Journal of Alzheimer's Disease 76 (2020) 691–701
DOI 10.3233/JAD-200108
IOS Press

Progression of Alzheimer's Disease by Self-Reported Cancer History in the Alzheimer's Disease Neuroimaging Initiative

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Accepted 4 May 2020

Abstract.
Background: Cross-sectional studies suggest self-reported cancer history is associated with decreased risk of Alzheimer's disease (AD). However, little is known about how self-reported cancer affects longitudinal AD progression, the primary outcome in clinical trials and observational studies.
Objective: To determine self-reported cancer history's effect on longitudinal AD progression in an observational study.
Methods: We utilized data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) to evaluate progression to AD by self-reported all-cancer, breast, prostate, colorectal, or non-melanoma skin cancer history. Linear mixed effects models were used to examine baseline differences and rates of progression on the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) by self-reported cancer history. Age at AD onset was examined using consensus clinical diagnoses with Cox proportional hazards regression.
Results: Among 1,271 participants, models revealed no significant differences in progression over time but did reveal significantly lower baseline ADAS-Cog score, indicating better cognition at a given age in those with self-reported cancer history. Cox models indicated those with self-reported cancer history had significantly later age of AD onset (HR: 0.67, 95% CI: 0.53–0.85) after adjustment for covariates.
Conclusion: Participants with self-reported cancer history entered ADNI with better cognition and later age of AD onset, but progressed similarly to participants without such history, indicating differences in AD between those with and without

[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at http://adni.loni.usc.edu/wp-content/themes/freshnews-devv2/documents/policy/ADNI_Acknowledgement_List%205-29-18.pdf

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self-reported cancer history emerge early in the disease course. Such differences in longitudinal progression by self-reported cancer history could affect AD trials and observational studies, given the current focus on early disease course. Further investigation is warranted with detailed longitudinal assessment of cancer and AD.

Keywords: Alzheimer's disease, cancer, cognitive impairment, disease progression, mild cognitive impairment

INTRODUCTION

Alzheimer's disease (AD) is associated with older age and comorbidities including diabetes, hypertension, and cardiovascular disease [1]. Cancer seems to have an inverse relationship with AD, primarily based on self-reported history of cancer among older adults [2–5]. Most studies have examined the cross-sectional relationship between self-reported cancer history and AD, which would not allow for determination of when in the course of AD this inverse relationship begins to occur. To date, no study has examined effects of self-reported cancer history on longitudinal AD progression. Differences in progression would be of particular importance for observational studies and clinical trials in AD, which focus on longitudinal outcomes.

To better understand the implications of cross-sectional findings for longitudinal studies, we examined progression of AD in patients with self-reported cancer history in an observational cohort study. We estimated the rate of decline on the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) based on self-reported cancer history overall and specifically in breast, prostate, colorectal, and non-melanoma skin cancers. We also estimated time to AD onset based on self-reported cancer history in this cohort. In addition, we estimated the age at which ADAS-Cog scores began to diverge between those with and without self-reported cancer history, due to potential pre-existing impairment in these groups. This initial analysis is intended to spur further research on the effect of cancer history on the progression of AD, particularly the implications for clinical trials and observational studies.

METHODS

Study population

Data used this manuscript were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu) downloaded August 27, 2018 [6]. ADNI began in 2003 as a public-private partnership under the leadership of Principal Investigator Michael W. Weiner, MD. The primary objective of the study has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure progression of mild cognitive impairment (MCI) and early AD [6]. For up-to-date information, see http://www.adni-info.org. ADNI is a longitudinal, multi-center observational study that continues today.

Inclusion criteria for the ADNI parent study are ages 55 through 90 years old at various stages of cognitive functioning (normal, MCI, and dementia due to AD), good overall health with no diseases preventing enrollment, and stable doses of permitted medications (including memory-related therapies) for four weeks prior to enrollment [6, 7]. Diagnoses of cognitive impairment were made following ADNI guidelines including NINDS-ADRDA criteria for probable AD [8] and Petersen criteria for MCI [9]. The ADNI study was reviewed and approved by Institutional Review Boards (IRBs) at each study site and written informed consent was obtained from each participant. This report was exempted from IRB approval by the UAB IRB.

A total of 1,271 participants with MCI or AD were used in the analysis. Participants were included in this analysis if they had two or more ADAS-Cog scores and were diagnosed as MCI or AD at baseline. Participants were excluded from this analysis if they were diagnosed as cognitively normal at baseline, or if they were missing information on dementia diagnosis, exam dates for baseline or follow-up ADAS-Cog scores, demographics, or baseline Mini-Mental State Examination scores. For the sub-analyses, participants were required to have *APOE* genotype information. For the survival analysis, participants were excluded if they lacked data on change in diagnosis (from MCI to AD).

