COMPARISON OF FUNCTIONAL AND COGNITIVE CAPACITY AMONG CANCER SURVIVORS AND CANCER-FREE INDIVIDUALS IN AN OLDER U.S. POPULATION

by
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Abstract

Background

The global population is aging rapidly, and cancer is one of the major health concerns of an aging population. Older cancer survivors can be challenged by the toxicities associated with cancer and its treatment in addition to the normal declines in functional and cognitive capacities due to aging. However, we only have limited data on whether older cancer survivors have worse functional and cognitive capacity profiles than their cancer-free counterparts.

Method

For this study, 7,459 participants from Health and Retirement Study (HRS) and completed functional capacity questionnaire between Feb 2016 to April 2018 were included, among which 1,238 are cancer survivors, and the rest are cancer-free. Answers from biennial HRS questionnaires were used for exposure and outcome ascertainment. Poisson regression models with robust variance were used to estimate the risk ratio (RR) for the association between cancer history and prevalence of functional and cognitive limitation. Stratified analysis by race/ethnicity was performed to explore potential race/ethnic group difference. Sensitivity analyses excluding demented participants were performed to evaluate the reliability of the primary analyses.

Results

A significant positive association was observed between cancer history and any

disability in basic ADLs (adjusted Risk Ratio = 1.09, 95% CI (1.01, 1.18). A significant positive association was observed between cancer history and any disability in IADLs (adjusted Risk Ratio = 1.11 (1.02, 1.22). Cognitive capacity did not differ significantly between cancer survivors and cancer-free participants. Low educational level, depressive symptoms within 12-month, and dementia history may also contribute to poor functional and cognitive capacities. Stratified analyses showed that non-Hispanic white has similar results to the analytic population. Because of group size, other race/ethnic groups do not show statistically significant associations, but the point estimate directions are similar to the analytic population except for gender. Sensitivity analysis results were similar to that of the primary analysis.

Conclusion

Older U.S. individuals with cancer history have reduced functional capacities but not cognitive capacity compared to older U.S. individuals without cancer history. More research is needed to study these differences and how to improve older cancer survivors' functional capacity, therefore optimizing health in elderly cancer survivors.

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1 Introduction

According to World Population Prospects 2019, by 2050, 1 in 6 people in the world will be over the age of 65, up from 1 in 11 in 2019 (United Nations, 2019). Cancer is one of the major health concerns of an aging population. In 2012, 47.5% of the total number of new cancer cases worldwide were adults aged 65 years and older, while only 8% of the world population was aged 65 years and older (Pilleron et al., 2019). In the U.S., more than 90% of cancer survivors are 50 years or older (American Cancer Society, 2019). The American Cancer Society estimated that the number of cancer survivors in the US will increase from 16.9 million in 2019 to more than 22.1 million by 2030 (American Cancer Society, 2019), and the majority of this increasing population will be older adults. Therefore, studies focused on understanding the impact of a cancer diagnosis specifically on older adults are urgently needed.

Older individuals are challenged by the toxicities associated with cancer and its treatment in addition to the normal declines in functional and cognitive capacities due to aging. (Mustian et al., 2012). It is unclear to what extent the diagnosis and treatment of cancer accelerate aging associated declines in functional and cognitive capacities.

There are studies that have investigated the association between cancer history, functional capacity limitations, and health-related outcomes. Sweeney's study on elderly female population pointed out that female cancer survivors were more likely to experience functional limitations than women with no cancer history (Sweeney et al., 2006). Blackwood et al. pointed out that basic ADLs disability, a measurement of

functional limitations, in older cancer survivors varied by age, stage, and cancer type with greater impairment with advanced age and stage cancer survivors, which also encouraged further research on ADLs disability among cancer survivors (Blackwood et al., 2020). Chavan and colleagues indicated that cancer survivors with more functional limitations and poorer self-rated health status had a higher hospitalization rate and higher risk of mortality compared to their cancer-free counterparts (Chavan et al., 2020). Reduced functional capacity in cancer survivors is also suggested to be a potential indicator of poorer quality of life (QOL) (Brekke, 2019).

Literatures have also indicated association between cancer history and cognitive failures. In a review of literature from 1970 to 2018, Coughlin and colleagues concluded that older breast cancer survivors suffer from cancer-related health issues including physical functioning and cognitive functioning (Coughlin et al., 2018). In a study comparing chemotherapy treated breast cancer survivors to their cancer-free counterparts for inflammation markers and cognitive performance differences, breast cancer survivors had a lower general cognitive performance even 20 years after treatment. (van der Willik et al., 2018). However, research studying cognitive impairment in cancer survivors was mainly conducted among breast cancer survivors and their counterparts, limited data are about cognitive disability among other cancer survivors and their counterparts (Guida et al,.2019).

A better understanding of the difference in functional and cognitive capacity profiles of U.S. older cancer survivors and their cancer-free counterparts is essential for more targeted and sophisticated impairment-oriented interventions and

rehabilitation for cancer survivors.

This project aimed to explore the potential prevalence difference in functional and cognitive capacity disability among older U.S. cancer survivors and cancer-free people. We hypothesize that cancer history is positively associate with poor functional and cognitive capacities, and lower educational level and dementia history may also associate with poor functional and cognitive capacities. Older age and recent depressive symptom could be potential confounders.

2 Methods

2.1 Study Population

The Health and Retirement Study (HRS, https://hrs.isr.umich.edu/) is a prospective cohort study of the older U.S. population (HRS profile, 2014) initiated by National Institute of Aging (NIA) and conducted by the Institute for Social Research (ISR) at the University of Michigan. HRS enrolled its first wave of participants in 1992, and then merged with Asset and Health Dynamics Among the Oldest Old (AHEAD) in 1998. HRS has been enrolling new participants every 6 years (Servais, 2004).

Study participants were recruited through household screening and the primary respondent was randomly selected from all age-eligible (⩾ 50 years of age) household members. The spouse or partner of the primary respondent was recruited regardless of age. Participants were interviewed face-to-face (FTF) by trained interviewer at baseline. Respondents are interviewed biennially, on topics of health, health-care usage, employment, economy, and family. Follow-up interviews are conducted in forms including telephone interview, FTF interview, enhanced FTF interview, internet surveys and self-administered mail surveys. The response rate for the 1992 baseline interview was 81.6%, and between 85-90% for the biennial interview from1994 through 2016. All aspects of the Health and Retirement Study have been approved by the University of Michigan Health Sciences and Behavioral Sciences Institutional Review Board (Ann Arbor, MI). For this study, we use publicly available deidentified data that was considered exempt by the Johns Hopkins School

of Public Health Institution Research Board.

