MEMORY PERFORMANCE OF BREAST CANCER SURVIVORS: ASSOCIATIONS WITH CAROTENOID INTAKE AND BRAIN-DERIVED NEUROTROPHIC FACTOR

by

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A thesis submitted to the Graduate Council of
Texas State University in partial fulfillment
of the requirements for the degree of
Master of Science
with a Major in Human Nutrition
August 2017

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ACKNOWLEDGEMENTS

To start, I would like to thank Dr. Krystle Zuniga for challenging me, acting as an excellent role model, and being a patient teacher throughout the research and writing process. Dr. Zuniga, your assistance in navigating this project was instrumental to me completing it, I am forever grateful for your mentorship this past year. To Dr. Michelle Lane and Dr. Ramona Salcedo-Price, thank you for your questions, insights pertaining to the study matter, and motivation to complete this project. My gratitude extends to all three members of my committee and the graduate professors at Texas State University who provided me with the skills and knowledge necessary to complete a project of this magnitude. To my graduate school friends, thank you for your encouragement and support throughout this entire process, I am fortunate to know each one of you. Lastly, I want to express my deepest gratitude to my parents: John, Jan, Paige, and Joe, my sisters: Megan and Kelsey and my partner Thomas for demonstrating an unwavering love and confidence in me and reminding me to remain grounded during this research project.

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I. INTRODUCTION

Prevalence and Impact of Cancer-related Cognitive Impairment on Cancer Survivors

Cancer survivors often experience physical and emotional side effects during cancer treatment and recovery, such as fatigue, sleep issues, anxiety, pain, anemia, nausea, and infections.[1,2] Frequently, cancer survivors report cognitive disturbances like impaired concentration, attention, and lapses in memory.[3–5] Cancer-related cognitive impairment (CRCI) is a term that describes the adverse cognitive side effects experienced by cancer patients and cancer survivors prior to, during, and after cancer treatment. Cognitive alterations vary based on the severity of impairment, pattern of onset, and domains of cognition affected. Evidence from longitudinal studies that utilized neuropsychological evaluations with baseline or pre-treatment assessments show that a portion of breast cancer patients demonstrate cognitive impairments prior to treatment.[6–8] Additional research in the breast cancer population shows that up to 75% of patients may be affected by declining cognitive function during cancer treatment and these declines can continue for months or years following treatment in a consistent minority (up to 35%) of cancer patients.[4] The adverse cognitive side effects can progress from the treatment period into recovery or may develop after the cancer treatments are completed.[9] In general, cancer patients face increased cognitive burdens at the onset of treatment and throughout active treatment periods.[10] Despite a majority of patients finding relief from CRCI shortly after treatment, post-treatment cognitive impairments may persist long after chemotherapy is completed.[11,12] These treatment-related cognitive sequelae can lead to negative changes in physical abilities, social activities, relationships, and may impact work achievements.[3,5,12,13] CRCI can negatively affect a cancer survivor's quality of life

and reduce their ability to focus, make decisions, formulate judgements, and solve problems.[3,10]

A majority of the research on CRCI has been conducted in the breast cancer population. Breast cancer is the most common cancer diagnosis among women in America.[14] The detection and treatment of breast cancer has become more effective, led to improved survival rates (89.7%, 5-year survival rate), and contributed to a growing number of survivors living after their cancer treatment has ended.[15] According to the American Cancer Society, there were approximately 3.5 million breast cancer survivors living in the United States at the beginning of 2016.[15] Long term cancer survivors are an important, and growing, segment of the population, of which a consistent minority is at risk for cognitive declines associated with cancer treatment. Therefore, it is important to examine which modifiable factors, such as nutrition, can reduce the comorbidities associated with cancer treatment.

II. LITERATURE REVIEW

Impact of Treatment Modality on CRCI

Additional factors impact the development of CRCI among cancer patients, including the treatment modality, as cognitive impairments are typically reported among patients treated with chemotherapy and radiation.[4] Still, self-reported difficulties in language and communication have been documented after hormonal therapy initiation in early stage breast cancer patients, suggesting that treatments besides chemotherapy can have negative effects.[16] A meta-analysis found poorer performance on assessments of executive function, motor function, and verbal memory among patients treated systemically compared with normative data or healthy controls.[17] A separate meta-analysis emphasized the impact of verbal and visuospatial declines among breast cancer patients compared with other domains that affect cancer survivors.[18] Among the systemic (chemotherapy, hormonal therapy, and/or targeted therapy) and local (surgery and/or radiation) treatment options for cancer, there is evidence to support additional negative cognitive impact from systemic treatments when compared with local therapies and/or healthy controls.[10,17,19,20] An early study by Ahles et al. (2002) found that breast and lymphoma cancer survivors who received systemic treatments had impaired neuropsychological performance on verbal memory tasks and psychomotor function compared with locally treated survivors at 5 years post treatment. Evidence reveals that systemic treatments for breast cancer can alter brain structure, which has been proposed to explain, in part, the cognitive alterations experienced by cancer survivors. Long term breast cancer survivors treated with the following adjuvant chemotherapy drugs; cyclophosphamide, methotrexate, and fluorouracil, with follow up on average 21.1 years

from diagnosis, presented with reduced tissue volumes for total brain and gray matter compared with age matched controls.[21] Additional support stems from studies that show reduced white matter and local gray matter volumes among patients evaluated shortly after chemotherapy treatment.[22,23] Although limited, insights from research studies using neuroimaging techniques suggest that structural changes that result from chemotherapy may account for some of the cognitive side effects experienced by patients and survivors.

It is evident that cognitive alterations are prevalent among cancer survivors (see review, Janelsins et al. 2011), and these symptoms are typically reported after chemotherapy treatment in the period soon after treatment has ended.[24] As of late, the prevalence of perceived cognitive dysfunction among cancer survivors, including breast cancer and several other types of cancer, is reported by nearly half of all cancer survivors per the LIVESTRONG survey. [25] Limited data has assessed the long-term cognitive burdens associated with a cancer diagnosis and concomitant treatments. However, several studies have found evidence of cognitive alterations present among cancer survivors at 10-20 years post cancer treatment. Yamada and colleagues (2010) evaluated the effects of chemotherapy on long term breast cancer survivors (>65 years old) compared with age, education, and IQ matched controls.[26] The evaluations took place at ten years post-chemotherapy and significant declines were documented in executive functioning, working memory, and divided attention.[26] A recent examination of the National Health and Nutrition Examination Survey (NHANES) data demonstrated that older cancer survivors (>60 years) performed worse on the Digit Symbol Substitution Test and had more subjective complaints pertained to memory function and concentration compared with individuals who had no history of cancer.[27] Heflin and colleagues evaluated the

long-term cognitive outcomes after being diagnosed with cancer among older cancer survivors compared with their disease-free twin. Cognitive deficits were more prevalent among cancer survivors, with documentation on average 14.06 years post diagnosis.[28] Lastly, breast cancer patients with exposure to adjuvant cyclophosphamide, methotrexate, and fluorouracil chemotherapy, 20 years prior to evaluations, performed worse on measures of processing and psychomotor speed, immediate and delayed verbal memory, and executive function than a healthy control group.[12] The relationship between cancer treatment and cognition, and the impact of additional moderating factors remains somewhat equivocal, warranting more research to improve cancer survivorship.

