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Cancer History Is Associated with Slower Speed of Cognitive Decline in Patients with Amnestic Cognitive Impairment

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Abstract.

Background: Several epidemiological studies report a negative association between Cancer and Alzheimer's disease (AD).

Objective: To characterize the trajectories of memory loss in individuals with early amnestic cognitive impairment with and without history of previous cancer.

Methods: Cognitive deterioration was assessed using the Montreal Cognitive Assessment (MoCA) or MoCA-Memory Index Score (MoCA-MIS) biannually in subjects with early amnestic cognitive impairment followed-up retrospectively from 2007 to 2021. History of Cancer was obtained from clinical records. Simple linear regressions of MoCA-MIS scores were calculated for each subject and analyzed with K-means cluster analysis to identify subgroups with different cognitive decline trajectories. χ^2 and *t* tests were used for descriptive categorical and continuous variables and mixed multiple linear regressions to determine cognitive decline covariates.

Results: Analysis of the trajectory of cognitive decline in 141 subjects with early amnestic cognitive impairment identified two subgroups: Fast ($n = 60$) and Slow ($n = 81$) progressors. At baseline Fast progressors had better MoCA-MIS ($p < 0.001$) and functionality (CDR $p = 0.02$, AD8 $p = 0.05$), took less anti-dementia medications ($p = 0.005$), and had higher depression rates ($p = 0.02$). Interestingly, Fast progressors slowed their speed of memory decline (from 1.6 to 1.1 MoCA-MIS points/year) and global cognitive decline (from 2.0 to 1.4 total MoCA points/year) when Cancer history was present.

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Conclusion: Two trajectories of amnestic cognitive decline were identified, possibly derived from different neurophysiopathologies or clinical stages. This study suggests that a history of previous Cancer slows down amnestic cognitive decline, specifically in a subgroup of subjects with depression at baseline and accelerated deterioration at follow-up.

Keywords: Alzheimer's disease, cognitive decline, cancer history, memory, mild cognitive impairment

INTRODUCTION

Several epidemiological studies have reported a negative association between Cancer and Alzheimer's disease (AD). Since early anatomopathological reports suggesting an inverse association between the occurrence of Cancer in AD patients [1, 2], there have been numerous studies corroborating an inverse relationship between the two disorders. Yamada et al. in 1999 reported lower odds ratios for Cancer in Japanese AD patients which was not observed for vascular dementia [3]. In two longitudinal studies, we reported that a history of Cancer reduces the risk of AD and conversely, the presence of AD reduces the risk of future Cancer [4, 5]. These results have been corroborated in several studies [6–16] and four meta-analyses [17–20]; however, a few reports have not found an inverse association [21–23].

In general, mutual protection between Cancer and AD has been observed for all types of Cancer, including skin Cancers. Furthermore, having more than one Cancer confers greater protection [10]. Interestingly, no association was observed with vascular dementia suggesting that the protection is related to neurodegeneration [3, 5, 8].

The mechanism by which AD and Cancer are inversely associated may be due to deregulation of common biological pathways in opposite directions [24–27]. Accordingly, inverse patterns of expression in AD and Cancer have been found in transcriptomic meta-analysis [13, 28]. Also, a lower likelihood of secondary AD diagnosis was found in Cancers that underexpressed Pin1, an enzyme that is overexpressed in Cancer and downregulated in AD [29]. Nevertheless, the possibility of underdiagnosis of Cancer in patients with dementia or other methodological biases has not been definitively excluded [30, 31].

Recently, Ospina-Romero et al. (2019) compared long-term memory trajectories in 14,583 subjects before and after an incident of Cancer, in comparison with patients without Cancer, showing that individuals who developed Cancer had better memory and slower cognitive decline than individuals of similar age who remained Cancer free [32]. However, it is still not well established if Cancer is a modifying factor in the rate of cognitive decline in already cognitively impaired subjects. Besides, it is not clear if there is a specific subgroup of patients that show this kind of benign cognitive trajectory.

In this study, we compared the trajectories of memory and cognitive decline of subjects with amnestic mild cognitive impairment (aMCI) and mild AD (mAD) with and without a clinical history of any type of Cancer, in order to evaluate the role of Cancer and type of Cancer in these courses. Since the trajectory of memory decline varies significantly among individuals with AD [33–35], we first performed a classificatory analysis of the different cognitive decline trajectories in our cohort.

METHODS

Study design and setting

This observational retrospective cohort research took place at Hospital Clínico de la Universidad de Chile (HCUCH) and Clínica Alemana de Santiago (CAS), both in Santiago, Chile, from 2007 to 2021. Electronic clinical records from both institutions were used to build the database for this study. HCUCH and CAS provide clinical care to upper- and middle-class socioeconomic status populations.

Eligibility criteria

Subjects with amnestic cognitive impairments were included if aged ≥ 58 years old, scored ≥ 11 points in the Montreal Cognitive Assessment (MoCA) and Clinical Dementia Rating sum of boxes (CDR-SOB)≤ 5. Exclusion criteria included moderate/severe AD, questionable cognitive impairment, non-amnestic MCI or non-AD dementia, severe auditory/visual impairment, or foreign language impairments. Also, patients with less than three MoCA-MIS evaluations were excluded from the analysis.

Clinical assessment

All aMCI and mAD subjects were evaluated by a single evaluator (MIB) in a standardized way in outpatient consultations at HCUCH and CAS. Subjects were followed-up over a maximum of 12.5 years. In this research, time was measured in semesters which was defined as a 6 ± 1-month time span. Therefore, only evaluations separated at least by 5 months each were considered.

Diagnosis of aMCI and mAD diagnosis were performed using the NIA-AA criteria [36]. Dementia status and severity were assessed using the CDR and CDR-SOB. In addition, an informant filled in the Alzheimer's Disease 8 (AD8) Questionnaire. All patients were tested with the MoCA [37], validated for the Chilean population [38], at the initial and on consecutive visits. Patients were assessed with a full MoCA test if seen 1 year after the previous evaluation, and, if seen in between (within 5 and 7 months from the previous assessment) they were evaluated with the MoCA memory index (MoCA-MIS) score [39], orientation and fluency with letter P. The three versions of the MoCA (with different sets of words for memory recall) were used in each evaluation to avoid a learning bias. The MoCA-MIS has a maximum of 15 points which is calculated as the sum of the number of words spontaneously recalled multiplied by 3, the number of words recovered with categorical clues multiplied by 2, and the number of words recalled by recognition multiplied by 1. MoCA-MIS was included due to its high sensitivity and specificity for amnestic cognitive impairment diagnosis.

