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Article

The Effect of Mediterranean Diet Adherence on the Relationship between Cognitive Performance and Cancer Survivorship

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Abstract: Purpose: Up to 75% of cancer survivors experience cognitive impairment from cancer or its treatment. No modifiable risk factor has been identified; however, a Mediterranean diet may be protective. We sought to determine if the relationship between Cognitive Performance and Cancer Survivorship depends on Mediterranean Diet adherence. **Methods:** We used cross-sectional data from the 2011-2012 and 2013-2014 cycles of the National Health and Nutrition Examination Survey. Mediterranean Diet adherence was defined as the aMed score which gives 1 point for intake above/below the sample-specific median for healthful/unhealthful food groups (range 0-9). Cognition was assessed via: (1) the Digit Symbol Substitution test assessing processing speed, attention, and working memory, (2) the Consortium to Establish a Registry for Alzheimer's disease (CERAD) assessing learning and short-term memory, and (3) the Animal Fluency test assessing executive function. Linear regression models adjusted for age, race, gender, comorbidities, smoking, total kilocalories, day and time of year of recall. **Results:** Among 2,450 participants, 385 had cancer. Mean age was 68.9 years (SE=0.2). The most common cancer was breast cancer (24%). The average aMed score was 3.5 (SE=0.1) in survivors versus 3.6 (SE= 0.1) in non-cancer controls. Cancer history was not associated with cognition ($p>0.05$). Among high aMed scores, cancer history was more negatively associated with animal fluency compared to low aMed scores (β (95% CI): -1.11 (-2.33, 0.12), $p=0.08$ for aMed*Cancer interaction term). **Conclusions:** Among high versus low aMed scores, positive cancer history was more negatively associated with cognition. Prospective studies are needed to confirm these results.

Keywords: cognition; NHANES; Mediterranean Diet; cancer

1. Introduction

Cognitive impairment associated with cancer or its treatment, called cancer related cognitive impairment (CRCI), has been shown to impact a substantial proportion of cancer survivors.[1–3] For example, among breast cancer survivors (BCS), the prevalence of CRCI 3-5 years after chemotherapy is 21%.[4] Those with CRCI suffer from reduced quality of life and increased rates of stress, anxiety, depression, and post-traumatic stress disorder, compared to cancer survivors without CRCI.[5–7] Pharmacological and non-pharmacological treatments for CRCI are still actively being identified and tested, but improving diet quality is a plausible intervention that has received relatively little attention.[8,9] Given that the number of persons in the United States (U.S.) with CRCI is expected to

increase due to improving cancer survival rates,[10] it is important to better understand whether the association between cancer survivorship and cognition varies by diet.

A recent systematic review of six studies found that fruit and vegetable consumption benefitted cognitive performance or reduced cognitive complaints among cancer survivors;[11] however, prior literature on the association between diet and cognition in cancer survivors is limited. For one, prior studies typically investigated subjectively- versus objectively- measured cognition, which may be related more to stress.[11,12] Additionally, the few studies investigating objective cognition and diet have a small sample size[13,14] (N=54-61) or were conducted in a country where population characteristics are different from those of the U.S.[15]

To address the limitations of prior literature and to better inform dietary interventions for treating CRCI, we used the National Health and Nutrition Examination Survey (NHANES) to determine if past cancer history is associated with objectively measured cognition and to test whether that association varies by diet. Prior literature demonstrated greater objective cognitive deficit in cancer survivors compared to non-survivors in NHANES (1999-2002 cycles).[16] Adherence to a Mediterranean Diet (Med Diet) has also been associated with higher cognitive scores in the majority of studies in cancer-free cohorts.[17] Thus, we hypothesized that past cancer history would be associated with a cognitive deficit and that this negative association would be mitigated among those with a higher adherence to a Med Diet.