Data collection

Demographic and clinical information

Demographic and clinical information was collected at baseline. Variables examined included sex,

race, age, education, and *APOE* genotype. Education level was total years of school [10]. Age in ADNI was not collected specifically, rather, birth year and birth month. To calculate age, we used the 15th of the month for all participants. Race, ethnicity (Hispanic versus non-Hispanic), sex, and marital status (married, widowed, divorced, never married, or unknown) were self-reported. Race was categorized into White versus non-White for this report.

Self-reported cancer history

Self-reported comorbidities were obtained from the ADNI medical history file. These variables were collected using standardized interview procedures across study sites by a nurse or other medical professional. Participants or caregivers were queried regarding current or previous diseases, which were recorded as system affected, description of the problem, dates of the problem, and whether it was current or resolved [10–12]. Our self-reported cancer history group consisted of all participants with self-reported previous malignancy (if the organ system code for "Malignancy" was positive). Additionally, Perl regular expressions [13] were used to search other organ systems to determine self-reports of cancers which may have been coded by the organ system affected (Supplementary Material). Perl regular expressions were also used to classify self-reported cancers into specific cancer types: breast, prostate, colorectal, and skin (not including melanoma). Although non-melanoma skin cancer is typically not part of cancer statistics, we have included it in our study based on results of previous analyses in the ADNI dataset [14]. An all-cancer group was also created to determine whether effects on progression of AD is a general effect of self-reported cancer or is specific to the type of cancer reported. Our reference group consisted of all ADNI participants without a self-reported history of cancer.

Alzheimer's disease progression

Alzheimer's Disease Assessment Scale-Cognitive Subscale

The ADAS-Cog [15] is a neuropsychological assessment evaluating memory, orientation, language, praxis, and word-finding difficulty. The scale is scored from 0 to 70 errors with higher scores indicating more cognitive impairment. Scores were collected at baseline and at follow-up visits every 6 months. A two-point difference is considered to be a significant change in most AD clinical trials [16].

Conversion to AD

For progression from MCI to AD, diagnostic summaries were collected via review of all visit documents across study sites by site principal investigators (PIs) who were medical professionals, usually a physician, trained in diagnostics of normal cognition, MCI, and various stages of AD. Diagnoses were adjudicated by the clinical monitor PI and the clinical conversion committee [10–12]. Participant status at each visit was categorized as stable, reverted, or converted, with the former two considered no progression and latter considered progression. Time to progression was calculated as the difference between the participant's visit date where conversion was documented and their birthdate. Additionally, participants who entered the study with AD were queried as to the self-reported onset of their AD symptoms. Only year was collected, so date of conversion was set as the middle of the year in which onset occurred (June 15). To calculate time to progression, the date of conversion was subtracted from participants' birthdate.

Statistical analysis

Bivariate analyses using t-tests and chi-square tests for continuous and categorical variables, respectively, were used to assess potential covariates. Fisher's exact test was used where expected cell counts were low for categorical variables. Linear mixed models (random coefficient models) [17] were used to examine progression on the ADAS-Cog by overall and specific self-reported cancer history status, adjusting for covariates of race, sex, education, with further adjustment for *APOE* $\varepsilon 4$ allele carrier status (positive or negative) in subanalyses. Age was used as the time variable for mixed modeling, centered on the mean age based on cognitive diagnosis (both AD and MCI, MCI only, or AD only). Separate age-centered time variables were created for each disease group. As non-melanoma skin cancer is often not included in cancer classifications, a sensitivity analysis was performed with an all-cancer group that did not include non-melanoma skin cancer. Instead, participants reporting only non-melanoma skin cancer were categorized as having no self-reported cancer for sensitivity analysis, while participants reporting non-melanoma skin cancer plus an additional cancer were retained in the self-reported all-cancer group due to the presence of another cancer type.

Kaplan-Meier analyses with log-rank tests were used to summarize the time to onset of AD based

on self-reported cancer history. Cox proportional hazards models were used to assess time to onset of AD by overall and specific self-reported cancer history controlling for relevant covariates, with censoring at the last recorded visit if progression had not occurred. Participant age was used as the time variable in this analysis. Education, baseline ADAS-Cog score, and *APOE* ε4 allele carrier status (positive or negative) were included in the final model regardless of statistical significance in bivariate analyses due to a priori knowledge of their association with cognitive decline [18–21]. Race was not included in Cox regression analysis. Over 90% of the ADNI cohort is White, non-Hispanic so adjusting for race in the model would not produce appropriate sample size in each group causing model convergence issues. Analyses included examination of proportional hazards assumptions. All statistical analyses were assessed at $\alpha = 0.05$ significance level using SAS Version 9.4 (SAS Institute, Inc., Cary, NC). SAS code is included in the Supplementary Material.