2.2 Study Design and Analytical Population

For this study, our eligible population was male and female participants 50 years or older at 2014 who enrolled in the HRS between 1992 and 2014, completed a baseline questionnaire, and have completed functional testing between Feb 2016 to April 2018.

Among 19,330 HRS cohort participants who were 50 years or older in 2014, 8,928 completed the Functional Limitations and Helpers questionnaire (Section G) and Cognition (Section D) between 2016-2018 and were therefore eligible for the current study. Participants with missing time of enrollment information (N=1,292) or time of 2014/2016 interview information (N=177) were subsequently excluded from analytic population. Therefore, the analytic population was 7,459 participants in total.

2.3 Primary Exposure

The primary exposure was cancer survivor history, and this was based on self-report. The participant was asked in Health Status (Section C since 2004, Section B before 2004) of the questionnaire about his/her cancer history every time he/she was interviewed (every 2 years). There are five questions asking cancer related status but answer for more than half of the participants was missing for three of five questions. We used the remaining two questions to determine cancer status: Has a doctor ever told you that you have cancer or a malignant tumor, excluding minor skin cancer (C018)? Has a doctor told you that you had NEW cancer or a malignant tumor, excluding minor

skin cancer since last interview(C024)? The participant was ascertained to have a cancer history if he/she EVER answered “Yes” to C018 and/or C024 in 2014 interview and did not dispute in 2016 interviews. Non-melanoma skin cancers were not counted as cancers for this study. Those participants without cancer history were classified as cancer-free individuals.

2.4 Outcome

The primary outcome of this study is functional capacity. Functional capacity was measured by disabilities in basic activities of daily living (ADLs) and instrumental activities of daily living (IADLs). In this study, ADLs were defined as dressing, walking, bathing, eating, getting in/out bed, and using toilet, and IADLs were defined as meal preparing, grocery shopping, making phone calls, taking medication, and managing money. In HRS, ADLs and IADLs were measured by Section G (Functional Limitations and Helpers) questionnaire. We used the functional capacity questionnaire answered at 2016 wave (interview conducted during Feb 2016 to April 2018) to ascertain the outcome. Participants were asked whether they had any difficulty in completing certain daily activity and whether they needed help with this daily activity. IADL responses of “yes” (has difficulty), “can't do,” and “don't do because of a health or memory problem,” and ADL responses of “yes,” “can't do,” and “don't do” were considered limitations. (Freedman et al., 2013). We dichotomized the outcome and ascertained the participant to have disability in ADLs and/or IADLs if we determined the participant to have disability of any daily activity within ADLs’ and/or IADLs’ realm.

For example, if participant A reported difficulty in eating, bathing, and managing money, and participant B reported difficulty only in preparing meals; we would determine that participant A had disability in both ADLs and IADLs, and participant B only had disability in IADLs. Examples of questions were showed in Table 5.

The secondary outcome of this study is cognitive capacity. We used self-reported memory, which was measured by question 101 in Cognition (Section D) questionnaire: How would you rate your memory at the present time? Participants would rate his/her memory as 1) Excellent, 2) Very good, 3) Good, 4) Fair, or 5) Poor. We collapse it into two categories: good versus poor memory. Therefore, participants who self-rated their memory as excellent, very good, or good were classified as having good memory, and participants who self-rated their memory as fair or poor were classified as having poor memory. Participants' working memory were measured by conducting immediate and delayed word recall. The participant was presented with a set of 10 words and asked to recall as many as he/she can immediately after the presentation, and after the participant answer another set of other questions (delayed recall). The variable was numerical, ranging from 0 to 10 for immediate and delayed recall, 0 to 20 for total recall. The outcome was then dichotomized into good versus poor working memory, and the cut point was determined by the medium number of correctly recalled words in cancer-free participants which was 5 for immediate recall, 4 for delayed recall, and 9 for total recall.

2.5 Demographic and comorbidity information

Demographic information was assessed by Section B (Demographic) questionnaire. Race/Ethnicity was ascertained when the participant was enrolled in the study. The participant was asked “Do you consider yourself Hispanic or Latino” and “What race do you consider yourself to be: White, Black or African American, American Indian, Alaska Native, Native Hawaiian, Pacific Islander, or something else?” The later question allowed select all that apply. We classified participant to be non-Hispanic White, Hispanic, Black, and others in this study. Education received by the participant was measured by asking “What is the highest grade of school or year of college you completed?” (B014) at enrollment, and the answer ranging from “no formal education” to “post-college (17+ years)”. The participant was also asked whether they get a high school diploma or have passed a high school equivalency test (B015). If the participant answered “some college” or “other in B014, follow-up questions on whether they received a college degree (B016) and highest degree earned (B017) was asked. We classified participants to have 4 levels of education: “less than high school”, “high school”, “college” and “graduate school”. The participant was ascertained to have “graduate school” education if they answered “Masters/MBA”, “Law”, “PhD”, “MD” to question B017, or “Post college (17+ years)” in B014. Among the remaining participants, we ascertained them to have “college” education if they answered “yes” to question B016 or answered “4 or more years college” to question B014. Among the remaining participants, we ascertained them to have “high school” education if they answered “yes” to question B015, or answered “12th grade”, “1-year college”, “2-years

college", "3-years college" to question B014. All other participants were ascertained to have "less than high school" education.

Other health-related information that could impact functional status was measured by Section C (Physical Health) questionnaire interviewed between Feb 2016 to April 2018. Question structure were similar to question C018 in Table 5. We dichotomized physical health variables to ever vs. never because these conditions like hypertension and diabetes are chronic conditions that has long-term effect and cannot be completely cured. For depression, a potential confounder, question C271 asked whether the participant ever had depression in lifetime, and question C150 asked whether the participant felt depressed within the last year. We ascertained the participant to ever be depressed if he/she answered "yes" to either of questions or ascertained him/her to be depressed within the last year if the participant answered "yes" to C150.