2. Methods

2.1. Overview

To test our hypotheses, we used NHANES data from 2011 to 2014. The design of NHANES has been published elsewhere.[18,19] Briefly, NHANES is an ongoing cross-sectional study that collects data every two years using a clustered, probability sampling design whereby participants are randomly selected in a four-stage procedure with over-sampling of specific groups of public health concern. After providing informed consent, participants are administered several questionnaires at home. These questionnaires collect data about demographics, physical activity, medical conditions, and other domains. Further examination takes place at a Mobile Examination Center where a physical examination, cognitive evaluation, and a 24-hour dietary recall are conducted. The physical exam includes blood work and measurement of height, weight, body composition, among others. The cognitive evaluation was administered to participants 60 years and older with no language or literacy requirements. No ethics approval was required as NHANES data is de-identified and publicly available.

2.2. Participant Selection

Participants in either the 2011-2012 or 2013-2014 waves of NHANES (N=19,931) were initially included. We selected these waves because they included the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Word List test, Digit Symbol Substitution Test (DSST), and Animal Fluency, measures of verbal episodic memory, processing speed, and verbal fluency which are frequently affected by cancer and cancer therapy.[20,21] Individuals < 60 years of age were excluded as they were not eligible for cognitive assessment (n=16,299). Additional exclusion criteria included: missing day 1 dietary recall (n=528), missing total kilocalories (kcal) (n=36), implausible kcal intake (<500 or >3500 kcal/day for women and <800 or >4200kcal/day for men[22]) (n=125), no saturated fat intake (a component for the Med Diet score, described below (n=1)), missing one or more cognitive tests or one or more trial within any test (n=335), unknown or missing cancer history (n=3), or a history of non-melanoma skin or brain cancer (n=154). Individuals remaining (n=2,450) constituted our sample for analysis.

2.3. Independent Variable: Past Cancer History

Past cancer history was determined with the following question: “Have you ever been told by a doctor or other health professional that you had cancer or a malignancy of any kind?” Participants could choose from 30 predefined cancer types.

2.4. Dependent Variables: Cognitive Performance

Cognitive performance included: (1) number correct on the DSST which assesses processing speed, sustained attention, and working memory, (2) number of words learned across three learning trials (CERAD-WL) and (3) a short delay (CERAD-DR) which assesses learning and short term memory, (4) total intrusions on the CERAD, and (5) number correct on the Animal Fluency test which assesses language and executive function.[23]

2.5. Confounders and Effect Modifier

We identified plausible confounders as age (right-censored at 80 years per NHANES design), race, ethnicity, household income, education, sex, smoking, and cardiometabolic disease. Cardiometabolic disease was captured under the variable comorbidity burden (range from 0-9) whereby a 1 was assigned if an individual had any of the following conditions: stroke, heart attack, angina, congestive heart failure, coronary heart disease, type 2 diabetes, high cholesterol, high blood pressure, or liver condition. Higher scores represent greater cardiometabolic disease burden. Mediators not controlled for in our regression models included minutes of moderate to vigorous physical activity (MVPA) per week, sleep hours per night, body mass index (BMI), and depressive symptoms.

In models testing the association between cancer survivorship and cognition Med Diet adherence was included as an effect modifier. Adherence was defined by the alternate Mediterranean Diet score (aMED),[24] modified to be compatible with 24-hour dietary recalls.[25] The score range is 0-9, with 1 point awarded for intake above the sex-specific median for vegetables, fruits, legumes, whole grains, nuts, seafood, and the ratio of monounsaturated fats to saturated fats, 1 point for intake at or below the sex-specific median for red meat and processed meats combined, and 1 point for moderate levels of alcohol consumption, i.e., 5-25g of ethanol per day for women and 10-50g of ethanol per day for men, and 0 points for any other level of intake for each of the 9 groups. Med Diet adherence was also treated as a binary variable dichotomized at the median of 3. High adherence was defined as a score > 3 and low adherence was defined as a score of 3 or less.

Additionally, we tested the extent to which the association between past cancer history and each measure of cognitive performance varied by age (<75 or ≥75).

2.5. Statistical Analysis.

We performed a descriptive analysis comparing cancer survivors to non-cancer controls on key variables (Table 1). We report means and standard errors for continuous variables and frequencies and percentages for categorical variables.