RESULTS

Bivariate analyses indicated those in the self-reported all-cancer history group were older, more likely to be White, have a diagnosis of MCI at baseline, and more likely to be married. Those with history of non-melanoma skin cancer were also more highly educated (Table 1). Table 2 includes the frequency of cancers among participants, including those with more than one cancer by group. A total of 52 participants had more than one cancer and a total of 9 had more than two cancers.

In mixed model analysis, no significant differences were seen in rate of progression over time on the ADAS-Cog for the self-reported all-cancer history group (β_{slope}: 0.06, 95% CI: –0.15, 0.27), regardless of baseline diagnosis (MCI or AD) (Table 3). This finding remained in sensitivity analyses that did not include non-melanoma skin cancer in the all-cancer group (β_{slope}: 0.02, 95% CI: –0.23, 0.27). However, self-reported history of cancer was associated with a statistically significant –4.42-point difference in

Table 1
Baseline Characteristics by Self-Reported Cancer History Status*

Variable	All ($n = 367$)	Breast ($n = 36$)	Prostate ($n = 103$)	Colorectal ($n = 29$)	Non-Melanoma Skin ($n = 165$)	No Cancer ($n = 904$)
Age (y)	**76.14 ± 7.00**	**75.50 ± 6.70**	**77.40 ± 6.44**	**79.38 ± 6.13**	**75.65 ± 7.34**	72.70 ± 7.76
Education (y)	15.97 ± 2.86	14.97 ± 3.07	16.02 ± 2.53	15.31 ± 3.33	**16.23 ± 2.94**	15.63 ± 2.89
Sex						
Male	**253 (68.94)**	**0**	**103 (100)**	17 (58.62)	**120 (72.73)**	487 (53.87)
Female	**114 (31.06)**	**36 (100)**	**0**	12 (41.38)	**45 (27.27)**	417 (46.13)
Race						
White	**357 (97.28)**	35 (97.22)	99 (96.12)	28 (96.55)	**160 (96.97)**	828 (91.59)
Non-White	**10 (2.72)**	1 (2.78)	4 (3.88)	1 (3.45)	**5 (3.03)**	76 (8.41)
Ethnicity						
Hispanic	1 (1.91)	1 (2.78)	3 (2.91)	0	1 (0.61)	34 (3.76)
Non-Hispanic	359 (97.82)	35 (97.22)	99 (96.12)	29 (100)	164 (99.39)	864 (95.58)
Unknown	1 (0.27)	0	1 (0.97)	0	0	6 (0.66)
Marital Status						
Married	**303 (82.56)**	23 (63.89)	**96 (93.20)**	20 (68.97)	137 (83.03)	694 (76.77)
Divorced	**33 (8.99)**	6 (16.67)	**4 (3.88)**	7 (24.14)	13 (7.88)	103 (11.39)
Widowed	**20 (5.45)**	4 (11.11)	**2 (1.94)**	2 (6.90)	10 (6.06)	78 (8.63)
Never Married	**7 (1.91)**	3 (8.33)	**0**	0	3 (1.82)	26 (2.88)
Unknown	**4 (1.09)**	0	**1 (0.97)**	0	2 (1.21)	3 (0.33)
Baseline Diagnosis						
Mild cognitive impairment	**282 (76.84)**	26 (72.22)	78 (75.73)	24 (82.76)	**133 (80.61)**	637 (70.46)
Alzheimer's Disease	**85 (23.16)**	10 (27.78)	25 (24.27)	5 (17.24)	**32 (19.39)**	267 (29.54)
APOE ε4 Status†						
Positive	183 (51.84)	19 (52.78)	**42 (42.42)**	15 (51.72)	84 (52.50)	477 (56.18)
Negative	170 (48.16)	17 (47.22)	**57 (57.58)**	14 (48.28)	76 (47.50)	372 (43.82)
Baseline ADAS-Cog Score‡	12.53 ± 6.42	**10.41 ± 5.08**	13.29 ± 6.59	**11.16 ± 4.92**	12.22 ± 6.07	13.20 ± 6.78

*Assessed at $\alpha = 0.05$ significance level using *t*-tests for continuous variables and chi-square tests for categorical variables (Fisher's exact tests where expected cell counts were low). Bold font indicates statistically significant differences compared to the no cancer column. Some variables may not sum to column total due to missingness in the variable: for the all cancer group ethnicity $n = 6$ are missing. †*APOE* ε4, apolipoprotein ε4 allele; not all participants had *APOE* ε4 genotyping ($n = 1202$). ‡ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale, scores range from 0 to 70. The All column includes 34 cancers which were not individually classified (367–333 = 34).