2.6 Statistical Analysis

The descriptive statistics of exposure, outcomes, demographic, and comorbidity information were calculated and presented absolute numbers and percentages, continuous variables were presented as mean (standard deviation) and median (IQR). Age was analyzed as categorical variable and was categorized into 10-year intervals. The youngest group (50-59 years of age) served as the reference group, and the oldest old was defined as those above 90 years old. The reference gender is female. The reference educational level was high school education. According to Educational

Attainment in the United States: 2019 table package, 89.61% of U.S. adults received high school or higher education. Categorical and binary variables were compared by Pearson's Chi-squared test. Continuous variables were compared using *t* tests. The following variables were treated as binary: gender (female, male), diabetes (ever, never), hypertension (ever, never), Smoking (current, non-current), alcohol consumption (ever, never), depression (ever, never), depressed within last year (yes, no), dementia (ever, never), hearing problem (ever, never) and osteoporosis (ever, never). The following variables were treated as categorical: race/ethnicity (non-Hispanic white, Hispanic, Black, others), and education (less than high school, high school, college, graduate school).

In this study, log binomial regression models were used, but they did not converge. Therefore, Poisson regression models with robust variance (an approximation to log binomial regression models when log binomial regression models did not converge) were used to estimate adjusted risk ratio (aRR) and 95% confidence interval (95% CI) for the association between cancer history and risk of having disability in basic ADLs and IADLs and having poor memory. Age and time from enrollment were adjusted for all models. In adjusted models, follow-up years (continuous), gender, age in 10 years, educational level, depressive symptoms within last 12-month, and dementia history were adjusted.

Stratified analysis by race/ethnicity groups were conducted because we want to explore whether there are racial differences for association between exposure and outcomes. Because smaller number of participants within each subgroup, the oldest

was redefined as 80 years and above, and educational level were dichotomized into less than high school versus high school degree and above. Adjusted RR and 95% CI were estimated using Poisson regression models with robust variance. Age, gender, time from enrolment, educational level (less to high school versus high school diploma and higher), depression within last year, and dementia were adjusted in stratified models.

Sensitivity analysis excluding demented participants were performed to evaluate the reliability of the primary analyses. Poisson regression models with robust variance were used and age, gender, time from enrolment, educational level (less to high school versus high school diploma and higher), depression within last year were adjusted.

Power and sample size analyses were performed to estimate the power of this analysis based on the analytic population size and the proportions of having ADLs/IADLs disabilities among cancer survivors and cancer-free individuals. One-sided hypothesis tests (cancer survivor having more limitations in ADLs/IADLs) with Type I error rate of 0.05 were performed using Chi-squared test.

Statistical significance refers to a 2-sided P value <0.05, and all the statistical analysis was performed using Stata 15 (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC.).

3 Results

3.1 Descriptive Results

The baseline demographics, comorbidities, and functional capacity disabilities are shown in Table 1. At the time of last survey, cancer survivors and cancer-free participants had mean ages of 74 years and 70 years, respectively. Cancer survivors were significantly older in age ($p<0.001$) and were more likely to be male.

Cancer survivors were more likely to be non-Hispanic White ($p<0.001$). Compared to cancer-free participants, a significantly higher proportion of cancer survivors reported college or higher (i.e., post-college graduate school) education ($p<0.001$).

Overall cancer survivors and cancer-free participants had similar comorbidity profiles. There was no significant difference between the prevalence of diabetes, hypertension, lifetime depression, dementia, and osteoporosis among cancer survivors and cancer-free participants. The prevalence of 12-month depressive symptoms and hearing problem were significantly different between cancer survivors and cancer-free participants, the p-value were <0.001 and 0.023, respectively. Among physical health problems, dementia (2.83% for cancer-free, 2.50% for cancer survivor), hearing problem (2.86% for cancer-free, 2.50% for cancer survivor), and osteoporosis (4.48% for cancer-free, 5.41% for cancer survivor) were rare (had a prevalence less than or close to 5%), while hypertension (73.57% for cancer-free, 74.72% for cancer survivor) was the most common comorbidity.

3.2 Functional Capacity

A significant positive association was observed between cancer history and any disability in basic ADLs (adjusted Risk Ratio = 1.09, 95% CI (1.01, 1.18). In the multivariable Poisson regression model with robust variance. In the age-adjusted model, the point estimate is similar (1.05), but the difference is not statistically significant (95% CI: 0.97, 1.14). For IADLs, the association is significant in the multivariable model, but not in the age-adjusted model: The point estimates and 95% CIs for age-adjusted and multivariable model are 1.06 (0.97, 1.16) and 1.11 (1.02, 1.22), respectively. Gender, age modelled as deciles, educational level, time between HRS cohort enrollment and outcome determination (follow-up years), depressive symptoms within last 12 months, and dementia history were adjusted for the multivariable model (See Table 2 and 3).

The risk of any disability in ADLs and IADLs among analytic population increased with age modelled as deciles. When compared to the youngest age group (50-59 years old), the oldest old group (90 years and older) had the highest aRR of 1.87 (95% CI, 1.57, 2.22) for risk of any disability in ADLs, and highest aRR of 2.54 (95% CI, 2.12, 3.04) for risk of any disability in IADLs. The interaction between continuous age and cancer history was not statistically significant, as well as the interaction between age categories (under 70 vs. equal or older than 70) and cancer history.

In the primary analysis, higher education showed a significant protective effect on successfully performing activities of daily living. The risk of any disability in ADLs and IADLs elevated by 1.30 (95% CI: 1.22, 1.39) and 1.38 (95% CI: 1.28, 1.48) times,

respectively, if the participant did not have a high school education. The risk of any disability in IADLs lowered to 0.85 (95% CI: 0.74, 0.98) if the participant had a college degree, suggesting potential benefit in IADL performance for people who completed higher education. The interaction between educational level (less than high school vs. high school or higher) and cancer history was not statistically significant.

Depression within last year and dementia were also positively associated with risk in poorer functional capacity. Comparing to participants who did not reported experiencing depressive symptoms within the last year, those who reported depressive symptoms within the last year had a 1.62 (95% CI: 1.52, 1.72) time risk of having any disability in basic ADLs, and a 1.70 (95% CI: 1.58, 1.83) time risk of having any disability in IADLs. Demented participants were more likely to have difficulty in performing ADLs and IADLs comparing to non-demented participants, the adjusted RR were 1.61 (95% CI: 1.43, 1.80) and 2.30 (95% CI: 2.09, 1.83), respectively. Sensitivity analysis excluding demented patients (N= 209) were conducted, and results were similar (data not presented).

