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Cancer in the Oldest-Old:
Risk of Dementia and Cognitive Decline

DISSERTATION

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for the degree of

DOCTOR OF PHILOSOPHY

in Epidemiology

by

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DEDICATION

To

Racheal Burgess, Aaron Burgess, Chris Nolen, Corey Nolen, Linda Moore and my family of Black and Indigenous people of color at UCI
for their unwavering love and ongoing support.

and to my squads
the Coffee Crew, Lindiwe, UCI Triathlon, AGS, the GAYBORHOOD and 4kokTeam PDX17
for our many adventures and high quality puzzle nights.

and lastly
to Canada, the two most amazing women I have the privilege of now calling my best friends
for years and years to come

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ABSTRACT OF THE DISSERTATION

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Doctor of Philosophy in Epidemiology

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Professor Karen L. Edwards, Chair

Disease burden increases with age. Cancer and dementia are two age-related chronic diseases that most commonly occur in older adults. They are also amongst the top 10 leading causes of death and disability in this age group. Despite the increased risk of comorbidity at older ages, it is unlikely for cancer and dementia to present in the same person at the same time. Surprisingly, evidence suggests that rates of dementia are lower in older adults with a history of cancer and vice versa. However, whether this pattern of inverse association holds true for the oldest-old, remains unclear. The oldest-old represent the fastest growing age group of the world's population yet have occupied only a small percentage of the population included in the published literature. The objective of this dissertation is to examine the relationship between cancer and dementia in the oldest-old using data from the 90+ Study at the University of California, Irvine.

An initial cross-sectional study was performed as a preliminary analysis using data from the 90+ study. A logistic regression model of 1525 oldest-old participants with a) no history of cancer or b) a history of cancer, were assessed for having dementia at baseline enrollment into the 90+ study. Results showed a 36% reduced odds of dementia in participants with a prior history of cancer at baseline. Building off these preliminary analyses, two studies were performed to further evaluate the overall research question about the relationship between

cancer and dementia in the oldest-old. Both research questions utilized data from the 90+ study. Specifically, the study population consisted of 761 older adults who were dementia free at baseline enrollment into the 90+ Study between 2003 to 2018.

The first research objective was to measure the risk of dementia in the oldest-old with a prior history of cancer compared to the oldest-old who remained cancer free. Using cox proportional hazards we estimated the cause-specific hazard ratio to address questions of etiology between the two diseases. The second research objective was to examine cognitive performance over time in participants with a history of cancer compared to those who remained cancer free. A linear mixed model for repeated measures was used to capture multiple longitudinal continuous outcomes in each of the groups.

Self-reported history of cancer was associated with a reduced rate of all-cause dementia in people aged 90 years and older as a function of the cause-specific hazard ratio. It was not associated with AD dementia. Although, the magnitude and direction of the association was similar to previous studies who found an inverse association. Additionally, we examined the role of type of cancer on the association between cancer and dementia, but the influence could not be determined in any definitive manner. In regard to cognitive performance, participants with a history of cancer showed slower rates of decline compared to participants who remained cancer free in global cognition and verbal fluency cognitive domains. No association in any other cognitive domain was found, largely due to missing information.

This is the largest study to date on cancer and dementia in a well-characterized cohort of the oldest-old. The results suggest that a history of cancer is associated with slower rates of cognitive decline over time. This, coupled with the magnitude and direction of the association between cancer and dementia suggests that a history of cancer does influence cognitive performance over time in the oldest-old. Furthermore, the inverse association suggests that a history of cancer may delay or protect from dementia in this particular age group. This research

into how age-related diseases influence the progression or prognosis of other age-related diseases is important when examining disease burden in the oldest age groups at highest risk for them. This research has the potential to influence healthcare screening practices in the oldest-old and how health care providers approach long-term and palliative care in patients with a history of cancer or diagnosed with dementia. Knowing whether a person in this age group is at greater or lesser risk of dementia as a result of their cancer history may influence how often they need to be screened for dementia and possibly whether or not signs of cognitive decline are attributed to dementia before ruling out other potential causes.

Introduction

Background

Cancer and cognition have a well-documented history. Cancer and cancer treatments have a negative association with cognition, where cancer and cancer treatments cause short-term and long-term dysfunction in multiple cognitive domains. Chemotherapy treatment is characterized by memory or cognitive deficits, otherwise referred to as “chemo-brain.” Elderly patient populations can be most at-risk for these deficits because of the presence of additional age-related cognitive deficits. Several studies of elderly populations with an average age range of 70-75 years old have found that a history of cancer was associated with increases in cognitive dysfunction when compared to similarly aged groups without a history of cancer (Heflin, 2005; Lange, 2014; Mandelblatt, 2014; Yamada, 2010). Additionally, one of these studies also found an increased risk of dementia in similarly aged populations with a history of cancer (Heflin, 2005). Dementia is a neurodegenerative disorder with multiple subtypes primarily affecting cognition. Notably, these studies on cancer, cognition and dementia have mostly been in breast cancer populations, have short follow-up periods, and have either completely excluded or included very few participants from the oldest-age groups.

In contrast, studies of multiple different cancers with longer follow-up times have shown significantly better cognitive performance in both memory and executive functioning associated with a history of cancer (Ospina-Romero, 2019; Gupta, 2019). In addition, studies of similar populations have also shown an inverse association between cancer and dementia (Driver, 2012; Bowles, 2017; Sun, 2020). The observation has been that the risk of dementia and primarily its most common subtype Alzheimer’s disease (AD) is lower in those with a history of cancer. There are several subtypes of dementia previously studied for their relationship with cancer, most of which do not show a stand-alone inverse association. AD is the exception; multiple studies have observed an inverse association between cancer and AD specifically. The inverse association

has also been observed in a neuroimaging study examining grey matter density (Nudelman, 2014), while a different study examining frontal brain volume also supports a possible inverse association (Gupta, 2019). In both studies participants with cancer had larger brain volumes then participants without cancer, suggesting that cancer may protect from atrophy in some areas of the brain which happens overtime and has been documented to effect cognitive performance.

It is suggested that different types of cancer may be more or less susceptible to brain changes, AD pathologies and cognitive problems. Gupta (2019) only observed larger volumes of frontal brain in participants with prostate cancer. They also found that only the survivors of invasive cancer types seemed to perform significantly better and achieve higher scores in various measures of executive functioning. Bowles (2017), found that less aggressive types of cancer or cancers diagnosed at earlier stages have a lower risk of AD compared to more aggressive late stage cancers. Both Driver (2012) and Sun (2020) observed that survivors of smoking related cancers had lower risk of AD. There is no strong explanation provided as to why there were differences between smoking and non-smoking related cancers, except that there may be a connection between carcinogenesis and neurodegeneration.

Biological Explanations of Inverse Association

The relationship between cancer and dementia is complicated, with many theories supporting a possible biological explanation for the inverse association. Cancer is a disease of abnormal cellular proliferation, while dementia is a disease of premature cellular death. The inverse relationship between cancer and dementia may be explained by shared pathways and underlying mechanisms of genetics, biology and physiology working in opposing directions for each disease. In this section we will briefly discuss some of the more common proposed biological explanations that support an inverse association between cancer and dementia.

There are 246 genes that overlap between cancer and dementia subtype AD (Rojas, 2020). Cancer and dementia need opposing genetic environments to exist. One example is the

pin1 protein folding gene required for cell division. Overexpressed pin1 leads to uncontrolled cellular growth (ie. cancer), but overexpressed pin1 also suppresses tau and amyloid B, two biomarkers of AD (Rojas 2020, Driver, 2014, Gargini, 2019). Therefore, when pin1 is overexpressed it can lead to cancer but may consequently suppress AD development. Similarly, the Wnt pathway, a cell survival pathway is also overexpressed in cancer, but under expressed in AD (Driver, 2014). Another gene is p53, a tumor suppressor gene that induces apoptosis in the presence of DNA damage. This gene also promotes cellular senescence which can reduce the regenerative potential in neurons (Driver, 2014; Martínez-Cué, 2020). P53 is underexpressed in cancer but overexpressed in dementia (Driver, 2014). The ubiquitin-proteasome system (UPS), a protein degrading system, also works in opposite ways for cancer and dementia. UPS is overexpressed in cancers. In fact the inhibition of UPS has been used to treat several forms of malignant cancers (Driver, 2014). In AD, the inhibition of UPS has been shown to increase the accumulation of tau and amyloid B in the brain (Hedge, 2019).

Another biological explanation involves mechanisms of energy production. Cells will undergo metabolic reprogramming in the face of mitochondrial dysfunction caused by the aging process (Demetrius, 2014). Glycolysis is the primary form of energy production in most tumor cells. In tumor cells, the Warburg Effect describes the process by which oxidative phosphorylation moves to aerobic glycolysis, resulting in increased glucose uptake and higher lactate production (Lanni, 2020; Liberti, 2016). This creates an environment where tumor cells can survive and grow in conditions with little to no oxygen. However, neurons are incapable of increasing energy production through glycolysis (Demetrius, 2014). Instead, neurons upregulate oxidative phosphorylation to increase energy production referred to as the Inverse Warburg Effect. In this model, neuronal cells compete for energy substrates (i.e. lactate), but there are not enough substrates to sustain every neuronal cell (Demetrius, 2014). The neuronal cells that don't produce enough energy undergo cellular death. That neuronal cell death may eventually progress to dementia. Demetrius and colleagues consider the Warburg Effect an "oncologic phenomenon"

and the Inverse Warburg Effect a “neuroenergetic phenomenon.” Ultimately, both the Warburg Effect and the Inverse Warburg Effect are forms of metabolic reprogramming triggered by the need for energy production due to mitochondrial dysfunction. But, energy production in cancer and dementia use different processes that work opposite one another, the up-regulation of glycolysis in tumor cells and the up-regulation of oxidative phosphorylation in neuronal cells.

While the role of shared genes and metabolic pathways are some of the most commonly studied explanations for the inverse association, there are several other possibilities. Signals on peripheral cells promoting cell proliferation might also send anti apoptotic (cell death) signals to neuronal cells (Rojas, 2020). Pavliukeviciene (2019) demonstrated that β amyloid inhibits the growth of some cancer cells in specific cell lines of specific tumor types (Pavliukeviciene, 2019). This is a result of either direct interaction with phospholipids on the membrane of cancer cells or the accumulation of β amyloid inside the cells themselves. Majd (2019) discuss that the activation of the PI3K/Akt/mTOR pathway in cell cycle re-entry may also help explain the inverse association (Majd, 2019). Under certain conditions, this pathway has been shown to promote both cellular proliferation and neuronal cell death. The pathway works similarly in both cancer and AD, where the hyperactivation or dysregulation of PI3K/Akt/mTOR pathway can lead to either cancer or AD. The difference, and what may explain the inverse, is the role of metabolic stress in this pathway. Cancer tissue uses energy that would otherwise be used for high energy demanded neurons. In doing so it also triggers an antioxidant defense of neurons that lowers risk of AD. However, non-cancer tissue (ie healthy tissue) will eventually undergo energy stress and reduced antioxidant enzymes associated with aging neurons, which can then lead to AD pathology.

Study Aims and Challenges

Despite growing evidence to suggest an inverse association between cancer and dementia and the potential that a history of cancer may delay memory decline, there are very few studies examining cancer and cognition in the oldest age groups. Therefore there is very little

knowledge of whether cancer and its' treatments have long-term effects on cognition and the risk of neurodegenerative disorders (i.e. dementia) in later stages of life, particularly amongst the oldest-old. Therefore this research study aims to examine the relationships between cancer, cognition and dementia in the oldest-old. Examining these relationships will come with several challenges. The first is survival bias. Survival bias is a type of selection bias in which the selection of groups or participants for analysis has been done in such a way that the sample is not representative of the whole population meant to be analyzed. Survival bias refers to the bias in which focus is given only on the groups of individuals that make it to the selection process, while those who could not make it past the selection process are overlooked. For example, our study seeks to understand the relationship between cancer, cognition and dementia. Therefore, if individuals with specific cancers do not survive long enough to be included in the selection process for participants, this is survival bias and can result in false conclusions. Survival bias may also be present in our study of the oldest-old because we are excluding anyone who does not survive to age 90. The next challenge will be competing risks. A competing risk refers to an event that either modifies the probability of the event of interest to take place or obstructs the observation of such event. The biggest competing risk for any study of cancer and dementia is death. Participants with a history of cancer might not survive long enough to get dementia and the higher rate of mortality in one group over another may bias the results. Lastly, diagnostic bias can also be a challenge for the study of cancer and dementia. Diagnostic bias refers to the bias that occurs when the perception of the researcher influences the diagnosis. This type of bias can take place when knowledge of an exposure, personal prejudice and subjective judgment of the researcher interfere in the diagnosis. Older adults are particularly susceptible to diagnostic bias if other prior comorbidities interfere in anyway with the diagnosis of another. Each of these challenges will be addressed where applicable in the specific aims for this research study. Finally, the dissertation research builds on a cross-sectional study evaluating the relationship between

history of cancer and dementia in the oldest-old. The results of the cross-sectional study are described in chapter 1 and serve as preliminary data for the dissertation research.

Aim 1: To determine the association between history of cancer and incidence of dementia and its major subtype, Alzheimer's disease (AD), in a cohort of older adults, 90 years and above, also referred to as the oldest old.

To address this aim, I used a cox proportional hazard regression model in a longitudinal cohort study of 761 participants from The 90+ Study at the University of California, Irvine. The 90+ Study is an ongoing longitudinal study from 2003 to present, which measures the health and well-being of individuals 90 years and above, also referred to as the oldest-old. Participants in our study were dementia free at baseline study enrollment. I measured the length of time between dementia free at baseline to incidence of dementia for each individual study participant. Participants were then separated into two unique groups of individuals with a history of cancer and individuals without a history of cancer. From here, I could compare the risk of dementia in each group to determine the association between history of cancer and dementia in the oldest-old. This is the largest study conducted to date in the oldest-old to examine the association between dementia and cancer and highlights the importance of including the oldest-old in research studies examining comorbidities.

After the evaluation of cancer and dementia, I wanted to understand how cognition could be specifically impacted by a history of cancer. For my next aim, I attempted to unravel which cognitive domains typically linked to dementia might help explain the association between cancer and dementia from the previous aim.

Aim 2: To compare the change in cognitive performance over time in older adults 90 years and above with a history of cancer to those with no history of cancer.

To address this aim, I used linear mixed models in a longitudinal cohort study of the same 763 participants from the 90+ Study who were dementia free at baseline study enrollment. For each participant, repeated measures of cognitive performance were collected from five different cognitive tests aimed at examining memory, attention, verbal fluency, executive function, and psychomotor speed. Like before, participants were then separated into two unique groups of individuals with a history of cancer and individuals without a history of cancer. I compared the change in cognitive performance over time in each group to determine whether a history of cancer was associated with changes in cognition in any of the five domains. This study provides a baseline understanding of whether cancer may be associated with changes in cognition over time in the oldest age groups. In addition to whether cognitive changes help to explain the association between cancer and dementia.

Overall, these research aims will contribute to our understanding of the relationship between cancer and dementia. My research aims will also contribute to our understanding of the risk of dementia in the oldest-old and how pre-existing conditions influence that risk. The knowledge contributions from these research aims will ultimately support the growing necessity for research studies on chronic disease in our oldest age groups.

Chapter 1: Preliminary Data: A Cross-Sectional Study of Cancer and Dementia in the Oldest-Old

1.1 Introduction

It was during the early 1990's that scientists first noticed that the presence of a Alzheimer's disease (AD) at death, determined by Kachaturian criteria of AD pathology, was less in people with cancer compared to people without cancer. Tirumalasetti (1991) performed a cross-sectional study using data from autopsy reports at the Willard Psychiatric Center in New York. They examined 210 autopsies over 10 years and found that patients with AD had less cancer on examination compared to patients without AD (Tirumalasetti, 1991). Cancer was determined at autopsy as any cancer present in the body and contributing to death. Tirumalasetti (2019) suspected that perhaps the trend could be explained by demographic factors (age, gender) which differed between the two groups. Nonetheless, it prompted further exploration into the relationship between cancer and AD. DeSouky (1992) used clinical data from the current population at the Willard Psychiatric Center, to run a cross-sectional study on cancer and AD, this time being sure to age-match to account for some of the demographic factors. Again, they found fewer diagnoses of cancers in patients with clinically diagnosed AD compared to patients without AD (DeSouky, 1992). Still, this was not enough information to justify or attribute these observations to a specific biological factor. Finally, in 1999, a larger scale study (n= 2222) in Japan examined the relationship between risk factors (e.g disease history) and dementia subtypes (AD and Vascular dementia (VaD)) using data from the Adult Health Study (AHS)(Yamada, 1999). Cancer was determined using medical records from biennial clinical examinations between 1958 to 1996, while dementia was diagnosed based on *DSM III/R* diagnostic criteria, determined by a screening panel of three neurologists and two internists between 1992 to 1996. The screening panel included two cognitive examinations. Following multivariate logistic regression analysis, the study found a decreased prevalence of AD in participants with cancer compared to those without (OR: 0.3, CI: 0.50-0.98) (Yamada, 1999). After which, they deduced that the reduced odds of AD in

people with prevalent cancers could be evidence of a protective effect or the effect of differential survival bias. Survivor bias suggests that mortality rates are higher for people with dementia or cancer, therefore they may not survive long enough to be diagnosed with a second disease, This bias would overestimate the odds ratio and give the perception of a reduced odds. Still, together these three studies from the 1990's struck new interest into the relationship between cancer and dementia, as well as the similarities between tumorigenesis and neurodegeneration.

To examine whether the inverse association between cancer and dementia exists in the oldest-old, we performed a cross-sectional analysis using data from The 90+ Study.

1.2 Methods

We performed a cross-sectional analysis using data from The 90+ Study, to assess the association of dementia and history of cancer. This cross sectional analysis utilized data from the baseline study enrollment visit beginning in January 2003. In our analysis, participants were excluded if missing information on history of cancer or dementia at the baseline visit. Dementia was determined by physician examination, self-report, or surrogate report for patients at the baseline visit (or study enrollment) (Corrada, 2008). There was a hierarchy for determining dementia based on the source of information: neurological exam, mini mental state exam (MMSE), informant questionnaires, and cognitive abilities screening instrument (CASI-short). Cancer was determined by self-report or by report by an informant if the participant was unable to give the information.

