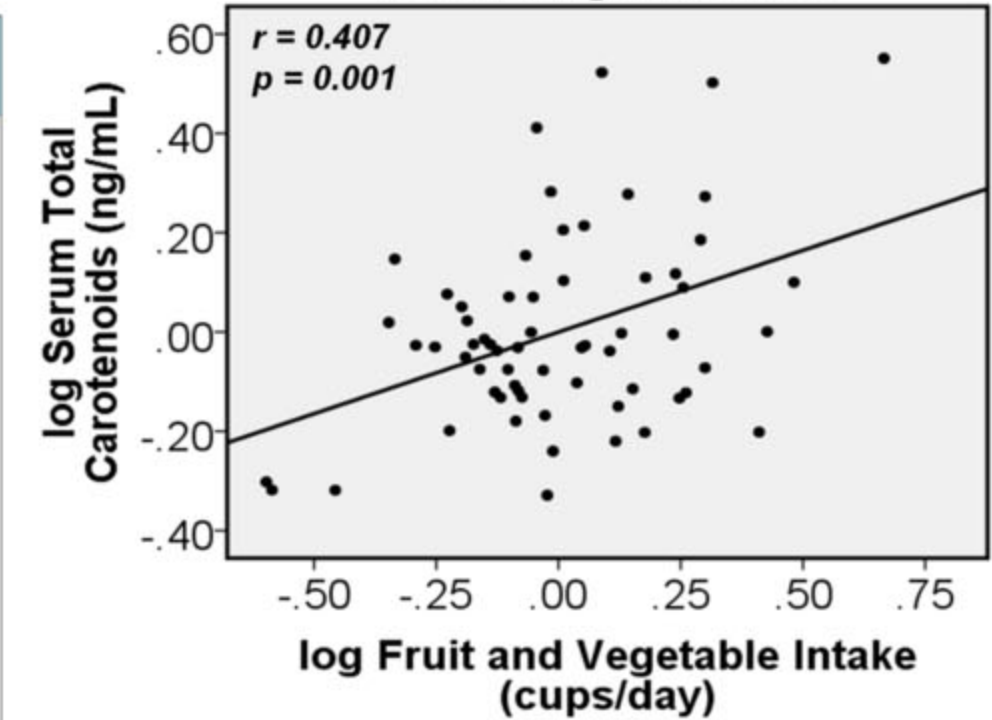
Results

Dietary Intake – Measured by Modified Block Food Frequency Questionnaire

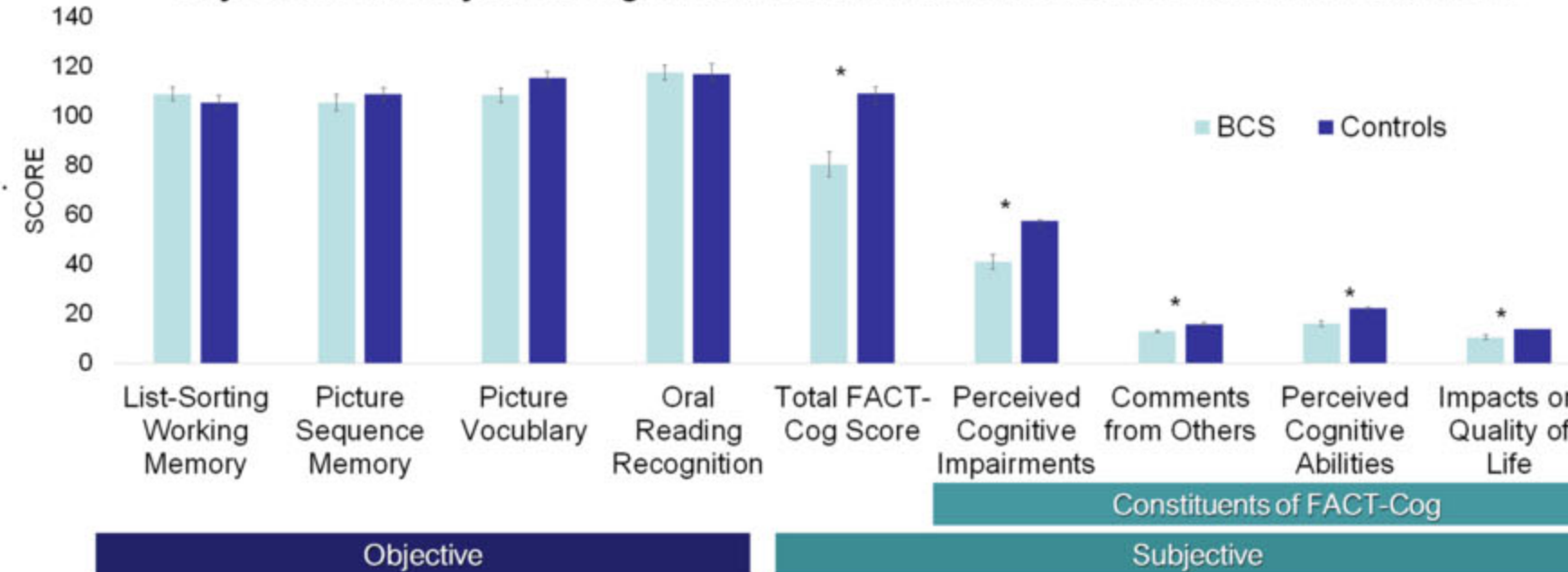
	Breast Cancer Survivors	Controls
Total Energy (kcal/day)	1745.4 (794.5)	1614.5 (587.7)
Carbohydrate (g/day)	192.0 (91.4)	179.2 (72.1)
Protein (g/day)	75.5 (34.8)	69.2 (24.7)
Fat (g/day)	76.2 (38.8)	69.8 (30.4)
Saturated Fat (g/day)	22.1 (11.2)	19.6 (10.5)
Monounsaturated Fat (g/day)	30.7 (15.6)	28.2 (11.4)