We used linear regression models to test the association between cancer survivorship and each measure of cognitive performance as well as for the significance of effect modifiers, which included aMed as a continuous or binary variable (Table 3) and age (<75 or ≥75) (Table 4). Model 1 was unadjusted. Model 2 adjusts for demographic characteristics only (education, sex, age, race, ethnicity, and income). Model 3 further adjusted for health and health behavior, i.e., diet-related variables (aMed score, kcals, day of recall, time of year of recall), smoking, and comorbidity burden.

We accounted for NHANES complex survey design of oversampling, clustering, and stratification by using the proper survey procedures. For linear regression models to test the association between cancer survivorship and cognition, we set alpha to 0.05. Alpha was set to 0.10 for interaction terms. All analyses were carried out with STATA version 17.0 (StataCorp LLC, College Station, TX, USA).

3. Results

Table 1 shows the sample characteristics. The mean age was 68.9 years (Standard Error [SE]: 0.2) with survivors being older than non-survivors. Survivors also had a higher prevalence of obtaining a four-year college degree (35.6% vs. 29.3%, respectively) and a higher proportion of cancer survivors versus non-survivors were non-Hispanic White individuals (84.9% vs. 77.9%).

Table 1. Sample CharacteristicsA.

	Overall		Cancer Survivor		Control	
	N (%) or Mean (SE)		N (%) or Mean (SE)		N (%) or Mean (SE)	
Age (Years)	68.9	0.2	70.8	0.4	68.5	0.2
Sex						
Male	1176	44.8%	185	41.9%	991	45.4%
Female	1274	55.2%	200	58.1%	1074	54.6%
Household Income						
≥ \$20,000	1746	83.1%	290	85.1%	1456	82.7%
< \$20,000	604	16.9%	80	14.9%	524	17.3%
Education						
< 9th	270	5.5%	35	4.1%	235	5.8%
9th-12th, No Diploma/GED	354	10.5%	39	6.2%	315	11.4%
HS Grad or GED	582	22.6%	86	21.6%	496	22.8%
Some College or Associates	684	31.0%	114	32.4%	570	30.7%
≥College Grad	558	30.4%	111	35.6%	447	29.3%
Race/Ethnicity						
Non-Hispanic White	1143	79.1%	223	84.9%	920	77.9%
Hispanic	478	7.3%	52	5.0%	426	7.8%
Non-Hispanic Black	608	8.8%	86	7.3%	522	9.1%
Other	221	4.8%	24	2.8%	197	5.2%
Smoker						
Never	1208	50.2%	166	44.6%	1042	51.3%
Former	930	39.1%	181	45.7%	749	37.8%
Current	311	10.7%	38	9.8%	273	10.9%
aMed Score (0-9)	3.6	0.1	3.5	0.1	3.6	0.1
Comorbidity Burden (0-8)B	1.8	0.0	1.9	0.1	1.7	0.0
Cancer TypeC						
Breast	92	3.8%	92	23.9%	0	0.0%
Prostate	88	3.6%	88	22.9%	0	0.0%
Melanoma	40	1.6%	40	10.4%	0	0.0%
Blood CancerD	16	0.7%	16	4.2%	0	0.0%
Multiple Cancers	36	1.5%	36	9.4%	0	0.0%
Childhood CancerE	2	0.1%	2	0.5%	0	0.0%
Cognition						
DSST Score	52.4	0.6	52.1	1.0	52.5	0.7
CERAD-WL	19.7	0.2	19.8	0.3	19.7	0.2
CERAD-DR	6.3	0.1	6.2	0.1	6.3	0.1
CERAD-Intrusions	0.6	0.0	0.6	0.1	0.6	0.0
Animal Fluency	18.1	0.2	18.1	0.4	18.1	0.2

ANs are unweighted and percentages, means, and SEs are weighted using the survey weights.

BComorbidity burden is the number of comorbidities a subject has. Comorbidities include stroke, heart attack, angina, congestive heart failure, coronary heart disease, type 2 diabetes, high cholesterol, high blood pressure, and liver condition.