Table 2
Frequency of Synchronous Cancers

	Breast	Prostate	Colorectal	Non-Melanoma Skin	Other	None
Breast	26	0	1	3	4	–
Prostate	0	80	2	11	4	–
Colorectal	1	2	13	3	5	–
Non-Melanoma Skin	3	11	3	123	19	–
Other	4	4	5	19	64	–
None	–	–	–	–	–	904

*Frequency does not add up to total sample size of 1271 due to a frequency of $n = 9$ with greater than 2 cancer types: Breast-colorectal-skin ($n = 1$), Prostate-colorectal-other ($n = 3$), Prostate-skin-other ($n = 3$), Breast-skin-other ($n = 1$), and Colorectal-skin-other ($n = 1$).

Table 3
Beta Estimates and 95% CI for Random Coefficients Models Based on Self-Reported History of Specific Cancer Types Regardless of Baseline Cognitive Diagnosis (MCI or AD)*

Cancer Type	β (95% CI)–Intercept	β (95% CI)–Slope
Model 1		
All Cancer versus No Cancer ($n = 1271$)	**–4.42 (–5.90, –2.94)**	0.06 (–0.15, 0.27)
Breast Cancer versus No Cancers ($n = 940$)	**–6.72 (–10.92, –2.53)**	0.33 (–0.25, 0.91)
Prostate Cancer versus No Cancers ($n = 1007$)	**–4.27 (–6.88, –1.65)**	–0.03 (–0.37, 0.31)
Colorectal Cancer versus No Cancers ($n = 933$)	**–10.76 (–15.69, –5.84)**	0.54 (–0.08, 1.16)
Non-Melanoma Skin Cancers versus No Cancers ($n = 1069$)	**–4.82 (–6.81, –2.84)**	0.04 (–0.22, 0.31)
Model 2		
All Cancer versus No Cancer ($n = 1202$)	**–4.17 (–5.67, –2.67)**	0.01 (–0.21, 0.23)
Breast Cancer versus No Cancers ($n = 885$)	**–6.27 (–10.41, –2.13)**	0.27 (–0.33, 0.86)
Prostate Cancer versus No Cancers ($n = 948$)	**–3.41 (–6.08, –0.75)**	–0.12 (–0.46, 0.23)
Colorectal Cancer versus No Cancers ($n = 878$)	**–10.81 (–15.68, –5.94)**	0.55 (–0.09, 1.18)
Non-Melanoma Skin Cancer versus No Cancers ($n = 1009$)	**–4.66 (–6.64, –2.68)**	0.02 (–0.25, 0.30)

*Estimated using linear random coefficients models of change in Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) with a random coefficient for time at $\alpha = 0.05$ significance level. Model 1: Adjusted for race (White versus Non-White), sex, and education. Model 2: Adjusted for variables in Model 1 plus *apolipoprotein* ε4 status (yes versus no). For sensitivity analysis with participants with only non-melanoma skin cancer history, estimates remained similar (intercept: β: –3.38, 95% CI: –5.11, –1.65; slope: β: 0.02, 95% CI: –0.23, 0.27). 95% CI, 95% confidence interval; MCI, mild cognitive impairment; AD, Alzheimer's disease.

intercept for ADAS-Cog score compared to no self-reported cancer history, after adjustment for race, sex, and education (95% CI: –5.90, –2.94). Again, this finding remained in sensitivity analyses that did not include non-melanoma skin cancer history in the all-cancer group ($\beta_{intercept}$: –3.38, 95% CI: –5.11, –1.65). Similar differences in intercepts were seen across self-reported cancer types [Breast: –6.72 (95%CI: –10.92, –2.53); Prostate: –4.27 (95% CI: –6.88, –1.65); Colorectal: –10.76 (95% CI: –15.69, –5.84); Non-Melanoma Skin: –4.82 (95% CI: –6.81, –2.84)]. Further adjustment for *APOE* ε4 status did not significantly change the results. Stratified analyses by baseline diagnosis showed that MCI patients had results similar to that observed in overall analyses within each self-reported cancer history category. However, in MCI patients with colorectal cancer history, there was evidence of a faster progression on ADAS-Cog over time [0.72, (95% CI: 0.04–1.40)] (Table 4). The AD group did not exhibit any significant differences in intercepts for ADAS-Cog score for overall or specific self-reported cancer history, nor any differences in rate of progression by self-reported cancer history type. These findings were unchanged in sensitivity analyses that did not include non-melanoma skin cancer in the all-cancer group. Figure 1 shows a graphical depiction of predicted ADAS-Cog scores by age based on unadjusted mixed model regression results.