Polyunsaturated fat (g/day)	17.5 (9.0)	17.0 (7.3)
Total dietary fiber (g/day)	21.2 (11.5)	22.6 (10.8)
Fruit (cups/day)	1.0 (0.8)	1.1 (0.9)
Vegetables (cups/day)	2.9 (1.8)	2.6 (1.6)
Total Carotenoid Intake (mg/day)	20.8 (13.5)	18.7 (10.3)

Mean (SD)

Serum Total Carotenoids Associated With Fruit and Vegetable Intake

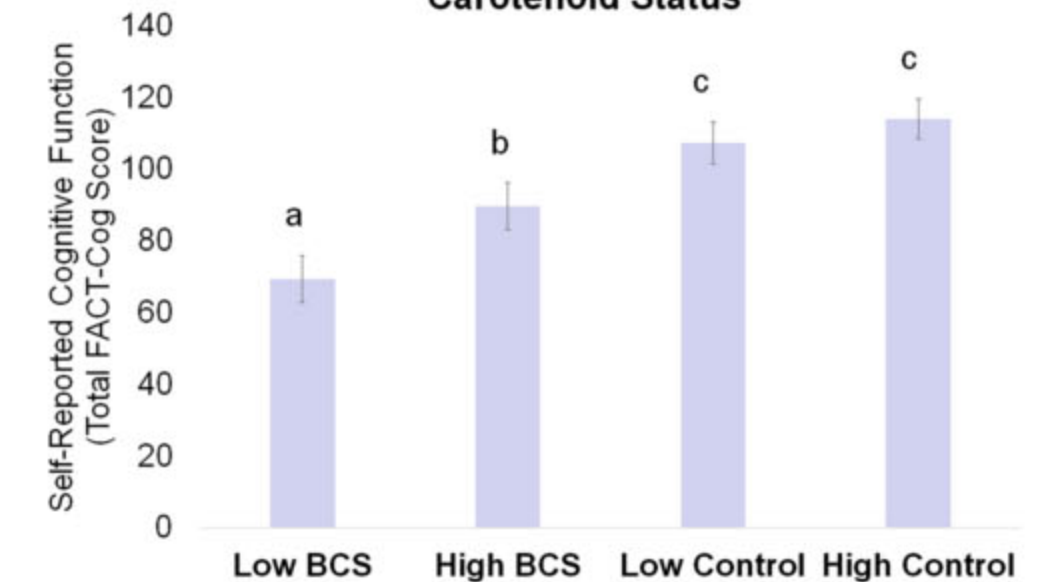


Objective and Subjective Cognitive Function in Controls and Breast Cancer Survivors