The crude association of the cross-sectional study was evaluated using a likelihood ratio chi-square test. Adjustment for gender and education was performed using a logistic regression model, where all cause dementia was the dependent variable and history of any cancer was the independent variable. Because age at diagnosis of cancer or dementia is unknown for most participants, we were not able to account for this in the model. Further, because age at study

enrollment is not a substitute for age at diagnosis of either condition, age was not included as a covariate in the model. All analyses were done using SAS 9.4 software.

1.3 Results

The logistic regression model included 1525 participants; 70 participants were excluded due to missing information. There were 836 people with no history of cancer at baseline. Over 40% (41.3%) of people with no history of cancer had dementia at baseline. There were 619 people with a history of cancer at baseline and 30.2% of people with a history of cancer had dementia at baseline. In addition to looking at any cancer, we stratified by the 6 most prevalent cancers in the study cohort (Table 1.1.). There were 36% reduced odds of dementia in participants with a history of any cancer. The odds did not change when non-melanoma skin cancer NMSC was excluded. When cancer was stratified by subtype, breast cancer was like any cancer (OR: 0.65 (0.44-0.95). Whereas colon and NMSC had a much larger reduced odds of dementia, approximately 65%. There was no statistically significant association for melanoma, prostate, or uterine cancer.

Table 1.1. The Odds Ratios of all-cause dementia in people with a history of cancer compared to people with no history of cancer stratified by cancer type

	No. of No Cancer	No. of Yes Cancer	**History of Cancer** No	Yes
Any Cancer	836	619	Reference	0.64 (0.50-0.80)
Any Cancer excluding non melanoma skin (NMSC)	836	424	Reference	0.68 (0.53-0.88)
Non melanoma skin cancer (NMSC)	836	275	Reference	0.46 (0.33-0.64)
Melanoma	836	68	Reference	0.78 (0.45-1.34)
Breast (Women only)	671	148	Reference	0.65 (0.44-0.95)
Prostate (Men)	165	49	Reference	0.71 (0.33-1.51)
Colon	836	78	Reference	0.44 (0.25-0.77)
Uterine (Women only)	671	52	Reference	0.73 (0.40-1.32)

*These are the results from a logistic regression adjusted for gender and education. All-cause dementia is the outcome and history of cancer as the main covariate of interest.

1.4 Discussion

There was a consistent inverse relationship between odds of all-cause dementia and several cancer types, adjusting for gender and education level. The inverse association between cancer and dementia was statistically significant for all cancer types except prostate, uterine and melanoma which had the smallest number of cases. Still, the association in all types trends towards a lower odds of dementia in people with cancer at baseline in people who are 90 years and older.

Although our results are consistent with the previous literature, there are a number of limitations when evaluating this association cross sectionally. Cross-sectional studies are designed to estimate prevalence at one point in time but do not have information regarding the temporal order of events. Thus, we can't make any inferences about causality or incidence of risk. Reporting bias is also a challenge with this study design because a person with dementia or severe cognitive may not remember a previous diagnosis of cancer. It is also possible that their informants were unable to report a cancer diagnosis on their behalf. Still, the biggest limitation of our cross sectional analysis is the inability to address concerns of competing risks. In an ageing population with multiple comorbidities, the competing risk of death is an important factor to consider.

Chapter 2: The Relationship Between Cancer and Dementia: A Prospective Cohort Study of the Oldest-Old

2.1 Introduction

In recent years, much attention has been paid to the relationship between cancer and dementia. Longitudinal studies have described a consistent inverse association, suggesting that a history of cancer may be associated with a lower risk of dementia (Ospina-Romero, 2020a; Ganguli, 2015). The mechanism underlying the association is unknown. Some researchers have hypothesized that risks associated with social determinants of health, for example physical activity, socioeconomic status, smoking and alcohol use, may be responsible, but this has since been discounted in more recent research that shows social determinants cannot fully explain the association (Ospina-Romero, 2021; Prinelli, 2018). Others have hypothesized that shared biological pathways between tumorigenesis and neurodegeneration (e.g., Pin1 (cell signaling), p53 (tumor suppressor), metabolic function, etc.) may be involved in this inverse association (Driver, 2014; van der Willik, 2018). One example is overexpression of the enzyme Pin1 which results in cell proliferation activation in multiple cancers. On the contrary, when Pin1 is under-expressed, it facilitates the buildup of tau and amyloid proteins present in Alzheimer's dementia (AD) pathologies (Driver, 2015). The characteristics of this common pathway and others, and their opposing roles in cancer and dementia, may point towards an etiological explanation for the inverse association. Still, some researchers have rejected biological explanations and have suggested that survival bias and incorrect model specification when accounting for competing risks may account for the inverse association.

Competing risks are events that occur before an event of interest that preclude the occurrence of the outcome of interest. Ignoring competing risks and unmeasured confounding on a competing event can introduce upwards bias on the risk estimates (Abdel-Qadar, 2018; Schuster, 2020) In studies of older adults, death is a common competing risk and accounting for

this potential bias is important. The two most common statistical approaches to minimize this bias are the cause-specific hazards function and the subdistribution hazards function (Noordzij, 2013). Briefly, the cause-specific hazard function assumes that censoring is non-informative, meaning that the time to censorship is unrelated to time to event. In this approach, participants who died are treated as censored observations, and are removed from the risk set. The assumption of non-informative censoring assumes that death has no impact on incidence of dementia (Allison, 2018; Wolbers, 2014). This approach is best used to answer epidemiological questions about etiology and will estimate the effect of history of cancer on the rate of dementia in participants who are dementia free (Austin, 2016). Whereas the subdistribution approach is best suited to answer questions about clinical prognosis and will estimate the effect of history of cancer on the absolute risk of dementia over time (Austin, 2016). Etiology is simply defined as the cause of something and examining etiology implies examining the underlying cause of why something happens. In support of a possible etiological link between cancer and dementia, it has been suggested that shared genes and biological pathways between tumorigenesis and neurodegeneration may play a role in presence of one disease over another. Our research question investigates whether history of cancer is associated with causing dementia, for which cause-specific hazard model is the more relevant method to investigate this question. It has also been reported that the cause-specific approach is more easily interpreted and provides a more natural interpretation of the results (So and Guo, 2018). Therefore, our decision to use the cause-specific HR as opposed to the alternative subdistribution HR, is because the two approaches fit with different types of research objectives.

Survival bias is another concern, especially in the oldest old and occurs if participants in a study are in some way different than participants who may not have survived to take part in the study. This can be true for participants, regardless of cancer history, who do not survive to age 90 and are not included in this study. Similarly, if participants with cancer experience death or are

removed from the study before they can be diagnosed with dementia, this can create survival bias. In a study from 2012, Driver (2012) showed a 20-30% reduced risk of dementia and AD dementia in people aged 65 years and older with a history of cancer. This study addressed concerns of survival bias by limiting their analysis of cancer and dementia to only those participants who survived to at least age 80. The results were no different than when they included participants who died before age 80, suggesting survival bias might not explain the inverse association.

To investigate the association between cancer and dementia and address these potential sources of biases, this study used data from The 90+ Study, one of the largest longitudinal studies of adults aged 90 years and older. We used a number of approaches to address potential biases and limitations including using the cause-specific method to account for competing risk of death, examining differences in risk of dementia by cancer subtype and separately for incident, prevalent and screening cancers with careful attention to adjustment of potential confounders. Despite the increased burden of cancer and dementia in this population, very few studies have evaluated this potential association in the oldest-old.

2.2 Methods

Participants

The 90+ Study, one of the largest cohorts of the oldest old, was the source population for this study. Eligibility included study enrollment between 2003-2018 and no history of dementia at baseline. All participants had a minimum of 1 follow-up visit with information on dementia status. At baseline, participants were asked about their medical history and given a physical examination and an in-person cognitive assessment. They were also asked to bring in any medication bottles to confirm medication name and prescribed dosage. For this analysis, we began with 1,525 participants and excluded those with a diagnosis of dementia at baseline (n=559) or prevalent or

incident brain and CNS tumors due to the potential impact on cognition (n=3). Similarly, individuals with acoustic neuroma (n=1), bone-head tumor (n=1) or meningioma (n=1) as well as those with missing information on either cancer or dementia (n=196) were also excluded from the study. Participants were followed from study entry until either 1) a diagnosis of incident dementia, 2) death, 3) loss to follow-up, or 4) the end of the study period.

Cancer Assessment

Prevalent cancer cases were identified by self-report using data from the medical history questionnaire collected at baseline. Participants were asked if they had ever been diagnosed with specific cancer types (breast, prostate, colon, uterine, melanoma, non-melanoma skin cancers (NMSC) and other). The responses were recorded as "yes," "no," "don't know" or in some cases where the question was not answered it would be reported as "not done." Participants who reported "other" were asked to specify the cancer type(s). Participants who reported a cancer diagnosis were also asked to specify the year of diagnosis. In total, 386 participants had 1 or more prevalent cancers identified at baseline. Incident cancers diagnosed during the study follow-up were also collected by self-report. In total, 68 participants had 1 or more incident cancers identified after baseline. Total prevalent and incident cancers by type included breast (n=89), prostate (n=43), colon (n=47), uterine (n=23), melanoma (n=55), non-melanoma skin (n=252), and other cancers (n=69). For our study, we combined intestinal and rectal cancers (n=3) with colon cancers to make a colorectal cancer group (n=50). In addition, cancers were dichotomized into "screening cancers" and "non-screening cancers". Screening cancers, including breast, prostate and colorectal cancers were those that are regularly screened for and as a result, are typically diagnosed at earlier stages with a higher likelihood of survival. Non-screening cancers included lymphoma, stomach and throat cancers. For participants with more than one cancer diagnosis, we used the first cancer diagnosed to classify both the cancer type and the screening cancer

group selection. One participant with a lipoma was reclassified from the prevalent cancer group to the no cancer group because this type of benign tumor is almost always non-cancerous.

Dementia Assessment

Our primary outcome, all-cause dementia, was defined as all diagnoses of dementia, regardless of etiology or subtype, including those with AD dementia. The clinical diagnosis of dementia in The 90+ Study has been well-described previously (Corrada, 2010). Briefly, all participants underwent an in-person baseline neurologic exam of mental status and functional abilities, performed by a trained physician or nurse practitioner. They also underwent a battery of neuropsychological tests that included the Mini-Mental Status Examination and Modified Mini-Mental Status Examination, The study preferred participants to have in-person follow-up biannual cognitive evaluations. For participants who could not have an in person follow-up examination, the assessment was done either via phone using the Cognitive Abilities Screening Instrument (CASI-short) (Teng, 1994) or through participant informants using the Dementia Questionnaire (DQ) (Kawas, 1994), and questionnaires asking about participant's cognitive status (Clark, 1996) and the functional abilities (Pfeffer, 1982; Katz, 1963). A diagnosis of dementia was determined using whatever information was available in a hierarchical order: neurological exam, MMSE, informant questionnaires, CASI-short. For the MMSE, age and education specific cutpoints derived for this cohort were used to assign a dementia diagnosis (Kahle-Wrobleski, 2007). For the neurological exam and informant questionnaires, a diagnosis of dementia followed the standard criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV). Briefly, these standards include impairment in memory and 1 or more cognitive domain (i.e. executive function, speech, movement, recognition) and impairments in social or occupational functioning.

Potential Covariates

Previous literature was used to determine possible covariates for use in our analysis. Ultimately, we selected covariate variables based on whether they were related to cancer and dementia in our particular cohort. Factors shown to be potentially associated with both the exposure and outcome variables of interest in both this cohort and others included age (Bland, 2018; Niccoli, 2012, Nolen, 2017; Corrada, 2010), gender (Dorak, 2012; Siegel, 2017; Prince, 2016; Brookmeyer, 2018), education (Montez, 2014; Mouw, 2008; Livingston, 2017; Vemuri, 2014), smoking (Koene, 2016; Anstey, 2007; Zhong, 2011), body mass index (BMI) (Kivimäki, 2018; Slade, 2012), hypertension (Koene, 2016; Walker, 2019; TZourio, 2007; Corrada, 2017; Walker, 2019), type 2 diabetes (T2DM) (Giovannucci, 2010; Tsilidis, 2015; Nolen, 2017; Huang 2014; Ohara, 2011; Gardner, 2013), depression (Spiegel and Giese-Davis, 2003; Jorm, 2001; Diniz, 2013; Byers, 2011; Spira, 2012), and cardiovascular disease (CVD) (Koene, 2016; Mehta, 2018; Armenian, 2016; Bertero, 2018; Roman, 2002; Almeida, 2001; Corrada, 2017. All potential covariates, except BMI, were self-reported at baseline.

Of note, BMI and smoking status were considered as potential confounders and assessed for their impact on the relationship between cancer and dementia. Height and weight measurements used to calculate BMI were often missing if a participant was interviewed at home or the participant was non-ambulatory. Similarly, smoking status was often missing from the dataset. Although, both smoking status and BMI were potential confounders, they were excluded from the final analysis due to too many missing values.

Finally, education was collected as a categorical variable: 1) did not complete 8th grade, 2) some high school, 3) high school graduate; 4) vocational school; 5) some college; 6) college graduate; 7) some graduate school; and 8) advanced degree. For these analyses, education was grouped into 1) Did not complete high school; 2) High school diploma; 3) Vocational and College; and 4) Advanced education/degree (defined as any type of graduate level or professional education).

2.3 Statistical Analysis

Baseline cohort characteristics were compared by cancer group using Pearson's chi-squared tests for categorical variables and two-sided t-tests for continuous variables. Cox proportional hazards models were used to examine the relationship between history of cancer and rate of dementia (all-cause dementia and AD dementia). Age was used as the timescale in each model. Cancer was coded as a time-dependent covariate, such that participants provided follow-up years to the "no cancer" group before cancer diagnosis and contributed time to the" incident cancer" group from the date of cancer diagnosis for the remainder of the follow-up period or until death.

Our primary analysis used Cox models with cause-specific hazard function, a widely used approach to account for competing risks. In this model, competing risks were accounted for by treating participants who died as censored observations, which were removed from the risk set. Participants who died did not contribute person-years to the study after death. Other methods, such as the Kaplan Meir, also censor observations and remove participants from the risk set who experience specific events (i.e. death) before the outcome of interest, but they do so in a way that ignores competing risks. The differences are in the types of assumptions with censoring. Kaplan Meir assumes independent censoring, meaning that censoring occurs at random and there is no difference in risk between censored participants and those who remain in the risk set. Competing risks violates the assumption of independent censoring because participants who experience the competing event are no longer at the same risk for the event of interest as those who remain in the risk set. Using Kaplan Meir in the presence of competing risks will overestimate the risk for the event of interest.

All models in our study compared the risk of all-cause dementia or AD dementia by cancer group. Model 1 was the unadjusted model. Model 2 adjusted for participant demographics

including age at baseline, education, and gender. In Model 3, we added baseline hypertension, diabetes, depression, and CVD to Model 2. Of note CVD was defined as the presence of 1 or more of the following conditions at baseline: Atrial fibrillation/other arrythmias, congestive heart failure, coronary artery disease, angina, heart valve disease, heart attack, myocardial infarction, or atrial fibrillation. Models 1-3 were repeated for pre-defined subgroup analysis including prevalent, incident, screening, and non-screening cancer groups. The best fit model from Models 1-3 was selected based on the minimum Akaike information criterion (AIC) value. The best-fit and unadjusted models were repeated, stratifying by 1) gender and 2) excluding NMSC for sensitivity analysis. NMSC is a cancer with a very high survival rate and rarely ever lethal. It is excluded as a form of sensitivity analysis because it may differ from other cancer types. We stratified by gender as a form of sensitivity analysis because this is a cohort of predominately women and there are specific cancers that impact women or men only that could impact the associations. Finally, all models were repeated by cancer type separately. Participants with multiple cancers were excluded from the analysis by cancer type.

Lastly, we examined survival bias. A survival analysis was performed to measure whether a history of cancer was associated with an overall increased risk of death in this study cohort. This analysis was performed to assess assumptions of survival bias which could impact the effect estimates in our study. We measured the overall risk of death to produce a plot like the Kaplan Meir plot which does not account for covariates. Participants in this approach remained in the analysis until their death or the study period ended, regardless of dementia status.

All statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC). Similar models to the ones performed in this study are presented in the following literature (So and Gao, 2018).

2.4 Results

Cohort characteristics

Characteristics for the 761 study participants are presented in Table 2.1. Women made up 69.4% of the study population, and most were white, well educated, between the ages of 90-95 at baseline. A little more than half (50.7%) had a history of cancer at baseline (prevalent cancer). Compared to participants who reported a history of cancer, those without a cancer history were significantly older at baseline (92.4 years versus 92.7 years). Other baseline demographics were not significantly different in the group with prevalent cancer compared to the group with no cancer at baseline, although the prevalent cancer group had slightly higher levels of education and were more likely to have a history of smoking, hypertension, CVD, depression and diabetes. A total of 257 participants were diagnosed with all-cause dementia. Dementia diagnoses by etiology: AD dementia (n= 154), vascular dementia (n= 28), mixed AD/vascular dementia (n= 25), other dementia (n= 23), or missing information on etiology (n=32). AD dementia was examined as a secondary outcome. Cases of mixed AD were excluded (n=17) from the AD dementia analysis.