Additional Factors that Moderate the Effect of Cancer Treatment on Cognition

Demographic factors like race, ethnicity, menopausal status, diet, age, education, and IQ may impact how cancer and cancer treatment affects cognitive function.[24,29–31] Symptoms that are commonly experienced during cancer treatment like stress, fatigue, lack of sleep, and lack of exercise will also impact an individual's ability to perform executive functions.[13] Executive functions encompass mental abilities like concentration, interference control, and regulating emotions, all of which support mental health and underlie success in vocational and social relationships.[13] These side effects correlate with self-reported cognitive impairments, but are not the only variables involved in the development of CRCI or perceived cognition since the cognitive impairments observed in studies usually remain significant after adjusting for psychological factors like anxiety, depression, or fatigue.[31] The onset and severity of CRCI varies on an individual basis, with evidence to suggest that age and cognitive reserve play a major role in a patient's development of CRCI.[32] Cognitive reserve may modulate the impact of age and cancer

treatment on cognitive performance.[9] Cognitive reserve is a term for the individual's capacity to recover from cognitive insults, and is influenced by biological and environmental factors like educational attainment, occupation, genetics, and lifestyle factors. Older age, exposure to chemotherapy, and lower pre-treatment cognitive reserve were significant predictors of worse performance on processing speed tasks among breast cancer patients compared with healthy controls and breast cancer patients without exposure to chemotherapy.[31] A longitudinal assessment of the standard adjuvant treatment regimen for breast cancer patients (5-fluorouracil, doxorubicin, and cyclophosphamide (FAC), with or without paclitaxel), on cognitive performance supports the potential impact of cognitive reserve on subsequent performance.[33] Interestingly, the researchers observed that the breast cancer patients who had pre-treatment declines on the Hopkins Verbal Learning Test, a measure of learning and memory, were more likely to experience post-treatment impairments. The researchers explained that cognitive reserve may protect an individual's ability to recover from cancer or cancer treatment-related cognitive insults.[33]

Cognition and Inflammation

Normal aging is accompanied by changes in brain volume and activation, cognitive function, and increased inflammation and oxidative stress in healthy adults.[34,35] Inflammation, in the absence of an acute infection, that persists over time characterizes several age-associated diseases, including Alzheimer's disease, macular degeneration, and type II diabetes. Age-related inflammatory changes, or "inflammaging", in the absence of pathological disease is known to impair memory.[36,37] There can be an elevation of pro-inflammatory markers like interleukin-6 (IL-6), interleukin-1β (IL-1β),

and tumor necrosis factor-alpha (TNF-α) during age-related disease states, reflecting the complex connectedness between inflammation, aging, and cognitive function.[38,39] Generally, age-associated cognitive declines affect the domains of executive function and episodic memory among healthy adults.[36,39] The brain has relatively few mechanisms to combat inflammation within the neural environment making it susceptible to detrimental effects from reactive oxygen species (ROS), including neuronal dysfunction and senescence.[40–42]

Additional evidence demonstrating the negative role of peripheral inflammation on brain health stems from the relationship between inflammation and neuropsychological disorders such as Alzheimer's disease, Parkinson's disease, or multiple sclerosis.[43,44] Aging and inflammatory markers have been independently associated with an increased risk of neuropsychological conditions like mild cognitive impairment and Alzheimer's disease.[38,45] Inflammation in the periphery can activate microglial cells in the brain.[46] This activation can either be supportive, by promoting proliferation of neural progenitor cells, or detrimental to neurogenesis by releasing pro-inflammatory cytokines.[46]

CRCI and Inflammation

The neurotoxic side effects of chemotherapeutic agents include 1) acute encephalopathy which causes confusion and altered behavior among the patient, 2) toxic leukoencephalopathy which is a disruption in white matter integrity resultant from myelin degradation and improper neurotransmitter function, and more commonly experienced are 3) perceived cognitive alterations which has been the topic of discussion thus far.[3,9] Inflammation plays a role in the pathogenesis of cognitive dysfunction, making it an

important target mechanism to investigate with regard to the cognitive side effects of cancer treatment.

One mechanism proposed for the side effects associated with chemotherapy is the increase of pro-inflammatory cytokines among cancer patients compared with control subjects.[47] These cytokines may be stimulated from physical factors such as the tumor or treatment method (surgical procedures, chemotherapy, or radiation therapy) and psychological factors such as fatigue or depression which develop during the cancer process.[5] Evidence supports the association between increased inflammatory markers like IL-6, IL-8, and monocyte chemoattractant protein (MCP)-1 and cognitive dysfunction in cancer patients treated with doxorubicin based chemotherapy.[48] Paclitaxel chemotherapy also induces differential expression of inflammatory markers such as IL-6, IL-8, and IL-10 among breast cancer patients compared with controls.[49] Patients with lymphatic system cancers exposed to chemotherapy also exhibit an increase in (IL-1ß) and cognitive dysfunction compared with healthy controls.[47,48] Ganz et al. conducted a prospective observational study that followed early breast cancer patients after initial treatments up to adjuvant endocrine therapy and examined cytokine levels and neuropsychological performance.[50] Elevated levels of TNF-α in patients exposed to chemotherapy at baseline was associated with more memory disturbances, with declines in TNF-α levels correlated with less disturbances over the year of follow up. Brain structural changes in the presence of altered cytokine levels have also been examined in the breast cancer population. There was a significant relationship between decreased hippocampal volume and increased TNF-α and reduced IL-6 was observed among breast cancer survivors compared with healthy controls.[51] Reduced verbal memory performance was also

observed among the breast cancer survivors and was associated with the altered hippocampal volumes and cytokine levels.[51]

Sufficient evidence (see review, Wang et al. 2015), affirms the correlation between changes in peripheral cytokines and cognitive dysfunction among chemotherapy-treated cancer patients. The precise mechanism underlying how peripheral increases in inflammatory cytokines impairs cognitive function is unknown. However, it is plausible that peripherally elevated cytokines may induce alterations among numerous neural substrates, including neurotransmitters and brain-derived neurotrophic factor (BDNF), in part by activating microglial cells to release pro-inflammatory cytokines to the neural environment.[11,52] Furthermore this inflammation may adversely affect adult hippocampal neurogenesis, which occurs throughout adulthood in the in the subgranular zone of the dentate gyrus, a region contained in the hippocampus of mammalian brains.[43,53] The hippocampus is a region in the brain recognized for its role in spatial and episodic memory formation.[54] Factors, like inflammation, that negatively affect adult hippocampal neurogenesis may contribute to the cognitive-related side effects that cancer survivors face during and after treatment.[55]

Adult Neurogenesis and Brain-derived Neurotrophic Factor

As discussed previously, alterations in brain structure and function occur with normal aging, and another molecule that may be associated with these processes is BDNF.[56] BDNF is a neurotrophin involved in long-term potentiation of synapses, which may modulate memory and learning capacity and stimulate neurogenesis.[56–58] Neurogenesis occurs throughout the lifespan but declines with advancing age.[56] Not only does neuroinflammation[59] affect neurogenesis, it is observed in non-human mammals

that, voluntary exercise and environmental stimuli will promote neurogenesis while stressors such as drugs, alcohol, or neurotransmitters like gamma-Aminobutryic acid will reduce neurogenesis.[46,53,54,59] Animal studies show that chemotherapy agents, like cyclophosphamide, can impair adult hippocampal neurogenesis and this reduction in neurogenesis parallels reduced performance on learning tasks.[55]