3.3 Cognitive Capacity

Unlike ADL, Cognitive capacity characterized by self-rated memory and working memory (tested by immediate and delayed word recall), did not differ significantly between cancer survivors and cancer-free participants (Table 4). In both age-adjusted and multivariable Poisson regression models with robust variance, the relative risk and adjusted relative risk for cancer survivor to have poorer self-rate memory were 0.99

(95% CI: 0.82, 1.07) and 1.04 (0.96, 1.11). For working memory, the RR and aRR for cancer survivors to have poorer working memory increased by 0.97 (95% CI: 0.92, 1.03) and 1.00 (95% CI: 0.94, 1.06), respectively, indicating no significant difference between cancer survivors' and their cancer-free counterparts'' working memory. Self-rated memory was not associated with age, but working memory declined with increased age. As expected, higher educational level showed a protective effect both on self-rated memory and working memory. Comparing to participants with high school degree, the aRR for having poor self-rated memory and poor working memory among participants with less than high school education was 1.47 (95% CI: 1.36, 1.58) and 1.38 (95% CI: 1.28, 1.48), respectively. People with college degree or higher had lower risk of having poor self-rate memory and poor working memory when compared to high school diploma owners. Depressive symptoms within 12-month were also associated to poorer self-rated and working memory, the aRR were 1.85 (95% CI: 1.72, 1.98) and 1.70 (95% CI: 1.58, 1.83), respectively.

3.4 Stratified Analysis

In the analytic population, a large portion of race/ethnicity information was missing. Stratified analyses were performed to explore the potential different associations of cancer history and functional capacity disability among different race/ethnic groups.

In the stratified analyses, a significant positive association were observed between cancer history and any disability in ADLs and in IADLs among non-Hispanic White

subgroup. The risk of having any disability ADLs and IADLs among non-Hispanic White cancer survivors, comparing to non-Hispanic White cancer-free participants, were 1.15 (95% CI: 1.03, 1.28) and 1.13 (95% CI: 1.01, 1.27) times higher, respectively. Similar positive associations were observed for Hispanic subgroup, but the association was not statistically significant: The aRR was 1.29 (95% CI: 1.00, 1.67) for ADLs and was 1.30 (95% CI: 0.97, 1.75) for IADLs. The association between cancer history and any disability in ADLs and IADLs was not statistically significant, but point estimate suggests potential trend. Comparing to Black cancer-free participants, Black cancer survivors' risk of having any disability ADLs and IADLs were 1.10 (95% CI: 0.92, 1.33) and 1.21 (95% CI: 0.98, 1.51) times higher, respectively (see Table 6).

Depression within last year and dementia history remained significant predictors of any disability in ADLs and IALDs for all race/ethnicity groups.

3.5 Sensitivity Analysis

As mentioned above, sensitivity analysis excluding demented participants (N=209) were conducted, and the point estimate and 95% confidence Interval were similar to the overall analyses.

3.6 Power and Sample Size Analysis

Power and sample size were performed separately for disabilities in ADLs/IADLs. Sample size, Type I error rate (α), and proportions of cancer survivors and cancer-free individuals having disabilities in ADLs/IADLs were known. The power of correctly

detecting difference between prevalence of having ADLs/IADLs limitation among cancer survivors and cancer-free individuals were 38.32% and 81.92%, respectively.

4 Discussion

4.1 Interpretation

To our knowledge, this study is the first national representative population-based study to compare the difference of self-reported disabilities in basic activity of daily living (ADLs), instrumental activity of daily living (IADLs), and cognitive capacity among males and female cancer survivors compared to cancer free individuals. The findings of this study indicated that older cancer survivors experience a higher prevalence of disabilities in ADLs and IADLs than similar aged cancer free individuals but not self-rated memory and working memory. Literatures indicated that percentage of experiencing difficulties ADL/IADL in age 65+ community population were 20-30% and 10-40% respectively, which are similar to the estimation from current study (35.2% for ADL and 28.71% for IADL) (Martin, Schoeni, & Andreski, 2010; Freedman et al., 2013; Bleijenberg, 2017).

Previous studies have indicated that cancer survivors are more likely to have more physical function limitation (defined as ≥2 out of 5 on the Rosow-Breslau scale or ≥4 out of 10 on the SF-36 physical function subscale) among Iowa women (Blair et al., 2019). Another study among Iowa women also indicated higher prevalence of functional limitations among women who had cancer compared to women who did not have cancer (Sweeney et al., 2006). An U.K. study found that cancer survivors are at higher risk of having mobility and ADL impairments (Williams et al., 2016). A systematic review on 20 studies focusing on breast cancer survivors also indicated

functional impairment burden (Bijker et al., 2018). The analysis of current study expends the knowledge on difference of ADL and IADL limitations between cancer survivor and cancer-free individuals.

Coughlin et al.'s review and van der Willik's study on cognitive impairment among breast cancer survivor have demonstrated association between breast cancer history and cognitive impairment. Von Ah concluded in her review on cognitive changes associated with cancer and cancer treatment that studies have found out that 44% of breast cancer survivors have clinically significantly memory deficits, cancer survivors reported cognitive impairment including impairments in memory, attention and concentration, speed of processing, and executive functioning (Von Ah, 2015). The estimated prevalence of mild cognitive impairment (MCI) varies from study to study (Ward, Arrighi, Michels, & Cedarbaum, 2012). For the purpose of this study, we want to explore the difference between cognitive capacity, rather than stick to a DSM-V diagnosis criterion, therefore the populational prevalence of MCI is not much relevant to our aim.

4.2 Strength and Limitation

There are several strengths of this study. While examining the difference between older cancer survivors and cancer-free individuals, this study also took demographic characteristics and comorbidity profile into consideration. The comorbidity and behavioral pattern of this analytic population are similar to the national statistics, validifying the reliability of national representativity of this analytic population.