Kaplan-Meier analysis of unadjusted time to event probabilities between the self-reported all-cancer history group compared to the no self-reported cancer history group showed differences between the curves that were statistically significant ($\chi^2 = 60.57$, $p \leq 0.0001$). Those with self-reported cancer history showed evidence of later age of onset of AD than those without self-reported cancer history (Fig. 2).

Consistent with Kaplan-Meier analyses, Cox regression showed a significantly later age of onset of AD in participants with any self-reported cancer history compared to those without any self-reported cancer history (HR: 0.68, 95% CI: 0.54–0.86) (Table 5). This association remained after adjustment for age, education, and baseline ADAS-Cog score

Table 4
Beta estimates and 95% CI for Random Coefficients Models Based on Self-Reported History of Specific Cancer Types by MCI or AD Diagnosis*

Cancer Type	β (95% CI)–Intercept	β (95% CI)–Slope
MCI—Without *APOE4*		
All Cancer versus No Cancer ($n = 919$)	**–3.80 (–5.32, –2.28)**	0.14 (–0.09, 0.37)
Breast Cancer versus No Cancers ($n = 663$)	**–5.23 (–9.66, –0.80)**	0.45 (–0.20, 1.11)
Prostate Cancer versus No Cancers ($n = 715$)	**–4.53 (–7.20, –1.86)**	0.06 (–0.30, 0.42)
Colorectal Cancer versus No Cancer ($n = 661$)	**–9.22 (–14.08, –4.36)**	**0.73 (0.07, 1.39)**
Non-Melanoma Skin Cancer versus No Cancer ($n = 770$)	**–3.80 (–5.80, –1.80)**	0.08 (–0.20, 0.37)
AD—Without *APOE4*		
All Cancer versus No Cancer ($n = 352$)	0.04 (–2.13, 2.20)	–0.20 (–0.46, 0.06)
Breast Cancer versus No Cancers ($n = 277$)	–2.85 (–8.55, 2.85)	–0.31 (–1.02, 0.40)
Prostate Cancer versus No Cancers ($n = 292$)	1.45 (–2.42, 5.33)	–0.26 (–0.67, 0.14)
Colorectal Cancer versus No Cancer ($n = 272$)	–6.12 (–19.04, 6.80)	0.03 (–1.23, 1.29)
Non-Melanoma Skin Cancer versus No Cancer ($n = 299$)	–0.45 (–3.81, 2.90)	–0.04 (–0.44, 0.35)
MCI—With *APOE4*		
All Cancer versus No Cancer ($n = 863$)	**–3.72 (–5.29, –2.15)**	0.09 (–0.15, 0.33)
Breast Cancer versus No Cancers ($n = 619$)	**–4.68 (–9.13, –0.23)**	0.39 (–0.28, 1.06)
Prostate Cancer versus No Cancers ($n = 668$)	**–3.96 (–6.73, –1.19)**	–0.03 (–0.41, 0.34)
Colorectal Cancer versus No Cancer ($n = 617$)	**–9.49 (–14.37, –4.61)**	**0.72 (0.04, 1.40)**
Non-Melanoma Skin Cancer versus No Cancer ($n = 721$)	**–3.84 (–5.88, –1.81)**	0.04 (–0.26, 0.34)
AD—With *APOE4*		
All Cancer versus No Cancer ($n = 339$)	0 (–2.21, 2.22)	–0.19 (–0.46, 0.07)
Breast Cancer versus No Cancers ($n = 266$)	–2.98 (–8.78, 2.83)	–0.31 (–1.03, 0.42)
Prostate Cancer versus No Cancers ($n = 280$)	1.46 (–2.50, 5.42)	–0.27 (–0.68, 0.14)
Colorectal Cancer versus No Cancer ($n = 261$)	–6.37 (–19.55, 6.80)	0.08 (–1.22, 1.38)
Non-Melanoma Skin Cancer versus No Cancer ($n = 288$)	–0.35 (–3.76, 3.06)	–0.02 (–0.42, 0.38)

*Estimated using linear random coefficients models of change in Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) with a random coefficient for time at $\alpha = 0.05$ significance level. Models adjusted for race (White versus Non-White), sex, education, and *apolipoprotein* ε4 status (yes versus no) if indicated. 95% CI, 95% confidence interval; MCI, mild cognitive impairment; AD, Alzheimer's disease.

(HR: 0.71, 95% CI 0.56–0.90), and in subanalyses adjusting for *APOE* ε4 status (HR: 0.67, 95% CI: 0.53–0.85) (Table 5). Self-reported prostate cancer and non-melanoma skin cancer history exhibited similar associations to the overall cancer history group even after full adjustment, but the later age of onset was not significant in those with self-reported breast or colorectal cancer history (Table 5).