Previous research has highlighted the important role of BDNF in the mammalian brain. BDNF binds to the receptor tropomyosin-related kinase receptor type B (TRKB), which is expressed throughout the brain including the cortex and hippocampal regions, where BDNF is most concentrated.[56] Without this receptor, as demonstrated in studies using animal knockout models, there is a cessation of neurogenesis in the presence of a non-functional TRKB receptor.[54] Additionally, investigations of the BDNF gene in humans reveals how important this growth factor is on hippocampal-dependent brain activity and function. Individuals with a single nucleotide polymorphism (SNP) in the gene encoding BDNF (a methionine substitution for valine), have reduced BDNF secretory activity, demonstrate decreased hippocampal activity and greater episodic memory impairments compared to individuals who are homozygous for the valine allele.[58,60] Erickson and colleagues (2010) detected that BDNF levels corresponded with hippocampal volume loss over time with age, and this decrease in hippocampal volume facilitated the spatial memory declines in a group of older adults without dementia.[56] Given the correlational evidence which suggests a relationship between BDNF and cognitive function exist in humans, in the proposed research the association between this neurotrophin and cognitive complaints among breast cancer survivors will be examined.

Effect of Nutrition on Cognition

Nutrition plays a vital role in brain health by: maintaining neural tissue and membrane structure, providing substrates for the synthesis of signaling molecules, and fueling metabolic processes.[34] Dietary components like B vitamins, vitamin D, omega-3 fatty acids, antioxidants like vitamin E, vitamin C, and dietary fiber have been shown to promote brain health.[40,61–64] In addition to isolated nutrients, various foods have been identified that maintain and promote cognitive function including cruciferous and green leafy vegetables, citrus fruits, fish, mushrooms, and high fiber breads.[65,66] In a prospective examination of dietary patterns and cognitive function, individuals with high dietary contribution from fruits and vegetables, whole grains, nuts, fatty fish, and low fat dairy had better cognitive performance compared to individuals with low intakes of such foods.[67] Following a dietary pattern inclusive of foods listed above, and reflective of the Dietary Guidelines for Americans, resulted in higher performance on the Modified-Mini State Examination, a measure of global cognitive function. Mounting evidence demonstrates an association between the consumption of a Mediterranean dietary pattern with a decreased risk of Alzheimer's disease and greater cognitive performance on neuropsychological test batteries in the aging population.[68] The Mediterranean diet emphasizes fruits and vegetables, with moderate dairy and low meat consumption, and high intakes of monounsaturated fats, mainly from olive oil and nuts. Fruits and vegetables are common components of dietary patterns that exhibit benefits to brain health, and are well regarded to reduce the risk of age-related chronic disease and mortality among older adults.[41,69] A systematic review by Loef and Walach provided evidence that higher vegetable intake was associated with lower rates of cognitive decline

and a decreased risk of dementia among a healthy aging population, in a handful of cohort studies.[70] Additional evidence from a recent meta-analysis supports the benefit of consuming greater amounts of fruits and vegetables, as there was an inverse association between consumption and risk of cognitive impairment and dementia among individuals over the age of 65 years.[71]

Furthermore, a benefit of fruit intake on specific aspects of cognition pertaining to semantic and episodic memory in an elderly population has been reported.[66] High fruit and vegetable intake among healthy older adults was associated with higher serum antioxidants, lower markers of oxidative stress, and higher performance on neuropsychological tests when compared with adults consuming lower intakes of fruits and vegetables.[61] These research studies provide some justification for recommendations to increase the consumption of fruits and vegetables for protecting cognitive function within the adult population. It is of interest to determine if the benefits of fruit and vegetable intake to cognition and antioxidant status observed among a healthy population would be seen in other populations that may face cognitive alterations such as cancer survivors. A recent cross sectional study found that increased fruit and vegetable consumption improved interference control, a measure of executive function among breast cancer survivors and age-matched controls.[72] Higher fruit and vegetable intake was associated with improved accuracy and reduced reaction time on the cognitive task of executive function, regardless of cancer status. Fruits and vegetables contain numerous bioactive compounds that confer health benefits to humans. Further investigation is warranted to isolate the compounds responsible for cognitive benefits observed with fruit

and vegetable consumption, as many compounds contained in fruits and vegetables likely interact to elicit the cognitive benefits seen in previous research.[73]

Carotenoids

One particularly important group of phytochemicals that are highly concentrated in fruits and vegetables, are carotenoids. Carotenoids are pigments found in green leafy vegetables, yellow-orange and red fruits or vegetables, and even egg yolks.[41] Carotenoids possess many physiological roles, such as acting as anti-inflammatory or antioxidant agents, have pro-vitamin A activity, ensure photoprotection of skin tissues, and are a major component of the macula lutea.[41,74] These pigments may also exert benefits for cognitive health, as some carotenoids have potent activity in scavenging free radicals, protecting lipid membranes from peroxidation, and reducing cellular inflammation.[63,74] Alpha and beta carotene, lycopene, lutein, zeaxanthin, and beta-cryptoxanthin are the main contributors to dietary carotenoid intake.[74,75] Carotenoid levels in the skin and serum are dependent on intake, bioavailability, and absorption.[75] Carotenoids accumulate in numerous sites in the body such as the retina, brain, and skin tissues and are transported to these sites via lipoproteins. Carotenoid levels, are often measured in the skin or blood, and these measurements correlate highly with self-reported dietary fruit and vegetable intake.[75]

Lutein and Zeaxanthin and Cognition

Carotenoids have not been extensively examined for their role in promoting cognition among healthy individuals or cancer survivors. Lutein and zeaxanthin have limited, yet promising, correlational support that suggests these specific carotenoids can reduce cognitive decline among aging populations. A prospective study identified that higher

intakes of cruciferous vegetables and green leafy vegetables were associated with higher scores on cognitive tests among older women compared with women with lower intakes.[76] These vegetable groups are rich sources of two major carotenoids, lutein and zeaxanthin which accumulate at higher degrees in brain tissue compared with other carotenoids.[35,41,76] The researchers reported that the protection conferred to memory performance from being in the highest quintile of intake, compared with the lowest, was equivalent to the difference of being about two years younger.[76] Furthermore, an investigation of plasma carotenoids demonstrated a relationship between low plasma levels of lutein and zeaxanthin with an increased probability of being in the lowest percentile (<25th percentile) of cognitive performance.[35] An observational study evaluating the cognitive performance and cerebellum carotenoid concentrations among centenarians found positive associations between lutein and zeaxanthin and performance on the Mini-Mental State Examination and verbal fluency tests, respectively.[77] Also, individuals in the same study who were diagnosed with mild cognitive impairment had lower brain concentrations of lutein compared with individuals who demonstrated normal cognitive functioning.[77] A double-blind, placebo-controlled intervention trial tested the effect of four months of docosahexaenoic acid, lutein, or combined supplementation on cognitive function in older women.[78] All supplemental interventions were associated with improved verbal fluency scores compared with baseline testing. Although limited, this evidence suggests that lutein and zeaxanthin play a possible role in maintaining brain health and future research is needed to assess the nature and extent of the current associations.[78]

Objectives

The primary aim of the research project was to examine and compare the cognitive performance of breast cancer survivors, by objective (NIH Cognition battery) and subjective measures (FACT-Cog), with healthy controls. A separate objective of the research study was to discover if any significant associations between lutein and zeaxanthin intake and memory performance and cognitive function exist. Based on the evidence that supports the role of lutein and zeaxanthin in promoting brain health among healthy older adults, the researchers hypothesized that lutein and zeaxanthin would be positively associated with subjectively and objectively assessed cognitive function. There is insufficient research which examines the association between lutein and zeaxanthin intake and cognitive performance or cognitive complaints among cancer survivors. Therefore, the first aim of the current research study was to address this gap in the literature. Secondly, the association between BDNF with cognitive performance will be evaluated. Our hypothesis was that lower BDNF would be associated with reduced cognitive performance (NIH Cognition Battery) and increased cognitive complaints (FACT-Cog) in both breast cancer survivors and healthy controls. The goal of this research was to advance the current understanding of how diet is related to brain health and formulate beneficial recommendations that may improve cancer survivors' quality of life.

