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ORIGINAL ARTICLE

Cognitive function in cancer survivors: analysis of the 1999–2002 National Health and Nutrition Examination Survey

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Abstract
Purpose Cancer and its treatment may affect cognitive function through a number of direct and indirect pathways including inflammation, lipid metabolism, vascular damage, and changes in the blood–brain barrier. While short-term treatment-related cognitive changes are well recognized, only limited research is available in older, long-term survivors of cancer.
Methods Using NHANES data from 1999 to 2002, 408 cancer survivors and 2639 non-cancer participants aged 60 years old and above were identified. Cognitive function of these groups were compared using the Digit Symbol Substitution Test (DSST) and self-reported problems with memory or confusion.
Results After adjustment for covariates, cancer survivors scored, on average, 1.99 points lower on the DSST compared to non-cancer survivors (−1.99, 95 % CI −3.94, −0.05). Cancer survivors also had 17 % higher odds of self-reporting problems with memory or confusion (OR 1.17, 95 % CI 0.89, 1.53).
Conclusion In this nationally representative sample of older US adults, cancer survivors had lower DSST scores than non-survivors and had more self-reported problems with memory or confusion.

Keywords Cancer survivors · Cognition · NHANES · Cognitive function

Introduction

There are currently over 13 million cancer survivors in the USA [1], and numbers are expected to grow with increasing cancer survival [2, 3]. Therefore, identifying the sequelae of cancer treatments that impact quality of life becomes increasingly important. Over the last two decades, systematic research has established cognitive impairment as a common sequela of cancer treatment. Up to 30 % of patients may experience cognitive impairment before treatment, 75 % may experience it during treatment, and up to 35 % of survivors will experience impairment months or years after treatment [4]. Several meta-analyses have demonstrated cancer survivors perform worse in the domains of memory, attention, executive function, processing speed, visual and verbal memory, and language compared to non-cancer survivors right after or within 1 year of treatment [5–7]. However, other studies have reported little differences between survivors and non-survivors or did not find differences between patients and controls [8–10]. Cognitive impairment may only affect a subgroup of patients or may range from subtle to more severe in nature. Additionally, not all domains are affected the same in patients who experience them, making future studies with large sample sizes especially important [9, 10]. Cancer and its treatment may affect cognitive function through a number of direct and indirect pathways including inflammation, lipid metabolism, vascular damage, and changes in the blood–brain barrier [11–13].

While the consequences of a cancer diagnosis and treatment on physical and mental health have been recognized as clinically meaningful [2, 14], the long-term consequences on

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cognition (>5 years following diagnosis) have been less well studied despite a 12–82 % prevalence of cognitive impairment in long-term cancer survivors [4] and evidence suggesting that long-term cognitive impairment is biologically plausible [12]. Koppelmans and colleagues evaluated 196 breast cancer survivors, on average 21 years post diagnosis. These survivors performed worse on tests of memory, processing speed, and executive function compared to non-cancer survivors [15]. Heflin and colleagues report that among 702 cancer survivor-non-cancer survivor twin pairs, cancer survivors were twice as likely to have any cognitive impairment (OR 2.1, 95 % CI 1.36, 3.24) up to 14 years after treatment [16]. Two meta-analyses examining cross-sectional studies of long-term survivors have identified memory, executive function, and processing speed as areas of impairment [17, 18]. While not all studies have reported cognitive deficits in short- and long-term survivors, executive function, processing speed, and attention appear most frequently. Differences in results between studies may be attributable to limited sample size, varying cancer and treatment histories, the variety of cognitive assessments used, and varying time intervals from treatment discontinuation. The lack of difference between survivors and non-survivors on objective neuropsychological assessments may also be due to the potential subtle nature of cognitive impairment in long-term survivors as many studies have reported an increase in self-reported cognitive complaints that are not related to objective measures [19].