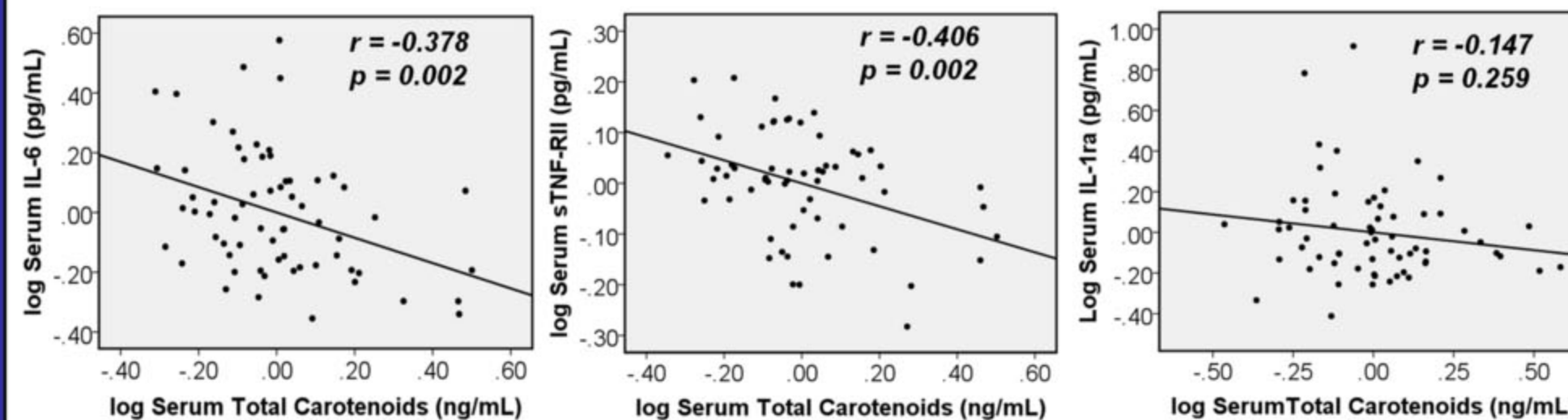
Estimated Marginal Means ± SE. Subjective function analyzed with Univariate ANCOVA, including age as covariate. Total FACT-Cog=0-132, *p<0.001

Perceived Cognitive Function by Total Serum Carotenoid Status



Estimated Marginal Means ± SE. BCS and healthy controls split into those with serum carotenoid levels ≤ median or >median. Univariate ANCOVA included age as covariate. Different letters indicate significant differences between groups as determined by post-hoc Fisher LSD (p<0.05). FACT-COG=0-132

Serum Total Carotenoids Correlated with Lower Levels of IL-6 and sTNFR-II



Partial correlations controlling for age, BMI, and moderate to vigorous physical activity.

Conclusions and Future Directions

- BCS have lower subjective cognitive function than healthy controls, which has been an early indicator of cognitive decline in other populations.
- Greater serum carotenoids in BCS were associated with greater subjective cognitive function in BCS, which may be clinically significant (minimal clinically important difference is Δ7-11 pts (Cheung, et al. J Clin Epi 2014)).
- Serum carotenoids were inversely associated with markers of inflammation.
- Future studies will test whether dietary carotenoids affect cognitive function in BCS via inflammation.
- Future research will explore how dietary patterns can reduce memory complaints and support cognitive health in BCS.

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