III. METHODS

A convenience sample of breast cancer survivors (BCS) (n=29) who completed primary treatment (chemotherapy, radiation therapy or both) within the past 60 months and age matched controls (n=38) with no history of a cancer diagnosis were recruited from the Austin, San Antonio, and San Marcos area using a variety of recruitment methods. Participants were recruited via local oncology clinics, support groups, print media (flyers), social networking sites, websites, and Texas State University's listserve. Any participant that contacted the research staff was telephoned, provided with a study description, and screened for eligibility. Additional inclusion criteria: female; 30-70 years old; no history of stroke, heart attack or transient ischemic attack; not currently pregnant; can speak, read, and write English; can attend all testing sessions; not blind or legally blind; nonsmoker; no current use of computer-based brain training games (e.g. Lumosity ®, BrainHQ ®). The exclusion criteria for this study included: male, < 30 or > 70 years of age, breast cancer survivor > 60 months from last treatment or currently undergoing primary treatment; breast cancer survivor never treated with chemotherapy and/or radiation; age-matched control with previous cancer diagnosis, history of stroke, heart attack or transient ischemic attack; currently pregnant; cannot speak, read or write English; blind or legally blind; cannot attend all testing sessions; current smoker; current use of computer-based brain training games (e.g. Lumosity ®, BrainHQ ®).

All participants were required to attend two testing sessions on separate days at the Nutrition and Physical Activity Lab at Texas State University (Family and Consumer Sciences Bldg, Rm 295A). At the first visit, the cognitive and physical assessments took place. Subjects were initially provided with two copies of the informed consent form;

both were signed and one was retained by the participant and one was kept by the experimenter. Next a research assistant administered the computer-based cognitive assessment; the National Institutes of Health Toolbox Cognitive Function Battery. This task took approximately 35 minutes.

Testing Measures

Anthropometric: Anthropometric measurements were taken in the following order: height, weight, and hip and waist circumference. Height and weight were measured using a digital stadiometer and floor scale. A tape measure was used to collect hip and waist circumference measurements. The researchers performed the calculation for body mass index (BMI) by dividing the individuals weight in kilograms by height squared (in centimeters). A questionnaire packet was provided for the participant to complete before returning 7-14 days after the initial visit. The second visit included the blood draw and dietary assessment.

Blood draw: Participants were fasted 10 hours prior to the appointment, at which a phlebotomist collected thirty milliliters (30 mL) of blood by venipuncture in the Student Health Center (phlebotomy room 159) at Texas State University.

Food Frequency Questionnaire: Participants completed a modified version of the 2005 Block food frequency delivered via NutritionQuest's online Data-on-Demand System.[79] This computer-based questionnaire took about 30-40 minutes to complete and the answers provided on this dietary questionnaire were reflective of intakes over the past 3 months. The questionnaire asked participants about their consumption of 110 food items, including portion size, and quantified the participants' fruit and vegetable intake as

well as specific carotenoid intake.[79] Participants that completed both testing appointments and returned all testing materials received $20 in cash.

Assessment of Cognitive Function**:** The National Institutes of Health Toolbox Neurological and Behavioral Function Cognitive Function Battery (NIHTB-CB) assesses five domains of cognition using seven test measures.[80] The cognitive domains and their corresponding test measures are indicated below in Table 1. Use of the NIHTB-CB enables researchers to compare scores of study participants with other studies that have utilized the same testing measures. The NIHTB-CB has high reliability and validity and has been widely used in various research applications to assess cognitive performance.[80] Episodic memory and working memory were tested by the picture sequence and list sorting working memory tasks, respectively. In the picture sequence task, participants were presented with illustrated objects or activities, and then asked to recall the sequential order of the items. The list sorting task assessed immediate recall, and provided the participant with pictures of foods and/or animals with written text and audio and then asks them to list the objects in size order (smallest to largest).[81]

Table 1. Test measures and cognitive domains included in the NIHTB-CB.

Cognitive Domain	NIHTB-CB Test Measure
Language	Picture Vocabulary Test Oral Reading Recognition Test
Episodic Memory	Picture Sequence Memory Test
Executive Function	Flanker Inhibitory Control and Attention Test Dimensional Change Card Sort Test
Working Memory	List Sorting Working Memory Test
Processing Speed	Pattern Comparison Processing Speed Test

The measures of memory function that were analyzed are underlined above.

Questionnaires

Participants completed a questionnaire packet which included measures of : demographics, cancer and health history, fatigue (FACIT-Fatigue)[82] self-reported cognitive function (FACT-Cog)[83], anxiety and depression (Hospital Anxiety and Depression Scale (HADS))[84], and well-being (FACT-GP).[85] The FACIT-Fatigue is a 13-item questionnaire that assessed symptoms of fatigue experienced within the past week. The FACT-Cog assessed perceived cognitive impairments experienced within the past week as well as asked the participants to rate the impact the perceived impairments have had on their quality of life.[83] The HADS scale is a self-assessment tool used to indicate the presence of symptoms of anxiety and/or depression. The FACT-GP is a 21-item questionnaire that assessed physical, social, emotional, and functional well-being.

Biological Specimen Collection and Analysis

Fasted blood samples for were collected via venipuncture into EDTA tubes, centrifuged, and the resultant serum was aliquoted and stored at -80º C for subsequent testing.

BDNF: Serum levels of BDNF were quantified using a Quantikine ELISA Human Free BDNF Immunoassay (R&D Systems, Minneapolis, MN), per the manufacturer's instructions.

Inflammatory Markers: Serum levels of interleukin-6 (IL6), soluble tissue necrosis factor- alpha receptor II (sTNF-α RII), and C-reactive protein (CRP) were quantified using their respective Quantikine ELISA Immunoassay kit (R&D Systems, Minneapolis, MN).

Carotenoids: Serum samples were sent to Baylor College of Medicine for analysis of lutein, zeaxanthin, beta and alpha- carotene, and lycopene by ultra-pressure liquid chromatography.