Table 2.1. Participant Characteristics by History of Cancer at Baseline (n=761)

Characteristic	**History of Cancer at Baseline**		
	No Cancer	Prevalent Cancer	p-value
Participants, n (%)	375 (49.3)	386 (50.7)	0.16
Follow-up years, mean (Range)	2.91 (0.01-10.2)	3.45 (0.45-13.1)	**0.01***
Age at baseline, median (Range)	92.7 (90.0-103.0)	92.4 (90.0-102.5)	**0.02***
Age at baseline, n (%)			
90-95 years	284 (75.7)	314 (81.4)	0.13
95-100 years	79 (21.1)	65 (16.8)	
100 – 103 years	12 (3.2)	7 (1.8)	
Gender (Female), n (%)	272 (72.5)	256 (66.3)	0.06
Race (White), n (%)	367 (97.9)	381 (98.7)	0.37

Education, n (%)			
Did not complete high school	19 (5.1)	27 (7.0)	0.21
High school diploma	70 (18.7)	54 (14.0)	
Vocational and College	224 (59.7)	231 (59.8)	
Advanced Education/Degree	62 (16.5)	74 (19.2)	
Medical History, n (%)			
Hypertension	212 (56.5)	230 (59.6)	0.22
Cardiovascular disease	158 (42.1)	183 (47.4)	0.14
Depression	42 (11.2)	43 (11.4)	0.54
Diabetes	28 (7.5)	31 (8.0)	0.21
Smoking history, n (%)			
Never smoker	197 (52.5)	196 (50.8)	0.61
Ever smoker	167 (44.5)	182 (47.2)	
Unknown smoking status	11 (3.0)	8 (2.0)	

As shown in Table 2.2, at the end of follow-up, 343 participants (45.1%) remained cancer free, 314 participants (41.3%) had 1 or more prevalent cancers at baseline and no additional incident cancers, 41 (5.4%) participants had 1 or more incident cancers but no prevalent cancer, and 27 participants (3.5%) had a history of both prevalent and incident cancers. An additional 36 participants (4.7%) were identified as having cancer but the onset date of diagnosis was unknown. When incident and prevalent cancer types were counted, approximately 33% of participants (n=139) had a history of more than one type of cancer. Almost half of all cancers were NMSC (43.4%) followed by breast (15.3%), melanoma (9.5%), colorectal (8.6%), prostate (7.4%), and uterine (3.9%). In those with a prevalent cancer only, 56.7% were NMSC. In the other groups, 61.0% of those with an incident cancer only and 77.8% of those with both an incident and prevalent cancer had a NMSC. There were more screening cancers in each of our groups (77-85%) compared to non-screening cancers.

Table 2.2. Participant characteristics stratified by cancer status at the end of study (n=761)

Characteristics	Cancer Groups				
	No Cancer	Prevalent cancer only	Prevalent + incident cancer	Incident cancer only	Unknown date of cancer
Participants, n (%)	343 (45.1)	314 (41.3)	27 (3.5)	41 (5.4)	36 (4.7)
Follow-up years, mean (Range)	2.97 (0.43-10.1)	3.49 (0.45-13.0)	4.92 (0.58-10.3)	3.29 (0.07-9.4)	1.92 (0.3-6.6)
Age at baseline, median (Range)	92.8 (90.0-103.0)	92.3 (90.0-102.5)	91.5 (90.0-97.1)	93.9 (90.5-102.7)	93.9 (90.0-100.9)
Age at baseline, n (%)					
90-95 years	255 (74.3)	258 (82.2)	23 (85.2)	35 (85.2)	27 (75.0)
95-100 years	76 (22.2)	50 (15.9)	4 (14.8)	6 (15.9)	8 (22.2)
100 – 103 years	12 (3.5)	6 (1.9)	-	-	1 (2.8)
Gender (Female), n (%)	250 (72.9)	206 (65.6)	19 (70.4)	28 (68.3)	25 (69.4)
Race (White), n (%)	335 (97.7)	309 (98.4)	27 (100)	41 (100)	36 (100)
Education, n (%)					
Did not complete high school	19 (5.5)	21 (6.7)	2 (7.4)	1 (2.4)	3 (8.3)
High school diploma	63 (18.4)	46 (14.7)	3 (11.1)	8 (19.5)	4 (11.1)
Vocational and College	209 (60.9)	185 (58.9)	19 (70.4)	23 (56.1)	19 (52.8)
Advanced Education/Degree	52 (15.2)	62 (19.7)	3 (11.1)	9 (22.0)	10 (27.8)
Medical History, n (%)					
Hypertension	194 (56.6)	187 (59.6)	15 (55.6)	24 (58.5)	22 (61.11)
Cardiovascular disease	145 (42.3)	146 (46.5)	10 (37.0)	17 (41.5)	23 (63.9)
Depression	40 (11.7)	36 (11.5)	2 (7.4)	1 (2.4)	6 (16.7)
Diabetes	26 (7.6)	25 (8.0)	1 (3.7)	3 (7.3)	4 (11.1)
Smoking history, n (%)					
Never smoker	182 (53.1)	158 (50.3)	15 (55.6)	20 (48.8)	18 (50.0)
Ever smoker	152 (44.3)	149 (47.5)	12 (44.4)	20 (48.8)	16 (44.4)
Unknown smoking status	9 (2.6)	7 (2.2)	-	1 (2.4)	2 (5.6)
[b]Cancer Count, n (%)					
One	-	221 (70.4)	-	36 (87.8)	22 (61.1)
Two	-	81 (25.8)	23 (85.2)	5 (12.2)	10 (27.8)
Three	-	11 (3.5)	3 (11.1)	-	4 (11.1)
Four or more	-	1 (0.3)	1 (3.7)	-	-
First cancer diagnosis, n (%)					
[a]Screening	-	269 (85.7)	21 (77.8)	34 (82.9)	21 (77.8)
Non-screening	-	45 (14.3)	6 (22.2)	7 (17.1)	6 (22.2)

[b]Cancer Type, n (%)					
Breast	-	71 (22.6)	12 (44.4)	3 (7.3)	2 (5.6)
Colorectal	-	39 (12.4)	2 (7.4)	3 (7.3)	6 (16.7)
Prostate	-	35 (11.2)	6 (22.2)	1 (2.4)	1 (2.8)
Uterine	-	15 (4.8)	2 (7.4)	1 (2.4)	5 (13.9)
Melanoma	-	38 (12.1)	3 (11.1)	5 (12.2)	9 (25.0)
Non-melanoma skin	-	178 (56.7)	21 (77.8)	25 (61.0)	28 (77.8)
Other	-	45 (14.3)	13 (48.2)	8 (19.5)	3 (8.3)

[a]Screening cancers include breast, prostate, cervical, NMSC, melanoma and colorectal cancers. Status is based on first diagnosis of cancer.
[b]Data reads as number of participants with specific number of cancers or specific type of cancer

Cancer and Risk of Dementia and AD Dementia

All-Cause Dementia:

Of the 761 study participants, 257 (33.8%) were diagnosed with dementia during follow-up. In participants with no history of cancer, 126 (36.7.%) developed all-cause dementia. In participants with prevalent cancer only, 100 (31.8%) developed all-cause dementia. In participants with prevalent and incident cancer, 7 (25.9%) developed all-cause dementia. In participants with incident cancer only, 9 (22.0%) developed all-cause dementia. As shown in Table 2.3, history of any cancer (prevalent or incident) was significantly associated with a lower risk of all-cause dementia in both unadjusted [HR=0.78 (0.61-0.99)] and adjusted model [model 3: HR=0.77 (0.59-0.99)]. Figure 2.1 shows the cumulative incidence of all-cause dementia for the any cancer group vs the no cancer group. The association was strongest in the history of both prevalent and incident cancers, which was associated with the lower risk of all-cause dementia in unadjusted [HR=0.45 (0.21-0.96)] and adjusted models [model 3: HR=0.42 (0.18-0.92)]. No significant association was demonstrated between incident cancer alone in relation to risk of all-cause dementia in unadjusted or adjusted models, although this effect size was notably closest to that of the prevalent and incident cancer group. Those with a history of screening cancers, although not

significant, had similar effect sizes as the any cancer group for the inverse association. The association was even stronger in non-screening cancers, although again it was not significant.

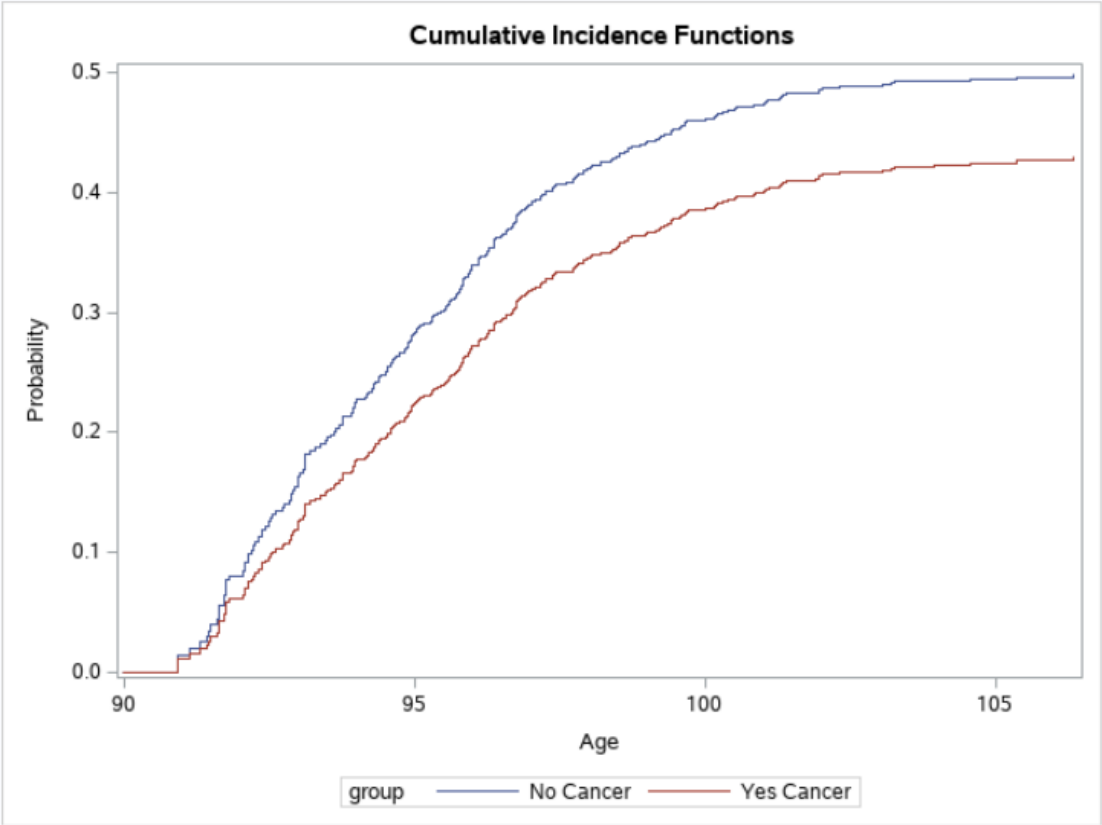
A sensitivity analysis was done to evaluate the role of NMSCs by excluding NMSCs from the “any cancer” group. Removing NMSC did not drastically alter the results. The rate of all-cause dementia [adjusted HR: 0.83 (0.62-1.11)] in participants with any cancer excluding NMSC compared to those without a history of cancer showed only a 5-6% difference from the results for any cancer. This suggests the inverse association is not likely to be driven entirely by including NMSC cancers. The lack of significance is likely driven by the decreased sample size after removing NMSC cancers.

Table 2.3. The association between history of cancer and rate of all-cause dementia using cox-proportional hazards models.

	Cause-specific hazard								
	Model 1 (Unadjusted)			Model 2			[1]Model 3		
	n	HR (95% CI)	P-value	n	HR (95% CI)	P-value	n	HR (95% CI)	P-value
No cancer	375	Reference	-	375	Reference	-	371	Reference	-
Any cancer	418	0.78 (0.61-0.99)	**0.05***	418	0.79 (0.61-1.01)	0.06	405	0.77 (0.59-0.99)	**0.04***
Any cancer - excluding NMSC	278	0.86 (0.65-1.13)	0.27	278	0.87 (0.65-1.14)	0.30	265	0.83 (0.62-1.11)	0.22
Prevalent cancer only	350	0.86 (0.66-1.11)	0.23	350	0.87 (0.67-1.13)	0.30	339	0.83 (0.63-1.08)	0.17
Incident cancer only	41	0.52 (0.25-1.02)	0.06	41	0.55 (0.27-1.10)	0.09	41	0.63 (0.31-1.28)	0.20
[2]Both Incident + Prevalent cancer	27	0.45 (0.21-0.96)	**0.04***	27	0.39 (0.17-0.86)	**0.02***	25	0.42 (0.18-0.92)	**0.03***
Screening cancer	355	0.80 (0.61-1.03)	0.08	355	0.80 (0.61-1.04)	0.10	344	0.79 (0.60-1.03)	0.08
Non-screening cancer	63	0.70 (0.42-1.14)	0.15	63	0.70 (0.42-1.16)	0.16	61	0.62 (0.36-1.07)	0.09

Any cancer refers to all cancers (prevalent and incident)
Model 2 is adjusted for age at baseline, gender, and education
Model 3 is adjusted for model 2 + baseline hypertension, diabetes, depression, and CVD.
[1]Best fit model
[2]This is a subgroup of participants who have both an incident and prevalent cancer. It does not include participants in the prevalent cancer only or incident cancer only groups

Figure 2.1. Cumulative incidence of all-cause dementia stratified by history of cancer



AD Dementia:

Of the 761 study participants, 154 (20.2%) were diagnosed with AD dementia during follow-up. Participants with non-AD dementia or were missing information on dementia etiology were excluded from this analysis. In participants with no history of cancer, 77 (22.4%) developed AD. In participants with prevalent cancer only, 59 (18.8%) developed AD. In participants with prevalent and incident cancer, 5 (18.5%) developed AD. In participants with incident cancer only, 6 (14.6%) developed AD. As shown in Table 2.4, the results for the association between history of cancer and AD dementia were very similar to the effect sizes for all-cause dementia in Table 2.3 across all cancer groups. Although, none of the associations reached statistical significance.

The cause-specific HRs ranged from 0.63-0.84 for most groups. Once again, like before, the prevalent and incident cancer group had the strongest association.

Table 2.4. The association between history of cancer and AD dementia using cox-proportional hazards models.

	Cause-specific hazard								
	Model 1 (Unadjusted)			Model 2			[1]Model 3		
	n	HR (95% CI)	P-value	n	HR (95% CI)	P-value	n	HR (95% CI)	P-value
No cancer	304	reference	-	304	reference	-	301	reference	-
Any cancer	350	0.73 (0.53-1.00)	0.05	350	0.76 (0.54-1.05)	0.10	343	0.75 (0.54-1.05)	0.09
Any cancer - excluding NMSC	229	0.80 (0.56-1.14)	0.22	229	0.83 (0.58-1.20)	0.32	222	0.84 (0.57-1.22)	0.35
Prevalent cancer only	289	0.80 (0.58-1.12)	0.20	289	0.86 (0.61-1.21)	0.38	284	0.83 (0.58-1.17)	0.29
Incident cancer only	36	0.52 (0.26-1.23)	0.13	36	0.55 (0.23-1.3)	0.17	36	0.64 (0.27-1.53)	0.32
[2]Both Incident + Prevalent cancer	25	0.44 (0.17-1.10)	0.08	25	0.40 (0.15-1.04)	0.06	23	0.44 (0.17-1.14)	0.09
Screening cancer	299	0.75 (0.53-1.03)	0.08	299	0.76 (0.53-1.06)	0.10	293	0.76 (0.53-1.06)	0.11
Non-screening cancer	51	0.63 (0.31-1.26)	0.19	51	0.69 (0.34-1.40)	0.30	50	0.63 (0.30-1.35)	0.24

Any cancer refers to all cancers (prevalent and incident)
Model 2 is adjusted for age at baseline, gender, and education
Model 3 is adjusted for model 2 + baseline hypertension, diabetes, depression, and CVD
[1]Best fit model
[2]This is a subgroup of participants who have both an incident and prevalent cancer. It does not include participants in the prevalent cancer only or incident cancer only groups

Cancer, Gender and Risk of Dementia and AD Dementia

When stratifying by gender (Table 2.5), we found a 21% reduction in risk of all-cause dementia in women with a history cancer [model 3: HR=0.79 (0.59-1.07)] and a 20% reduced risk of AD dementia [model 3: HR=0.80 (0.54-1.18) vs no history of cancer. We found a 34% reduction in risk of all-cause dementia in men with a history cancer [model 3: HR=0.6 (0.38-1.15)] and a 33% reduced risk of AD dementia [model 3: HR=0.67 (0.33-1.33) vs no history of cancer. None of these associations reached statistical significance.

Table 2.5. The association between history of cancer and rate of all-cause dementia and AD dementia using cox-proportional hazards models stratified by gender

	Cause-specific hazard					
	All-cause dementia					
	Model 1 (Unadjusted)			**Model 3 (Adjusted)**		
	n	HR (95% CI)	P-value	n	HR (95% CI)	P-value
Men						
No Cancer	103	reference	-	103	reference	-
Any Cancer	140	0.74 (0.44-1.23)	0.24	136	0.66 (0.38-1.15)	0.15
Women						
No Cancer	272	reference	-	268	reference	-
Any Cancer	278	0.80 (0.60-1.06)	0.11	269	0.79 (0.59-1.07)	0.13

	AD dementia					
	Model 1 (Unadjusted)			**Model 3 (Adjusted)**		
	n	HR (95% CI)	P-value	n	HR (95% CI)	P-value
Men						
No Cancer	87	reference	-	87	reference	-
Any Cancer	122	0.72 (0.38-1.36)	0.30	119	0.67 (0.33-1.33)	0.24
Women						
No Cancer	217	reference	-	214	reference	-
Any Cancer	228	0.73 (0.50-1.06)	0.10	224	0.80 (0.54-1.18)	0.25

Model 3 is adjusted for age at baseline, gender, education, baseline hypertension, diabetes, depression and CVD

Cancer Types and Risk of Dementia and AD dementia

When estimating the cause-specific HR there were no significant associations between breast, colorectal, prostate, uterine or melanoma cancers with either all-cause dementia or AD dementia in our study cohort (Tables 2.6a and 26b). In fact, given the size of the CIs in this analysis it is likely that there were sample size limitations. Still, NMSCs (which made up most of the cancers in our study) showed a 34% lower rate of all-cause dementia [model3: HR: 0.66 (0.45-0.96)] in participants with cancer compared to those without a history of cancer. NMSCs showed no significant association with the rate of AD dementia, although the effect size is nearly identical to that of all-cause dementia.

Table 2.6a. The association between history of cancer and rate of all-cause dementia using Cox-proportional hazards models stratified by cancer type.