Only two studies have examined all types of cancer, in older adult survivors, and cognitive function, both from the Health and Retirement Study (HRS). Data from the 2002 wave of the HRS report no significant difference between cancer survivors and non-cancer survivor participants on the Telephone Interview for Cognitive Status; which is sensitive to dementia and focuses on the domains of attention, memory, and visuospatial processing [20]. Further analysis of the 2006 wave found that survivors performed 0.22 points higher on a total cognition score compared to non-cancer survivor participants (B=0.22, SE 0.13). This total cognition score summed results from a large battery of tests covering the domains of learning, memory, attention, language, and processing speed, among others. Additionally, similar effect sizes were reported when stratified by length of survival (long-term survivors (DEF) B=0.276, SE 0.131; short-term survivors B=0.10, SE 0.28) [21]. Both of these studies employed summary measures of cognition that may not have accurately characterized the cognitive impairment of this population as not all patients will have deficits in the same cognitive domains.

Researchers have hypothesized that older adults may be more susceptible to treatment-induced cognitive impairment, reporting that older patients, with a lower baseline on WRAT-3 reading score, who receive chemotherapy perform worse on measures of processing speed compared to those not exposed to chemotherapy as late as 18 months after chemotherapy [22]. However, it remains unclear if cognitive impairment later in life is associated with a history of cancer regardless of age at diagnosis. As a larger proportion of our population continues to age and the number of cancer survivors continues to grow, evaluating the effect of cancer on cognition later in life is imperative [1].

In order to examine the association between a history of cancer and cognitive impairment in older adults (>60 years), we utilized the National Health and Nutrition Examination Survey (NHANES), taking advantage of a large nationally representative sample that includes all types of cancers. Focusing our analysis on perceived cognitive function and objective assessment of processing speed, attention, executive function, learning, and working memory [23].

Methods

Study population

The NHANES is a survey designed to provide information regarding population demographics, health, and nutrition based on a sample representative of the US population. The survey is conducted by trained professionals and includes an in-home interview as well as a medical examination consisting of laboratory testing and medical questionnaires. In this cross-sectional design, using all adults aged 60 years and older from NHANES 1999 to 2002, we examined cancer history in relation to performance on the Digit Symbol Substitution Test (DSST, n=2547) and self-reported functional limitation due to difficulty remembering or periods of confusion (n=3047).

Cognition

Cognitive function is a broad concept, which can be separated into several domains: attention, executive function, visuospatial skill, learning, and memory [24]. In NHANES cycles from 1999 to 2002, the DSST was administered to all participants 60 years of age or older. The DSST consists of rows of blank boxes with a number above each box randomly selected between 1 and 9. Additionally, there is a code box in which the numbers 1 through 9 appear with a symbol beneath them. The participant is asked to enter the matching symbol into the blank boxes below the corresponding number, completing as many as they can within 120 s. The participant's score is the number of boxes filled correctly [25]. The DSST calls on several interrelated cognitive domains for its completion. A participant must be able to quickly compare and process the code box and blank boxes (processing speed), focus on this task for 120 s (attention), recall the corresponding symbol (memory), and quickly shift between pairs (executive function) [26]. Several epidemiologic studies have reported cancer patients performing worse on neuropsychological tests for

these domains compared to healthy participants [27, 28]. Thus, the DSST served as our primary outcome measuring cognitive function.

Five hundred participants did not complete the DSST and are excluded from these analyses. Among these 500, 173 were in an environment that was too distractive to take the test, 54 participants refused the test, 151 were unable to complete the sample test and thus did not take the DSST, and 63 did not complete the DSST for other reasons. Among those unable to complete the sample, 74 were due to physical limitations (e.g., impaired vision), and 54 were due to cognitive limitations. Lastly, among the 54 participants unable to complete the DSST due to cognitive limitations, only 6 were cancer survivors (11.1 %).

In addition to the DSST assessment, participants were asked: "{Are you/Is SP} limited in any way because of difficulty remembering or because {you/s/he} experience {s} period of confusion?" Participants were able to respond "yes," "no," "don't know," or "refused." Only 7 participants reported "don't know" while 1 participant was missing a response to this variable and was excluded from these analyses. This question may be more closely related to survivors' perceived memory performance as a proxy to impact on quality of life and may reflect a decline in cognition even though they still perform in the normal range on neuropsychological assessments [29]. It has been used to measure the prevalence of cognitive impairment in large population surveys [30].