CNot all cancer types are shown. Breast, prostate, and melanoma were the three most common cancers.

DBlood cancer is defined as having a history of leukemia, blood cancer, or lymphoma/Hodgkin’s Disease.

EChildhood cancer is defined as being diagnosed with cancer at less than 20 years of age.

Table 2 shows the association between past cancer history and cognitive performance. In the unadjusted model (model 1), past cancer history was not associated with DSST Score (β : 0.42; 95% [Confidence Interval [CI]: -2.95, 2.12), CERAD-WL (β : 0.10; 95% CI: -0.31, 0.51), CERAD-DR (β : -0.12; 95% CI: -0.39, 0.15), CERAD-Intrusions (β : -0.11; 95% CI: -0.38, 0.16), or Animal Fluency (β : -0.07; 95% CI: -0.75, 0.62).

In models adjusted for demographic characteristics (model 2) the results were generally similar in magnitude and direction and were not statistically significant. Models additionally adjusted for health (model 3) tended to be the lowest in magnitude and were also not statistically significant.

Table 2. Regression EstimatesA for Modeling of Cognition by Past Cancer History.

DSST Score	Cancer history β (95% CI)	<i>p</i>
Model 1: Cancer history	-0.42 (-2.95, 2.12)	0.74
Model 2: Model 1 + DemographicsB	-0.47 (-2.52, 1.58)	0.64
Model 3: Model 2 + Health & Health BehaviorC	0.04 (-1.83, 1.91)	0.97
CERAD-WL	Cancer history β (95% CI)	<i>p</i>
Model 1: Cancer history	0.10 (-0.31, 0.51)	0.63
Model 2: Model 1 + DemographicsB	0.27 (-0.15, 0.69)	0.20
Model 3: Model 2 + Health & Health BehaviorC	0.30 (-0.12, 0.72)	0.16
CERAD-DR	Cancer history β (95% CI)	<i>p</i>
Model 1: Cancer history	-0.12 (-0.39, 0.15)	0.38
Model 2: Model 1 + DemographicsB	-0.01 (-0.31, 0.28)	0.93
Model 3: Model 2 + Health & Health BehaviorC	0.00 (-0.29, 0.28)	0.98
CERAD-Intrusions	Cancer history β (95% CI)	<i>p</i>
Model 1: Cancer history	0.06 (-0.14, 0.26)	0.54
Model 2: Model 1 + DemographicsB	0.05 (-0.16, 0.26)	0.63
Model 3: Model 2 + Health & Health BehaviorC	0.06 (-0.16, 0.27)	0.59
Animal Fluency Score	Cancer history β (95% CI)	<i>p</i>
Model 1: Cancer history	-0.07 (-0.75, 0.62)	0.85
Model 2: Model 1 + DemographicsB	-0.13 (-0.70, 0.44)	0.65
Model 3: Model 2 + Health & Health BehaviorC	-0.03 (-0.58, 0.53)	0.93

Table 2 | Shown are estimates of the coefficients for past cancer history for each of the five cognitive scores for each model used.

AEstimated using ordinary least squares regression, except for CERAD Intrusions for which Poisson regression was used.

BDemographics: age, race, gender, income, education.

CHealth and Health Behavior: Diet, smoking, and comorbidity burden.

Table 3 shows whether the association between past cancer history and cognition varied by aMed as both a continuous and dichotomous variable (low vs. high Med Diet adherence). The association between past cancer history and cognition, as measured via Animal Fluency and CERAD-Intrusions, varied by aMed dichotomized at the median (β : -1.11, 95% CI: -2.33, 0.12 for Animal Fluency; β : 0.62, 95% CI: 0.04, 1.19 for CERAD-Intrusions) at the $\alpha = 0.10$ level; the inverse relationship between past cancer history and cognitive performance was stronger at higher levels of Med Diet adherence compared to lower levels.

Table 3. AssociationA of Past Cancer History with Cognition by Med Diet Adherence.