DISCUSSION

In this secondary analysis of the ADNI observational cohort, participants with self-reported cancer history and MCI at baseline had an approximately 4-point lower difference in mixed model intercepts after controlling for covariates. This suggests that ADAS-Cog score for those with self-reported cancer history was lower for a given age compared to those with no self-reported cancer history in the MCI sample, corresponding to less cognitive impairment in the former. Further analysis of the mixed model suggests no difference in slopes of ADAS-Cog scores (rate of cognitive decline) over time between the self-reported cancer history and no self-reported cancer history groups. However, due to heterogeneity among cancer types, the self-reported all-cancer results must be interpreted with caution. Separate analysis by specific self-reported cancer type revealed similar results to the self-reported all-cancer history analysis after adjustment for relevant covariates, except for self-reported colorectal cancer. In those with AD at baseline, no significant differences in ADAS-Cog intercepts (score at a given age) and slope (rate of cognitive decline) were seen for overall and specific self-reported cancer history groups. Additionally, consistent with previous literature [14], self-reported cancer history in ADNI was associated with later age of onset of AD after adjusting for education, baseline ADAS-Cog score, and *APOE* ε4 status for self-reported overall, prostate, and non-melanoma skin cancer, though not for self-reported breast and colorectal cancer. Sensitivity analyses that did not include self-reported non-melanoma skin cancer in the all-cancer group yielded similar results regardless of baseline cognitive diagnosis. Collectively, these results indicate that participants with self-reported cancer history do not have greater progression of cognitive impairment in AD than participants with

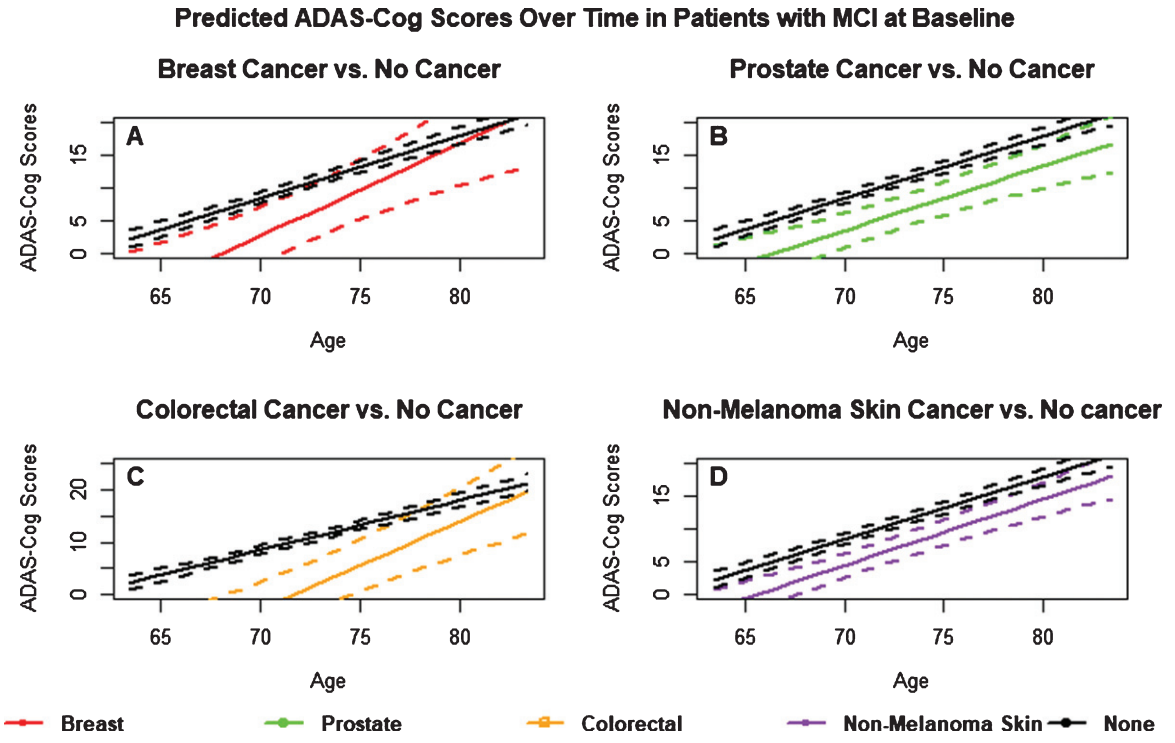

Fig. 1. Predicted ADAS-Cog Scores Over Time by Self-Reported Cancer History in MCI. The group with no self-reported cancer history begins with a higher Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) score, indicating worse cognition at baseline, but progresses similar to the group with self-reported cancer history. ADAS-Cog scores were predicted over time using unadjusted linear mixed effects models.

no self-reported cancer history. During the course of MCI, those with self-reported cancer history also progressed at a similar rate to those without self-reported cancer history. Thus, differences in cognitive scores between those with and without self-reported cancer history appear to develop early in the course of their cognitive trajectories. These results are consistent with the inverse relationship between AD and self-reported cancer history in cross-sectional analyses [2–5], but our analysis expands on these results by examining the timing of this effect.