	Cause-specific hazard					
	All-Cause dementia					
	Model 1 (unadjusted)			Model 3 (adjusted)		
	n	HR (95% CI)	P-value	n	HR (95% CI)	P-value
No cancer	272	reference	-	268	reference	-
Breast	44	1.15 (0.71-1.86)	0.57	42	1.06 (0.63-1.76)	0.83
No cancer	103	reference	-	103	reference	-
Prostate	17	1.08 (0.40-2.85)	0.88	14	0.76 (0.22-2.54)	0.66
No cancer	375	reference	-	371	reference	-
Colorectal	22	0.77 (0.33-1.76)	0.53	21	1.02 (0.44-2.35)	0.96
No cancer	375	reference	-	371	reference	-
Melanoma	14	0.85 (0.27-2.70)	0.79	14	0.92 (0.28-3.00)	0.89
No cancer	375	reference	-	371	reference	-
NMSC	140	0.65 (0.45-0.93)	**0.02***	140	0.66 (0.45-0.96)	**0.03***
No cancer	272	reference	-	268	reference	-
Uterine	8	0.88 (0.27-2.82)	0.83	8	0.99 (0.29-3.32)	0.99

Model 3 is adjusted for age at baseline, gender, education, baseline hypertension, diabetes, depression and CVD

Table 2.6b. The association between history of cancer and rate of AD dementia using Cox-proportional hazards models stratified by cancer type.

	Cause-specific hazard					
	AD dementia					
	Model 1 (unadjusted)			Model 3 (adjusted)		
	n	HR (95% CI)	P-value	n	HR (95% CI)	P-value
No cancer	217	reference	-	214	reference	-
Breast	31	0.84 (0.41-1.71)	0.64	31	0.83 (0.40-1.38)	0.61
No cancer	87	reference	-	87	reference	-
Prostate	15	0.88 (0.25-3.07)	0.83	13	0.89 (0.22-3.53)	0.87
No cancer	304	reference	-	301	reference	-
Colorectal	20	0.97 (0.39-2.43)	0.95	19	1.34 (0.53-3.40)	0.53
No cancer	304	reference	-	301	reference	-
Melanoma	14	1.17 (0.36-3.73)	0.79	14	1.27 (0.38-4.20)	0.70
No cancer	304	reference	-	301	reference	-
NMSC	121	0.62 (0.39-0.98)	0.04	121	0.64 (0.39-1.02)	0.06
No cancer	217	reference	-	214	reference	-
Uterine	6	0.70 (0.09-5.15)	0.72	6	0.72 (0.09-5.50)	0.75

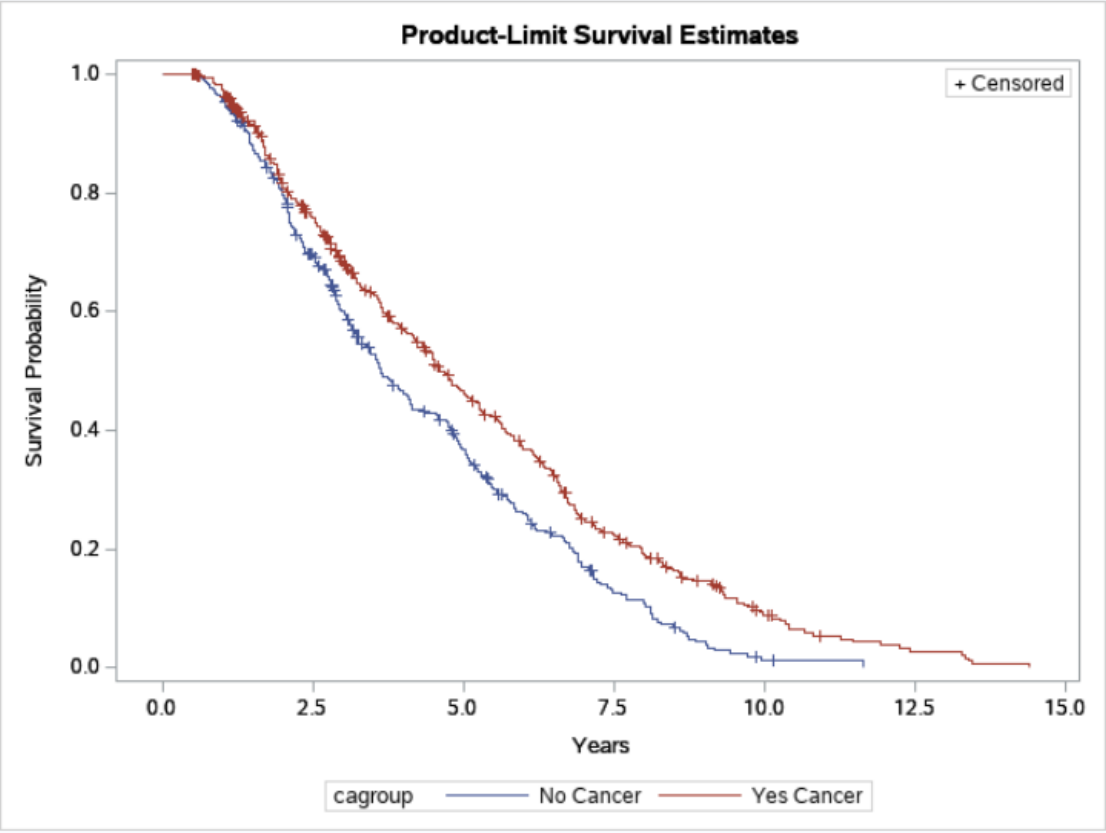
Model 3 is adjusted for age at baseline, gender, education, baseline hypertension, diabetes, depression and CVD

History of Cancer and the Rate of Death

Kaplan Meir Survival Analysis

Using survival analysis, we measured the overall rate of death for participants with and without a history of cancer. This analysis is different than the one above because participants were not censored at the time of dementia diagnosis. Therefore this analysis includes person years after dementia diagnosis. Moreover, it includes data points on participants diagnosed with cancer after their dementia diagnosis, which changed the final number of participants with a history of cancer from 420 to 438 and participants who remained cancer free from 343 to 325. 77.9% (n=341) of participants with a history of cancer died compared to 82.5% (n=268) of participants with no history of cancer. As shown in Figure 2.2, participants with a history of cancer survived longer in our study cohort than those without a history of cancer (p<000.1).

Figure 2.2. Kaplan Meir Survival Estimates by History of Cancer



2.5 Discussion

In this well-characterized cohort of men and women, aged 90 years and older, we found a significant inverse association between cancer and rate of all-cause dementia. Importantly, these results are from the largest US cohort study of the oldest-old and show an approximately 23% lower rate of all-cause dementia in participants with a history of any cancer compared to those without a history of cancer. This study also found that participants with a combined prevalent and incident cancer, had the lowest rate of all-cause dementia. When evaluated by cancer type, this study found only NMSC was significantly associated with a 34% lower rate of all-cause dementia. Notably, the associations in AD dementia for any cancer, combined prevalent and incident cancers, and NMSC had similar effect sizes but did not reach statistical significance.

These findings are consistent with previous studies, including the Framingham Heart Study (Driver, 2012), which found a 20-30% reduced risk of dementia in people with a history of cancer (age 68-96 years, mean 77 years), and several other studies of cancer and dementia among those 60+ years old (Roe, 2010; Musicco, 2013; White, 2013; Freedman, 2016; Sun, 2020). The point estimates in our study for the association between any cancer and all-cause dementia HR=0.77 (0.59-0.99), as well any cancer and AD dementia HR=0.77 (0.54-1.05), is similar in magnitude. Furthermore, our sub-analysis of incident cancers found that the rate of dementia is much lower in participants with incident cancers only (HR: 0.63 (0.31-1.28) and combined prevalent and incident cancers (HR: 0.42 (0.18-0.92). Although, all the results did not reach significance, similar studies found stronger associations of similar magnitude (HR: 0.58, 95% CI = 0.35-0.97) when examining incident cancers (Chamberlain, 2021).

The results in NMSCs are consistent with other studies (White, 2013; Schmidt, 2017; Steinerman, 2011; Ibler, 2018). It has been suggested that environmental factors associated with NMSC, including outdoor physical activity and vitamin D exposure may explain this decreased rate of dementia (Moore, 2016; Moehrle, 2008). Although analyses stratified by cancer type did

not reach statistical significance for types other than NMSC, the effects were in the same direction and of similar magnitude as previous studies (Frain, 2013; Papageorgakopoulos, 2017) and power may have been limited for these other individual cancer types. However, sensitivity analysis was performed by excluding NMSC and cancer-dementia results remained significant.

While several previous studies have shown differences between men and women (Hanson, 2017; Freedman, 2016; Frain, 2017; Realmuto, 2012), we did not find any evidence to support this in our study cohort. When stratified by gender the results of the associations in all-cause and AD dementia were similar.

Because methodologic issues, including survival bias, diagnostic bias, confounding and competing risks may also explain the cancer-dementia association, we paid careful attention to these issues. First, confounding was addressed in this study by adjusting for variables known to be associated with both the exposure and outcome, including age, education, gender, hypertension, diabetes, depression, and CVD. After adjustment, the inverse association between cancer and all-cause dementia remained significant. While it is possible that residual confounding may still account for part of the association, it is unlikely to account for all of the association. In this longitudinal study the cohort was evaluated on a regular basis using standard neurological assessments by trained physicians and nurse practitioners and it is unlikely that those with and without cancer were assessed differentially. This would have combatted any diagnostic bias from subjective measures by researchers. Furthermore, we excluded 559 people at baseline due to a diagnosis of dementia, thus excluding those for whom recall of cancer diagnosis before baseline would be less accurate. Another concern, related to survival bias, was whether cancer severity and clinical prognosis may impact risk of dementia differently. To address this, screening and non-screening cancers were evaluated separately. Compared to non-screening cancers, screening cancers have higher 5- and 10-year survival rates and are generally diagnosed at younger ages and earlier stages. Consistent with others (Frain, 2013), we found a significant

decrease in rate of dementia in both the screening and non-screening cancer groups. Additionally, our current study performed analyses for incident and prevalent cancers as well as screening and specific cancer types, and continued to find evidence of an inverse relationship, including when analyses were limited to NMSC, a cancer with high survival rates.

As discussed by Ospina-Romero (2020a), an additional challenge in evaluating the association between cancer and dementia is concern about competing risks (Ospina-Romero, 2020a). Specifically, participants with cancer have a higher rate of death compared to those without cancer and may not survive long enough to be diagnosed with dementia. Competing risks can bias the association by overestimating the effect and seemingly making the rate of dementia even lower in the cancer group than it is. After a separate analysis of history of cancer and death, we did not find any evidence of death impacting our study estimates. It is possible that death from cancer may not be as great a concern in the oldest old compared to younger age groups when it comes to the cancer and dementia relationship. People who survive to age 90 and older are likely different than those who die at younger ages, and as a group are at greater risk of death than younger age groups. Therefore we can infer that at age 90 the risk of dying from cancer is no different than the risk of dying from other health complications. A study published in 2008 using the Health and Retirement study data found that chronic conditions were not a strong predictor of death in adults 90-99 years, but rather functional limitations were better indicators (Lee, 2008).

A more recent study from 2020 used simulations to model the cancer-dementia relationship in cancer free and dementia free older adults 65+ years, to examine whether competing risks could explain the inverse association (Hayes-Larson, 2020). They found that any bias induced by competing risks, including in cancers with high mortality rates, were not large enough to explain the inverse association. Rather, it would take some unknown or unmeasured risk factor that protects from cancer mortality and dementia incidence, to introduce enough bias to affect the estimates of the inverse association. Likewise, Ospina-Romero (2020a) found that

competing risks were unlikely to explain the inverse association between cancer and AD, after a meta-analysis of 22 studies showed an overall mean 11% lower risk of AD for participants with a history of cancer (Ospina-Romero, 2020a). In this meta-analysis they investigated biases using directed acrylic graphs of causal structures that demonstrate how biases, like competing risks could affect association estimates in a positive or negative direction.

The best approach for our specific research question was to use the cause-specific HR. The cause-specific HR method to estimate the association between two events is used to answer epidemiological questions of etiology (Austin, 2016; Lau, 2009) and is a more "natural interpretation" of the data (Guo, 2018). The second method, the subdistribution HR approach, is better suited to predict clinical diagnosis or an individual's risk, like a clinical prediction model (Austin, 2016; Lau, 2009; Lee, 2016). Because of the shared genes and biological pathways between tumorigenesis and neurodegeneration, our question about the association between cancer and dementia is focused more on etiology than prediction. For this reason, we chose to use the cause-specific method. The cause-specific hazard estimates the effect of covariates on the rate of dementia (outcome) occurrence in participants who have not yet experienced death (competing event) or dementia (event of interest). The cause-specific hazard function also assumes non-informative censoring, meaning that the death from cancer has no impact on incidence of dementia (Allison, 2018; Wolbers, 2014). There is no test available to determine if censoring is non informative or informative. Unfortunately, there is also currently no reliable method to estimate risk if there is informative censoring (Allison, 2018). However, when censoring is informative the estimated risk from the cause-specific method is less biased than other proposed methods. Moreover, when using the cause-specific method under the possibility of informative censoring, the analysis should control for covariates that are common risk factors for both the competing event (death) and the event of interest (dementia). Most researchers agree

that the use of the cause-specific hazard function is the preferred approach to address etiologic questions (Wolbers, 2014; Austin and Fine, 2017).

Finally, we examined survival bias through survival analysis. We estimated the overall survival rate of participants with cancer and participants without cancer for the full period that they were in the 90 Plus study. This includes additional person-years after dementia diagnosis that were not included in our cause-specific hazard model for risk of dementia. This meant that even after they were diagnosed with dementia, they continued in the survival analysis until they died, or the study ended. Participants with cancer survived longer over time than participants without cancer. Given that participants with a history of cancer were less likely to die, the argument around death as a competing risk being a significant factor in the association is unlikely to be true. If it had been, we would have observed a substantial increased rate of death among those with cancer compared to those without cancer. The results of the survival analysis demonstrate that having a history of cancer did not put participants at greater risk of death in this study cohort.

Limitations and Strengths

While this is one of the largest cohorts of the oldest-old, the generalizability of this study may be limited due to the nature of The 90+ Study population, which is a predominantly white, female, and well-educated cohort, and these results may not apply to racially diverse populations. Yet it is worth noting that most of the oldest-old population are women and therefore our results represent the true gender make-up of this population, but it may lead to challenges when making inferences about men in this age group. Different races may be burdened by specific risk factors that are not represented in the 90+ study and the specific characteristics of cancers in this study population. Secondly, while we controlled for confounding and accounted for potential biases, most of the covariates used in our models were baseline measures which limited our ability to account for time-varying effects . For future studies, the use of time-varying covariates from the

90 Plus study will allow for a more comprehensive understanding of temporal relationships because it would be possible to examine how their effect changes throughout the follow-up period. The effect of specific risk factors that change after baseline could have confounded death rates or rates of dementia in the study sample, changing the magnitude of the inverse association in either direction. The study was also limited by the self-report of cancer diagnosis that could result in underreporting. Epidemiologists have argued against the use of self-reported cancer in epidemiological studies (Bergmann, 1998). This may be a particular issue in older adults with memory and cognitive problems, who may forget if/when they had cancer in the past. In our study, 41.1% (n=314) of participants were considered cognitively impaired non dementia (CIND) at baseline, although there were no significant differences between CIND for participants with and without cancer. Still, this could have introduced ascertainment or recall bias into our study, resulting in an overestimation of the association. We have seen similar biases in studies where cancer is measured as a time-independent variable (Roe, 2005; Hanson, 2016). Still, it's unlikely that these biases could fully explain the inverse association, given that self-report of cancer in the United States has been shown to be accurate (Dominguez, 2007; Parikh-Patel, 2003). Furthermore, because cancer is self-reported we did not have sufficient information on stage or cancer treatments. The stage of cancer and type of treatment have different short and long term effects on cognition (Janelsins, 2014). Most studies report late-stage cancers and treatments using chemotherapy increase risk for cognitive impairment (Ahles, 2012; Biglia, 2012; Vitali, 2017). Surprisingly, recent studies of cancer and dementia, show that late-stage cancers (Bowles, 2017) and chemotherapy treatment (Frain, 2017) were independently associated with a lower risk of dementia and AD dementia. A closer look at the mechanisms underlying the inverse association may explain the effect that stage and treatment have on the overall association between cancer and dementia.

This study has a number of strengths. First, The 90+ Study is one of the largest cohorts of the oldest-old nationwide and were able to leverage the rich data on this well-characterized cohort, regular clinical assessments with rigorous and standardized approaches to diagnosis of dementia and AD dementia, long-term follow-up that all allowed careful assessment of the study question and ability to address many of the previously identified methodological challenges in evaluating the association between cancer and dementia. Specifically, the diagnosis of dementia was determined by clinical evaluation at multiple study visits and not taken from claims or registry data, and therefore maybe more reliable and consistent across all participants. An in-person clinical evaluation at baseline makes it less likely that our cohort included anyone with dementia at baseline. Additionally, because of the short interval between follow-up visits, it is less likely that cases of incident dementia were missed. Multiple study visits also allowed for the detection of incident cancers, and incident cancer could be included a time-dependent variable. Another study strength was our examination of cancer types individually. The significant inverse association between NMSC and dementia is less susceptible to survival bias because NMSC has a high survival rate.

We were able to confirm an inverse association between cancer and rates of all-cause and AD dementia in a study cohort of participants aged 90 and greater. As the fastest growing age group worldwide, it is important to understand the impact of health conditions on aging adults because life expectancy and chronic disease play an important role in public health programming and policy.

Chapter 3: The Relationship Between Cancer and Cognitive Decline: A Longitudinal Cohort Study of the Oldest-Old

3.1 Introduction

Previous studies have shown a consistent and inverse association between cancer and risk of dementia (Driver, 2012). We have recently confirmed this association in a community-based cohort of the oldest-old, a group of men and women, aged 90 years and older, followed from 2003-2018, and dementia-free at baseline (unpublished). These results appear contradictory to some evidence that cancer and cancer treatment are associated with an increase in cognitive impairment. Approximately 16%-75% of adults with solid tumors report cognitive problems in memory, attention, processing speed and executive function before and after cancer diagnosis (Pendergrass, 2018; Asher, 2015) and more than 20 longitudinal studies have found evidence of accelerated cognitive impairment in cancer survivors (Ahles, 2012; Pendergrass, 2018). However, most of these studies were limited to younger cohorts of breast cancer survivors only and follow-up was limited to 3-12 months post diagnosis.