This study has several limitations. First of all, cancer history was self-reported and physician confirmation was not made. Although efforts were made to reduce the number of misreporting, there might still be limited misclassification of cancer history status. Second, due to the nature of the HRS, large portion of missed information on specific cancer type and cancer treatment does not allow us to analyze how cancer type and cancer treatment would influence functional and cognitive capacities. Additionally, with no physician confirmation and electronic health record available, the specific time of cancer diagnosis was unavailable for analysis, so that we cannot estimate how time from cancer diagnosis would influence the current association. Also, the cross-sectional design makes it difficult to interpret the association identified. Some demographic characteristics and comorbidity profile differences between cancer survivor and cancer-free individuals were identified in this study. Though adjusted for potential confounders, we cannot draw any casual conclusion without a longitudinal study design.

4.3 Conclusion

The goal of this study to examine and quantify the difference in functional and cognitive capacity disability among cancer survivors compared to older U.S. cancer-free individuals. In general, older U.S. individuals with cancer history have poorer functional capacities but not cognitive capacity than older U.S. individuals without cancer history. This suggests the importance of assessing functional capacity in cancer survivors early and that cancer survivors may need for intense rehabilitation to

maintain activities of daily living, which is important for independence. In July 2018, the National Cancer Institute convened basic, clinical, and translational science experts for a think tank titled “Measuring Aging and Identifying Aging Phenotypes in Cancer Survivors.” The think tank pictured future research to study cancer survivors’ long-term and late-emerging effects of cancer and related treatment on aging endpoints (Guida et al., 2019). Poorer functional capacity among cancer survivors has been associated with higher hospitalization rate, higher re-hospitalization rate, and higher mortality (Chavan et al., 2020). More research is needed to study the synergistic relationship between cancer and aging, therefore optimizing health in elderly cancer survivors.

Table 1. Basic Characteristics of Cancer Survivors and Cancer-free participants

Characteristic	Cancer Free (N=6,221)	Cancer Survivor (N=1,238)	P-value
Age			<0.001
Mean (SD)	70.50 (10.13)	74.32 (9.80)	
Median (IQR)	69 (62-78)	75 (67-82)	
Gender			0.056
Male	2,175 (34.96)	468 (37.80)	
Female	4,046 (65.04)	770 (62.20)	
Race & Ethnicity			<0.001
Non-Hispanic White	2,804 (45.44)	567 (68.15)	
Hispanic	349 (5.66)	36 (4.33)	
Black	736 (11.93)	95 (11.42)	
Others	275 (4.46)	31 (3.73)	
Missing	2,007 (32.52)	103 (12.38)	
Education			<0.001
Less than High School	1,586 (25.49)	240 (19.39)	
High School	3,480 (55.94)	711 (57.43)	
College	545 (8.76)	133 (10.74)	
Graduate School	462 (7.43)	127 (10.26)	
Missing	148 (2.35)	27 (2.18)	
Diabetes			0.576
Ever	2,160 (34.72)	420 (33.93)	
Never	4,055 (65.18)	818 (66.07)	
Missing	6 (0.13)	0	
Hypertension			0.353
Ever	4,563 (73.57)	925 (74.72)	
Never	1,650 (26.33)	313 (25.28)	
Missing	8 (0.13)	0	
Alcohol Consumption			0.735
Ever	2,913 (46.83)	573 (46.28)	
Never	3,305 (53.13)	664 (53.63	
Missing	3 (0.05)	1 (0.08)	
Smoking			<0.001
Current	893 (14.35)	128 (10.34)	
Non-current	5,327 (85.63)	893 (89.66)	
Missing	1 (0.02)	0	
Lifetime Depression			0.760
Yes	2,685 (43.09)	529 (42.73)	
No	3,530 (56.83)	709 (57.27)	
Missing	6 (0.10)	0	
12-month Depression			0.027
Yes	1,487 (23.90)	260 (21.00)	
No	4,717 (75.82)	975 (78.76)	

Missing	17 (0.27)	3 (0.24)	
Dementia			0.484
Ever	178 (2.86)	31 (2.50)	
Never	6,037 (97.04)	1,207 (97.50)	
Missing	6 (0.10)	0	
Hearing Problem			0.023
Ever	159 (2.86)	46 (2.50)	
Never	6,062 (97.44)	1,192 (97.50)	
Missing	1 (0.10)	0	
Osteoporosis			0.154
Ever	279 (4.48)	67 (5.41)	
Never	5,929 (95.31)	1,167 (94.26)	
Missing	13 (0.21)	4 (0.32)	
Any Disability in Basic ADLs			0.178
Yes	2,172 (34.91)	457 (36.91)	
No	4,050 (65.09)	783 (63.09)	
Any Disability in Instrumental ADLs			0.010
Yes	1,746 (28.11)	393 (31.74)	
No	4,472 (71.89)	845 (68.26)	
Self-rated Poor Memory			0.894
Yes	2,630 (42.28)	521 (42.08)	
No	3,584 (57.61)	716 (57.84)	
Missing	7 (0.11)	1 (0.08)	
Poor Working Memory			0.116
Yes	3,069 (49.33)	641 (51.78)	
No	3,152 (50.67)	597 (48.22)	
Year Since Last Interview			0.053
Mean (SD)	2.14(0.40)	2.11 (0.36)	
Median (IQR)	2 (2-2)	2 (2-2)	

Table 2: Age adjusted risk ratio (RR) and adjusted risk ratio (aRR) and 95% confidence interval (95% CI) of having any disability in basic activity of daily livings (ADLs) among cancer survivors and cancer-free participants.

	Age-Adjusted[a]		Adjusted[b]	
	RR (95% CI)	P-value	aRR (95% CI)	aP-value
Cancer history				
No	ref (1)		ref (1)	
Yes	1.05 (0.97, 1.14)	0.265	1.09 (1.01, 1.18)	0.030
Gender				
Male	1.05 (0.99, 1.12)	0.100	1.09 (1.03, 1.17)	0.005
Female	ref (1)		ref (1)	
Age[c]				
50-59			ref (1)	
60-69			1.09 (0.99, 1.20)	0.087
70-79			1.08 (0.93, 1.24)	0.313
80-89			1.32 (1.14, 1.53)	<0.001
90 and above			1.87 (1.57, 2.22)	<0.001
Education				
Less than High School	1.38 (1.29, 1.47)	<0.001	1.30 (1.22, 1.39)	<0.001
High School	ref (1)		ref (1)	
College	0.91 (0.80, 1.03)	0.127	0.89 (0.79, 1.01)	0.064
Graduate School	0.92 (0.81, 1.05)	0.199	0.92 (0.81, 1.05)	0.227
Depression				
Never	ref (1)		ref (1)	
Within last year	1.69 (1.59, 1.80)	<0.001	1.62 (1.52, 1.72)	<0.001
Dementia				
No	ref (1)		ref (1)	
Yes	1.77 (1.58, 1.97)	<0.001	1.61 (1.43, 1.80)	<0.001

a Adjusted for age

b Adjusted for follow-up years (continuous), gender, age in 10 years, educational level, depression symptoms within last 12-month, and dementia history.

c Age at 2016 interview.