History of Cancer and its temporality were obtained from clinical charts and remote anamnesis. Only subjects who had Cancer history at their first MoCA assessment were included. So, subjects that developed Cancer after enrollment were not considered in the Cancer group. In cases where the patient had developed more than one type of Cancer in his previous medical history, only the time of presentation of the first Cancer was considered. The Cancer origin defined Cancer type, here divided in Skin (squamous cell carcinoma, basal cell carcinoma, and melanoma) or Non-Skin (prostate, testicle, breast, ovary, cervix, larynx, lung, kidney, bladder, gastric, intestine, colon, leukemia, lymphoma, and thyroid) subtypes.

Baseline sociodemographic data (age, education, and sex), family history of AD dementia, baseline comorbidities (hypothyroidism, depression, type 2 diabetes [DM2], high blood pressure [HBP], hypercholesterolemia) and treatment status (acetylsalicylic acid, memantine and/or acetylcholinesterase [AChE] inhibitors) were also obtained from clinical records. Depression diagnosis was confirmed using Structured Clinical Interview for DSM-IV, Research Version (SCID-RV) [40].

The principal research outcomes were total MoCA and MoCA-MIS scores trajectories in time, considering the retrospective presence or absence of Cancer diagnosis in the clinical history of the subjects.

Standard protocol approvals, registrations, and patient consents

Sociodemographic and clinical data were collected directly from clinical charts to an Excel datasheet providing a numeric code for each participant ensuring anonymity. Research was evaluated and accepted by HCUCH and CAS Research Ethics Committee and granted a waiver for consent.

Descriptive statistics

A two-column table was used for descriptive statistics using mean and standard deviation (SD) for continuous variables and absolute and relative frequencies for categorical variables. Amnestic subjects with or without Cancer were compared using χ^2 tests for categorical variables and two-tailed unpaired Student *t* tests for continuous variables. 95% confidence intervals (CI) were included for both analyses as a measure of precision and an $\alpha < 0.05$ was considered significant. GraphPad Prism version 9.2.0 (2021) was used for these purposes.

Analytic statistics

To detect different trajectories of memory and global cognitive loss, we first used simple linear regressions of the MoCA-MIS scores (0 to 15 points) along time (1 to 25 semesters) for each participant assuming linear trend, using Intercept, Slope, and R^2 to describe trajectories. The intercept denotes an approximation of memory status prior to the first medical consultation (i.e., semester 0); Slope denotes the rate of MoCA-MIS points lost per semester, and R^2 the shape of the MoCA-MIS scores trajectory. For instance, high R^2 denotes a linear decline, while low R^2 values denote non-linear or noisy trajectories. As mentioned in inclusion criteria, we removed all participants with less than three MoCA-MIS observations, because regressions with 2 points would produce a perfect R^2 and that a two-points estimation

would be highly sensitive to measurement error. MoCA-MIS was used for group classificatory purposes due to its specificity for memory assessment and the higher number of observations accumulated during follow-up.

Following individual regression analysis, we used classification algorithms which cluster (or group) similar trajectories based on Intercept, Slope and R^2 without a gold standard or proposed outcome (hence an unsupervised rationale). The NbClust R library was used to explore the number of clusters (or groups) to extract. The two most voted solutions from a total of 30 different methods included in this package were explored. Using principal component analysis, we projected the clusters into the two components which explained more variance and selected those that were more apart from each other (e.g., polygons that did not overlap, and with higher distances of cluster borders). Based on the K-Means algorithm with 25 random starting points, clusters were obtained.

The following step was to characterize the groups obtained by the algorithm. We then characterized these groups using the Intercept, Slope, R^2, as well as with other socio-demographic and morbidity data. Groups were named according to their characteristic trajectories as "Fast and Slow Progressors".

In order to analyze the evolution over time between groups, the impact of Cancer on the trajectories of the Fast and Slow Progressors groups was evaluated. Mixed linear models (MLM) were used to control for repeated measures with each cluster obtained independently. Dependent variables were MoCA-MIS and MoCA total score. Independent variables were time (semesters), age (years), education (years), Cancer (as a dummy variable, using absence of Cancer as reference), and drugs used (as dummy variables, using no drug usage as reference). A random intercept and a random slope (time based) were defined. This means that we modeled all participants assuming that they would show differences in their initial scores and individual trajectories as part of inter individual differences. To evaluate if on top of that variability independent variables might contribute not only to differences on intercept but also to the rate of memory loss (e.g., if Cancer slowed down the rate of memory loss), an interaction of time with all independent variables was included.

Finally, based on the pruned models (models without non-significant regressors), the MLM model was reevaluated using the type of Cancer variable grouped in Skin Cancer versus Non-Skin Cancer, with absence of Cancer as reference.

Models were pruned using a backward method and fitted using the Bound Optimization by Quadratic Approximation (BOBYQA) [41]. Marginal R^2 (variance explained by fixed effects) and conditional R^2 (variance explained by the whole model) were estimated using Nakagawa-Schielzeth's method and extensions [42–44]. In general terms, marginal R^2 is the explained variance due to the predictors used in the regression model, while conditional R^2 includes also the variance explained by interindividual differences. The variance not explained by the model is because of noise (i.e., instrument imprecision or non-specified sources of variability), or because the trajectories do not follow a linear shape.

To control for the potential impact of early mortality on the slopes of the above-mentioned models, a survival analysis was included. Survival curves were estimated using Cox Proportional-Hazards Model for the whole sample, with and without Cancer groups and for the Fast and Slow subgroups.

To find out if there were any family biological links in our data between the family history of Cancer and AD with the presence of Cancer in our cohort, we performed independent logistic regressions.

Finally, to strengthen the analysis, we performed a sensitivity analysis to hidden bias on the interaction coefficient to assess how large the effect of an unobserved confounder should be in order to explain away our findings [45, 46].

Statistical analyses were performed using Project R software (2021). Clustering was performed using NbClust and reshape2. MLM were performed using lme4, lmerTest, Optimx, and MuMIn. Survival curves were estimated using survival and survminer. Finally, plots were performed using ggplot 2.

RESULTS

Participants

From a total of 2,049 subjects with cognitive related reasons for consultation, 1,419 had only one evaluation or unmet inclusion criteria of being ≥ 58 years old, scoring ≥ 11 points on MoCA and a CDR-SOB ≤ 5.