Cancer history

Cognitive function in cancer survivors may be affected by both processes related to cancer etiology and consequences of cancer treatment. However, there is evidence to suggest the latter may have a greater impact [31, 32]. Therefore, we are using cancer history as a surrogate measure of exposure to chemotherapies and radiation treatments that may have had a lasting impact on a participant's cognition. Because the majority of skin cancers are non-melanoma and not treated with these modalities, participants reporting a history of skin cancer have been excluded.

Covariates

A priori, the following variables were identified as potential confounders of the relationship between cancer history and cognitive function: age, education, gender, and ethnicity. Education, gender, and ethnicity have been shown to predict performance on neuropsychological tests in cancer survivors and will be included as covariates in these analyses [33, 34]. Not only is an older person more likely to have experienced cancer, age effects have been reported with the DSST, with a sharp decline in score after age 60 [25]. Therefore, age was assessed as a confounder as well as an effect modifier with cancer history. The DSST has been strongly correlated with self-reported general health [30], and cancer survivors are more likely to self-report poor or fair health status. Therefore, we explored self-reported health status as a covariate influencing the association between cancer history and cognitive function either as a confounder or a mediator.

Statistical analysis

All statistical analyses were done using SAS version 9.3 (SAS Institute, Cary, NC), using survey procedures with appropriate sample weights. Descriptive statistics for covariables were calculated in the overall population and in relation to cancer history. Cancer history was assessed as a dichotomous variable (yes/no) and as a categorical variable distinguishing between long-term survivors (those 5 or more years since diagnosis), short-term survivors (those less than 5 years from diagnosis), and no history of cancer. Using linear regression, we assessed the relationship between the continuous DSST score and any history of cancer as well as long and short-term survivors compared to those with no history of cancer. Logistic regression was used to examine the odds of self-reported memory problems or confusion in those with any history of cancer, long-, or short-term survivorship to those with no history of cancer. Two regression models were run: a crude model and a model adjusting for a priori selected covariates. We computed 95 % confidence intervals (CI) as a measure of statistical precision. In order to examine the effect modification of cancer history by age and interaction term was included in the models mentioned above, and stratum specific estimates were generated for those less than 75 years old and those 75 or more years old.

Results

Participant characteristics according to cancer history are presented in Table 1. Participants with a history of cancer were, on average, 11.57 years post diagnosis and 52 participants reported having more than one cancer. Cancer survivors were significantly older and more highly educated. Cancer survivors scored slightly worse on the DSST (44.07 vs. 46.27). A higher percentage of survivors self-reported problems with memory or confusion (13.3 vs. 11.30 %).

Table 2 shows mean difference in DSST score and relative odds of self-reported memory problems in cancer survivors compared to non-cancer participants. On average, cancer survivors scored 2.19 points lower on the DSST compared to those with no history of cancer (B=−2.19; CI=−4.73, 0.34). After adjustment for covariates, cancer survivors scored, on average, 1.99 points lower on the DSST compared to non-survivors (CI=−3.94, −0.05). Upon categorizing cancer history into short- (<5 years) and long-term (5 or more years),

Table 1 Participant characteristics according to self-reported problems with memory or confusion and mean DSST score according to participant characteristics

Characteristic	Overall	History of cancer	
		Yes	No
N=3047	3047	408 (14.84)	2639 (85.15)
Age (years)	71.00 (0.25)	72.87 (0.56)	70.67 (0.26)
Sex			
Male	1487 (42.1)	221 (45.7)	1266 (54.2)
Female	1560 (57.8)	187 (41.5)	1373 (58.4)
Education[1]			
<HS	1398 (33.4)	140 (27.3)	1258 (34.4)
HS	676 (28.5)	96 (27.8)	580 (28.6)
Some college	553 (21.0)	94 (24.2)	459 (20.5)
College or >	408 (16.9)	77 (20.5)	331 (16.3)
Ethnicity			
NH-White	1623 (79.2)	274 (84.8)	1349 (78.3)
Mexican American	666 (3.3)	44 (1.5)	622 (3.6)
Hispanic	131 (5.5)	15 (4.3)	116 (5.7)
NH-Black	559 (8.9)	67 (6.8)	492 (9.3)
Other	68 (2.9)	8 (2.3)	60 (3.0)
General health status[2]			
Excellent	386 (14.6)	40 (10.6)	346 (15.3)
Very good	685 (26.1)	70 (16.8)	615 (27.7)
Good	982 (32.5)	142 (38.7)	840 (31.4)
Fair	734 (19.3)	110 (2.7)	624 (1.1)
Poor	256 (7.3)	46 (10.2)	210 (6.8)
DSST score (*n*=2547)	45.95 (0.59)	44.07 (1.06)	46.27 (0.67)
Self-reported memory or confusion problems			
Yes	398 (11.6)	53 (13.3)	345 (11.30)
No	2641 (88.3)	355 (86.6)	2286 (88.6)