The findings from this analysis emphasize the need for more detailed longitudinal follow-up studies of cancer and AD. Studies of cancer among AD patients have focused mostly on self-reported cancer history, which is limited by potential recall bias inherent in self-report. Self-reported cancer history is further limited by lack of detailed information about the cancer treatments and staging which would be useful in assessing any relationship between treatment and cognition at AD onset. Studies of AD among cancer patients have focused on cross-sectional follow-up AD assessment in individuals with documented cancer history. This approach has its own limitations in

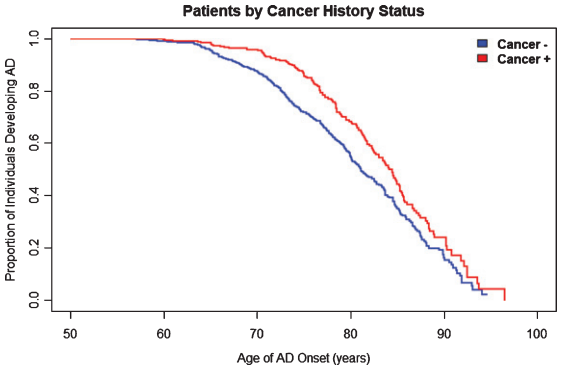

Fig. 2. Kaplan-Meier Analysis by Self-Reported Cancer History. Participants with MCI and self-reported cancer history (Cancer+) have a later age of onset of AD compared to those without self-reported cancer history (Cancer –) in subset of participants with measured *APOE* ε4 status ($n = 1202$).

that it could be subject to survivor bias, where patients with cancer may die prior to assessment and diagnosis of AD, and does not provide information on longitudinal progression of AD.

The findings from this analysis must also be viewed in the context of what is known about short-term

Table 5
Hazard Ratios (HR) and 95% CI for Time-to-Onset of AD Based on Self-Reported Cancer History ($n = 1202$)*

Comparison	HR	95% CI	p
All-Cancer versus No Cancer			
Without *APOE4*	0.71	0.56–0.90	**0.0040**
With *APOE4*	0.67	0.53–0.85	**0.0009**
Breast Cancer versus No Cancer			
Without *APOE4*	0.67	0.30–1.52	0.3419
With *APOE4*	0.65	0.29–1.47	0.3013
Prostate Cancer versus No Cancer			
Without *APOE4*	0.60	0.41–0.89	**0.0113**
With *APOE4*	0.59	0.40–0.87	**0.0085**
Colorectal Cancer versus No Cancer			
Without *APOE4*	0.96	0.56–1.65	0.8795
With *APOE4*	0.88	0.51–1.52	0.6465
Non-Melanoma Skin Cancer versus No Cancer			
Without *APOE4*	0.74	0.55–1.01	0.0579
With *APOE4*	0.71	0.52–0.96	**0.0273**

*Assessed using Cox proportional hazards models at the $\alpha = 0.05$ significance level. Models adjusted for education in years and baseline Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) score, and *apolipoprotein (APOE4)* $\varepsilon 4$ status (yes or no) if indicated ($n = 858$ with *APOE4*). 95% CI, 95% confidence interval; AD, Alzheimer's disease.

cognitive effects of cancer. Cancer is associated with cognitive deficits prior to, during, and after treatment. Evidence is mixed for how long these may last [22, 23] and prognosis for cognitive deficits may differ based on treatment modality [24]. The cognitive deficits observed in cancer patients include executive function, verbal skills, and memory [22–25]. Similar patterns of deficits are observed in AD progression and worsen over time [26]. Since cancer patients may already possess symptoms in similar domains, progression of AD would intuitively be more rapid than the general population. However, our results indicate that this may not be the case. This is in contrast to pre-existing cognitive deficits due to other disorders, which are usually associated with higher risk of AD [27]. While it is possible that some of these discrepancies arise due the limitations of self-report, studies have indicated relatively high sensitivity and specificity in self-reported cancer history compared to cancer registries, especially for the cancers under study in this project [28–30]. This further emphasizes the need for detailed longitudinal studies of cancer and AD to determine if the results of our analysis are due to cancer itself or to the self-reporting of cancer history.