Exclusion criteria were applied to the remaining 630 subjects, which included moderate/severe AD ($n = 49$), questionable cognitive impairment ($n = 42$), non-amnestic MCI ($n = 91$) or non-AD dementia (including frontotemporal dementia ($n = 38$), Lewy bodies dementia/Parkinson's disease dementia ($n = 37$), primary progressive aphasia ($n = 63$), vascular

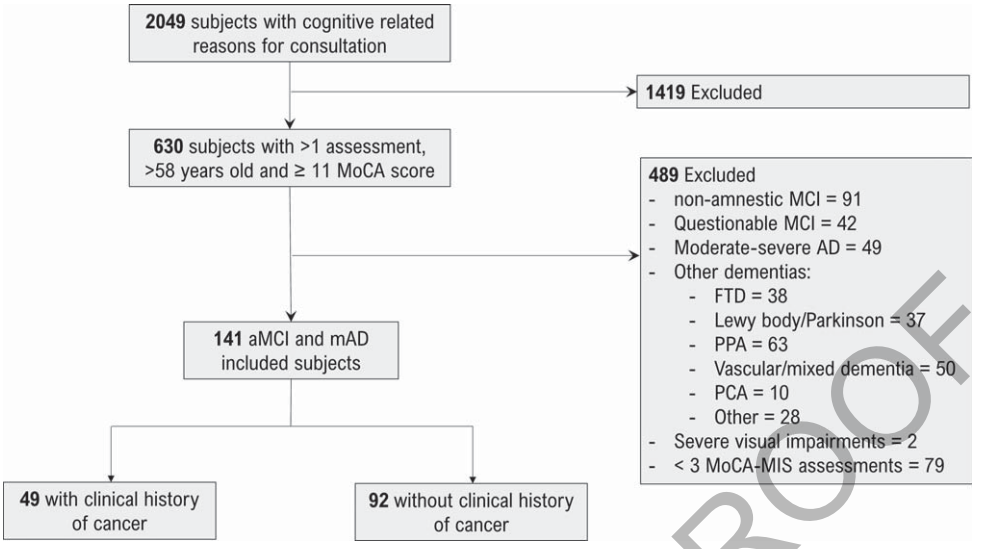

Fig. 1. Selection of the Study Sample. aMCI, amnestic mild cognitive impairment; mAD, mild Alzheimer's disease; FTD, frontotemporal dementia; PCA, posterior cortical atrophy; PPA, primary progressive aphasia; MoCA, Montreal Cognitive Assessment; MIS, Memory Index Score.

dementia/mixed dementia ($n = 50$), posterior cortical atrophy ($n = 10$), other forms of degenerative dementia ($n = 28$), and severe auditory, visual, or foreign language impairments ($n = 2$). After applying inclusion and exclusion criteria 220 subjects with aMCI or mAD subjects were included in the database. But, since estimations of a slope with only two MoCA-MIS assessments would be highly sensitive to measurement error, patients with less than three evaluations ($n = 79$) were excluded and a final sample of 141 subjects were selected. Of them, 49 subjects had clinical history of Cancer and 92 did not (Fig. 1).

Baseline description

Our final sample of 141 aMCI and mAD subjects had an average of 73.5 (SD = 6.4) years, 13.5 (SD = 4.3) educational years, and 93 (66.0%) of them were female (Table 1). Other baseline cognitive and medical descriptions of subjects are available in Table 1. Sociodemographic and clinical missing data represented 1.25% of the final database, which included subject's memory biases or unavailability from clinical records.

After dividing and comparing groups according to their previous Cancer history, at study entry the group with Cancer history ($n = 49$) demonstrated a higher proportion of men ($p = 0.006$) and was older than the Non-Cancer group ($p = 0.002$). They had similar total MoCA and MoCA-MIS scores; however, the group with Cancer history performed better in Attention ($p = 0.012$) and Delayed Recall ($p = 0.014$) MoCA subdomains. There were no differences in the CDR ($p = 0.537$) and CDR-SOB ($p = 0.427$) at baseline between groups, but the informant reported a better AD8 score in the Cancer group ($p = 0.006$). Also, no differences were obtained in comorbidities and treatment status between groups (Table 1).

Cancer diagnosis was made on average 6.8 (SD = 6.5) years (range 0 to 35 years) before their first clinical assessment. Out of the total subjects with Cancer, 26.5% had Skin-related Cancers (basal cell carcinoma $n = 10$, squamous cell carcinoma $n = 0$, and melanoma $n = 4$) and the rest had Non-Skin Cancers (prostate = 12, colon $n = 8$, breast $n = 8$, and others = 12). Five subjects had clinical history of 2 different types of Cancer (Supplementary Table 1).

Trajectories of memory decline

Participants had a mean follow-up of 8.9 semesters (SD = 4.3; range 2 to 25 semesters), representing 626 MoCA-MIS and 545 total MoCA measurements. Therefore, each subject had a mean of 4.44 MoCA-MIS and 3.87 total MoCA evaluations. On average, one MoCA-MIS and 0.87 total MoCA were performed every year per subject.

Since the trajectories of memory decline showed relevant variability among participants, our first aim was to characterize and group the different

Table 1
Baseline Description of Subjects

	Total Sample	With Cancer	Without Cancer	p^a
n	141	49	92	
Sociodemographic Data				
Age (y), mean (SD)	73.5 (6.4)	75.6 (6.2)	72.4 (6.3)	0.006**
Education (y), mean (SD)	13.5 (4.3)	12.8 (4.7)	13.9 (4.0)	0.157
Sex (Female), *n* (%)	93 (66.0)	24 (49.0)	69 (75.0)	0.002**
Cancer Status				
Cancer, *n* (%)	49 (34.8)	—	—	—
Cancer type (skin), *n* (%)	13 (9.2)	13 (26.5)	—	—
Clinical Description				
Family history of AD, *n* (%)	51 (36.2)	15 (30.6)	36 (39.1)	0.316
MoCA total score (0–30), mean (SD)	21.0 (3.9)	21.8 (3.9)	20.6 (3.9)	0.068
Visuospatial (0–5), mean (SD)	3.5 (1.3)	3.6 (1.2)	3.5 (1.3)	0.493
Naming (0–3), mean (SD)	2.6 (0.7)	2.5 (0.7)	2.7 (0.7)	0.267
Attention (0–6), mean (SD)	4.8 (1.3)	5.2 (1.1)	4.6 (1.3)	0.012*
Language (0–3), mean (SD)	2.3 (0.8)	2.2 (0.9)	2.3 (0.7)	0.473
Fluency (words), mean (SD)	13.5 (4.6)	12.7 (4.8)	13.9 (4.5)	0.132
Abstraction (0–2), mean (SD)	1.5 (0.6)	1.4 (0.6)	1.6 (0.6)	0.064
Delayed recall (0–5), mean (SD)	1.0 (1.4)	1.4 (1.6)	0.8 (1.2)	0.014*
MoCA-MIS (0–15), mean (SD)	7.9 (2.0)	8.5 (3.9)	7.6 (3.0)	0.134
Orientation (0–6), mean (SD)	4.7 (1.5)	4.8 (1.6)	4.6 (1.5)	0.517
CDR score (0–3), mean (SD)	0.6 (0.2)	0.6 (0.2)	0.6 (0.2)	0.537
CDR-SOB score (0–18), mean (SD)	1.8 (1.1)	1.7 (1.3)	1.9 (1.1)	0.427
AD8 score (0–8), mean (SD)	4.8 (2.0)	4.1 (1.9)	5.1 (1.9)	0.006**
Comorbidities				
Hypothyroidism, *n* (%)	48 (34.0)	20 (40.8)	28 (30.4)	0.215
DM2, *n* (%)	40 (28.4)	13 (26.5)	27 (29.3)	0.724
HBP, *n* (%)	59 (41.8)	23 (46.9)	36 (39.1)	0.371
Hypercholesteremia, *n* (%)	57 (40.4)	20 (40.8)	37 (40.2)	0.945
Depression, *n* (%)	87 (61.7)	30 (61.2)	57 (62.0)	0.932
Pharmacological Treatment				
ASA, *n* (%)	27 (19.1)	8 (16.3)	19 (20.7)	0.534
Anti-Dementia Medications				
None, *n* (%)	25 (17.7)	11 (22.4)	14 (15.2)	0.284
Anti-AChE, *n* (%)	24 (17.0)	10 (20.4)	14 (15.2)	0.435
Memantine, *n* (%)	24 (17.0)	8 (16.3)	16 (17.4)	0.873
Both, *n* (%)	68 (48.2)	20 (40.8)	48 (52.2)	0.199