Statistical Analysis

Significant differences in participant characteristics were determined using an independent t-test for continuous variables and approximate significance of the phi coefficient for categorical variables. Pearson correlations were used to test for significant relationships between variables such as fatigue, anxiety, depression, age, education, and BMI. Multiple hierarchical regression analysis was then performed to assess the associations between the predictor variables (serum lutein and zeaxanthin, BMI, anxiety, depression) and the outcome variable (subjective and objective cognitive function). Median splits categorized BCS and controls into low (BCS, 163.2 μG/L or less) (controls, 214.72 μG/L or less) or high (BCS, more than 163.2 μG/L) (controls, more than 214.72 μG/L) serum lutein and zeaxanthin status groups. FACT-Cog scores were compared between the cancer survivors with high and low lutein and zeaxanthin status and non-cancer controls using univariate analysis of covariance (ANCOVA).

ANCOVA was used to assess for group differences in serum levels of IL-6, CRP, sTNF-αRII, and BDNF while adjusting for age and BMI. Partial correlations were performed to test for significant relationships between BDNF, serum lutein and zeaxanthin, inflammatory markers, and subjective and objective measures of cognition while adjusting for BMI and age.

IV. RESULTS

Table 2 displays demographic information for the BCS and healthy controls. BCS and control subjects were similar in age, BMI, race, ethnicity, education, and income. The BCS and controls had a mean age of 50.10 $\pm$ 10.06 years and 50.79 $\pm$ 10.04 years, respectively. Most of the participants were white, with more than 4 years of college level education, and a reported income of greater or equal to $60,000/year. In terms of treatment modality, all BCS received surgery, and an equal number of patients received chemotherapy and/or radiation therapy (37.9%, n=11), compared with chemotherapy (34.5%, n=10) or radiation alone (27.6%, n=8). More than half of the BCS received hormonal therapy (65.5%, n=19) and 75.9% (n=22) reported to be post-menopausal. The average time since last treatment was 18.62 months, or approximately 1.5 years.

Table 2. Demographic characteristics of BCS and controls

	BCS N=29	*Control N=38*	Significance
Age (Mean, SD)	50.10, 10.06	50.79, 10.04	.8
BMI kg/m^2 (Mean, SD)	29.70, 6.3	27.28, 7.6	.2
White (n, %),	20 (69.0)	33 (86.8)	.1
Hispanic or Latino (n, %)	6 (20.7)	9 (23.7)	.8
$\geq$ 4 year college degree (n,%)	20 (69.0)	32 (84.2)	.1
Income $\geq$ \$60,000	16 $^{\emptyset}$ (55.1)	29 $^{\emptyset}$ (78.4)	.1
post-menopausal (n,%)	22 (75.9)	-	
Breast Cancer Stage (n,%)			
DCIS	3 (10.3)	-	
Stage 1	8 (27.6)	-	
Stage 2	11 (37.9)	-	
Stage 3	6 (20.7)	-	
Unknown	1 (3.4)	-	
Tumor Characteristics (n. %)			
ER positive	17 (58.6)	-	
HER2 positive	6 (20.7)	-	
Treatment (n,%)			
Chemotherapy Only	10 (34.5)	-	
Radiation Only	8 (27.6)	-	
Chemotherapy plus radiation	11 (37.9)	-	
Hormone therapy	19 (65.5)	-	
Surgery	29 (100)	-	

Table 2. Continued.

Time since last treatment- months (Mean, SD)	18.62(16.3) -

ø= Participant "chose not to answer" (cancer n=3) (control n=1)

Psychological Health and Well-Being in BCS and Controls

An independent sample t-test demonstrated differences in reported values between the BCS and controls on several psychological variables (Table 3). BCS had significantly greater fatigue, anxiety, and depression. Additionally, BCS had significantly lower scores on the FACT-GP for physical, emotional, and functional well-being compared with healthy controls (higher scores indicate better well-being).

Table 3. Psychological health and well-being in BCS and controls

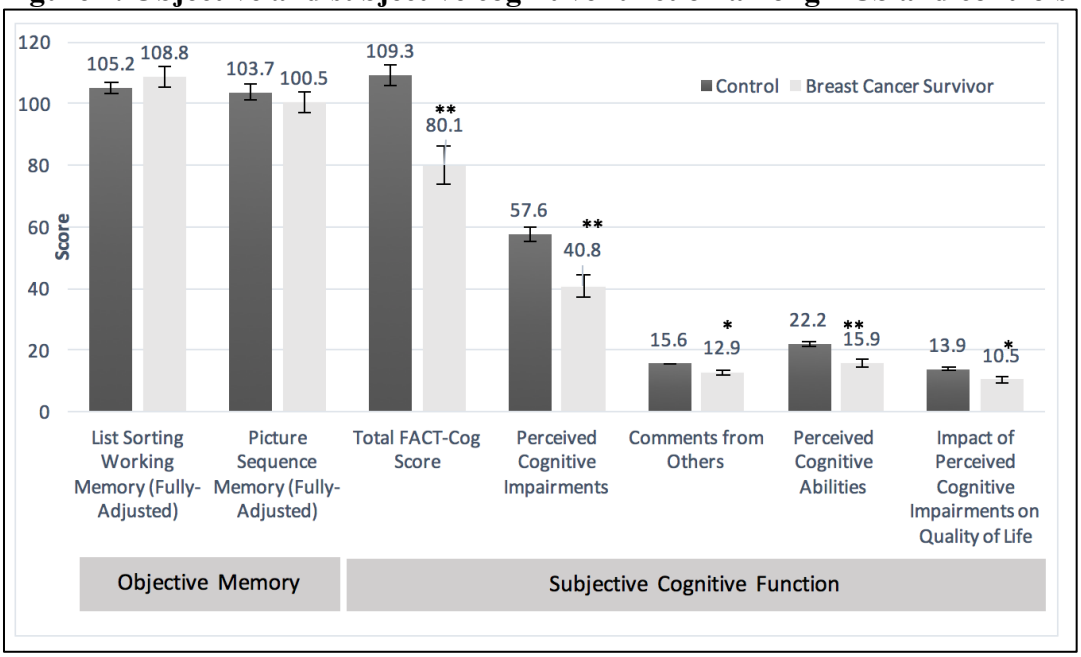
	Group	N	Mean	SD	*t*	*df*	*p*
Fatigue	BCS Control	29 38	32.2 44.3	15.6 7.4	-4.216	65	<.001
Anxiety	BCS Control	29 38	8.4 6.7	2.8 2.4	2.610	65	.011
Depression	BCS Control	29 38	7.3 5.7	3.2 2.3	2.329	65	.023
Well-being Total Score	BCS Control	29 38	58.2 70.0	17.2 10.6	-3.457	65	.001
Physical Well-being	BCS Control	29 38	17.0 21.7	6.0 2.0	-4.523	65	<.001
Emotional Well-being	BCS Control	29 38	10.7 13.8	4.2 2.2	-3.882	65	<.001
Functional Well-being	BCS Control	29 38	16.5 19.3	5.5 4.7	-2.274	65	.026

Cognitive Function in BCS and Age-matched Controls

Fully-adjusted scores were used in this analysis to compare the score of the participant to scores from a normative sample that adjusted for age, gender, race, ethnicity, and

education.[86] Overall, over half (53.7%, n=67) of the participants were above the 75th percentile for List Sorting Working memory and Picture Sequence Memory (58.5%, n=65). BCS and controls performed similarly on the List Sorting Working Memory, t(65)=1.046, p=.300 and Picture Sequence Memory task, t(63)= -.769, p=.445. BCS reported more cognitive complaints on subjective measures of cognitive function, including the total score on the FACT-Cog and all four sub-scales of the questionnaire (perceived cognitive impairments, comments from others, perceived cognitive abilities, and impact of perceived cognitive impairments on quality of life).