Table 3: Age adjusted risk ratio (RR)and adjusted risk ratio (aRR) and 95% confidence interval (95% CI) of having any disability in instrumental activity of daily livings (IADLs) among cancer survivors and cancer-free participants.

	Age-Adjusted[a]		Adjusted[b]	
Characteristic	RR (95% CI)	P-value	aRR (95% CI)	aP-value
Cancer history				
No	ref (1)		ref (1)	
Yes	1.06 (0.97, 1.16)	0.219	1.11 (1.02, 1.22)	0.016
Gender				
Male	0.99 (0.92, 1.07)	0.812	1.02 (0.95, 1.10)	0.497
Female	ref (1)		ref (1)	
Age[c]				
50-59			ref (1)	
60-69			0.95 (0.85, 1.08)	0.445
70-79			1.05 (0.88, 1.24)	0.601
80-89			1.57 (1.32, 1.87)	<0.001
90 and above			2.54 (2.12, 3.04)	<0.001
Education				
Less than High School	1.47 (1.36, 1.58)	<0.001	1.38 (1.28, 1.48)	<0.001
High School	ref (1)		ref (1)	
College	0.86 (0.74, 0.99)	0.036	0.85 (0.74, 0.98)	0.026
Graduate School	0.74 (0.63, 0.87)	<0.001	0.75 (0.63, 0.88)	<0.001
Depression				
Never	ref (1)		ref (1)	
Within last year	1.85 (1.72, 1.98)	<0.001	1.70 (1.58, 1.83)	<0.001
Dementia				
No	ref (1)		ref (1)	
Yes	2.54 (2.31, 2.78)	<0.001	2.30 (2.09, 2.54)	<0.001

a Adjusted for age

b Adjusted for follow-up years (continuous), gender, age in 10 years, educational level, depression symptoms within last 12-month, and dementia history.

c Age at 2016 interview.

Table 4: Age adjusted risk ratio (RR)and adjusted risk ratio (aRR) and 95% confidence interval (95% CI) of poor self-rated and working memory among cancer survivors and cancer-free participants.

	Self-rated Memory		Working Memory	
Characteristic	RR[a] (95% CI)	aRR[b] (95% CI)	RR[a] (95% CI)	aRR[b] (95% CI)
Cancer history				
No	ref (1)	ref (1)	ref (1)	ref (1)
Yes	0.99 (0.82, 1.07)	1.04 (0.96, 1.11)	0.97 (0.92, 1.03)	1.00 (0.94, 1.06)
Gender				
Male	1.08 (1.02, 1.14)	1.12 (1.06, 1.18)	1.23 (1.17, 1.28)	1.26 (1.21, 1.32)
Female	ref (1)	ref (1)	ref (1))	ref (1))
Age				
50-59		ref (1)		ref (1)
60-69		1.01 (0.93, 1.10)		1.17 (1.07, 1.28)
70-79		0.99 (0.87, 1.11)		1.47 (1.31, 1.64)
80-89		0.93 (0.81, 1.05)		1.97 (1.77, 2.21)
90 and above		0.88 (0.74, 1.06)		2.39 (2.11, 2.70)
Education				
Less than High School	1.47 (1.39, 1.55)	1.42 (1.35, 1.50)	1.44 (1.38, 1.50)	1.40 (1.34, 1.46)
High School	ref (1)	ref (1)	ref (1)	ref (1)
College	0.86 (0.77, 0.97)	0.86 (0.77, 0.96)	0.80 (0.72, 0.88)	0.78 (0.71, 0.86)
Graduate School	0.69 (0.60, 0.79)	0.69 (0.60, 0.79)	0.60 (0.52, 0.68)	0.59 (0.52, 0.66)
Depression				
Never	ref (1)	ref (1)	ref (1)	ref (1)
Within last year	1.38 (1.30, 1.46)	1.29 (1.22, 1.37)	1.24 (1.18, 1.30)	1.18 (1.12, 1.24)
Dementia				
No	ref (1)	ref (1)	ref (1)	ref (1)
Yes	1.91 (1.76, 2.06)	1.77 (1.63, 1.93)	1.49 (1.39, 1.61)	1.40 (1.29, 1.51)

a Adjusted for age

b Adjusted for follow-up years (continuous), gender, age in 10 years, educational level, depression symptoms within last 12-month, and dementia history.

c Age at 2016 interview.

Table 5: Sample questions from Health and Retirement Study Questionnaire

Question Number	Question text
C018	Has a doctor ever told you that you have cancer or malignant tumor, excluding minor skin cancer? 1. Yes 3. Disputes previous wave record, but now has condition 4. Disputes previous wave record, does not have condition 5. No 8. Don't know 9. Refuse
C019	In the last two year, have you seen a doctor about your cancer? 1. Yes 5. No 8. Don't know 9. Refuse
C020	We want to know about any cancer treatment that may have taken place during the last two years. In the last two years, have you received any treatment for cancer? 1. Yes 5. No 8. Don't know 9. Refuse
C024	Since your last interview, has a doctor told you that you had a new cancer or malignant tumor, excluding minor skin cancer? 1. Yes 5. No 8. Don't know 9. Refuse
C026	In which organ or part of your body did your cancer start? 1. Organ/Body Part: 8. Don't know 9. Refuse
C028	In what year was your (most recent) cancer diagnosed? 1. Year 8. Don't know 9. Refuse
C029	In what month was that 1. Month