AChE, acetylcholinesterase; ASA, acetylsalicylic acid; AD, Alzheimer's disease; AD8, Alzheimer Disease 8 Questionnaire; CA, cancer; CDR, Clinical Dementia Rating Scale; CDR-SOB, Clinical Dementia Rating Scale – Sum of Boxes; DM2, Type 2 diabetes; HBP, high blood pressure; MoCA, Montreal Cognitive Assessment; MIS, Memory Index Score. [a]*p* values for comparison using *t* tests for quantitative variables and χ^2 test for qualitative variables. $^*p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$.

trajectories of cognitive decline of all participants. So, MoCA-MIS scores were analyzed using individual linear regressions followed by cluster analysis. Using this method two clusters were identified, denoting differences in the rate of memory loss over time. As shown in Fig. 2A, we detected a first group named Fast Progressors with a higher memory loss rate (steeper negative Slope; $M=-0.95$, SD = 0.73), a higher baseline MoCA-MIS score (higher Intercepts $M=11.74$, SD = 3.01) and a closer proximity to linear trend in memory loss rate (higher goodness-of-fit Marginal/Conditional R^2 values = 0.47 / 0.77). The other group, named Slow Progressors, showed a slower rate of memory loss (close to zero Slope; $M=-0.06$, SD = 0.41), and lower baseline MoCA-MIS scores (lower Intercepts; $M=6.58$, SD = 2.53). Also, their trajectories showed lower goodness-of-fit R^2 values (Fast / Slow R^2 = M = 0.76, SD = 0.19 / $M=0.25$, SD = 0.24), pointing to progressions with slopes close to zero and departure from a linear trend.

When assessing the MLM results, both groups showed significant memory decline in their MoCA-MIS scores over time, with a higher rate in Fast Progressors, which lost around 1.6 (out of 15) MoCA-MIS points per year (Table 2; $\beta=-0.82$ [–0.94 – –0.69] MoCA MIS points/semester; $p<0.001$). On the other hand, Slow Progressors lost 0.22 (out of

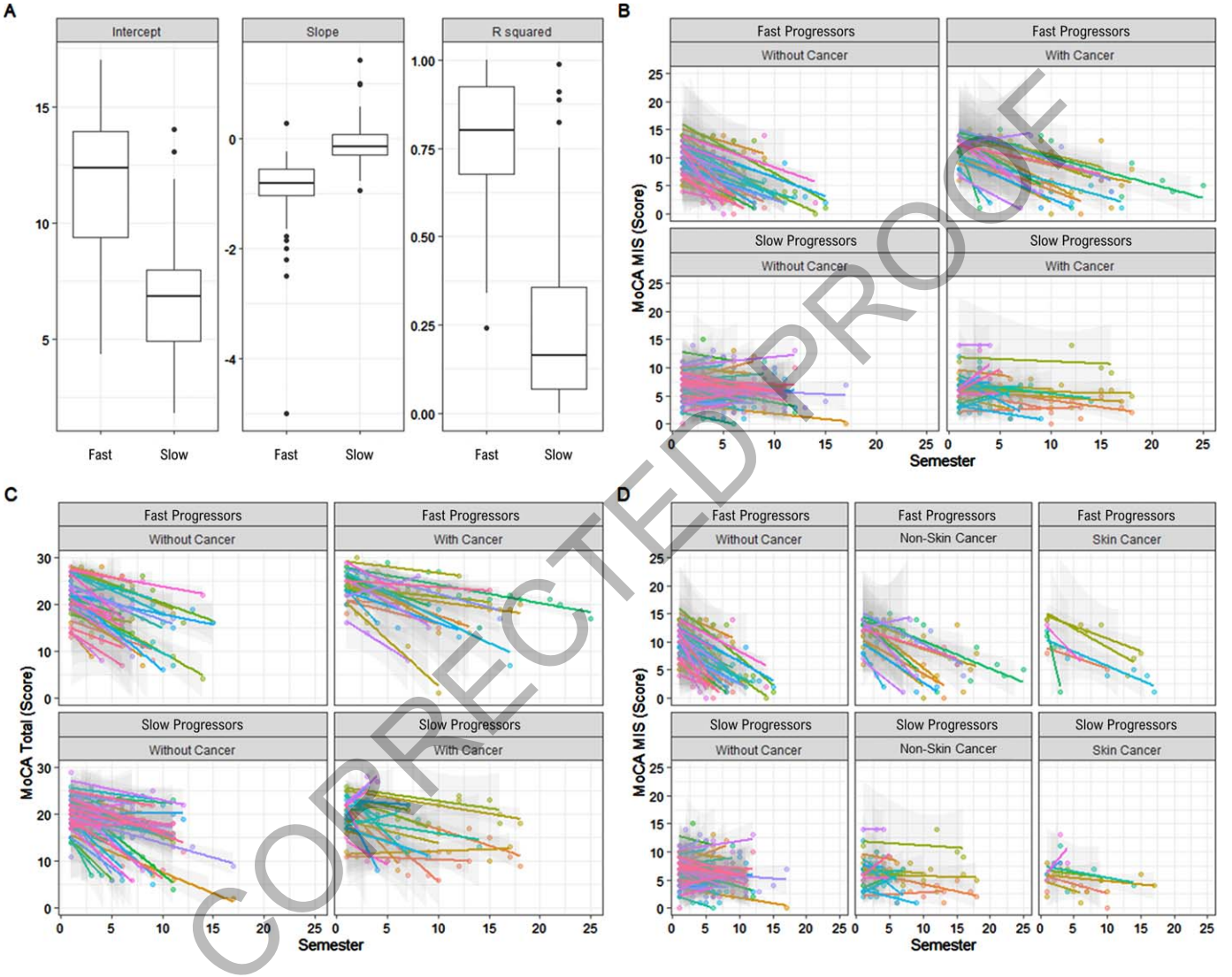

Fig. 2. Characterization of Fast and Slow Progression Groups with or without Cancer. A) Clusters were obtained using the intercept, slope, and R2, of each patient's linear regression model of MoCA-MIS versus Semester. B) Each individual regression model presented by group and by the presence of Cancer. C) Regression models of Total MoCA Score separated in the same fashion (not used in clustering procedure). D) Individual linear models for MoCA-MIS by subgroup, but splitting the Cancer variable into Skin Cancer, Non-Skin Cancer, and without Cancer.