Recently, it has been suggested that the impact of cancer on cognitive performance may be specific to certain cognitive domains. For example, Gupta (2019) examined cognitive performance in older adults with and without cancer (mean age 67.4 and 60.8 years, respectively) in the Framingham Heart Study Offspring cohort (Gupta, 2019). History of any cancer was significantly associated with better scores in executive function using Trail Making Test B but significantly worse on verbal learning and memory tasks using the Verbal Paired Associates, a subtest of the Wechsler Memory Scale. In contrast, a larger population based study of 14,000 older (50+) participants from the Health and Retirement Study found that those with an incident cancer had a 10.5% slower rate of memory decline in the 10 years before their diagnosis compared to participants who remained cancer free (Ospina-Romero, 2019). After cancer diagnosis, there was a momentary short-term acceleration in loss of memory in approximately the

2 years following diagnosis. Over time memory improved until the rate was similar to memory decline before diagnosis. This ultimately led to an overall 3.9% slower rate of memory decline after cancer diagnosis in those with an incident cancer compared to participants who remained cancer free. This suggests that the time of decline relative to cancer diagnosis may be relevant. Perhaps the protective effect of cancer on cognition is only present during a designated time before and after diagnosis. Additional support for time being an important factor in cancer's effect on cognition comes from the cancer and dementia literature. Previous studies have shown that cancer seems to be most protective against dementia in the earliest years following cancer diagnosis (Ording, 2020; Hanson, 2017). Together, these results may explain why incident cancers seem to be more protective against cognitive decline and dementia than prevalent cancers (Ospina-Romero, 2019; Frain, 2017; Bowles, 2017).

A better understanding of the association between cancer and cognitive performance may help to elucidate a functional mechanism for the inverse association between cancer and dementia. This study will examine the longitudinal association between cancer diagnosis and cognitive performance in a large group of men and women, aged 90 years and older, from The 90+ Study and evaluate potential differences by multiple cognitive domains, cancer types, and time since initial cancer diagnosis.

3.2 Methods

Participants

The source population for this study was The 90+ Study, one of the largest longitudinal population-based cohorts of the oldest old, and has been described elsewhere (Corrada, 2008; Corrada, 2010). Briefly,1525 participants were recruited from the 1980 Leisure World Cohort Study in Laguna Woods, CA. Initial participants had to be age 90 or older as of January 1, 2003. Exclusion criteria for the present analysis included (1) a diagnosis of dementia at baseline, (2) missing self-reported information on history of cancer, and (3) history of brain and CNS tumors

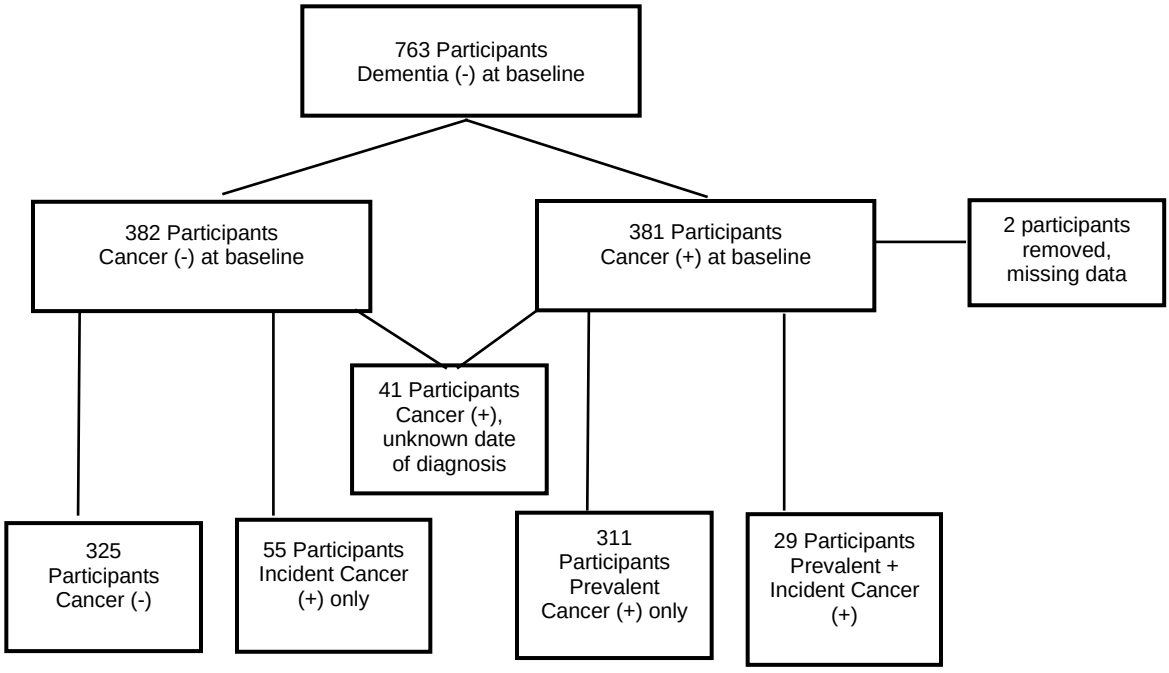
(n=3), acoustic neuromas (n=1), bone-head tumors (n=1) or meningiomas (n=1).Inclusion criteria included a minimum of 1 score on one of the selected cognitive tests at an in-person follow-up visit. For this analysis the participants were followed from entry into the 90+ study until either 1) death, 2) loss to follow-up, or 3) the end date from which this analysis concluded. This study was approved by the University of California, Irvine Institutional Review Board.

At baseline, participants were asked about their demographics given, a physical examination and an in-person cognitive assessment. Medical history (ie depression, cardiovascular disease, hypertension and diabetes) was self-reported. They were also asked to bring in any medication bottles to confirm reported medication names and prescribed dosages. Subsequent interviews after baseline gathered the same information. *Cancer Assessment*

A history of cancer was identified by self-report using data from the medical history questionnaire collected at baseline. History of cancer may have also been reported by an informant if the participant was unable to give the information. Participants were asked if they had ever been diagnosed with cancer and their responses were recorded as “yes,” “no,” “don’t know” or in some cases where the question was not asked it would be reported as “not done.” Participants who reported “other” were asked to specify the cancer type(s). The interviewer asked this question for each cancer type. Incident cancers after baseline were also self-reported through follow-up questionnaires administered on average every 6 months.

Cancer cases were divided into prevalent and incident cancer groups for subgroup and sensitivity analysis. Prevalent cancers were defined as cancers diagnosed before baseline study enrollment. Incident cancers were defined as cancers diagnosed after baseline study enrollment.

Figure 3.1. Flow chart of study population



Cognitive Performance Testing

A battery of standardized tests was used to evaluate cognition in this study cohort. In-person neuropsychological assessments were conducted at baseline and every 6 months on average at follow-up by trained and certified psychometrists using a battery of neuropsychological tests. We selected 5 tests based on their frequency of use in both the cancer and dementia literature (Hodgson, 2014; Tsoi, 2014) and validation in adults aged 90 years and older (Whittle, 2007; Kahle-Wrobleski, 2007). Cognitive tests used included Mini-Mental State Examination (MMSE), Modified Mini-Mental State (3MS) examination, California Verbal Learning Test (CVLT), Trail Making Test (TMT) and the Animal Fluency Test (Animal Fluency). Global cognition was measured using the MMSE and 3MS. The five domains measured in this study were 1) memory (using CVLT-free recall and CVLT-long delay), 2) attention (using TMT-A), 3) verbal fluency (using Animal Fluency), 4) executive function (using TMT-B) and 5) psychomotor speed (using TMT-C).

On the 3MS and MMSE, participants are asked a series of questions and are awarded points for correct answers. The questions are a combination of word lists, arithmetic, basic motor skills and language comprehension. There are five sections of the CVLT: 4 trials of immediate and 1 trial of delayed recall after 10 minutes of nonverbal distractions. In each section the participant is asked to remember a list of 9 randomly ordered words and repeat them back verbally. The 90+ Study modified this test by giving the words both verbally and visually to participants, whereas the original version only included the words being read out loud (Whittle, 2007). The TMT consists of 3 parts, parts A, part B, and part C. TMT-A measures attention. TMT-A consists of a series of circles with numbers where participants are asked to draw lines to connect the numbered circles in chronological order (1, 2, 3, 4,...). TMT-B measures executive function. TMT-B consists of a series of circles with both numbers and letters. Participants were asked to draw lines to connect the circles in order, alternating between numbers and letters (1, A, 2, B,...). TMT-C measures psychomotor speed. Participants were asked to trace a dotted line connecting 25 empty circles using a colored marker. The three parts are timed (measured in seconds) independently and the shorter it takes for a participant to finish the better their performance. Finally, for the animal fluency test, participants were given 60 seconds to name as many animals as they could. They received 1 point for each correct item and the higher the score, the better their performance.

Each test was administered to participants in the 90+ study in a specific order for the neuropsychological assessment. As a result, tests administered earlier in the neuropsychological assessment had more repeated measures/time points for use in this research study. Tests administered later had fewer repeated measures/time points and for some participants were missing entirely for the length of their follow-up period. Missing data was often due to participant fatigue or sensory (hearing or visual) impairments.

3.3 Statistical Analysis

Chi-square for categorical variables and two-sample t-tests for continuous variables were performed to compare baseline characteristics and baseline cognitive test scores between participants with and without cancer.

Linear mixed effects models evaluated differences in rates of change in cognitive test performance for participants with and without a history of cancer. Random intercepts and slopes of cognitive performance were included in our models to accommodate the intraclass correlations among repeated measures from the same individual. Each model compared participants with a history of cancer to those with no history of cancer. The interaction between cancer and time tests the difference in annual change rates in performance on cognitive tests between participants with a history of cancer and participants with no history of cancer. All adjusted models included baseline age, education, gender, and self-reported medical history of hypertension, depression, diabetes and cardiovascular disease collected at baseline and used as fixed effects in our adjusted model.

Models 1 and 2 measured the rate (slope) of cognitive performance over time between participants with no history of cancer and participants with a history of cancer. We calculated the annual rate of cognitive performance for each test in each cognitive domain. Model 1 is our unadjusted model. Model 2 is adjusted for baseline age, education, gender, baseline hypertension, cardiovascular disease, depression and diabetes. The primary analyses compared participants with any cancer (prevalent or incident) at the end of the study period to participants who remained cancer free. In our previous aim, cancer was a time-dependent variable. However, cancer is not time dependent in this study. Rather the cancer groups are decided based on cancer status at the end of the study. This was decided because previous studies have shown that cancer can affect rates of cognitive decline in participants with cancer, multiple years before their cancer

diagnosis. Therefore we wanted to capture the time between baseline enrollment and incident cancer diagnosis and attribute that time to the appropriate cancer group.

A sensitivity analysis excluding participants with non-melanoma skin cancer (NMSC) only was also performed. NMSCs were excluded from our sensitivity analysis because these cancers are less lethal, less likely to require pharmacotherapy interventions or radiation and generally have favorable prognosis compared to other cancers. Therefore, NMSC may not have the same effects on cognition as other cancers. We also stratified our groups by cancer type.

Subgroup analyses were performed to independently assess participants with prevalent cancer and participants with incident cancer. Participants with both prevalent and incident cancers were excluded. We then ran a different subgroup analysis excluding participants with prevalent cancer, to assess the change in cognitive performance pre- and post- incident cancer diagnosis. To do this we excluded participants with a prevalent cancer and participants with more than one incident cancer. Cognitive performance from baseline enrollment to diagnosis of incident cancer made up the measurements for the pre- incident cancer group and cognitive performance after incident cancer diagnosis made up the measurements in the post- incident cancer group.

Finally, we ran a sensitivity analysis to assess the change in cognitive performance for participants whose first cancer was 0-5 years, 6-10 years, 11-15 years, 16-20 years, 21+ years before baseline. Participants with more than one cancer were excluded from these analyses. Excluding participants with multiple different cancers diagnosed at different ages prevented the overlapping of the different time categories.

Trail making tests A,B,&C were excluded from the analyses of cancer type, prevalent and incident cancers, and time (years) between first cancer diagnosis and baseline, because of missing data. The first studies in our battery, the MMSE, 3MS, and Animal Fluency had completion rates of 99.8, 93.6% and 99.3%, respectively. The non-completion rates on the final

tests in our battery were 76.9% (TMT-A), 63.3% (TMT-B) and 72.7% (TMT, C). Statistical analyses were performed using SAS 9.4M2. All *P*-values are two-tailed. Statistical significance was defined as $P \leq 0.05$.

3.4 Results

As shown in Table 3.1., this cohort of oldest old participants were predominately white, female and well educated. Compared to those without as history of cancer, participants with cancer were significantly younger (92.4 years vs 92.7 years; p=0.02), had longer follow-up (3.15 years vs 2.71 years; p=0.001) and were a smaller proportion of women (66.3% vs 73.5%; p=0.03). Differences by history of cancer were not seen in education level, or medical history, including hypertension, cardiovascular disease, diabetes, or depression.

As shown in Figure 3.1, at baseline, 381 (49.9%) participants had a history of prevalent cancer and 382 (51.1 %) participants had no history of cancer at baseline. During follow-up, 55 participants from the initial cancer free group were diagnosed with an incident cancer, and 29 participants with a prevalent cancer were diagnosed with a new, incident cancer. At the end of follow-up, there were 311 prevalent only cancers, 55 incident only cancers, 29 prevalent and incident cancers combined, and 325 participants remained cancer free.

Of the 294 (38.6%) participants who reported having only one type of cancer, 151 had nonmelanoma skin cancer (NMSC) (51.3%). This was followed by 44 breast cancer cases (14.9%), 15 melanoma cases (5.1%), 21 colorectal cancers (7.1%), 19 prostate cancers (6.4%) and 8 uterine cancers (2.7%). The remaining 36 participants (12.2%) had an “other” cancer. We did not do separate analyses on cancers in the other group. When grouped by time since cancer diagnosis, 17.7% (n=52) were diagnosed 0-5 years before baseline, 12.9% (n=38) were diagnosed 6-10 years before baseline, 12.9% (n=38) were diagnosed 11-15 years before baseline, 9.2% (n=27) were diagnosed 16-20 years before baseline, 21.7% (n=64) of participants

were diagnosed more than 20 years ago, 16.7% (n=49) were diagnosed after baseline and 26 participants (8.8%) were missing information on time of first cancer and were excluded from the analyses.

Table 3.1. Characteristics of study population by history of cancer at the end of study

Characteristic	History of cancer at end of study period		
	No Cancer	Yes Cancer	p-value
Participants, n (%)	325 (42.7)	436 (57.3)	
Follow-up, yrs, median, (Range)	2.71 (0.01-11.5)	3.15 (0.01-13.8)	**0.001***
Baseline Age, yr, median, (Range)	92.7 (90.0-102.3)	92.4 (90.0-103.0)	**0.02***
Age at baseline (n, %)			0.12
90-95 years	245 (75.4)	353 (81.0)	
96-99 years	69 (21.2)	75 (17.2)	
100+ years	11 (3.4)	8 (1.8)	
Gender, F , (n, %)	239 (73.5)	289 (66.3)	**0.03***
Race, White, (n, %)	318 (97.9)	430 (98.6)	0.42
Education, (n, %)			0.32
Did not complete high school	17 (5.2)	29 (6.7)	
High school diploma	59 (18.2)	65 (14.9)	
Vocational and College	198 (60.9)	257 (58.9)	
Advanced Education/Degree	51 (15.7)	85 (19.5)	
Cognitive Status at Baseline			0.09
Normal	161 (49.5)	240 (55.0)	
[1]CIND	142 (43.7)	172 (39.5)	
Not reported	22 (6.8)	24 (5.5)	
Medical History (n, %)			
Hypertension	187 (57.5)	255 (58.5)	0.53
Cardiovascular disease	138 (42.5)	203 (46.6)	0.26
Depression	38 (11.7)	47 (10.8)	0.69
Diabetes	24 (7.4)	35 (8.0)	0.18

[1]CIND= Cognitively impaired not dementia

*P-value is measure of the difference between the two groups . Significance is p<0.05

In table 3.2. participants with a history of cancer at the end of the study period had significantly higher mean baseline scores on the MMSE (26.8 vs 26.3; p=0.03), 3MS (89.7 vs 88.3; p=0.04), CVLT-free recall (24.8 vs 23.5; p=0.01), and Animal Fluency test (13.7 vs 12.9; p=0.01). No significant differences between those with and without cancer was seen for baseline CVLT-long delay, TMT-A, TMT-B or TMT-C scores.

Table 3.2. Baseline cognitive test scores by history of cancer at end of study

Cognitive Test	**History of cancer at end of study period**				
	No Cancer		Yes Cancer		
	Participants (n)	Cognitive Tests Scores, (Mean, SD)	Participants (n)	Cognitive Tests Scores (Mean, SD)	p-value
MMSE	325	26.3 (3.00)	436	26.8 (2.46)	**0.03***
3MS	325	88.3 (9.72)	436	89.7 (8.33)	**0.04***
CVLT-Free Recall	310	23.5 (5.75)	418	24.8 (5.24)	**0.01***
CVLT-Long Delay	309	5.20 (2.58)	415	5.53 (2.54)	0.09
TMT-A	276	67.1 (33.8)	378	66.7 (33.5)	0.88
TMT-B	217	169.1 (76.1)	296	166.0 (74.0)	0.64
TMT-C	267	28.8 (14.9)	370	28.7 (15.5)	0.94
Animal Fluency	324	12.9 (4.04)	436	13.7 (4.39)	**0.01***

MMSE: mini-mental status examination; 3MS: modified mini-mental status examination; CVLT: California Verbal Learning Test; TMT: Trail Making test; Animal Fluency: Animal Fluency Test

There was a significant difference in annual decline in global cognition and verbal fluency, but not in the other cognitive domains measured (Table 3.3) for participants with cancer compared to participants without cancer. Participants with cancer declined significantly slower than the no cancer group. Compared to those without cancer, participants with a history of cancer had significantly slower rates of annual decline in global cognition measured by the MMSE (Model 2 multiply-adjusted difference=0.16 points/year, p=0.04), 3MS (Model 2 multiply-adjusted difference=0.70 points/year, p=0.01) and verbal fluency (Model 2 multiply-adjusted Animal

Fluency test difference=0.16, p=0.01). Although annual rate of decline by cancer history was faster in the those without a history of any cancer for memory and attention, differences did not reach the level of statistical significance in either unadjusted or adjusted models. Exclusion of NMSCs from these analyses eliminated all significant differences in annual cognitive decline between the groups by cancer history. Figure 3.2 illustrates the slopes of each adjusted model for all cancers in the different cognitive domains. Visually you can see the differences between the slopes for global cognition and verbal fluency, which are not seen in the other cognitive domains.