Figure 1. Objective and subjective cognitive function among BCS and controls



Values are mean ± SEM, * <.01, ** <0.001.

Dietary and Serum Lutein and Zeaxanthin

BCS (M = 7089.8 ± 5848.7 mcg) and controls (M = 5618.5 ± 3622.7 mcg) had similar dietary intakes of lutein and zeaxanthin (Table 4). Dietary lutein and zeaxanthin was positively correlated with total fruit and vegetable intake in both BCS, R=.793, p=<.001, and controls, R=.834, p=<.001. BCS and controls consumed an average of 5.82 ± 3.5

servings of fruit and vegetables per day with no significant differences in diet composition for micro or macronutrients, besides dietary cholesterol intake being slightly higher in the cancer group (t (64) =2.041, p=.045).

Table 4. Dietary and serum lutein and zeaxanthin measurements in BCS and controls

Variable	Group	Mean ± SD	t-value	df	*p*
Dietary lutein & zeaxanthin intake (mcg/day)	BCS Control	7089.8 ± 5848.7 5618.5 ± 3622.7	1.259	64	.213
Serum lutein & zeaxanthin (µg/l)	BCS Control	241.8 ± 224.7 235.2 ± 119.2	-.873	63	.386
Total serum carotenoids (µg/l)	BCS Control	1176.2 ± 899.2 1183.5 ± 611.4	-0.039	63	.969

Correlations between serum lutein and zeaxanthin and dietary variables in the BCS and control groups are reflected in Table 5. After controlling for BMI, serum lutein and zeaxanthin correlated with dietary lutein and zeaxanthin, total fruit and vegetable intake, daily servings of vegetables, My Pyramid vegetables (dark green, cups), My Pyramid vegetables (not legumes/potatoes, cups), and other My Pyramid vegetables (including tomatoes, cups) in the total sample.

Table 5. Correlations between serum lutein and zeaxanthin and dietary variables among the total sample

Serum Lutein and Zeaxanthin (µG/L)	Dietary Lutein and zeaxanthin (mcg)	Daily servings of Vegetables	Daily servings of fruit & fruit juices (cups)	My Pyramid veg- not legumes/ (cups)	My Pyramid veg- dark green (cups)	My Pyramid veg- orange (cups)	My Pyramid veg- potato (cups)	My Pyramid veg- other, incl. tomatoes (cups)	Total Fruit and vegetables (servings)
Correlation (R)	.342	.447	.189	.440	.331	.197	-.005	.423	.449
p	.006	<.001	.134	<.001	.008	.119	.971	.001	<.001
df	62	62	62	62	62	62	62	62	65

Relationship of Serum Lutein and Zeaxanthin and Cognitive Function

Serum lutein and zeaxanthin in BCS and controls did not correlate with fully-adjusted List Sorting Working Memory or Picture Sequence Memory scores (data not shown). Additionally, after controlling for age, correlations between serum lutein and zeaxanthin and Total Fact-Cog score, were not significant in the BCS (R=.086, p=.669) or control group (R=.195, p=.255). Hierarchical regression analyses were used to assess the ability of serum lutein and zeaxanthin to predict memory performance when including additional covariates. Serum lutein and zeaxanthin was not correlated with fully-adjusted List Sorting Working Memory, in the regression model with the addition of confounders such as BMI, anxiety, and depression among the controls and total sample. The regression model that included serum lutein and zeaxanthin, BMI, anxiety, and depression significantly predicted fully-adjusted List Sorting Working Memory in the BCS group, F (4,23) =3.822, p=.016. (Table 6). Note that serum lutein and zeaxanthin is not a

significant predictor, only anxiety significantly predicts working memory performance when all four variables are included in the model.

Table 6. Summary of simple regression analyses for variables predicting list sorting working memory performance

	BCS		*Control*		*Total*	
Variable	ß	Sig	ß	Sig	ß	Sig
Serum lutein and zeaxanthin	-.250	.215	-.151	.416	-.128	.351
BMI	-.138	.474	-.071	.706	-.017	.901
Anxiety	-.526	.012	-.153	.398	-.279	.045
Depression	-.217	.284	.122	.503	-.104	.466
R^2	.295		-.061		.052	
F	3.822*		.484		1.885	

*** p<.05**

Table 7 shows the results of the linear regression analyses between serum lutein and zeaxanthin, BMI, anxiety, depression and Picture Sequence Memory. There was no statistically significant relationship between the variables used to predict memory performance among BCS, controls, or the total sample.

Table 7. Summary of simple regression analyses for variables predicting picture sequence memory

	BCS		*Control*		*Total*	
Variable	ß	Sig	ß	Sig	ß	Sig
Serum lutein and zeaxanthin	-.028	.905	-.101	.607	-.028	.905

Table 7. Continued.

BMI	-.114	.621	-.171	.389	-.114	.621
Anxiety	-.153	.515	-.086	-.463	-.153	.515
Depression	-.230	.344	.106	.562	-.230	.344
R^2	-.019		-.086		-.019	
F	.873		.328		.873	

Table 8 shows the results of the linear regression analyses between serum lutein and zeaxanthin, age, BMI, anxiety, depression and Total FACT-Cog score. Despite the combination of variables used to predict memory performance among BCS, controls, or the total sample being significant, the beta coefficients for serum lutein and zeaxanthin (primary predictor) failed to reach significance. Age, BMI, anxiety, and depression were significant predictors of FACT-Cog scores in the analysis for the total sample while age, BMI, and anxiety were significant predictors of FACT-Cog scores among the BCS.

Table 8. Summary of simple regression analyses for variables predicting perceived cognitive impairments

	BCS		*Control*		*Total*	
Variable	ß	Sig	ß	Sig	ß	Sig
Serum lutein and zeaxanthin	-.221	.133	.078	.600	-.118	.247
Age	.556	<.001	-.046	.747	.282	.003
BMI	-.307	.036	-.096	.518	-.219	.032
Anxiety	-.348	.029	-.354	.014	--.436	<.001

Table 8. Continued.

Depression	-.129	.377	-.452	.003	-.295	.005
R^2	.631		.388		.504	
F	10.226**		.5.555**		14.007**	

*** p<.05, **p<.01.**

Association Between Lutein and Zeaxanthin Status and Objective and Subjective Cognition

Participants were categorized as having low or high serum lutein and zeaxanthin status based on a median split of serum lutein and zeaxanthin levels in their respective group (median serum level of 163.2 μG/L for the BCS and 214.72 μG/L for the Control group). There was a statistically significant main effect of lutein and zeaxanthin status on Total FACT Cog Scores, F (3,57) =12.441, p=<.001 (Table 9). Eta for lutein and zeaxanthin group was 0.434 which represents a large effect. Reverse scoring on the FACT-Cog means that higher scores reflect higher levels of perceived cognitive function and quality of life. The significant differences among the four groups, as indicated by pairwise comparisons using the Least Significant Difference (LSD) test are listed in Table 9 below. BCS with low lutein and zeaxanthin status did not have significantly different Total FACT Cog scores compared to BCS with high lutein and zeaxanthin status (p=.991). BCS with high lutein and zeaxanthin status had significantly lower total FACT-Cog scores than control participants with low lutein and zeaxanthin status (p<.001), and control participants with high lutein and zeaxanthin status (p<.001). Controls with low lutein and zeaxanthin status had significantly higher total FACT-Cog scores than BCS with low lutein and zeaxanthin status (p<.001) and high lutein and

zeaxanthin status (p<.001), but did not have significantly different scores compared with controls with higher lutein and zeaxanthin status (p=.338). Controls with high lutein and zeaxanthin status had significantly higher total FACT-Cog scores than BCS with low lutein and zeaxanthin status (p<.001) and BCS with high lutein and zeaxanthin status (p<.001).