Table 2
Mixed Linear Model Results of MoCA-MIS and Total MoCA for Fast and Slow Progressors and their Interaction with Cancer

	MoCA-MIS				MoCA-Total			
[-6pt] Predictors	Fast Progressors		Slow Progressors		Fast Progressors		Slow Progressors	
[-6pt]	Estimates (CI)	*p*	Estimates (CI)	*p*	Estimates (CI)	*p*	Estimates (CI)	*p*
Intercept (MoCA score)	12.14 (10.60 – 13.68)	< 0.001***	9.16 (7.66 – 10.66)	< 0.001***	20.3 (17.25 – 23.36)	< 0.001***	21.94 (19.58 – 24.30)	< 0.001***
Age (y)	–	–	–	–	–	–	–	–
Education (y)	–	–	–	–	0.28 (0.08 – 0.48)	0.005**	–	–
Time (Semester)	–0.82 (–0.94 – –0.69)	< 0.001***	–0.12 (–0.18 – –0.05)	0.001**	–0.97 (–1.15 – –0.79)	< 0.001***	–0.71 (–0.88 – –0.54)	< 0.001***
Cancer (With Cancer)	1.08 (–0.40 – 2.55)	0.153	–	–	1.88 (0.15 – 3.61)	0.033*	–	–
Memory Medications								
Anti-AchE	–1.03 (–3.15 – 1.09)	0.34	–2.24 (–4.09 – –0.39)	0.018*	–0.7 (–3.31 – 1.91)	0.598	–1.2 (–4.12 – 1.72)	0.419
Memantine	–3.01 (–5.13 – –0.89)	0.005**	–3.19 (–5.03 – –1.34)	0.001**	–3.71 (–6.26 – –1.16)	0.004**	–3.75 (–6.65 – –0.84)	0.012*
Both	–1.7 (–3.39 – 0.00)	0.05*	–2.71 (–4.31 – –1.11)	0.001**	–1.41 (–3.55 – 0.73)	0.196	–0.18 (–2.71 – 2.36)	0.892
Time (Semester): Cancer (With Cancer)	0.23 (0.07 – 0.39)	0.004**	–	–	0.28 (0.02 – 0.54)	0.032*	–	–
Patients (*n*)	60		81		60		81	
Measurements (*n*)	273		353		243		302	
Marginal R^2 / Conditional R^2	0.47 / 0.77		0.09 / 0.49		0.37 / 0.88		0.28 / 0.86	

AChE, acetylcholinesterase; CI, 95% Confidence Interval; MoCA, Montreal Cognitive Assessment; MIS, Memory Index Score. Columns represent dependent variables, MoCA-MIS or Total MoCA, in Fast and Slow Progressors while each row represents regressors or predictors. Blank cells indicate variables that were tested but removed from the model due to non-significant results. The interaction between time and Cancer (i.e., Time [Semester]: Cancer [With Cancer]) denotes the change in the rate of score loss due to Cancer presence. Time (Semester) and Time (Semester): Cancer (With Cancer) interaction regression coefficients can be read as score points by semester, while the remaining variables contribute globally and independently to the semester (given their dummy variable nature). $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

15) MoCA-MIS points per year (Table 2; β = –0.12 [–0.18 – –0.05] MoCA MIS points/semester; $p = 0.004$). A similar pattern was found for global cognitive decline measured by total MoCA score, but the difference in progression was not as strong as for MoCA-MIS; Fast Progressors lost around 2 points (out of 30) of total MoCA score per year (Table 2; β = –0.97 [–1.15 – –0.79] Total MoCA points/semester; $p < 0.001$), while Slow Progressors lost around 1.4 points (out of 30) per year (Table 2; β = –0.71 [–0.88 – –0.54] Total MoCA points/semester; $p < 0.001$)

There were no significant differences in age of the participants in Fast and Slow Progression groups neither in total baseline MoCA nor MoCA-MIS scores ($p > 0.05$), therefore, age was removed from the models. Education contributed only to the starting total MoCA score in Fast Progressors (Table 2; β = 0.28 [0.08 – 0.48] Total MoCA points; $p = 0.005$). Specifically, Fast Progressors started with 0.28 points more of total MoCA per year of education. Therefore, a ten-year education background would contribute 2.8 points of total MoCA score. In contrast, Slow Progressors showed no protective effect for educational background.

Regarding medication, all drugs showed a negative contribution to total MoCA and MoCA-MIS at baseline, regardless of the group, indicative of the status of the patients at the time in which medications were prescribed (Table 2). In general, AChE inhibitors had a small effect, in most cases not different from zero (no difference compared to no-medication; Table 2; Fast Progressors β = –1.03 [–3.15 – 1.09] MoCA MIS points; $p = 0.34$) except for MoCA-MIS in Slow Progressors where the use of AChE inhibitors was associated with a loss of 2 MoCA-MIS points (Table 2; β = –2.24 [–4.09 – –0.39] MoCA MIS points; $p = 0.018$). Memantine use was associated with a greater memory and cognitive deterioration in Fast and Slow Progressors, showing an impact of 3 (Fast progressors: β = –3.01 [–5.13 – –0.89] MoCA MIS; $p = 0.001$) to almost 4 (β = –3.71 [–6.26 – –1.16] Total MoCA points; $p = 0.004$) points less in initial scores of total MoCA and MoCA-MIS. Finally, concomitant use of both drugs was associated with lower MoCA-MIS scores, both in Fast (β = –1.7 [–3.39 – –0.00] MoCA MIS points; $p = 0.05$; β = –1.41 [–3.55 – –0.73] Total MoCA points; $p = 0.196$) and Slow Progressors (β = –2.71 [–4.31 – –1.11] MoCA MIS points; $p = 0.001$; β = –0.18 [–2.71 – 2.36] Total MoCA points; $p = 0.89$), being greater in the latter (Table 2).

Association with Cancer

The presence of Cancer history showed a significant contribution counteracting the rate of memory loss over time (depicted as the interaction Time [Semester]: Cancer [with Cancer]) in the group of Fast Progressors. This interaction indicates that patients slowed their MoCA-MIS decline from 1.6 points to 1.1 points per year (a countereffect of $\beta = 0.23$ [0.07 – 0.39] MoCA-MIS points/semester; $p = 0.004$). The same pattern was observed for total MoCA score, where the expected loss of around 2 points per year was reduced to 1.4 points (Table 2; $\beta = 0.28$ (0.02 – 0.54) MoCA MIS points/semester; $p = 0.032$). Cancer history also contributed to a higher baseline total MoCA score ($\beta = 1.88$ [0.15 – 3.61] Total MoCA, $p = 0.033$).