Model 3: Model 2B + Health and Health BehaviorC	Cancer history*aMed β (95% CI)	<i>p</i>
DSST Score	-0.46 (-1.37, 0.45)	0.31
CERAD-WL	-0.12 (-0.49, 0.25)	0.51
CERAD-DR	-0.07 (-0.25, 0.12)	0.47
CERAD-Intrusions	0.15 (-0.06, 0.35)	0.15
Animal Fluency Score	-0.28 (-0.63, 0.07)	0.12

Model 3: Model 2B + Health and Health BehaviorC	Cancer history*aMed_High_vs_Low β (95% CI)	<i>p</i>
DSST Score	-2.41 (-5.87, 1.05)	0.17
CERAD-WL	0.50 (-0.83, 1.84)	0.45
CERAD-DR	-0.14 (-0.74, 0.46)	0.63
CERAD-Intrusions	0.62 (0.04, 1.19)	0.04
Animal Fluency Score	-1.11 (-2.33, 0.12)	0.08

Table 3 | Shown are estimates of the coefficients for the interaction terms of past cancer history with aMed as a continuous variable and with aMed as a binary variable for each of the five cognitive scores for the fully adjusted model.

A Estimated using ordinary least squares regression, except for CERAD-Intrusions for which Poisson regression was used.

B Model 1 (Cancer hx) + Demographics (age, race, gender, income, education).

C Health and Health Behavior: Diet, smoking, and comorbidity burden.

Table 4 presents results for the Cancer history*age interaction. The association between past cancer history and cognition, as measured by CERAD-DR, varied by age (β : 0.81; 95% CI: 0.16, 1.45). The effect of past cancer history on cognition was higher at a higher age compared to a lower age.

Table 4. AssociationA of Past Cancer History with Cognition by Age.

Model 3: Model 2B + Health and Health BehaviorC	Cancer history*(≥ 75 years vs. < 75 years) β (95% CI)	<i>p</i>
DSST Score	2.80 (-1.23, 6.83)	0.17
CERAD-WL	0.75 (-0.45, 1.94)	0.21
CERAD-DR	0.81 (0.16, 1.45)	0.02
CERAD-Intrusions	0.03 (-0.50, 0.56)	0.91
Animal Fluency Score	0.68 (-0.90, 2.26)	0.39

Table 4 | Shown are estimates of the coefficients for the interaction terms of past cancer history with age as a binary variable for each of the five cognitive scores for the fully adjusted model.

A Estimated using ordinary least squares regression, except for CERAD-Intrusions for which Poisson regression was used.

B Model 1 (Cancer hx) + Demographics (age, race, gender, income, education).

C Health and Health Behavior: Diet, smoking, and comorbidity burden.

4. Discussion

Using NHANES data from the 2011-2012 and 2013-2014, we show that past cancer history is not significantly associated with cognitive performance after adjusting for several potential confounders, including age and diet. This differs from our hypothesis that cancer survivors would have poorer cognitive performance compared to non-cancer controls. Williams and colleagues used NHANES data from 1999-2002 and reported that cancer survivors have worse performance on DSST compared to non-cancer controls.[16] The difference between the results of our study and that of Williams et al. may be attributable to reduced cancer-related mortality that occurred continuously from the early-1990's to 2011.[40] Reductions in cancer mortality have occurred due to advances in cancer prevention, early detection, and treatment,[40] suggesting that cancers are being diagnosed at earlier stages, resulting in less aggressive treatments. In turn, this may result in less CRCI over time and less of an effect of cancer in our study compared to earlier ones, such as Williams et al.. A larger sample size may be better-powered to detect the potentially smaller differences in cognition between cancer survivors and non-cancer controls.