Table 3.3. Slope of Cognitive Performance over time by history of cancer and cognitive domain

		Model 1: Unadjusted			**Model 2:** Adjusted	
	N	Annual rate of change (CI)	*p-value	N	Annual rate of change (CI)	*p-value
Global Cognition						
MMSE						
All cancers						
History of cancer						
Yes	436	-0.64 (-0.74, 0.54)		421	-0.81 (-0.91, -0.70)	
No	325	-0.75 (-0.88, 0.63)		321	-0.97 (-1.10, -0.85)	
Difference in slopes	761	0.11 (-0.03, 0.27)	0.13	743	0.16 (0.006, 0.32)	**0.04***
All cancers exc. NMSC						
History of cancer						
Yes	286	-0.69 (-0.82, -0.55)		272	-0.88 (-1.02, -0.74)	
No	325	-0.75 (-0.88, -0.62)		321	-0.98 (-1.12, -0.85)	
Difference in slopes	611	0.06 (-0.11, 0.25)	0.48	593	0.10 (-0.08, 0.28)	0.27
3MS						
All cancers						
History of cancer						
Yes	436	-2.21 (-2.54, -1.89)		422	-2.74 (-3.08, -2.41)	
No	325	-2.75 (-3.15, -2.36)		321	-3.44 (-3.86, -3.04)	
Difference in slopes	761	0.54 (0.03, 1.05)	**0.03***	743	0.70 (0.19, 1.22)	**0.01***
All cancers exc. NMSC						
History of cancer						
Yes	286	-2.40 (-2.84, -1.97)		272	-2.98 (-3.43, -2.52)	
No	325	-2.76 (-3.17, -2.34)		321	-3.48 (-3.92, -3.04)	

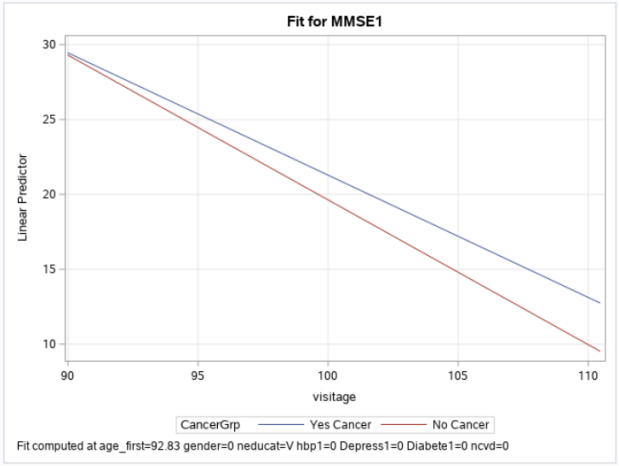
Difference in slopes	611	0.35 (-0.25, 0.95)	0.25	593	0.49 (-0.10, 1.10)	0.10
Memory						
CVLT, Free Recall						
All cancers						
History of cancer						
Yes	418	-0.43 (-0.56, -0.30)		407	-0.45 (-0.58, -0.31)	
No	310	-0.50 (-0.66, -0.33)		306	-0.47 (-0.65, -0.30)	
Difference in slopes	728	0.06 (-0.14, 0.27)	0.53	713	0.02 (-0.18, 0.23)	0.81
All cancers exc. NMSC						
History of cancer						
Yes	275	-0.44 (-0.61, -0.28)		262	-0.46 (-0.64, -0.29)	
No	310	-0.50 (-0.67, -0.34)		306	-0.47 (-0.65, -0.29)	
Difference in slopes	585	0.05 (-0.17, 0.29)	0.62	568	0.007 (-0.23, 0.24)	0.94
CVLT, Long Delay						
All cancers						
History of cancer						
Yes	415	-0.22 (-0.28, -0.17)		404	-0.25 (-0.31, -0.19)	
No	309	-0.26 (-0.33, -0.19)		305	-0.28 (-0.36, -0.21)	
Difference in slopes	724	0.03 (-0.05, 0.12)	0.38	709	0.03 (-0.05, 0.12)	0.49
All cancers exc. NMSC						
History of cancer						
Yes	271	-0.24 (-0.31, -0.17)		260	-0.28 (-0.33, -0.19)	
No	309	-0.26 (-0.33, -0.19)		305	-0.29 (-0.37, -0.21)	
Difference in slopes	580	0.02 (-0.07-0.11)	0.68	565	0.02 (-0.07-0.11)	0.81
Verbal Fluency						
Animal Fluency						
All cancers						
History of cancer						
Yes	436	-0.55 (-0.64, -0.47)		423	-0.61 (-0.69, -0.52)	
No	324	-0.69 (-0.79, -0.58)		320	-0.77 (-0.88, -0.66)	
Difference in slopes	760	0.13 (-0.002, 0.26)	0.05	743	0.16 (0.02, 0.30)	**0.01***
All cancers exc. NMSC						
History of cancer						
Yes	286	-0.60 (-0.71, -0.50)		272	-0.66 (-0.77, -0.55)	
No	324	-0.68 (-0.78, -0.57)		320	-0.77 (-0.88, -0.66)	
Difference in slopes	610	0.07 (-0.07, 0.22)	0.32	592	0.11 (-0.03, 0.25)	0.14
Attention						
TMT-A						

All cancers						
History of cancer						
Yes	378	5.29 (4.27, 6.30)		370	6.35 (5.25, 7.45)	
No	276	5.48 (4.20, 6.76)		272	6.81 (5.41, 8.20)	
Difference in slopes	654	-0.19 (-1.82, 1.44)	0.81	642	-0.45 (-2.12, 1.20)	0.58
All cancers exc. NMSC						
History of cancer						
Yes	250	5.81 (4.50, 7.13)		242	7.26 (5.83, 8.69)	
No	276	5.33 (4.01, 6.66)		272	7.00 (5.53, 8.47)	
Difference in slopes	526	0.47 (-1.3, 2.34)	0.61	514	0.26 (-1.64, 2.16)	0.78
Executive Function						
TMT-B						
All cancers						
History of cancer						
Yes	296	10.08 (8.23, 11.93)		289	11.65 (9.68-13.62)	
No	217	8.86 (6.15, 11.57)		213	10.75 (7.82-13.68)	
Difference in slopes	515	1.22 (-2.05, 4.50)	0.46	503	0.90 (-2.42, 4.23)	0.59
All cancers exc. NMSC						
History of cancer						
Yes	199	10.57 (8.10, 13.05)		193	11.90 (9.22-14.58)	
No	217	8.94 (6.17, 11.71)		213	10.37 (7.31-13.44)	
Difference in slopes	418	1.63 (-2.07, 5.34)	0.38	406	1.52 (-2.25, 5.31)	0.42
Psychomotor Speed						
TMT-C						
All cancers						
History of cancer						
Yes	370	1.88 (1.45, 2.31)		362	2.13 (1.69, 2.58)	
No	267	1.87 (1.32-2.43)		263	2.26 (1.68, 2.84)	
Difference in slopes	637	0.003 (-0.69, 0.69)	0.99	625	-0.13 (-0.81, 0.55)	0.70
All cancers exc. NMSC						
History of cancer						
Yes	245	1.66 (1.11, 2.21)		237	1.89 (1.32, 2.45)	
No	267	1.81 (1.25, 2.37)		263	2.19 (1.59, 2.78)	
Difference in slopes	51	-0.14 (-0.93, 0.63)	0.70	500	-0.30 (-1.05-0.45)	0.43

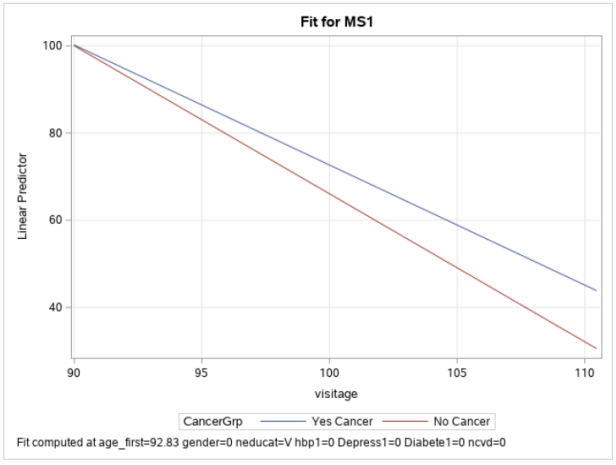
Model 1 is unadjusted
Model 2 is adjusted for age at baseline, education gender, hypertension, depression, diabetes and cardiovascular disease;
*P-value is measure of the difference between the two slopes. Significance is $p<0.05$

Figure 3.2. Slopes of Cognitive Performance over time by history of cancer and cognitive test

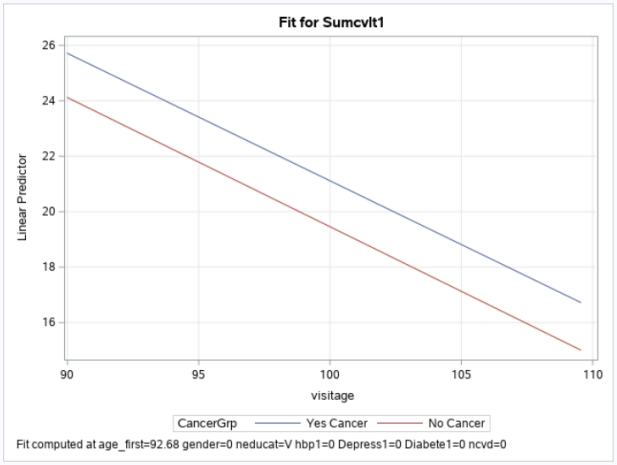
A. MMSE



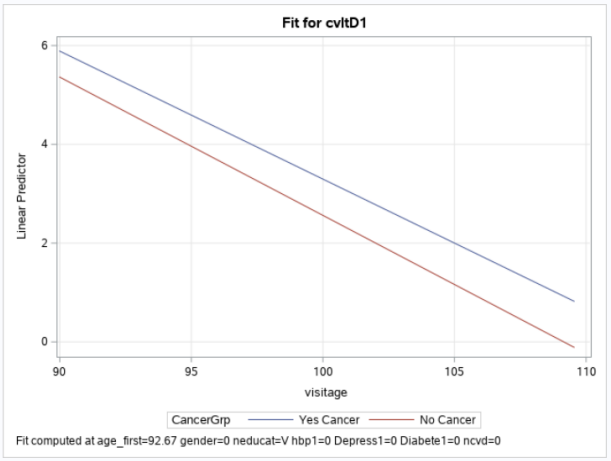
B. 3MS



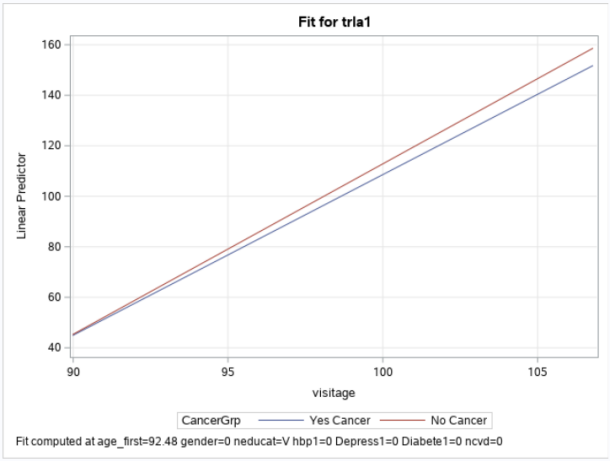
C. CVLT, Free Recall



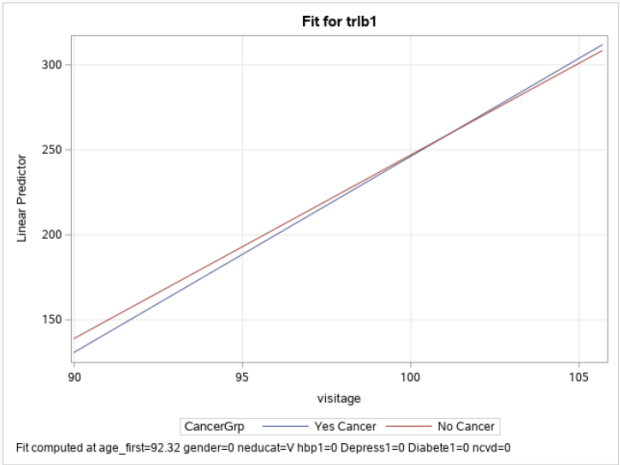
D. CVLT, Long Delay



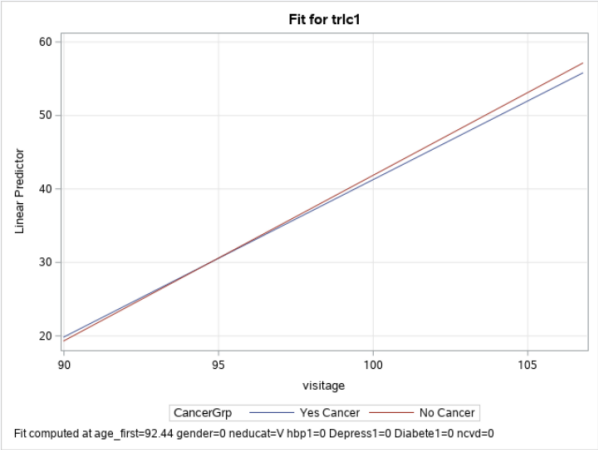
E. TMT-A



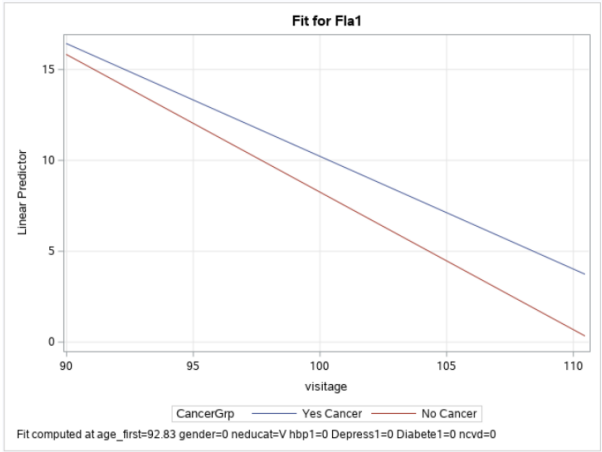
F. TMT-B



G. TMT-C



H. Animal Fluency



Cognitive performance for individual cancer types

Data presented below is from the adjusted model. Table 3.4 shows the comparison of annual cognitive decline by cancer site. NMSC, breast, and colon cancers were associated with a significantly slower rate of cognitive decline in the areas of global cognition as measured by MMSE and 3MS compared to participants without cancer. Interestingly, melanoma was associated with a faster rate of cognitive decline in global cognition for participants with cancer, although it was only significant for the MMSE. Only NMSC and colon cancers were associated with slower rates of cognitive decline in memory measured with the CVLT, Long Delay test. Finally, only NMSC was associated with slower rates of cognitive decline in verbal fluency on the Animal Fluency test. Trail making tests A,B,&C were excluded from these analyses due to missing information.

Table 3.4. Annual Slopes of cognitive change over time by type of cancer and cognitive domain

	Model 1: Unadjusted			Model 2: Adjusted		
	N	Annual rate of change (CI)	*p-value	N	Annual rate of change (CI)	*p-value
Global Cognition						
MMSE						
Breast						
History of cancer						
Yes	44	-0.58 (-0.89, -0.27)		42	-0.61 (-0.77, -0.45)	
No	239	-0.75 (-0.90, -0.62)		235	-0.87 (-0.96, -0.79)	
Difference in slopes	285	0.17 (-0.16, 0.51)	0.31	278	0.26 (0.08, 0.44)	**0.01***
Prostate						
History of cancer						
Yes	19	-0.87 (-1.54, -0.19)		16	-0.68 (-0.95, -0.41)	
No	86	-0.67 (-1.00, -0.34)		86	-0.83 (-1.04, -0.62)	
Difference in slopes	106	-0.20 (-0.94, 0.55)	0.60	103	0.15 (-0.19, 0.48)	0.39
Colon						
History of cancer						
Yes	21	-0.66 (-1.09, -0.79)		20	-0.53 (-0.78, -0.26)	
No	325	-0.75 (-1.26, -0.87)		321	-0.88 (-0.95, -0.79)	
Difference in slopes	346	0.09 (-0.43, 0.63)	0.71	341	0.35 (0.07, 0.62)	**0.01***
NMSC						
History of cancer						
Yes	145	-0.60 (-0.72, -0.39)		144	-0.59 (-0.66, -0.52)	
No	328	-0.75 (-0.88, -0.64)		323	-0.85 (-0.93, -0.78)	
Difference in slopes	473	0.15 (-0.05, 0.34)	0.15	468	0.26 (0.16, 0.46)	**0.01***
Melanoma						
History of cancer						
Yes	15	-1.05 (-1.64, -0.42)		15	-1.20 (-1.49, -0.90)	
No	325	-0.74 (-0.88, -0.61)		321	-0.88 (-0.96, -0.79)	
Difference in slopes	340	-0.31 (-0.91, 0.31)	0.31	336	-0.32 (-0.62, -0.02)	**0.04***
3MS						
Breast						
History of cancer						
Yes	44	-2.16 (-3.18, -1.13)		42	-2.15 (-2.66, -1.64)	
No	239	-2.76 (-3.22, -2.30)		235	-2.98 (-3.26, -2.72)	
Difference in slopes	283	0.60 (-0.52, 1.73)	0.29	277	0.83 (0.27, 1.40)	**0.01***
Prostate						
History of cancer						
Yes	19	-2.72 (-4.86, -0.59)		16	-2.38 (-3.21, -1.54)	
No	86	-2.61 (-3.67, -1.56)		86	-2.89 (-3.54, -2.24)	
Difference in slopes	105	-0.11 (-2.51, 2.28)	0.92	102	0.51 (-0.51, 1.53)	0.33