Fast Progressors showed the model with highest marginal pseudo-R^2 (0.47), where predictors explained 47% of the variance for MoCA-MIS, meaning that cognitive decline along time, Cancer, and AD medication explained about half of the variability observed. In the case of Total MoCA the variability was lower (37%), and it also included education as a significant predictor of trajectory. In contrast, Slow Progressors, showed a low marginal pseudo-R^2 for MoCA-MIS (0.09) explaining 9% of data variability. For Total MoCA this improved up to 28%, mainly explained by time variable (i.e., cognitive decline on time). Conditional pseudo-R^2 represents the variance explained by the predictors and by patients' variability (interindividual differences) in their trajectories. The low conditional pseudo-R^2 for MoCA-MIS in Slow Progressors are indicative of departure from linear trend, which can be attributed to other sources of variability not evaluated in this study, or that these patients had nonlinear trajectories. These values are consistent with the results obtained with simple linear regressions and reported in Fig. 2A, as Slow progressors presented lower R^2s.

The individual trajectories of the MoCA-MIS in both groups (Fig. 2B) show the impact of Cancer on slowing the rate of memory loss in Fast Progressors and not in Slow Progressors. Nonetheless, it is also possible that the effect found was not present in all patients, where some high-rate memory loss can be seen in Fast Progressors with Cancer as well. Consistent with the R^2 values shown in Fig. 2A and the conditional pseudo-R^2 in Table 2, Slow Progressors presented more variability (lower conditional pseudo-R^2) in their trajectories both for MoCA-MIS (0.49) and total MoCA (0.86; Fig. 2B and 2C, respectively).

During follow-up, 22 subjects (15.6% of the total sample) died. Interestingly, there was no early mortality of subjects with Cancer in the survival analysis ($\beta = 0.366$, HR = 1.443, 95%CI = 0.615–3.381, $p = 0.4$) (Fig. 3).

Finally, trying to further explore a biological link between AD and Cancer, we ran a logistic regression analysis with family history of Cancer and family history of AD, and no significant relationship was found ($p = 0.81$ and $p = 0.74$, correspondingly).

Given the observational nature of the study, a sensitivity analysis to hidden bias was conducted. The objective of this analysis is to estimate how large potential unobserved confounders should be in order to explain away our findings and yield a non-statistically significant difference between the rate of progression of patients with and without cancer. Following Frank et al. (2013) [46], we found that an unobserved confounder should explain 28.2% and 6.2% of the effect of the progression over time between cancer and non-cancer patients for Fast Progressors, which is equivalent to switching 7 (out of 23) and 3 (out of 23) patients to an effect of 0 for MoCA-MIS and Total MoCA, respectively. For the MoCA-MIS findings, which is highly related to the evolution into AD, results appear to be robust to potential hidden bias, providing additional evidence that a spurious correlation is less likely, even though still possible.

Effect of Cancer type in fast progressors

As the next step, we focused on the significant effects of Cancer found in Fast Progressors and wondered if there is a particular type of Cancer that determines this effect. So, the MLM analysis was repeated, introducing the Cancer variable split into Skin and Non-Skin Cancer subgroups, considering that previous research had studied this variable separately [4, 47]. It is important to consider the participation of Skin Cancer, since it is the most frequent type of Cancer in white population [48] and also has a good prognosis (except for melanoma), diminishing the chance that patients die before they reach the age of risk of cognitive deterioration. In this case, in both groups, Skin and Non-Skin, Cancer had a significant effect of slowing down the decline in MoCA-MIS over time, being slightly higher for Skin Cancer (Skin Cancer: $\beta = 0.27$ [0.02–0.52], $p = 0.036$ versus Non-Skin Cancer: $\beta = 0.24$ [0.07 – 0.52]; $p = 0.005$; Table 4 and Fig. 2D). For total MoCA, the effect of type