Table 9. Impact of serum lutein and zeaxanthin on subjective and objective memory impairments among BCS and controls

	Low LZ BCS	High LZ BCS	Low LZ Control	High LZ Control
Fully-adjusted List Sorting Working Memory	109.7 ± 19.2	108.1 ± 15.8	106.4 ± 11.4	103.9 ± 11.1
Fully-adjusted Picture Sequence Memory	97.6 ± 20.1	104.1 + 16.7	104.7 + 13.3	103.7 ± 16.2
Total FACT-Cog Score	79.1 ± 5.6[a]	79.2 ± 5.6[a]	107.5 ± 4.8[b]	114.2 ± 4.9[b]

Different letters indicate significantly different at the p<.05 level.

BDNF and Objective and Subjective Cognitive Function

There were no significant differences in serum BDNF (mean ± SD) among the BCS (1405.39 ± 507.53 pg/mL) or control (1434.87 ± 406.95 pg/mL) groups, t(64)=-.262, p=.794. Results from partial correlations, after controlling for age, indicated that BDNF was not associated with objective or subjective measures of cognition in the total sample, Table 10.

Table 10. Partial correlations between objective and subjective memory among the total sample

BDNF	*List Sorting Working Memory*	*Picture Sequence Memory*	*FACT-Cog Total*
Correlation	.009	-.179	-.086
Sig (2-tailed)	.947	.160	.501
N	64	64	64

Inflammatory Markers

Mean differences in inflammatory markers among BCS and controls are reported in Table 11. Results from the ANCOVA revealed that there were no significant differences in serum IL-6, soluble TNF alpha receptor 2, or C-Reactive protein (CRP) among the BCS and controls.

Table 11. Mean values of inflammatory markers in BCS and controls

	Group	N	Mean	St Dev	*F*	*p*
IL-6 (pg/mL)	BCS Control	28 38	2.7 2.1	1.8 1.5	.811	.371
Soluble TNF-alpha receptor 2 (pg/mL)	BCS Control	28 34	3064.2 2695.2	773.4 607.1	3.647	.061
CRP (ng/mL)	BCS Control	24 36	2175.9 3175.5	1540.6 2612.4	1.662	.203

Table 12 displays the correlations between serum lutein and zeaxanthin, inflammatory markers, and BDNF. After adjusting for age and BMI there were no significant associations between serum lutein and zeaxanthin and levels of inflammatory markers or BDNF.

Table 12. Correlations between serum lutein and zeaxanthin, inflammatory markers, and BDNF in BCS and controls

Serum Lutein and Zeaxanthin		IL-6	Soluble TNF receptor 2	CRP	BDNF
Correlation	BCS	-0.346	-0.372	-.236	.137
Sig. (2-tailed)		.083	.061	.291	.504
N		28	28	24	28
	Control				
Correlation		.009	-.063	.154	.104
Sig. (2-tailed)		.958	.735	.392	.551
N		38	34	36	38

V. DISCUSSION

Comparison of Memory Performance among BCS and Controls

Subjective, but not objective, measures of cognitive function were significantly different among BCS and controls. The BCS had higher self-reported impairments in cognitive function. These findings are consistent with previous literature showing a predominance of perceived cognitive impairments among patients or survivors rather than objectively measured impairments.[25,52,87] Often objective measures of cognitive performance do not correlate with self-reported declines, and this was observed in the current sample.[87] Although, the cancer survivors were not experiencing objective impairments in memory it is still important to acknowledge the perceived impairments that were reported as these symptoms can negatively impact quality of life.[52] Furthermore, daily or "everyday" functioning is more closely linked with self-reported cognition than objectively measured cognition.[88] Suggesting that, the subjective measures may provide a broader assessment of cognitive function and is an important indicator of how cancer survivors are affected by CRCI.

Additionally, in line with prior studies, psychological variables such as anxiety and depression, correlated with self-reported cognitive complaints.[87] Since the FACT-Cog assesses self-perceived declines in domains like attention and language it is possible that objective tests on memory did not fully capture the impairments that BCS reported. Only two objective measures of cognition were utilized; the List Sorting Working Memory and Picture Sequence Memory task, thus, potential changes in other domains of cognition were not assessed. Limited recent evidence suggests that BCS who are susceptible to CRCI may be more likely to demonstrate cognitive declines in verbal or

visual domains. [18] Continued research is needed to evaluate which domains are consistently affected among the cancer survivors.

Another factor which impacts cognitive performance is the time between treatment and cognitive assessments. The average time since last treatment in the BCS group was 18.24 months or approximately 1.5 years. In some studies, researchers observed that cognitive complaints resolve within this period of time, yet other studies have found documented impairments long after treatment cessation (10-20 years).[6,12,20,31] Thus it seems unlikely that the similarities in objective performance in BCS and controls observed in this sample can be explained by the time since treatment. The sample participants were also young, with mean sample age of 50.5 $\pm$ 10.0 years, and prior research has suggested that older cancer survivors may be particularly vulnerable to cognitive complaints, while younger survivors have a greater ability to recover from cancer treatment-related cognitive insults.[31,32] Our sample may have had very few individuals experiencing objective declines in cognition as most participants had high performance on the neuropsychological assessments. Over half of the BCS and controls were above the 75th percentile for performance on the List Sorting Working Memory and Picture Sequence Memory tasks.

Associations between Lutein and Zeaxanthin Status and Cognitive Function

Serum lutein and zeaxanthin was not a significant predictor of List Sorting Working Memory, Picture Sequence Memory, or perceived cognitive function among the BCS, controls, and total sample. Although the regression models for List Sorting Working Memory in the BCS and perceived cognitive impairments in all three groups reached overall significance, the beta coefficients for serum lutein and zeaxanthin failed

to reach significance. Anxiety was a predictor of cognitive function among the BCS for list sorting working memory and among the BCS and total sample for self-reported cognitive function score. In addition, depression was a significant predictor of self-reported cognitive function in the total sample. Previous research has demonstrated that psychological variables such as anxiety and depression can influence self-reported cognitive function, as these symptoms are often associated in studies and known to have confounding potential.[52,87,88]

The results from the ANCOVA indicated that serum lutein and zeaxanthin status was not associated with perceived cognitive impairments or objective memory performance. Our hypothesis that higher serum levels of lutein and zeaxanthin would be associated with improved memory performance (thus higher scores on the FACT-Cog) was not observed among both groups. The results do not provide preliminary evidence for higher lutein and zeaxanthin serum levels being positively associated with self-perceived cognition in BCS. Additional analyses may consider broadening the examination to total carotenoids to see if any relationships exist between cognitive outcomes, including the measures listed above, and other types and combinations of carotenoids, not exclusively lutein and zeaxanthin.