Table 5 cont.: Sample questions from Health and Retirement Study Questionnaire

Question Number	Question text
ADL	Here are a few more everyday activities. Please teel me if you have any difficulty with theses because of physical, mental, emotional or memory problem. Again, exclude any difficulties you expect to last less than three months.
G014	Because of a health or memory problem do you have any difficulty within dressing, including putting on shoes and socks? 1. Yes 5. No 6. (if vocal) Can't do 7. (if vocal) Don't do 8. Don't know 9. Refuse
G015	Does anyone ever help you dress? 1. Yes 5. No 8. Don't know 9. Refuse
IADL	
G041	Because of a health or memory problem do you have any difficulty preparing a hot meal? 1. Yes 5. No 6. (if vocal) Can't do 7. (if vocal) Don't do 8. Don't know 9. Refuse
G043	Does anyone help you prepare hot meals? 1. Yes 5. No 8. Don't know 9. Refuse

Table 6: Adjusted risk ratio (aRR) and 95% confidence interval (95% CI) of having any disability in basic and instrumental activity of daily livings (ADLs and IADLs) among cancer survivors and cancer-free participants, stratified by race & ethnicity.

	Race and Ethnicity group*							
	Non-Hispanic White (N=3,579)		Hispanic (N=406)		Black (N=882)		Others (N=318)	
Characteristic	ADLs	IADLs	ADLs	IADLs	ADLs	IADLs	ADLs	IADLs
Cancer history								
No	ref (1)	ref (1)	ref (1)	ref (1)	ref (1)	ref (1)	ref (1)	ref (1)
Yes	1.15 (1.03, 1.29)	1.13 (1.01, 1.27)	1.29 (1.00, 1.67)	1.30 (0.97, 1.75)	1.10 (0.92, 1.33)	1.21 (0.98, 1.51)	1.07 (0.73, 1.55)	0.93 (0.59, 1.47)
Gender								
Female	ref (1)	ref (1)	ref (1)	ref (1)	ref (1)	ref (1)	ref (1)	ref (1)
Male	1.20 (1.08, 1.32)	1.10 (0.99, 1.22)	1.07 (0.85, 1.34)	0.89 (0.69, 1.16)	0.94 (0.79, 1.13)	1.16 (0.72, 1.87)	0.93 (0.70, 1.22)	1.08 (0.77. 1.50)
Age								
50-59	ref (1)	ref (1)	ref (1)	ref (1)	ref (1)	ref (1)	ref (1)	ref (1)
60-69	1.02 (0.73, 1.42)	0.96 (0.67, 1.37)	2.69 (0.54, 13.49)	1.68 (0.30, 9.51)	1.04 (0.73, 1.48)	0.76 (0.50, 1.14)	1.09 (0.73, 1.62)	1.03 (0.56, 1.90)
70-79	1.05 (0.73, 1.50)	1.12 (0.77, 1.65)	3.01 (0.60, 15.15)	2.97 (0.51, 17.39)	1.08 (0.70, 1.65)	0.75 (0.45, 1.17)	0.89 (0.49, 1.61)	0.81 (0.37, 1.81)
80 and above	1.46 (1.02, 2.10)	1.91 (1.31, 2.79)	3.14 (0.62, 15.80)	3.97 (0.68, 23.18)	1.28 (0.83, 1.98)	1.16 (0.72, 1.87)	1.32 (0.72, 2.40)	1.76 (0.80, 3.87)
Education								
High School and above	ref (1)	ref (1)	ref (1)	ref (1)	ref (1)	ref (1)	ref (1)	ref (1)
Less than High School	1.18 (1.04, 1.33)	1.45 (1.29, 1.63)	1.89 (1.42, 2.52)	1.85 (1.34, 2.55)	1.16 (0.99, 1.35)	1.22 (1.01, 1.46)	1.13 (0.88, 1.46)	1.70 (1.22, 2.33)
Depression								
Never	ref (1)	ref (1)	ref (1)	ref (1)	ref (1)	ref (1)	ref (1)	ref (1)
Within last year	1.38 (1.48, 1.55)	1.50 (1.33, 1.68)	2.03 (1.64, 2.51)	1.45 (1.15, 1.84)	1.83 (1.58, 2.11)	1.82 (1.51, 2.19)	1.41 (1.10, 1.81)	1.69 (1.22, 2.33)
Dementia								

No	ref (1)	ref (1)	ref (1)	ref (1)	ref (1)	ref (1)	ref (1)	ref (1)
Yes	1.79 (1.48, 2.15)	2.59 (2.24,2.99)	1.40 (0.98, 1.99)	1.67 (1.22, 2.27)	1.48 (1.08, 2.03)	2.44 (1.93, 3.07)	1.73 (1.19, 2.51)	2.03 (1.39, 2.98)

*Adjusted for age in decile, gender, time from enrolment, educational level (less to high school versus high school diploma and higher), depression within last year, and dementia history.

Table 7: Adjusted risk ratio (aRR) and 95% confidence interval (95% CI) of interaction terms in basic and instrumental activity of daily livings (ADLs and IADLs) among cancer survivors and cancer-free participants.

Cancer History *	ADL	IDAL	Self-rated Mem	Working Mem
	aRR[a] (95% CI)	aRR[b] (95% CI)	aRR[a] (95% CI)	aRR[b] (95% CI)
Age (cont.)	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)	1.00 (1.00, 1.01)
>70	0.97 (0.83, 1.14)	0.92 (0.76, 1.11)	1.04 (0.89, 1.21)	1.03 (0.89, 1.18)
Sex	1.00 (0.85, 1.17)	1.15 (0.96, 1.37)	1.07 (0.93, 1.24)	1.14 (1.02, 1.27)
12-month depression	1.01 (0.86, 1.18)	1.06 (0.89, 1.27)	0.87 (0.74, 1.01)	0.95 (0.84, 1.08)

References

Bijker, R., Duijts, S. F. A., Smith, S. N., de Wildt-Liesveld, R., Anema, J. R., & Regeer, B. J. (2018). Functional impairments and work-related outcomes in breast cancer survivors: A systematic review. Journal of Occupational Rehabilitation, 28(3), 429–451.

Blackwood, J., Karczewski, H., Huang, M. H., & Pfalzer, L. (2020). Katz activities of daily living disability in older cancer survivors by age, stage, and cancer type. Journal of Cancer Survivorship: Research and Practice, 14(6), 769–778.