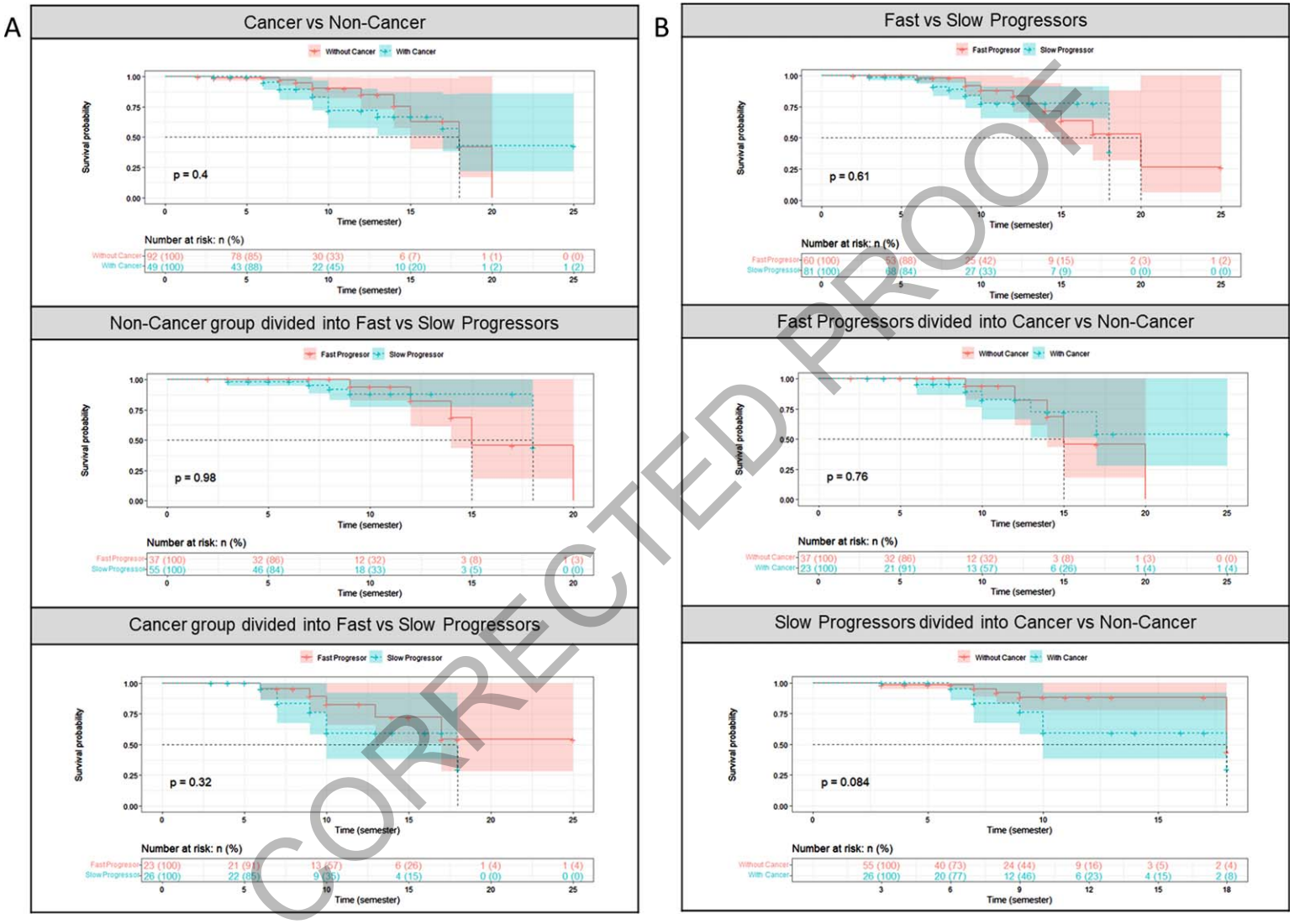

Fig. 3. Survival Curves of Fast vs Slow Progressors and Cancer versus Non-Cancer groups. A) Survival curves of the whole sample of Cancer versus Non-Cancer groups and subgroups and (B) the whole sample of Fast versus Slow Progressors groups and subgroups. Lines represent median mortality rate, crosses depict drop-out and colored shades indicate 95% confidence intervals.

Table 3
Description of Subjects per Classificatory Group and Cancer Condition

	All ($n=141$)			Fast Progressors ($n=60$)			Slow Progressors ($n=81$)		
	Fast progressors	Slow Progressors	p^a	Without Cancer	With Cancer	p^a	Without Cancer	With Cancer	p^a
n	60	81	—	37	23	—	55	26	—
Sociodemographic Data									
Age (y), mean (SD)	73.7 (6.4)	73.4 (6.5)	0.843	73.2 (6.3)	74.4 (6.7)	0.457	71.9 (6.4)	76.6 (5.7)	0.002**
Education (y), mean (SD)	13.5 (4.4)	13.5 (4.3)	0.989	13.8 (3.6)	13.0 (5.5)	0.425	14.2 (4.3)	12.7 (4.1)	0.241
Sex (Female), *n* (%)	39 (65.0)	54 (66.7)	0.836	27 (75.0)	11 (47.8)	0.049*	41 (74.5)	13 (50.0)	0.029*
Cancer Status									
Cancer, *n* (%)	23 (38.3)	26 (32.1)	0.442	—	—	—	—	—	—
Cancer type (skin), *n* (%)	6 (10.0)	7 (8.6)	0.947	—	6 (26.1)	—	—	7 (26.9)	—
Clinical Description									
Family history of AD, *n* (%)	21(35.0)	30 (37.0)	0.803	12 (33.3)	8 (34.8)	0.851	23 (41.8)	7 (26.9)	0.195
MoCA total (0–30), mean (SD)	22.4 (4.0)	20.0 (3.6)	<0.001**	21.6 (4.3)	23.5 (3.3)	0.074	19.9 (3.5)	20.3 (3.9)	0.569
Visuospatial (0–5), mean (SD)	3.7 (1.4)	3.4 (1.2)	0.267	3.7 (1.4)	3.6 (1.4)	0.713	3.3 (1.3)	3.7 (1.0)	0.203
Naming (0–3), mean (SD)	2.6 (0.7)	2.6 (0.6)	0.797	2.6 (0.7)	2.6 (0.7)	0.770	2.7 (0.6)	2.5 (0.7)	0.213
Attention (0–6), mean (SD)	4.9 (1.2)	4.8 (1.4)	0.59	4.7 (1.3)	5.2 (0.9)	0.080	4.6 (1.3)	5.2 (1.4)	0.078
Language (0–3), mean (SD)	2.3 (0.8)	2.3 (0.8)	0.924	2.3 (0.7)	2.2 (1.0)	0.638	2.3 (0.7)	2.2 (0.8)	0.600
Fluency (words), mean (SD)	13.3 (5.0)	13.7 (4.3)	0.667	14.2 (5.4)	11.9 (3.8)	0.084	13.8 (3.7)	13.4 (5.5)	0.742
Abstraction (0–2), mean (SD)	1.6 (0.6)	1.4 (0.6)	0.237	1.6 (0.5)	1.4 (0.6)	0.155	1.5 (0.6)	1.3 (0.6)	0.183
Delayed recall (0–5), mean (SD)	1.8 (1.5)	0.4 (0.8)	<0.001**	1.5 (1.6)	2.4 (1.4)	0.012*	0.4 (0.7)	0.5 (1.1)	0.630
MoCA-MIS (0–15), mean (SD)	10.2 (2.8)	6.3 (2.6)	<0.001**	9.4 (2.8)	11.3 (2.5)	0.010**	6.4 (2.4)	6.0 (3.0)	0.501
Orientation (0–6), mean (SD)	5.0 (1.4)	4.5 (1.6)	0.034*	4.8 (1.6)	5.4 (1.0)	0.069	4.6 (1.4)	4.3 (1.9)	0.433
CDR (0–3), mean (SD)	0.6 (0.2)	0.7 (0.3)	0.017*	0.6 (0.2)	0.5 (0.2)	0.233	0.6 (0.3)	0.7 (0.3)	0.368
CDR-SOB (0–18), mean (SD)	1.5 (1.0)	2.0 (1.2)	0.005**	1.7 (1.0)	1.1 (0.8)	0.011**	1.9 (1.1)	2.2 (1.3)	0.284
AD8 (0–8), mean (SD)	4.4 (2.0)	5.1 (2.0)	0.053*	4.7 (2.2)	3.8 (1.5)	0.126	5.4 (1.7)	4.3 (2.2)	0.030*
Comorbidities									
Hypothyroidism, *n* (%)	21 (35.0)	27 (33.3)	0.836	11 (30.6)	9 (39.1)	0.453	16 (29.1)	11 (42.3)	0.239
DM2, *n* (%)	17 (28.3)	23 (28.4)	0.994	10 (27.8)	7 (30.4)	0.776	17 (30.9)	6 (23.1)	0.466
HBP, *n* (%)	25 (41.7)	34 (42.0)	0.971	14 (38.9)	11 (47.8)	0.446	22 (40.0)	12 (46.2)	0.600
Hypercholesteremia, *n* (%)	24 (40.0)	33 (40.7)	0.929	11 (30.6)	12 (52.2)	0.082	25 (45.1)	8 (30.8)	0.209
Depression, *n* (%)	44 (73.3)	43 (53.1)	0.015*	27 (75.0)	16 (69.6)	0.776	29 (52.7)	14 (53.8)	0.925
Pharmacological Treatment									
ASA, *n* (%)	11 (18.6)	16 (19.8)	0.832	6 (16.2)	5 (21.7)	0.591	13 (23.6)	3 (11.5)	0.202
Anti-Dementia Medications									
None, *n* (%)	17 (28.3)	8 (9.9)	0.005**	8 (21.6)	9 (39.1)	0.143	6 (10.9)	2 (7.7)	0.651
Anti-AChE, *n* (%)	10 (16.7)	13 (16.0)	0.923	6 (16.2)	4 (17.4)	0.906	8 (14.5)	6 (23.1)	0.343
Memantine, *n* (%)	10 (16.7)	14 (17.3)	0.923	8 (21.6)	2 (8.7)	0.192	8 (14.5)	6 (23.1)	0.343
Both, *n* (%)	23 (38.3)	45 (55.6)	0.043*	15 (40.5)	8 (34.8)	0.656	33 (60.0)	12 (46.2)	0.242

