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Recent cancer treatment and memory decline in older adults: An analysis of the 2002–2012 Health and Retirement Study

Krystle E. Zuniga [a,*], Nicholas J. Bishop [b]

[a] Nutrition and Foods, Family and Consumer Sciences, Texas State University, 601 University Drive, San Marcos, TX 78666, USA
[b] Family and Child Development, Family and Consumer Sciences, Texas State University, San Marcos, TX, USA

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ABSTRACT

Objective: Few studies have examined the impact of cancer treatment on cognitive trajectories in the growing population of older adults diagnosed with and surviving cancer. This study examined whether recent cancer and its treatment accelerated memory decline in older adults.
Materials and Methods: We conducted a secondary analysis of observations drawn from the Health and Retirement Study (2002–2012), a population-based sample of older adults in the United States. Changes in immediate (IWR) and delayed word recall (DWR) scores were estimated by latent growth modeling in individuals who never had cancer ($n = 10{,}939$) or had been diagnosed with cancer between 2000 and 2002 and received treatment with some combination of radiation and/or surgery ($n = 240$), chemotherapy only ($n = 34$), or chemotherapy and some combination of radiation and/or surgery ($n = 64$).
Results: In the period immediately following treatment, individuals reporting a recent cancer treated with chemotherapy and surgery/radiation experienced significantly more rapid decline in IWR ($b = -0.34$, $SE = 0.17$, $p = 0.047$) and DWR ($b = -0.38$, $SE = 0.19$, $p = 0.049$) than the non-cancer group. Sensitivity analyses addressing mortality selection and memory-related disease at baseline attenuated the strength of these associations. There were no other statistically significant differences in estimated linear or quadratic slope by cancer status or treatment.
Conclusion: Our results support a potential association between recent cancer treatment and trajectories of memory decline in older adults and provide guidance on the interpretation of statistical estimates from panel studies of health and aging.

1. Introduction

More than 74% of the 15.5 million cancer survivors currently living in the U.S. are 60 years of age or older [1]. Cancer therapies result in side effects that may have long-term impacts on health, potentially accelerating the aging process and associated declines in physical and cognitive health [2]. Cancer-related cognitive impairments may affect multiple cognitive domains, leading to slower processing speed, memory lapses, difficulty concentrating and multitasking, and confusion [3]. Moreover, older cancer survivors with pre-existing age-related cognitive impairment may be at greater risk of worsening cognitive dysfunction due to cancer treatment compared to their younger counterparts [4].

Age is a well-established, non-modifiable risk factor for cognitive decline and is commonly associated with biological alterations such as immune dysfunction, systemic inflammation, hormonal imbalance, DNA damage, oxidative stress, and blood -brain barrier damage [3]. Additionally, aging is associated with declines in grey and white matter integrity and changes in volume and activity of the frontal lobe and hippocampus, resulting in negative impacts on working memory, processing speed, and executive function [5]. The biological alterations typically observed in cancer patients are similar to the changes observed during aging, most notably oxidative stress, inflammation, and cognitive impairment. Based on these overlapping processes of cancer and aging, it has been hypothesized that cancer and its treatments may accelerate physical and cognitive aging [3]. The phase shift hypothesis suggests that cancer treatment causes an initial cognitive change, and then cognitive decline follows normal aging; whereas the accelerated aging hypothesis suggests that cancer treatment accelerates the normal cognitive decline associated with aging. The majority of longitudinal studies in cancer survivors have examined short-term cognitive changes (up to 3 years post-treatment), failing to observe long-term cognitive trajectories and determine if deficits in cognitive function may reemerge when exacerbated by age-related brain changes [6–9].

Evidence suggests that recent cancer and its treatment impacts cognitive decline in older adults and there are shared pathways between cancer and aging. However, few studies have examined the long-term impacts of cancer treatment on cognitive trajectories in the growing

* Corresponding author at: Texas State University, 601 University Drive, San Marcos, TX 78666, USA.
E-mail addresses: k_z17@txstate.edu (K.E. Zuniga), nicholas.bishop@txstate.edu (N.J. Bishop).

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population of older adults diagnosed with and surviving cancer. Therefore, longitudinal studies in older, newly diagnosed cancer patients and survivors are needed to determine whether cancer and its treatment exacerbate the cognitive decline associated with normal aging. We conducted a secondary analyses of the Health and Retirement Study to examine the impact of a recent cancer and its treatment on trajectories of memory in a representative sample of community-dwelling older Americans.

2. Methods

2.1. Survey Design and Sample Selection

Observations were drawn from the Health and Retirement Study (HRS), a nationally-representative panel study designed to collect transdisciplinary data on older adults beginning in 1992 with biennial follow-up [10]. The HRS is sponsored by the National Institute on Aging (grant number NIA U01AG009740) and is conducted by the University of Michigan. The HRS was approved by the University of Michigan Institutional Review Board and participants provided informed consent at enrollment. Texas State University's Institutional Review Board determined that analyses of HRS data were exempt from review. In association with the NIA and the Social Security Administration, the RAND Corporation developed a cleaned data file containing imputed wealth and income measures (version O) [11]. The HRS survey is collected using both face-to-face and telephone interviews, with cognitive scores being shown not to differ by interview mode [12]. To account for complex sampling design and to produce nationally-representative estimates, person-level analysis weights from 2002, household identification number accounting for nesting of observations, and stratification adjustments for standard errors were included in all analyses.