Blair, C. K., Jacobs, D. R., Jr, Demark-Wahnefried, W., Cohen, H. J., Morey, M. C., Robien, K., & Lazovich, D. (2019). Effects of cancer history on functional age and mortality. Cancer, 125(23), 4303–4309.

Bleijenberg, N., Zuithoff, N. P. A., Smith, A. K., de Wit, N. J., & Schuurmans, M. J. (2017). Disability in the individual ADL, IADL, and mobility among older adults: A prospective cohort study. The Journal of Nutrition, Health & Aging, 21(8), 897–903.

Brekke, M. F., la Cour, K., Brandt, Å., Peoples, H., & Wæhrens, E. E. (2019). The association between ADL ability and quality of life among people with advanced cancer. Occupational Therapy International, 2019, 2629673.

Chavan, P. P., Kedia, S. K., Mzayek, F., Ahn, S., & Yu, X. (2020). Impact of self-assessed health status and physical and functional limitations on healthcare utilization and mortality among older cancer survivors in US. Aging Clinical and Experimental

Research. doi:10.1007/s40520-020-01654-5

Freedman, V. A., Spillman, B. C., Andreski, P. M., Cornman, J. C., Crimmins, E. M., Kramarow, E., … Waidmann, T. A. (2013). Trends in late-life activity limitations in the United States: an update from five national surveys. Demography, 50(2), 661–671.

Guida, J. L., Ahles, T. A., Belsky, D., Campisi, J., Cohen, H. J., DeGregori, J., … Hurria, A. (2019). Measuring Aging and Identifying Aging Phenotypes in Cancer Survivors. Journal of the National Cancer Institute, 111(12), 1245–1254.

Katz, S. (1963). Studies of illness in the aged: The index of ADL: A standardized measure of biological and psychosocial function. JAMA: The Journal of the American Medical Association, 185(12), 914.

Major Depression. (n.d.). Retrieved April 12, 2021, from Nih.gov website: https://www.nimh.nih.gov/health/statistics/major-depression.shtml

Martin, L. G., Schoeni, R. F., & Andreski, P. M. (2010). Trends in health of older adults in the United States: past, present, future. Demography, 47 Suppl, S17-40.

Miller, K. D., Nogueira, L., Mariotto, A. B., Rowland, J. H., Yabroff, K. R., Alfano, C. M., … Siegel, R. L. (2019). Cancer treatment and survivorship statistics, 2019. CA: A Cancer Journal for Clinicians, 69(5), 363–385.

Mustian, K. M., PhD, Sprod, L. K., PhD, Janelsins, M., PhD, Peppone, L. J., PhD, Mohile, S., MD, Director, A. P. A., … Associate Professor, Physical Exercise, Activity and Kinesiology (PEAK) Laboratory, James P Wilmot Cancer Center, University of Rochester School of Medicine and Dentistry, Rochester, New York, US. (2012).

Exercise recommendations for cancer-related fatigue, cognitive impairment, sleep problems, depression, pain, anxiety, and physical dysfunction—A review. Oncology & Hematology Review, 08(02), 81.

Na, L., Pan, Q., Xie, D., Kurichi, J. E., Streim, J. E., Bogner, H. R., … Hennessy, S. (2017). Activity limitation stages are associated with risk of hospitalization among medicare beneficiaries. PM & R: The Journal of Injury, Function, and Rehabilitation, 9(5), 433–443.

Pergolotti, M., Deal, A. M., Williams, G. R., Bryant, A. L., Bensen, J. T., Muss, H. B., & Reeve, B. B. (2017). Activities, function, and health-related quality of life (HRQOL) of older adults with cancer. Journal of Geriatric Oncology, 8(4), 249–254.

Pilleron, S., Sarfati, D., Janssen-Heijnen, M., Vignat, J., Ferlay, J., Bray, F., & Soerjomataram, I. (2019). Global cancer incidence in older adults, 2012 and 2035: A population-based study: Global cancer incidence in older adults. International Journal of Cancer. Journal International Du Cancer, 144(1), 49–58.

Products - data briefs - number 289 - October 2017. (2019, June 6). Retrieved April 12, 2021, from Cdc.gov website: https://www.cdc.gov/nchs/products/databriefs/db289.htm

Servais, M. (2004). Overview of HRS Public Data Files for Cross-sectional and Longitudinal Analysis. Retrieved from https://hrs.isr.umich.edu/publications/biblio/5835

Siegel, R. L., Miller, K. D., Fuchs, H. E., & Jemal, A. (2021). Cancer statistics, 2021. CA: A Cancer Journal for Clinicians, 71(1), 7–33.

Sonnega, A., Faul, J. D., Ofstedal, M. B., Langa, K. M., Phillips, J. W. R., & Weir, D. R. (2014). Cohort profile: The health and Retirement Study (HRS). International Journal of Epidemiology, 43(2), 576–585.

Sweeney, C., Schmitz, K. H., Lazovich, D., Virnig, B. A., Wallace, R. B., & Folsom, A. R. (2006). Functional limitations in elderly female cancer survivors. Journal of the National Cancer Institute, 98(8), 521–529.

United Nations. (2019). World Population Prospects 2019: Highlights. UN.

US Census Bureau. (n.d.). U.S. census Bureau releases new Educational Attainment data. Retrieved from https://www.census.gov/newsroom/press-releases/2020/educational-attainment.html

van der Willik, K. D., Koppelmans, V., Hauptmann, M., Compter, A., Ikram, M. A., & Schagen, S. B. (2018). Inflammation markers and cognitive performance in breast cancer survivors 20 years after completion of chemotherapy: a cohort study. Breast Cancer Research: BCR, 20(1), 135.

Von Ah, D. (2015). Cognitive changes associated with cancer and cancer treatment: state of the science. Clinical Journal of Oncology Nursing, 19(1), 47–56.

Ward, A., Arrighi, H. M., Michels, S., & Cedarbaum, J. M. (2012). Mild cognitive impairment: disparity of incidence and prevalence estimates. Alzheimer's & Dementia: The Journal of the Alzheimer's Association, 8(1), 14–21.

Williams, K., Jackson, S. E., Beeken, R. J., Steptoe, A., & Wardle, J. (2016). The impact of a cancer diagnosis on health and well-being: a prospective, population-based study: The impact of a cancer diagnosis on health and well-being. Psycho-

Oncology, 25(6), 626–632.