Evaluation of Dietary Lutein and Zeaxanthin Intake and Serum Lutein and Zeaxanthin Status

The notion that carotenoids serve an important role in maintaining the health of cancer survivors is rooted in the physiological functions of carotenoids and their accumulation in neural tissues. It is possible that the protective effects of carotenoids may be reserved to those with low intakes of carotenoids. In our sample, dietary intake and

serum values of lutein and zeaxanthin were high and similar among both BCS and controls. For comparison, the average serum concentrations of the adult female population ages 3 years and older in the US with similar demographic characteristics was reported to be 131 μg/L in 2001-2002, whereas BCS and controls had mean values of 241.8 ± 224.7 μg/L and 235.2 ± 119.2 μg/L, respectively.[89] Therefore, the benefits of carotenoid intake may already be occurring among participants in the study. Furthermore, this contributed to limited variation in carotenoid intake and serum levels which may explain, in part, the lack of association between lutein and zeaxanthin status and objective or subjective measures of cognition. Notably, 39.3% of the BCS were meeting recommendations to consume at least 5 servings of fruits and vegetables which is higher than the reported 18.2% of BCS meeting 5-A-Day recommendations in the American Cancer Society's Study of Cancer Survivors-II national survey conducted in 2007.[90] Therefore, participants in the current sample may not be representative of the BCS population and it is possible that these shared dietary habits, among BCS and controls, influenced their willingness to participate in the study and thus biased the results.

It is important to note that the carotenoid status of an individual will vary depending on their levels of oxidative stress, individual ability to absorb and metabolize carotenoids and meal composition surrounding carotenoid ingestion.[74,91] Also, there are genetic components that affect an individual's ability to utilize and accumulate carotenoids.[91] Besides sampling serum or tissue to measure lutein and zeaxanthin levels, measuring macular pigment optical density (MPOD), i.e. retinal lutein and zeaxanthin may be a more optimal method for assessing relationships between lutein and zeaxanthin and cognition.[92,93] MPOD levels are associated with brain concentrations of carotenoids

and in comparison, serum levels have shorter half-lives in circulation compared with tissue levels that can reflect longer term carotenoid status.[75] Continued research is needed to understand how the selection and variability of tissue, serum, or retinal biomarkers might influence findings related to the present and future research surrounding these compounds.

Relationships Between Inflammatory Markers, BDNF, and Cognitive Function

There was no relationship between BDNF and the following variables: objective memory performance, subjective cognitive function, and serum lutein and zeaxanthin. As previously observed in older populations, positive correlations have been observed between BDNF levels and cognitive function to suggest that BDNF may be associated with memory performance.[56,58,60] However, our sample was relatively young, small in size, and lacked significant differences in levels of circulating BDNF. Although some studies demonstrate a positive relationship between BDNF and cognitive performance, other investigations lack evidence of positive associations between BDNF and memory performance among healthy adults, similarly to the results observed in the current study.[94–96]

Prior research has documented increases in several inflammatory markers among cancer patients and survivors compared with non-diagnosed counterparts.[48,49,51] Cytokine-related changes in cognition have been observed in a number of studies, suggesting that inflammation may mediate differences in objective or subjective cognition among cancer survivors.[11,50] There were no significant relationships between serum lutein and zeaxanthin and inflammatory cytokines among the BCS or controls. Since there were no observed differences among inflammatory markers in BCS and

controls, the researchers cannot report on any relationships between carotenoids, inflammation, and memory or self-reported functioning. Future studies should examine additional inflammatory markers and cognitive domains, not limited to working and episodic memory, to gain a greater understanding of the relationship between inflammation and cognition among BCS.

Strengths and Limitations

The strengths of this study include utilization of the NIHTB Cognition Battery and FACT-Cog for assessing cognitive function. The NIHTB Cognition Battery provides scores that are relevant for comparing our sample participants with the general healthy population. This allowed us to determine that the BCS and controls were high performers on the objective memory tasks, which gave insights as to why there may not have been objective differences. In this study, objective measures of cognitive function were similar among BCS and controls with significant differences observed only on subjective measures of memory performance. By using validated questionnaires to assess perceived cognitive function, fatigue, and well-being, our results further demonstrate that BCS experience difficulties in these areas. Another strength was the use of serum analyses to corroborate the dietary carotenoid data and provide objective information about the carotenoid status of BCS sampled in this study. As alterations in cognitive function were expected to exist in the current sample, it was essential to have an objective assessment of dietary intake. The use of serum measurements assisted the researchers, yet the measurement can be limited as the absorption of carotenoids is affected by several factors (previously discussed) and serum levels provide a short-term method to evaluate the

dietary habits of the sample participants. Up until now, no studies have investigated the relationship between lutein and zeaxanthin status and cognitive function in BCS.

A limitation of this study included the study design and sample size. The cross-sectional nature of this study allowed for evaluations of how current dietary intakes, serum carotenoids, inflammatory markers, and circulating BDNF correlate with memory function, but causal inferences could not be drawn. The sample was relatively small, which likely contributed to the insignificant differences between diet and cognition observed in this study. Although serum BDNF was analyzed in our sample, SNP's for genes including BDNF, apolipoprotein E (APOE) or catechol-O-methyltransferase (COMT) were not evaluated. Prior research has shown that genetic variations in these genes correlate with reduced or enhanced memory performance.[58] Therefore, the researchers cannot account for the potential impact that these SNP's may have on cognitive performance or circulating levels of BDNF in the sample. Lastly, the researchers did not assess for interactions between predictor or outcome variables with variables including: physical activity, body composition, or other dietary factors. A recent study demonstrated that higher fitness level was associated with better working memory performance among young adults.[97] Levels of the biomarkers CRP and BDNF had mediation and moderation effects, respectively, on the relationship between memory performance and fitness level for individuals with the highest VO_2max levels. This study demonstrates the importance of assessing various predictor variables and biomarkers when examining cognitive performance. Lastly, the researchers only assessed two objective measures of memory function, working and episodic memory. In comparison, the FACT-Cog is a comprehensive survey that assesses self-perceived decrements in not

only memory, but other domains like language, concentration, attention, and thinking abilities.[98] For this reason, it is likely that a combination of perceived cognitive changes occurring in the BCS were not reflected in the objective assessments which measured working memory and episodic memory.

Summary

The findings from this study contribute to a growing body of literature that observes less favorable perceived cognitive function among BCS compared with controls. The research aimed to gather evidence of a beneficial relationship between lutein and zeaxanthin intake and status and cognition, so that more specific dietary recommendations could be made to improve cancer survivor's quality of life. There were some inconsistent findings in the present study with previous literature as the BCS did not have higher levels of inflammatory markers compared with controls. Furthermore, the limited variation in lutein and zeaxanthin serum levels and dietary intake among the two groups likely influenced the ability of researchers to draw conclusions about how these compounds are related to objective or subjective cognitive function.

Future research should include a larger sample of cancer survivors with greater variations in carotenoid intake and status which would enable researchers to better understand how these compounds may benefit certain individuals and if they are neuroprotective. Additional research is needed to improve the current understanding of which dietary modifications can benefit cancer survivors' quality of life or cognitive outcomes. It may be more plausible to approach this research question utilizing specific types of fruit and vegetables, as a combination of nutrients and phytochemicals found in recommended foods likely interact to elicit benefits. Also, these targeted recommendations may be more practical and effective in the cancer survivor population, and dietary solutions such as these are in demand as the number of BCS continues to grow.

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