Colon						
History of cancer						
Yes	21	-2.73 (-4.46, -1.11)		20	-1.98 (-2.79, -1.15)	
No	325	-2.75 (-3.22, -2.37)		321	-2.99 (-3.24, -2.74)	
Difference in slopes	346	0.02 (-1.76, 1.81)	0.97	341	1.01 (-0.17, 1.86)	**0.02***
NMSC						
History of cancer						
Yes	151	-2.08 (-2.59, -1.55)		150	-1.89 (-2.11, -1.66)	
No	325	-2.72 (-3.11, -2.33)		321	-2.91 (-3.14, -2.67)	
Difference in slopes	476	0.64 (-0.01, 1.30)	0.05	471	1.02 (0.70, 1.33)	**0.01***
Melanoma						
History of cancer						
Yes	15	-3.37 (-5.37, -1.37)		15	-3.79 (-4.72, -2.86)	
No	325	-2.72 (-3.15, -2.27)		321	-2.99 (-3.24, -2.73)	
Difference in slopes	340	-0.65 (-2.70, 1.39)	0.52	336	-0.80 (-1.75, 0.14)	0.09
Memory						
CVLT, Free Recall						
Breast						
History of cancer						
Yes	43	-0.50 (-0.92, -0.09)		41	-0.45 (-0.67, -0.20)	
No	226	-0.53 (-0.74, -0.35)		222	-0.63 (-0.75, -0.50)	
Difference in slopes	269	0.03 (-0.41, 0.50)	0.89	263	0.18 (-0.72, 0.44)	0.15
Colon						
History of cancer						
Yes	17	-0.66 (-1.40, 0.06)		17	-0.38 (-0.75, -0.01)	
No	310	-0.45 (-0.63, -0.29)		306	-0.57 (-0.69, -0.46)	
Difference in slopes	327	-0.21 (-0.96, 0.54)	0.58	323	0.19 (-0.19, 0.58)	0.33
NMSC						
History of cancer						
Yes	145	-0.44 (-0.65, 0.23)		144	-0.42 (-0.53, -0.31)	
No	310	-0.46 (-0.64, -0.29)		306	-0.55 (-0.66, -0.44)	
Difference in slopes	455	0.02 (-0.02, 0.28)	0.86	451	0.13 (-0.02, 0.28)	0.09
Melanoma						
History of cancer						
Yes	15	-0.46 (-1.23, -0.31)		15	-0.34 (-0.77, 0.10)	
No	310	-0.46 (-0.63, -0.28)		306	-0.57 (-0.68, -0.45)	
Difference in slopes	325	0.00 (-0.79, 0.78)	0.99	321	0.23 (-0.21, 0.68)	0.30
CVLT, Long Delay						
Breast						
History of cancer						

Yes	42	-0.29 (-0.46, -0.12)		40	-0.31 (-0.41, -0.21)	
No	225	-0.30 (-0.38, -0.22)		221	-0.34 (-0.40, -0.29)	
Difference in slopes	267	0.01 (-0.18, 0.19)	0.96	261	-0.03 (-0.08, 0.14)	0.60
Colon						
History of cancer						
Yes	17	-0.16 (-0.48, 0.15)		17	-0.10 (-0.26, 0.07)	
No	309	-0.24 (-0.32, -0.17)		305	-0.31 (-0.37, -0.26)	
Difference in slopes	326	0.08 (-0.25, 0.40)	0.63	322	0.21 (0.04, 0.38)	**0.01***
NMSC						
History of cancer						
Yes	144	-0.20 (-0.28, -0.09)		143	-0.23 (-0.27, -0.18)	
No	309	-0.25 (-0.33, -0.19)		305	-0.30 (-0.35, -0.25)	
Difference in slopes	453	0.05 (-0.04, 0.18)	0.34	449	0.07 (0.01, 0.14)	**0.03***
Melanoma						
History of cancer						
Yes	15	-0.37 (-0.69, -0.05)		15	-0.36 (-0.55, -0.16)	
No	309	-0.25 (-0.32, -0.18)		305	-0.31 (-0.36, -0.26)	
Difference in slopes	324	-0.12 (-0.45, 0.20)	0.46	320	-0.05 (-0.24, 0.15)	0.64
Verbal Fluency						
Animal Fluency						
Breast						
History of cancer						
Yes	44	-0.51 (-0.76, -0.25)		42	-0.54 (-0.69, -0.39)	
No	238	-0.63 (-0.76, -0.53)		234	-0.69 (-0.77, -0.61)	
Difference in slopes	282	0.12 (-0.15, 0.40)	0.38	276	0.15 (-0.12, 0.32)	0.07
Colon						
History of cancer						
Yes	21	-0.71 (-1.15, -0.29)		20	-0.64 (-0.88, -0.39)	
No	324	-0.67 (-0.77, -0.56)		324	-0.73 (-0.80, -0.66)	
Difference in slopes	345	-0.04 (-0.49, 0.40)	0.90	345	0.09 (-0.16, 0.35)	0.09
NMSC						
History of cancer						
Yes	151	-0.51 (-0.60, -0.32)		150	-0.52 (-0.59, -0.44)	
No	324	-0.68 (-0.79, -0.59)		320	-0.70 (-0.78, -0.63)	
Difference in slopes	475	0.17 (-0.01, 0.33)	0.05	470	0.18 (0.08, 0.28)	**0.01***
Melanoma						
History of cancer						
Yes	15	-0.57 (-1.02, -0.13)		15	-0.57 (-0.84, -0.29)	
No	324	-0.66 (-0.78, -0.57)		320	-0.73 (-0.80, -0.66)	
Difference in slopes	339	0.09 (-0.36, 0.54)	0.70	335	0.16 (-0.11, 0.44)	0.25

Model 1 is unadjusted
Model 2 is adjusted for age at baseline, education and gender, hypertension, depression, diabetes and cardiovascular disease

Cognitive performance for prevalent and incident cancers

Table 3.5 shows the annual decline in cognitive performance stratified by incident versus prevalent cancer. Prevalent cancer was significantly associated with a slower annual decline in global cognition and verbal fluency compared to those without any cancer. In those without cancer, MMSE scores declined 0.25 points/year faster than participants with a prevalent cancer. (p=0.01; CI=0.08-0.43) and 3MS scores declined 0.86 points/year faster in those with prevalent cancer (p=0.003; CI=0.26-1.48). Similarly, verbal fluency decline was slower in those with prevalent cancer (Model 2 multiply-adjusted rate of decline 0.20 points/year; p=0.02, CI=0.04-0.36). History of a prevalent cancer was not related to annual changes in memory performance compared to those without cancer. Incident cancers were not associated with annual changes in any measure of global cognition, memory, or verbal fluency.

Table 3.5. Annual Slopes of Cognitive change over time in prevalent vs incident cancer cases

		Model 1: Unadjusted			**Model 2: Adjusted**	
	N	Annual rate of change (CI)	*p-value	N	Annual rate of change (CI)	*p-value
Global Cognition						
MMSE						
Prevalent Cancer						
History of cancer						
Yes	219	-0.56 (-0.68, -0.44)		211	-0.72 (-0.84, -0.59)	
No	325	-0.75 (-0.87, -0.63)		321	-0.97 (-1.09, -0.84)	
Difference in slopes	544	0.19 (0.01-0.34)	**0.04***	532	0.25 (0.08, 0.43)	**0.01***
Incident Cancer						
History of cancer						
Yes	50	-0.75 (-1.05, -0.58)		49	-0.88 (-1.12, -0.62)	
No	325	-0.75 (-0.87, -0.63)		321	-0.97 (-1.09, -0.84)	
Difference in slopes	375	0.00 (-0.26-0.28)	0.99	370	0.09 (-0.17-0.37)	0.53
3MS						
Prevalent Cancer						
History of cancer						
Yes	219	-2.06 (-2.52, -1.59)		211	-2.58 (-3.06, -2.09)	
No	325	-2.72 (-3.12, -2.32)		321	3.44 (-3.86, -3.02)	
Difference in slopes	534	0.66 (0.04-1.27)	**0.03***	532	0.86 (0.26, 1.48)	**0.01***
Incident Cancer						
History of cancer						
Yes	50	-2.52 (-3.41, -1.63)		49	-2.88 (-3.77, -2.00)	
No	325	-2.72 (-3.12, -2.32)		321	-3.44 (-3.86, -3.02)	
Difference in slopes	375	0.20 (-0.77,-1.17)	0.69	370	0.56 (-0.40, 1.52)	0.25
Memory						
CVLT, Free Recall						
Prevalent Cancer						
History of cancer						
Yes	209	-0.38 (-0.56, -0.26)		202	-0.42 (-0.59, -0.23)	
No	310	-0.48 (-0.64, -0.31)		306	-0.46 (-0.63, -0.28)	
Difference in slopes	635	0.10 (-0.15-0.34)	0.44	621	0.04 (-0.20, 0.29)	0.72
Incident Cancer						
History of cancer						
Yes	47	-0.39 (-0.76, -0.15)		47	-0.40 (-0.74, -0.07)	
No	310	-0.48 (-0.64, -0.31)		306	-0.46 (-0.63, -0.28)	
Difference in slopes	374	0.09 (-0.30, 0.46)	0.63	369	-0.06 (-0.31, 0.43)	0.75
CVLT, Long Delay						
Prevalent Cancer						
History of cancer						
Yes	207	-0.21 (-0.27, -0.14)		300	-0.25 (-0.32, -0.16)	

No	309	-0.26 (-0.33, -0.19)		305	-0.28 (-0.38, -0.09)	
Difference in slopes	631	0.05 (-0.05,-0.15)	0.38	617	0.03 (-0.07, -0.14)	0.53
Incident Cancer						
History of cancer						
Yes	47	-0.21 (-0.28, -0.13)		47	-0.24 (-0.38, -0.16)	
No	309	-0.26 (-0.33, -0.19)		305	-0.28 (-0.38, -0.09)	
Difference in slopes	373	0.05 (-0.11,-0.21)	0.56	368	0.04 (-0.12, 0.20)	0.62
Verbal Fluency						
Animal Fluency						
Prevalent Cancer						
History of cancer						
Yes	219	-0.50 (-0.64, -0.38)		211	-0.55 (-0.67, -0.43)	
No	324	-0.67 (-0.80, -0.56)		320	-0.75 (-0.88, -0.65)	
Difference in slopes	543	0.17 (0.01, 0.33)	**0.04***	531	0.20 (0.04, 0.36)	**0.02***
Incident Cancer						
History of cancer						
Yes	50	-0.54 (-0.77, -0.32)		49	-0.60 (-0.82, -0.37)	
No	324	-0.67 (-0.80, -0.56)		320	-0.75 (-0.88, -0.65)	
Difference in slopes	374	0.13 (-0.11,0.39)	0.30	369	0.15 (-0.09, 0.40)	0.21

Model 1 is unadjusted
Model 2 is adjusted for age at baseline, education, gender, hypertension, depression, diabetes and cardiovascular disease

Cognitive performance for before and after incident cancers

To assess timing of cognitive decline with respect to cancer occurrence, we compared differences in annual cognitive performance in pre, and post-incident cancer diagnosis to those without a history of cancer (Table 3.6). There was a consistent trend of slower rates of cognitive decline pre-incident cancer compared to the noncancer group. Not all the results reached significance. There was a consistent trend of faster rates of cognitive decline post-incident cancer compared to the noncancer group. No results for MMSE, 3MS, CVLT-Free Recall, CVLT-Long Delay, or Animal Fluency tests reached statistical significance.

Verbal fluency and memory (CVLT, Free Recall only) showed faster annual decline in the noncancer group compared to those in the incident cancer group before their cancer diagnosis [(Verbal Fluency: difference in annual decline 0.47 (0.13-0.80; p=0.01)) and [(Memory: difference in annual decline 0.57 (0.01-1.12; p=0.04)]. Differences in annual 3MS performance between pre-incident cancer and noncancer groups were significant in our unadjusted model. After adjustment for known confounders, no significant differences were seen when comparing 3MS performance scores prior to incident cancer diagnosis with the noncancer group.

Table 3.6. Annual Slopes of Cognitive change in cognition over time, before and after incident cancer

		Model 1: Unadjusted			**Model 2: Adjusted**	
	N	Annual rate of change (CI)	*p-value	N	Annual rate of change (CI)	*p-value
Global Cognition						
MMSE						
Before incident cancer						
History of cancer						
Yes	49	-0.38 (-0.75, -0.007)		48	-0.73 (-1.11, -0.35)	
No	325	-0.75 (-0.88, -0.63)		321	-0.94 (-1.08, -0.80)	
Difference in slopes	374	0.37 (-0.02, 0.77)	0.06	369	0.21 (-0.17, 0.60)	0.28
After incident cancer						
History of cancer						
Yes	49	-0.88 (-1.18, -0.59)		48	-1.06 (-1.36, -0.77)	
No	325	-0.75 (-0.88, -0.63)		321	-0.94 (-1.08, -0.80)	
Difference in slopes	374	-0.13 (-0.46, 0.18)	0.40	369	-0.12 (-0.44, 0.20)	0.45
3MS						
Before incident cancer						
History of cancer						
Yes	49	-1.06 (-2.26, 0.13)		48	-2.17 (-3.38, -0.95)	
No	325	-2.75 (-3.15, -2.35)		321	-3.33 (-3.77, -2.89)	
Difference in slopes	380	1.69 (0.42, 2.95)	**0.01***	375	1.16 (-0.09, 2.42)	0.07
After incident cancer						
History of cancer						
Yes	49	-2.99 (-3.94, -2.04)		48	-3.49 (-4.44, -2.54)	
No	325	-2.75 (-3.15, -2.35)		321	-3.33 (-3.77, -2.89)	
Difference in slopes	380	-0.24 (-1.27, 0.79)	0.65	375	-0.16 (-1.17, 0.86)	0.76

Memory						
CVLT, Free Recall						
Before incident cancer						
History of cancer						
Yes	42	0.07 (-0.44, 0.58)		41	0.15 (-0.38, 0.68)	
No	310	-0.46 (-0.63, -0.30)		306	-0.42 (-0.60, -0.23)	
Difference in slopes	352	0.53 (0.004, 1.07)	**0.04***	347	0.57 (0.01, 1.12)	**0.04***
After incident cancer						
History of cancer						
Yes	42	-0.85 (-1.24, -0.49)		41	-0.84 (-1.27, -0.39)	
No	310	-0.46 (-0.63, -0.30)		306	-0.42 (-0.60, -0.23)	
Difference in slopes	352	-0.39 (-0.81, 0.04)	0.07	347	-0.42 (-0.88, 0.05)	0.08
CVLT, Long Delay						
Before incident cancer						
History of cancer						
Yes	42	-0.07 (-0.29, 0.14)		41	-0.14 (-0.36, 0.07)	
No	309	-0.25 (-0.33, -0.18)		305	-0.26 (-0.34, -0.19)	
Difference in slopes	351	0.18 (-0.04, 0.41)	0.12	346	0.12 (-0.10, 0.35)	0.29
After incident cancer						
History of cancer						
Yes	42	-0.38 (-0.55, -0.22)		41	-0.41 (-0.58, -0.25)	
No	309	-0.25 (-0.33, -0.18)		305	-0.26 (-0.34, -0.19)	
Difference in slopes	351	-0.13 (-0.31, 0.05)	0.17	346	-0.15 (-0.33, 0.03)	0.10
Verbal Fluency						
Animal Fluency						
Before incident cancer						
History of cancer						
Yes	49	-0.14 (-0.45, 0.18)		48	-0.26 (-0.59, 0.06)	
No	324	-0.67 (-0.77, -0.57)		320	-0.73 (-0.85, -0.62)	
Difference in slopes	373	0.53 (0.20, 0.87)	**0.01***	368	0.47 (0.13, 0.80)	**0.01***
After incident cancer						
History of cancer						
Yes	49	-0.69 (-0.93, -0.45)		48	-0.77 (-1.01, -0.53)	
No	324	-0.67 (-0.77, -0.57)		320	-0.73 (-0.85, -0.62)	
Difference in slopes	373	-0.02 (-0.28, 0.24)	0.88	368	-0.04 (-0.30, 0.22)	0.78

Model 1 is unadjusted

Model 2 is adjusted for age at baseline, education, gender, hypertension, depression, diabetes and cardiovascular disease

Cognitive performance for date of first cancer

Table 3.7 shows the stratified analyses by date of first cancer, relative to baseline. The trend we see in these results is that the rate of cognitive decline is faster in the prevalent cancer groups whose first cancer was closer to baseline study enrollment compared to groups whose prevalent cancer was further from baseline study enrollment. Those with cancer diagnosed more than 20 years before the baseline visit had a significantly slower annual rate of decline for the MMSE (Model 2 adjusted difference 0.44/year; p=0.01 (0.15, 0.73), 3MS (Model 2 adjusted difference 1.59/year; p=0.01, (0.69, 2.63), and Animal Fluency (Model 2 adjusted difference 0.33/year; p=0.01 (0.08, 0.58) compared to those without cancer. Comparison between the noncancer group and those with cancer diagnosed 20 years prior to enrollment found borderline significant differences for CVLT-Free Recall (Model 2 adjusted difference 0.30/year; p=0.10, (-0.06, 0.67). No significant association was found between cancer diagnosed after enrollment or cancer diagnosed less than 20 years before baseline compared to those without cancer for any cognitive domain tested.