Our analysis tested for effect modification by aMed revealing that the association of past cancer history with cognition varies based on aMed adherence (as a binary variable). Specifically, the negative association of past cancer history with Animal Fluency Score and CERAD-Intrusions is stronger at higher levels of Med Diet adherence compared to lower levels. This also deviates from our hypothesis that any objective cognitive deficit associated with past cancer history would be lower (or null) with higher adherence to a Med Diet. However, in a 26-week randomized controlled clinical trial among 143 early-stage breast cancer survivors undergoing chemotherapy and radiation, participation in a diet and physical activity intervention increased cognitive flexibility significantly more compared to a usual care group.[41] In a cross-sectional study among breast cancer survivors (post-treatment) and non-survivors, vegetable and/or fruit consumption was positively associated with executive functioning.[14] These and, to our knowledge, all other studies investigating cognition and diet in cancer survivors have been in breast cancer survivors. NHANES includes all cancer types and treatments which may have led to our conflicting results compared to prior studies. It would be beneficial to investigate cancer-specific results in a larger cohort.

Past cancer history also interacted with age whereby the association of cancer survivorship with CERAD-DR was higher at a higher age (≥ 75 years) compared to a lower age (<75 years). In a recent analysis of the Health and Retirement Study cohort, cancer survivors had significantly higher memory scores than non-cancer controls *before* diagnosis, suffered a loss in memory capacity immediately after diagnosis that equalized their memory with that of non-survivors, but over the next decade maintained a slower rate of memory decline after diagnosis compared to non-cancer controls.[44] Cancer survivors in this NHANES cohort may have had a similar memory trajectory, and this may account for the inability to detect memory differences between survivors and non-cancer controls until older age.

The strengths of this study include the use of a large, nationally representative dataset. It is also the first to our knowledge to investigate the interaction of diet with past cancer history on cognition using a nationally representative dataset. Moreover, it is the first to report CERAD and Animal Fluency scores for cancer survivors using NHANES data.

Our study, however, is not without limitations. Because the data is cross-sectional, causality cannot be determined and residual confounding cannot be ruled out, though we did include a bevy of relevant confounders. Secondly, we were unable to provide estimates for different cancers and treatments as treatment data was not collected and not enough survivors of any cancer were available to conduct a meaningful statistical analysis. Given that not all cancer treatments, e.g., non-CNS radiation, result in cognitive impairment,[45] our results may have been affected by the inclusion of survivors who would not generally be expected to have cognitive impairment from cancer treatment. Future larger studies would be able to identify better which cancers and treatments are related to cognitive impairment.

This study is the first, to our knowledge, to use NHANES data from 2011-2014 to examine the association between past cancer history and cognitive performance. We show that past cancer history is not significantly associated with cognitive performance, even after controlling for several confounders. However, Med Diet adherence and age interacted with past cancer history. Specifically, the association of past cancer history with cognitive performance is lower at higher (versus lower) levels of Med Diet adherence, and the association of past cancer history with CERAD-DR is higher at a higher age (≥ 75 years) compared to a lower age (<75 years). Several reasons for these findings were proposed, such as the use of a highly heterogeneous population in terms of cancer type, but to confirm these suspicions, larger, prospective studies in older cancer survivors are needed.

Data availability statement: The data and data analysis scripts underlying this article are available in Box, at <https://uofi.box.com/s/tjc8yop079y3u11umj1kzv3jv9gki4hf>. The datasets were derived from sources in the public domain: NHANES at <https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/default.aspx?BeginYear=2011> and <https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/default.aspx?BeginYear=2013>.

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L.T.-H.; Project administration, A.M.; Resources, V.O., Software, V.O.; Supervision, V.O. and L.T.-H.; Validation, V.O.; Visualization, A.M. and V.O.; Writing—original draft, A.M.; Writing—review and editing, all authors. All authors have read and agreed to the published version of the manuscript.

Ethics Approval: This is a secondary data analysis of NHANES 2011-2014 which was approved by the National Center for Health Statistics Ethics Review Board (protocol #2011-17) and which was conducted in accordance with United States Federal Regulations, 45CFR46 subparts A through D.

Consent to Participate: Informed consent was obtained from all individual participants included in the study.

Consent to Publish: This manuscript contains no individual person's data in any form and as such the requirement for consent to publish is not applicable to this study.

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Conflicts of Interest: The authors declare no relevant competing interest.

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