These results clarify the implications of self-reported cancer history for observational studies and treatment trials for individuals with AD. Participants in AD studies with self-reported cancer history have a similar rate of progression of AD as those without self-reported cancer history. Thus, longitudinal studies of the course of AD, and treatment trials examining the effects of interventions on AD progression, would seem to not be affected by self-reported cancer history of the participants. However, given the small sample sizes for specific self-reported cancer types in our analysis, this conclusion should be interpreted as preliminary, and differences between individuals with and without self-reported cancer history may be apparent in larger studies. Participants in AD studies with self-reported cancer history also have fewer cognitive deficits at baseline and later age of onset for AD. Thus, as clinical trials for AD increasingly shift to treatment in the earliest stages of the disease, self-reported cancer history may assume a much greater importance as a confounder of treatment effects. The 4-point baseline difference in cognition between participants with and without self-reported history of cancer is greater than the typical effect size for cholinesterase inhibitors, and similar to the effect size for other potential confounders in AD clinical trials [20, 31, 32]. If self-reporting does not seem to be a driver of our results, this could have implications for identifying factors which may predispose those with cancer history to future development of AD, and identify the need for more focused treatment of AD cognitive deficits in trial participants with prior cancer.

Strengths and limitations

This study has several notable strengths. First, this study is the first to examine longitudinal progression based on self-reported cancer history and specific self-reported cancers rather than previous studies examining only cross-sectional associations. Longitudinal analysis allows for examination of rates of progression using slopes (rate of cognitive decline) and intercepts (level of impairment at a particular age) in mixed models, while cross-sectional analyses cannot distinguish between the two. Secondly, participants in self-reported cancer and no cancer history groups come from the same primary study base, increasing internal validity. Thirdly, data collection procedures are highly standardized across study sites limiting potential for information bias.

The primary limitation to consider is that cancer history was determined via self-report, which can be inaccurate compared to objectively confirmed cancers via biopsy or imaging as noted above; verification of cancer diagnoses through medical records

would strengthen findings. Other limitations include potential selection biases, in that most cancer survivors included in ADNI would be less advanced or in remission longer than the general population. This would be due to study exclusion criteria and likelihood that participants with more advanced cancers would be deceased prior to developing MCI or AD. This selection bias would correspond to less invasive, less damaging treatments and more time to recover from potential cancer-related cognitive impairment, resulting in less severe cognitive deficits for those with cancer history enrolled in ADNI compared to those with cancer history in the general population. We do not know the extent to which this bias would influence self-reported cancer history. Cognitive effects of cancer and/or chemotherapy, as well as MCI, could have affected ability to self-report cancer status and recall details about their cancers [33, 34], and would limit our ability to specifically attribute cognitive deficits to cancer, chemotherapy, or AD. Furthermore, age of onset in the AD group is self-reported and not measured, which could bias the results if inaccurate. We were also unable to adjust for comorbidities in our analysis due to lack of detailed data in many ADNI participants for calculating a comorbidity score. This is similar to previous analyses in ADNI assessing cognition and brain abnormalities in cancer [14]. Additionally, while the results from specific self-reported cancer history analyses show no evidence of a difference in cognitive decline over time, sample size was limited for each self-reported cancer type and even further limited when also stratifying by baseline diagnosis. Some of the association in the self-reported all-cancer history analyses could be driven by self-reported cancers not specifically examined in this analysis. However, the self-reported cancers included in this analysis are very common and would be expected to reflect the most common self-reported cancer types seen in a general clinic setting. Most importantly, use of an AD observational study like ADNI does not allow us to draw epidemiological inferences such as whether or not cancer is a risk factor for AD.

In conclusion, these analyses suggest that, in observational studies of AD, self-reported all-cancer history is associated with better cognitive scores at a given age in AD patients, but no difference in disease progression over the course of AD. These results echo previous cross-sectional studies indicating an older age of onset for those with self-reported cancer history and with self-reported history of specific cancer subtypes, but this is also the first study focusing specifically on the relationship between self-reported cancer and longitudinal AD progression. Our results demonstrate the need for detailed longitudinal studies of cancer history and and how this affects AD and its progression to clarify complex relationship between the two diseases.

ACKNOWLEDGMENTS

Funding for this report was provided by NIH R01 AG057684 (MEF, GRC, LSS, REK) and by NIH R01 AG037561 (GRC, LSS, REK). The funding agency has no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript.

Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.; Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California.

Authors' disclosures available online (https://www.j-alz.com/manuscript-disclosures/20-0108r2).

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JAD-200108.

Previous presentation

Alzheimer's Association International Conference, July 14-18, 2019, Los Angeles, CA, USA

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