[1] 12 subjects missing education information

[2] 104 subjects missing self-reported health status

compared to non-survivors, long-term survivors had a lower mean difference in DSST score (B=−2.83; CI=−5.66, 0.005) as did short-term survivors (B=−0.83; CI=−4.27, 2.60). This trend continued upon adjustment for covariates (short-term B=−1.18, CI=−3.15, 1.14; long-term B=−2.38, CI=−4.57, −0.18).

Cancer survivors had 1.19 times the relative odds of self-reporting problems with memory or confusion compared to those without a history of cancer (odds ratio (OR)=1.19; CI=0.94, 1.51, data not shown). After adjustment for covariates, cancer survivors had 17 % increased odds of self-reporting problems with memory or confusion compared to non-survivors (OR=1.17; CI=0.89, 1.53). Being a long-term survivor was associated with higher relative odds of self-reported problems with memory or confusion compared to non-survivors (OR=1.49; CI=1.09, 2.04). However, short-term survivors had lower odds compared to non-survivors (OR=0.61; CI= 0.33, 1.15) and neither association persisted after adjustment for covariates (short-term OR=0.65, CI=0.31, 1.34; long-term OR=1.41, CI=0.99, 2.02).

When self-reported health status was added as a covariable in modeling either outcome, the results became null suggesting that self-reported health may be moderating the association between cancer history and cognitive impairment (DSST B=−1.02; CI=−2.99, 0.94; self-reported cognition OR=0.97; CI=0.75, 1.25). Stratum specific results for age categories are reported in Table 3 along with *p* values for the interaction term between cancer history and age. Results suggest that age modifies the association between cancer diagnosis and cognitive outcomes, with a larger effect size in the younger group (<75 years). Among those younger than 75, cancer survivors performed 3.25 points lower on the DSST compared to non-cancer survivors (B=−3.25; CI=−5.88, −0.62). However this difference was only 0.18 points lower among those 75 or older (B=−0.18; CI=−2.94, 2.57; p=0.11). A similar trend was observed for self-reported cognition. Among those older than 75, cancer survivors had 19 % lower odds of self-reported problems with memory or confusion compared to non-cancer survivors (OR=0.81; CI=0.51, 1.29). However, among younger than 75, cancer survivors had 71 % increased odds of self-reported problems with memory or confusion (OR=1.71; CI 1.01, 2.80; p=0.09).

Discussion

In this nationally representative sample of older US adults, cancer survivors performed worse on an objective test of processing speed, attention, executive function, learning, and working memory after adjustment for age, gender, education, and ethnicity. Our findings also suggest that cancer survivors have higher odds of self-reporting problems with memory or confusion; however, this association failed to achieve statistical significance except when examined in only those between 60 and 75 years old.

Consistent with our findings, Keating et al. report that older US adult (>55 years) cancer survivors and non-survivors did not differ in self-reported memory status (29.6 vs. 30.4 % reporting excellent or very good memory, p=0.55) [20]. Interestingly, a separate study done in NHANES waves from 2001 to 2006 using all participants over the age of 40 found that those with a history of cancer had 40 % higher odds of self-reported memory problems compared to those without a history of cancer (OR 1.4, 95 % CI=1.08, 1.83) after adjusting for age, gender, ethnicity, general health status, and income [35]. Upon the addition of those aged 40 to 59 to our analysis we saw a similar effect size (OR 1.23, 95 % CI=0.91, 1.67). When our analysis was stratified, among those aged 40–59, survivors had a 77 % greater relative odds of self-reported memory problems compared to non-survivors, while among those 60 and above, there was only a 13 % increase in relative