Table 3.7. Annual Slopes of Cognitive changes over time in participants with cancer by time of first cancer

		Model 1: Unadjusted			**Model 2: Adjusted**	
	N	Annual rate of change (CI)	*p-value	N	Annual rate of change (CI)	*p-value
Global Cognition						
MMSE						
Time since cancer dx						
History of cancer						
No	325	-0.75 (-0.88, -0.64)	0.00	321	-0.97 (-1.11, -0.83)	0.00
Yes, After baseline	49	-0.75 (-1.09, -0.57)		48	-0.88 (-1.15, -0.61)	
Difference in slopes		-0.00 (-0.29, 0.29)	0.99		-0.09 (-0.20, 0.39)	0.53
Yes, 0-5 years before baseline	52	-0.65 (-0.94, -0.35)		51	-0.81 (-1.11, -0.52)	
Difference in slopes		0.10 (-0.21, 0.42)	0.52		0.16 (-0.16, 0.48)	0.32

Yes, 6-10 years before baseline	38	-0.61 (-0.93, -0.26)		37	-0.69 (-1.03, -0.35)	
Difference in slopes		0.14 (-0.21, 0.42)	0.41		0.28 (-0.07, 0.64)	0.12
Yes, 11-15 years before baseline	38	-0.57 (-1.03, -0.34)		36	-0.77 (-1.12, -0.41)	
Difference in slopes		0.18 (-0.18, 0.55)	0.33		0.20 (-0.17, 0.58)	0.27
Yes, 16-20 years before baseline	27	-0.78 (-1.17, -0.40)		25	-0.98 (-1.39, -0.58)	
Difference in slopes		-0.02 (-0.42, 0.38)	0.91		-0.01 (-0.43, 0.40)	0.95
Yes, More than 20 years before baseline	64	-0.35 (-0.62, -0.09)		62	-0.53 (-0.80, -0.27)	
Difference in slopes		0.40 (0.10, 0.69)	**0.01***		0.44 (0.15, 0.73)	**0.01***
3MS						
Time since cancer dx						
History of cancer						
No	325	-2.72 (-3.17, -2.37)	0.00	321	-3.44 (-3.95, -3.10)	0.00
Yes, After baseline	49	-2.52 (-3.57, -1.87)		48	-2.88 (-4.03, -2.35)	
Difference in slopes		0.19 (-0.88, 0.98)	0.69		0.56 (-0.59, 1.26)	0.25
Yes, 0-5 years before baseline	52	-2.53 (-3.51, -1.55)		51	-3.01 (-4.06, -2.10)	
Difference in slopes		0.19 (-0.81, 1.29)	0.72		0.42 (-0.60, 1.50)	0.41
Yes, 6-10 years before baseline	38	-2.41 (-3.49, -1.28)		37	-2.68 (-3.82, -1.58)	
Difference in slopes		0.31 (-0.79, 1.56)	0.60		0.76 (-0.36, 2.01)	0.20
Yes, 11-15 years before baseline	38	-2.12 (-3.63, -1.36)		36	-2.82 (-4.37, -2.05)	
Difference in slopes		0.60 (-0.93-1.48)	0.33		0.62 (-0.90-1.53)	0.32
Yes, 16-20 years before baseline	27	-2.30 (-3.63, -1.08)		25	-2.97 (-4.42, -1.80)	
Difference in slopes		0.42 (-0.92-1.75)	0.54		0.47 (-0.94-1.77)	0.50
Yes, More than 20 years before baseline	64	-1.31 (-2.19, -0.43)		62	-1.85 (-2.75, -0.97)	
Difference in slopes		1.40 (0.49, 2.42)	**0.01***		1.59 (0.69, 2.63)	**0.01***
Memory						
CVLT, Free Recall						
Time since cancer dx						
History of cancer						
No	310	-0.48 (-0.64, -0.32)	0.00	306	-0.46 (-0.65, -0.31)	0.00
Yes, After baseline	47	-0.39 (-0.73, -0.05)		47	-0.40 (-0.76, -0.06)	

Difference in slopes		0.09 (-0.28, 0.47)	0.62		0.06 (-0.31, 0.43)	0.74
Yes, 0-5 years before baseline	48	-0.71 (-1.10, -0.33)		48	-0.71 (-1.09, -0.32)	
Difference in slopes		-0.23 (-0.63, 0.19)	0.27		-0.24 (-0.66, 0.17)	0.24
Yes, 6-10 years before baseline	36	-0.50 (-0.93, -0.08)		35	-0.49 (-0.92, -0.07)	
Difference in slopes		-0.02 (-0.48, 0.42)	0.91		-0.03 (-0.49, 0.42)	0.88
Yes, 11-15 years before baseline	37	-0.39 (-0.85, 0.06)		35	-0.45 (-0.91, 0.02)	
Difference in slopes		-0.08 (-0.40, 0.67)	0.72		0.01 (-0.47, 0.51)	0.94
Yes, 16-20 years before baseline	24	-0.35 (-0.84, 0.13)		22	-0.38 (-0.88, 0.11)	
Difference in slopes		0.12 (-0.38, 0.64)	0.62		0.08 (-0.44, 0.60)	0.76
Yes, More than 20 years before baseline	64	-0.09 (-0.40, 0.24)		62	-0.16 (-0.49, -0.17)	
Difference in slopes		0.39 (0.03, 0.76)	0.03		0.30 (-0.06, 0.67)	0.10
CVLT, Long Delay						
Time since cancer dx						
History of cancer						
No	309	-0.26 (-0.33, -0.19)	0.00	305	-0.28 (-0.36, -0.21)	0.00
Yes, After baseline	47	-0.21 (-0.35, -0.07)		47	-0.24 (-0.39, -0.10)	
Difference in slopes		0.04 (-0.11, 0.21)	0.56		0.04 (-0.11, 0.19)	0.62
Yes, 0-5 years before baseline	47	-0.27 (-0.44, -0.10)		47	-0.29 (-0.46, -0.12)	
Difference in slopes		-0.01 (-0.19, 0.17)	0.88		-0.01 (-0.18, 0.17)	0.90
Yes, 6-10 years before baseline	35	-0.23 (-0.41, -0.04)		34	-0.24 (-0.43, -0.06)	
Difference in slopes		0.03 (-0.16, 0.23)	0.76		0.04 (-0.15, 0.23)	0.71
Yes, 11-15 years before baseline	37	-0.34 (-0.55, -0.16)		35	-0.38 (-0.58, -0.19)	
Difference in slopes		-0.08 (-0.29, 0.13)	0.44		-0.10 (-0.31, 0.10)	0.38
Yes, 16-20 years before baseline	24	-0.14 (-0.36, 0.04)		22	-0.20 (-0.43, -0.01)	
Difference in slopes		0.12 (-0.11, 0.34)	0.31		0.08 (-0.16, 0.28)	0.51
Yes, More than 20 years before baseline	64	-0.12 (-0.25, 0.02)		62	-0.17 (-0.29, -0.01)	
Difference in slopes		0.14 (-0.02, 0.30)	0.09		0.11 (-0.02, 0.29)	0.16
Verbal Fluency						
Animal Fluency						

Time since cancer dx						
History of cancer						
No	324	-0.67 (-0.79, -0.58)	0.00	320	-0.76 (-0.89, -0.66)	0.00
Yes, After baseline	49	-0.54 (-0.74, -0.30)		48	-0.60 (-0.80, -0.37)	
Difference in slopes		0.13 (-0.07-0.40)	0.30		0.16 (-0.05, 0.42)	0.22
Yes, 0-5 years before baseline	52	-0.65 (-0.92, -0.40)		51	-0.70 (-0.96, -0.45)	
Difference in slopes		0.02 (-0.25-0.31)	0.90		0.06 (-0.21, 0.34)	0.69
Yes, 6-10 years before baseline	38	-0.51 (-0.80, -0.23)		37	-0.47 (-0.75, -0.18)	
Difference in slopes		0.16 (-0.13-0.47)	0.29		0.28 (-0.005, 0.60)	0.06
Yes, 11-15 years before baseline	38	-0.56 (-0.97, -0.38)		36	-0.63 (-1.04, -0.45)	
Difference in slopes		0.11 (-0.29-0.33)	0.50		0.13 (-0.28, 0.34)	0.41
Yes, 16-20 years before baseline	27	-0.50 (-0.83, -0.19)		25	-0.62 (-0.96, -0.30)	
Difference in slopes		0.17 (-0.16-0.51)	0.33		0.14 (-0.20, 0.48)	0.42
Yes, More than 20 years before baseline	64	-0.33 (-0.54, -0.09)		62	-0.43 (-0.64, -0.18)	
Difference in slopes		0.34 (0.09, 0.60)	**0.01***		0.33 (0.08, 0.58)	**0.01***

Model 1 is unadjusted
Model 2 is adjusted for age at baseline, education, gender, + hypertension, depression, diabetes and cardiovascular disease

3.5 Discussion

In this longitudinal cohort of the oldest-old adults, we found an inverse association between history of cancer and cognitive decline. Compared to those without cancer, participants with a history of cancer had a significantly slower annual rate of decline in global cognition and verbal fluency. To our knowledge, we are the first to show a slower annual rate of verbal fluency decline among those with a history of cancer. This finding is consistent with several recent studies of cognitive decline in older adult cancer survivors. Gupta (2019) found that participants with invasive cancers performed better on executive function tasks compared to people without cancer. Then Ospina-Romero (2019) found that people with cancer performed better on memory

tasks and had slower rates of decline overtime. Still, others have shown conflicting results where history of cancer has no effect on long term decline, or the cognitive decline is worse. However, much of these studies were limited by a shorter duration of follow-up period, small sample sizes, differences in measurement tests and focused primarily on treatment-related effects in young populations of breast cancer (Iconomou, 2004; Lange, 2019a; Lange, 2019b; Le Rhun, 2015; Hutchinson, 2012).

This study also demonstrated that only prevalent cancers, when compared to incident cancers were associated with a slower rate of decline in global cognition and verbal fluency. Further evidence suggests this relationship is more complicated. It seems that the time interval since cancer diagnosis differentially affects cognitive function and is supported by our analyses of prevalent vs incident cancers, pre-incident vs pos-incident cancers, and our analysis of duration since first cancer diagnosis. In our analysis of prevalent vs incident cancers we found that participants with prevalent cancer declined slower in global cognition compared to participants without cancer. Whereas participants with incident cancers had similar rates of decline. Prevalent cancers are cancers diagnosed earlier in life. Suggesting that the time of cancer diagnosis may play a role in the rate of decline over time. Breaking down prevalent cancers into 5-year time intervals, we found that the group that declined at the slowest rate were participants whose cancer was first diagnosed more than 20 years before baseline. Similar studies looking at memory in older adults (Lange, 2014) and a recent review on cancer and cognition (Pendergrass, 2018) also support the idea that the timing of an individual's cancer diagnosis impacts cognitive performance in the long-term.

Looking solely at incident cancers, our findings which compared annual rates of cognitive decline before (pre-) and after (post-) incident cancer diagnosis showed that cognitive decline in both memory and verbal fluency was slower before incident cancer diagnosis and then accelerated after incident cancer diagnosis. Overall, participants without cancer had significantly

faster rates of cognitive decline compared to pre- incident cancer. Yet, slower rates of decline compared to post- incident cancer which never reached a significant difference in slopes. Ospina-Romero (2019) found similar results in their study on memory and incident cancers where prior to cancer diagnoses, rates of decline were slower. Then immediately following an incident cancer diagnosis there was an acceleration in cognitive decline, which overtime changed and showed slower rates of memory decline in people with cancer compared to those without (Ospina-Romero, 2019). Notably, the Ospina-Romero (2019) study was larger than ours, it included a younger population (age 50+, mean age 66.4 years versus median age 92 years in our study), a different distribution of women (58% versus 69% in our study), and did not include multiple cognitive domains. However, the consistency between their findings and ours is promising and supports the assumption that time of cancer diagnosis factors into its effect of cognitive performance.

Ultimately, looking at cognitive decline immediately following an incident cancer is challenging. Cognition following a cancer diagnosis is subject to treatment effects (Magnuson, 2016) which may or may not resolve over a predictable amount of time. In one study of women with breast cancer, aged 65 years and older, 39% (n=11) showed declines in cognition between baseline and 6 months after chemotherapy, particularly in domains of visual memory, attention, and psychomotor speed (Hurria, 2006). Similarly another study of older women with breast cancer (aged >60 years) showed significant declines in processing speed (measured by Trail Making Test) up to 18 months after chemotherapy compared to a cancer-free group and breast cancer survivors not receiving chemotherapy (Ahles, 2010). While verbal ability (measured by D-KEFS Verbal Fluency Test) declined in the first month, it gradually improved over the next year. Surprisingly, treatment with hormonal therapy showed evidence of acute but worse declines in verbal memory (measured by CVLT-II) compared to the cancer-free group and breast cancer survivors treated with chemotherapy. Additionally, the effects of treatment for other cancers, such

as colon cancer and multiple myeloma on cognitive function found that older age groups with less education were most at-risk for treatment-related cognitive declines (Jones, 2013; Cruzado, 2014).

The analyses performed on cognitive performance stratified by cancer site had varied results, with several cancers showing slower rates of cognitive decline in different cognitive domains. Except for melanoma cancer, which seemed to show trends of faster rates of cognitive decline compared to those without cancer in some but not all cognitive domains. Notably, not all the results reached statistical significance. It is possible that the varied results are due to sample size limitations in different cancer sites. Despite the varied results we can infer that cancer, regardless of type, has some impact on cognitive performance. The impact on different cognitive domains does not seem to be cancer type specific.

This is the first longitudinal study to examine long term effects of cancer on cognition in older adults with prevalent cancers more than 20 years before baseline. When stratified by time since cancer diagnosis, we found that those diagnosed at least 20 years before the baseline cognitive function measurement showed a significant slower rate of annual cognitive decline. It is possible that differential follow-up times across the different subgroups may introduce survival bias if participants whose cancers were diagnosed earlier in life die before evidence of cognitive decline. This is unlikely in our study, as the median (range) years of follow-up time for each of the cancer groups in this analysis were similar: ‘No cancer’ 4.63 (11.52), 'After baseline' 6.49 (13.34), '5 Years or Less from baseline' 5.03 (12.96), ‘6-10 years from baseline' 5.74 (10.05), '11-15 years from baseline' 5.15 (9.26), '16-20 years from baseline' 5.37 (10.42), '20 or more years from baseline' 6.31 (12.60). In fact the prevalent cancers more than 20 years before baseline had some of the longest follow-up times compared to other groups.

NMSCs are generally nonfatal cancers with a high survival rate, it has been suggested that inclusion of participants with NMSCs only would eliminate a potential survival bias. In our study, the cancer-cognitive function association remained when looking only at NMSCs, increasing the likelihood of a true effect. NMSCs are very common and are often detected only by chance. As a result, they are underreported (Eisemann, 2014) and it is possible that the true effect may be greater than we were able to report in this study.

As previously reported, participants in the 90+ study have higher rates of non-completion towards the end of a battery of tests (Whittle, 2007), and was also seen in our study. This limited our ability to assess the domains of executive function, attention, or psychomotor speed. In addition, while we were able to show an association between all cancers and cognitive function, we were limited by sample size to investigate further by cancer type. The lack of a standardized assessment or neuropsychological test battery for use in older adult cancer populations makes comparisons between studies difficult. Finally, our study population was predominantly white with high levels of education, potentially limiting the generalizability of these findings.

In addition to the limitations above, this study had several strengths. The use of repeated clinical measures of cognitive performance to measure longitudinal change was a strength of our study. The 90 + study does evaluations every 6 months, maximizing the amount of data available in the follow-up time in a cohort where follow-up is not long due to high mortality. Longer follow-up times provided information on the temporal relationship of cancer and cognition missing from previously published cross-sectional studies and short-term longitudinal studies (Hutchinson, 2012). In addition, our sample size allowed us to examine time-intervals for prevalent cancers. Lastly, we were able to look at more than one cognitive domain associated with dementia and its subtype AD in a large population of the oldest-old.

Currently neuropsychological testing is not routinely performed in older adults with cancer. New guidelines by the National Comprehensive Cancer Center (NCCN), however have recommended cognitive screening as part of a routine geriatric assessment in oncology. Implementation of this practice could help us understand the long-term effects of cognition in cancer survivors. To our knowledge, this is the only study to examine long-term effects of cancer in older adults using the 3MS or MMSE. The MMSE and the 3MS is the most common screening tests for dementia and cognitive abilities (Tsoi, 2015). Over time different testing measures have been created as alternatives to the MMSE and 3MS in order to measure cognition in various populations. Each of which have been validated in different groups but not all have been validated against one another, making it difficult to compare results between studies. Future studies and research on cancer and cognition should standardize which tests should be used for analysis or at the minimum use the most common testing measurements. A strength of The 90+ Study is that slight modifications were made to the tests to allow for testing individuals with sensory impairment (ie enlarged bolded font and words shown as they were read out loud) and used shortened version of tests to minimize fatigue. Modifications and order of testing in the testing battery were performed to compensate for fatigue, vision and hearing impairment that might compromise test performance in this age group. Modification of these tests made them suitable for use when measuring cognition in the oldest-old. More detailed information on testing procedures and scoring is provided in previous literature (Kahle-Wrobleski, 2012; Melikyan, 2019).

Conclusion

Our study examined the relationships between cancer and dementia and cancer and cognitive performance in the oldest old. At the start, we hypothesized that a history of cancer would be associated with decreased rates of dementia in our study cohort. Our results support our hypothesis. Using the cause-specific hazard method we ran time-to-event analysis on a cohort of 761 older adults aged 90 years and above who were free from dementia at baseline and with or without a history of cancer at baseline. This is the largest study conducted to date in the oldest-old to examine the association between dementia and cancer and the results support an approximate 20% lower rate of all-cause dementia and AD dementia in participants with a history of cancer compared to those without a history of cancer. Like previous studies, when cancer groups were stratified, the strongest associations were amongst participants with incident cancers. We performed multiple subgroup analysis to examine different biases, such as survival bias and death as a competing risk. A history of cancer was associated with longer survival rates and lower rates of death before dementia diagnosis. The results of these subgroup analysis support a true inverse association that is not due to known confounding, competing risk of death, or diagnostic bias.

Multiple linear mixed models were used to evaluate repeated measures of cognitive performance and to calculate the rate of change in cognitive performance for individual cognitive tests in each of our cancer groups. A history of cancer was associated with slower rates of cognitive decline compared to cancer free participants in some (ie global cognition and verbal fluency) but not all cognitive domains (ie memory, executive function, psychomotor speed) associated with dementia and its subtype AD. Our results also showed that cancer seemed to be protective against cognitive decline in the months before a cancer diagnosis and then accelerated cognitive decline in the months directly following cancer diagnosis. Still, the slowest rates of decline were amongst participants whose cancer was first diagnosed earlier in life. Which may

suggest that any protective effects of cancer on cognition may be time restrictive or is only evident during certain periods pre- and post- cancer diagnosis. Our results indicate that it is plausible that the pattern of protection may change over time.

This is the largest study conducted to date in the oldest-old to examine the association between cancer and dementia. Overall, our results show that there is an inverse association between cancer and dementia in the oldest-old. Evidence of slower cognitive decline in different cognitive domains in participants with cancer also provides support for the inverse association. Given these findings, further studies to understand the basis of these findings and any underlying mechanisms responsible for the inverse association are warranted.

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