To examine whether recent cancer and treatment status was associated with variation in trajectories of word recall in older adults, this study utilized outcome data measured from 2002 to 2012 with all covariates being measured in 2002. Surveys before 2002 restricted the number of cancer treatment types the respondent could select, with the 2002 survey and later waves allowing respondents to select as many cancer treatment types as were applicable. The initial sample in 2002 including 20,159 observations was reduced by removing individuals that were not identified as being a member of an HRS study-cohort based on age or had missing age values in 2002 ($n = 2994$). Due to scarcity of observations at the oldest ages, individuals age 100 and older at any wave were removed ($n = 60$). Those that had missing data on either the 2002 immediate or delayed word recall scores ($n = 2142$), had missing data on 2002 cancer and treatment status ($n = 1467$), or reported a cancer diagnosis between 2000 and 2002 and reported no cancer treatment ($n = 56$) or treatment only for symptoms associated with cancer such as pain, nausea, or rashes ($n = 46$) were also removed. To compare word recall among individuals recently diagnosed with cancer against those who did not report developing a cancer over the period observed, participants reporting a cancer diagnosis in the year 2000 or before ($n = 213$) or a cancer diagnosis between 2004 and 2012 ($n = 1694$) were removed. Finally, 210 observations with missing data on baseline covariates were removed, resulting in a final analytic sample size of 11,277.

2.2. Measures

Immediate word recall (IWR) and delayed word recall (DWR) scores were used as measures of memory and fluid processing abilities. The IWR and DWR tests are free recall tasks measuring the construct of episodic verbal memory and are shown to be sensitive to changes in fluid cognitive abilities [13,14]. Respondents were asked to recall words from a list of 10 common nouns (e.g. lake, car, army) with the number of words correctly recalled providing the IWR score. Interviewers read from one of four randomly assigned word lists and subsequent administrations used a different word list for the three following waves [15]. The DWR score was calculated as the number of words correctly recalled after approximately 5 min of other survey questions being asked. When modeling change in IWR and DWR, a count of previous word recall tests, beginning in the first HRS wave in 1992, was included as a time-varying covariate in all models.

The focal predictor variable was a combined measure indicating whether the respondent reported a new cancer diagnosis in the two years prior to the 2002 interview, and if so, what type of treatment they received. Respondents were placed in mutually exclusive categories representing those reporting no cancer in the past two years, those who reported cancer and either reported treatment through radiation or surgical methods, chemotherapy treatment as their only form of treatment, or chemotherapy in addition to radiation and/or surgery. The no cancer group was used as reference in all analyses.

A number of variables measured in 2002 were included as covariates. All analyses controlled for respondents' age, gender, race/ethnicity, and marital status. Other covariates included education, longest occupational tenure, retirement status, obesity (a body mass index (BMI) of 30 kg/m^2 or greater), vigorous physical activity, alcohol consumption (non-drinkers (reference group), moderate drinkers (males:1–14 drinks per week, females: 1–7 drinks per week), and heavy drinkers (males: >14 drinks per week, females: >7 drinks per week), limitations in activities of daily living (ADLs) and instrumental activities of daily living (IADLs), and a sum of chronic conditions (high blood pressure, diabetes, lung disease, heart disease, stroke, psychiatric problems, and arthritis). Any diagnosis of a memory-related disease was included to control for pre-existing memory impairments. Analysis of descriptive statistics included bivariate ANOVA with Tukey post-hoc tests to test mean differences across cancer status and treatment types and chi-square with pairwise statistical tests using the Bonferroni correction for multiple testing to identify significant differences in categorical variables across cancer status and treatment groups.

2.3. Statistical Methods

Mplus version 7.3 was used to estimate separate conditional nonlinear latent growth trajectories of IWR and DWR [16]. Latent growth modeling (LGM) builds on a structural equation modeling framework allowing the estimation of change over time using latent variables [17]. Nested model fit testing of unconditional growth models indicated that the quadratic model best fit the observed data for both measures of memory. In our model, the latent linear slope represents immediate change in the period directly following baseline measurement, and the latent quadratic slope represents rate of change at later periods of observation [18]. The alpha level used to identify statistically significant estimates was $p < 0.05$.

The x-axes of the latent growth models were specified using individually-varying time scores based on age. Individual time scores were defined as participants' age at each interview centered on the grand mean age at baseline measurement in 2002, divided by 10. This specification of time allows the mean intercept to be interpreted as the average word recall score at the mean age of the sample in 2002, and the mean linear and quadratic latent slopes to represent change in word recall over a 10-year period of increase in age.

Maximum likelihood estimation with robust standard errors was used as the estimator in all analyses, accommodating both non-normality and data missing at random (MAR). When observing developmental change in older adults, mortality selection may bias parameter estimates when dropout is associated with the outcome of interest [19,20]. The challenges of accurately estimating cognitive trajectories in the presence of mortality selection are especially difficult considering the increased risk of death related to cognitive decline, cancer diagnosis, and variation in treatment based on cancer type, stage, and other conditions. To examine the influence of mortality selection on the parameter estimates of interest, we conducted sensitivity analyses using a pattern

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