Table 2 Mean difference in DSST score and odds of self-reported problems with memory and confusion in those with a history of cancer compared to those without

	Mean difference in DSST score (95 % CI)	Odds of self-reported problems with memory or confusionOR (95 % CI)
N	2539	3024
History of cancer		
Yes vs. no	−1.99 (−3.94, −0.05)	1.17 (0.89, 1.53)
Short-term	−1.18 (−3.50, 1.14)	0.65 (0.31, 1.34)
Long-term	−2.38 (−4.57, −0.18)	1.41 (0.99, 2.02)
Age (75+ vs. <75)	−11.87 (−13.01, −10.73)	2.63 (2.01, 3.44)
Gender (vs. female)	−4.14 (−5.64, −2.64)	1.11 (0.84, 1.47)
Education		
<HS (ref)	0.0 (ref)	1.00 (ref)
HS	10.58 (8.62, 12.54)	0.59 (0.39,0.88)
Some college	14.21 (12.59, 15.83)	0.52 (0.32, 0.85)
College or >	19.51 (17.93, 21.09)	0.29 (0.35, 0.97)
Ethnicity		
NH-White	0.0 (ref)	1.00 (ref)
Mexican American	−9.13 (−11.59, −6.68)	1.76 (1.28, 2.42)
Hispanic	−13.24 (−16.12, −10.35)	1.88 (1.13, 3.11)
NH-Black	−13.45 (−15.29, −11.60)	1.22 (0.86, 1.74)
Other	−2.89 (−8.90, 3.11)	1.84 (0.75, 4.52)

Models are mutually adjusted for age, gender, education, ethnicity, and self-reported general health status

odds. In our original analysis, which was restricted to those 60 and above, after stratifying by those below and above 75 years of age our associations attenuated in the older age group, suggesting that age is acting as an effect modifier of the association between cancer history and self-reported memory problems. Although those 75+ were a median of 7 years post diagnosis and those between 60 and 75 years were 5.5 years post diagnosis, it seems unlikely that a 1.5-year difference would account for the difference in association seen across these two groups. We hypothesize that having cancer may accelerate cognitive decline in younger participants but have less of an impact on older adults.

After adjustment for covariates, we found a significant negative association between cancer history and DSST score which is inconsistent with two studies that have reported findings from two different waves of the US Health and Retirement Study. The first, using the 2002 wave, found no difference in proportion of long-term cancer survivors (more than 4 years since diagnosis) and non-survivors in each quartile of total cognition score (p=0.92) [20]. The second (using the 2006 wave) found that those with a history of cancer scored 0.22 points higher on the total cognition score, although not statistically significant. They also report that long-term survivors scored significantly higher compared to non-survivors (B=0.27, SE 0.13) whereas we report here long-term and short-term survivors performed worse on average compared to non-survivors. The difference in direction of association may be attributable to the difference in neuropsychological assessment. The HRS utilized a global measure of cognition whereas this analysis utilizes an assessment sensitive to the domains of processing speed, executive function, and attention [25].

Table 3 Mean difference in DSST score and odds of self-reported problems with memory and confusion in those with a history of cancer compared to those without stratified by age (younger than 75 years or 75 years and older)

	N (%) cancer survivors	Mean difference in DSST score (95 % CI)	Odds of self-reported problems with memory or confusion OR (95 % CI)
N (%)	408 (14.8 %)	2539	3024
History of cancer (yes vs. no)			
Among <75 years	189 (17.7 %)	−3.25 (−5.88, −0.62)	1.71 (1.01, 2.80)
Among ≥75 years	219 (11.0 %)	−0.18 (−2.94, 2.57)	0.81 (0.51, 1.29)
p value for interaction		0.11	0.09

Models adjusted for age, gender, education, and ethnicity

In this population, self-reported health status may be a mediator of the association between cancer history and cognitive function. Upon the addition of self-reported health status to our adjusted model estimating the difference in DSST scores, the effect size attenuated to 1 and was no longer significant (B=−1.02; CI=−2.99, 0.94). Similarly, when health status was added to models estimating odds of self-reported memory of confusion the association became null (OR=0.97; CI= 0.75, 1.25). The attenuation of results indicates mediation by self-reported health status that may reflect comorbidities that are a result of cancer and also influence cognitive function [36]. Self-reported health status appears to be an important variable that should be measured in future studies examining cognitive impairment.

We lacked information on treatment type and duration; instead, we used cancer history as a surrogate measure of these exposures. While we excluded participants with skin cancers that likely only received resection, it is possible that a substantial number of participants reporting cancer may have not received chemotherapy or radiation. Studies that have compared chemotherapy-treated patients to locally treated patients have reported that those treated with chemotherapy perform worse on tests of cognitive function [32, 37]. Our inability to make this classification may have masked the true association. However, it has been hypothesized that the cancer itself causes inflammatory mechanisms resulting in cognitive impairment [31]. Therefore, our large heterogeneous sample of cancer survivors adds to the discussion of whether it is the total cancer experience or treatment with chemotherapy that results in cognitive impairment.

Sample size limitations did not allow for analysis by cancer type, limiting our ability to compare our findings to the majority of existing literature primarily done in breast cancer survivors. Additionally, DSST analyses were restricted to those 60 years and older and stratifying by age indicated the younger (<75 years) survivors in our analysis performed worse than younger non-survivors. However, this effect was not seen in the older participants (≥75) indicating that a large proportion of the effect size was attributable to effect modification by age. We hypothesize that in this population, the effect of age on cognitive function outweighs the effect of cancer history. Further, we were unable to objectively quantify the effect of cancer history on cognition in a younger age group that may be more sensitive to cancer-related impairment. It is also important to note that the self-reported cognitive impairment is by definition subjective and illustrates an individual's perceived cognitive difficulties in their daily life and have not consistently correlated with objective measures [19, 38–40]. Self-reported cognitive impairment has also been associated with anxiety and depression (which were unavailable for this analysis); however, the directions of these associations are not well defined and may actually be due to reverse causality. Still, subjective measures of cognitive impairment remain important as they correlate well with quality of life measure, and many cancer survivors that self-report cognitive impairment also report they are significantly bothered by these complaints [41].

This is the only study to examine domain-specific cognitive deficits in a large, nationally representative, older population of long-term cancer survivors. We report here deficits in a test of processing speed, attention, executive function, learning, and working memory. The use of the DSST in this study is advantageous as it is a brief and sensitive test of these domains; particularly the functioning of attentional processes. Impairment in these domains has been associated with decreased social role functioning and community engagement [42] as well as increased difficulty reading and driving [43]. All of these activities are important in maintaining quality of life and autonomy, especially in older adults [36]. While the number of older cancer survivors (60+) continues to grow, studies on cognitive impairment in this group are limited. These results add to the discussion of whether older survivors experience cognitive impairment and whether it is due to cancer-related toxicity or biological age. We provide evidence that cancer survivors over 60 years of age are at higher risk for cognitive impairment compared to other older adults. Further, we report those between 60 and 75 years experience a higher rate of impairment compared to those 75+, suggesting a possible threshold effect with biological age or the fact that those between 60 and 75 may be closer in time to their completed treatment. While many studies have examined the short-term effects of cancer therapy on cognition, relatively little has been done in long-term survivors, especially older long-term survivors. The cancer survivors in this sample on average were 12 years from diagnosis and we were able to stratify results by long- and short-term (<5 years) survivors. We found some indication that length of survival may be an effect modifier as long-term survivors were somewhat more likely to self-report memory problems and also scored lower on the DSST (Table 2).

Conclusion

Our study indicates that long-term cancer survivors suffer more cognitive impairment than non-cancer survivors, but study limitations may have masked a more pronounced association. Future longitudinal studies should utilize heterogeneous groups of cancer survivors and should place importance on a large age range to examine age effects, as well as use a comprehensive battery of neuropsychological tests.

Compliance with ethical standards

Conflict of interest The authors declare they have no competing interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

Informed consent Informed consent was obtained from all individual participants included in this study upon their enrollment into NHANES.

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