AChE, acetylcholinesterase; ASA, acetylsalicylic acid; AD, Alzheimer's disease; AD8, Alzheimer Disease 8 Questionnaire; CA, cancer; CDR, Clinical Dementia Rating Scale; CDR-SOB, Clinical Dementia Rating Scale – Sum of Boxes; DM2, Type 2 diabetes; HBP, high blood pressure; MoCA, Montreal Cognitive Assessment; MIS, Memory Index Score. [a]p values for comparison using t tests for quantitative variables and χ^2 test for qualitative variables. *$p<0.05$, **$p<0.01$, ***$p<0.001$.

of Cancer was lost when splitting Cancer variables. This discrepancy may be explained by the reduced number of observations in the Skin Cancer group, and also by a less robust effect compared to the one detected with MoCA-MIS.

Clinical description of subjects with and without Cancer in the Fast and Slow Progressor subgroups

Table 3 shows the mean and SD of the measured cognitive scores, Cancer status, sociodemographic and clinical characteristics of the Fast and Slow Progressor subgroups. There were no differences in age, education, sex, family history of AD, or Cancer prevalence between the two subgroups. The most distinctive differences were better cognitive measures in the Fast Progressor subgroup as determined by a better baseline total MoCA ($p<0.001$), Delayed Recall ($p<0.001$), and MoCA-MIS ($p<0.001$) scores and lower CDR ($p=0.017$), CDR-SOB ($p=0.005$), and AD8 ($p=0.05$) scores; in all indicating that Fast Progressors had better cognition at study entry than Slow Progressors, without significant age or sex differences. Regarding the different domains

Table 4
Mixed Linear Models Results Considering the Type of Cancer

Predictors		MoCA-MIS		MoCA-Total	
		Estimates (CI)	*p*	Estimates (CI)	*p*
Intercept (MoCA score)		10.61 (9.63 – 11.59)	< 0.001***	21.4 (18.46 – 24.34)	< 0.001***
Age (y)		–	–	–	–
Education (y)		–	–	0.26 (0.06 – 0.47)	0.01*
Time (Semesters)		–0.81 (–0.94 – –0.69)	< 0.001***	–0.86 (–0.99 – –0.72)	< 0.001***
Cancer Type	Non-Skin	1.61 (–0.04 – 3.27)	0.056	–	–
	Skin	1.09 (–1.53 – 3.70)	0.415	–	–
Time (Semesters): Cancer Type (Non-Skin)		0.24 (0.07 – 0.40)	0.005**	–	–
Time (Semesters): Cancer Type (Skin)		0.27 (0.02 – 0.52)	0.036*	–	–
Memory Medications	Anti-AChE	–	–	–0.83 (–3.49 – 1.84)	0.544
	Memantine	–	–	–4.16 (–6.74 – –1.58)	0.002**
	Both	–	–	–1.65 (–3.84 – 0.54)	0.139
Patients (*n*)		60		60	
Measurements (*n*)		273		243	
Marginal R^2 / Conditional R^2		0.42 / 0.76		0.39 / 0.90	

AChE, acetylcholinesterase; CI, 95% Confidence Interval; MoCA, Montreal Cognitive Assessment; MIS, Memory Index Score. Columns represent dependent variables (MoCA-MIS or Total MoCA), while each row represents regressors or predictors. Blank cells are variables that were tested but removed from the model due to non-significant results. The interactions between time and Cancer type (i.e., Time [Semester]: Cancer Type [Non-Skin], Time [Semester]: Cancer Type [Skin]) denotes the change in the rate of score loss due to each type of Cancer present. Time (Semester), Time (Semester): Non-Skin, and Time (Semester): Skin interaction regression coefficients can be read as score points by semester, while the remaining variables contribute globally and independently to the semester (given their dummy variable nature). $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

of the MoCA, Fast and Slow Progressors had similar scores, except for better results in Orientation ($p = 0.034$) and Delayed Recall ($p < 0.001$) in Fast Progressors. The two groups were also similar in their comorbidities (hypothyroidism, DM2, HBP, and hypercholesterolemia), except for depression prevalence ($p = 0.015$), which was higher in Fast Progressors. Pharmacological treatment also presented differences; Slow Progressors had a higher proportion of patients taking both memantine and AChE inhibitors ($p = 0.043$) and fewer patients taking neither of them ($p = 0.005$), in accordance with a more advanced cognitive decline in this group. In all, Fast and Slow Progressors were alike in most variables explored but for a better cognitive status and higher proportion of depression in Fast Progressors (Table 3).

The presence of Cancer was associated with a significant difference of sex with higher prevalence of males in the Cancer groups, both in Fast ($p = 0.049$) and Slow Progressors ($p = 0.029$; Table 3, and also evidenced in Table 1). In addition, in Fast Progressors, Cancer was associated with better Delayed Recall ($p = 0.012$) and MoCA-MIS ($p = 0.01$) scores, and better CDR-SOB average score ($p = 0.011$) compared with Non-Cancer Fast Progressors (Table 3). Finally, Slow Progressors with Cancer were older ($p = 0.002$) and had better AD8 scores ($p = 0.03$) compared with Non-Cancer Slow Progressors (Table 3).

Survival analyses

Finally, considering the advanced age of these patients and the presence of metabolic and Cancer comorbidities, we performed a survival analysis with the intention of evaluating whether there was any distortion in data attributable to early mortality. As shown in Fig. 3, there were no significant differences, neither in the analyses of Fast and Slow Progressors ($\beta = 0.2425$, HR = 1.274, 95%CI = 0.5346–3.038, $p = 0.61$), with and without Cancer ($\beta = 0.366$, HR = 1.443, 95%CI = 0.615–3.381, $p = 0.4$), nor in their subgroups (Fig. 3B). On the other hand, to rule out sex bias in mortality, we repeated this analysis using this variable without finding significant differences (All: $\beta = -0.073$, HR = 0.929, 95%CI = 0.389–2.218, $p = 0.87$; Without Cancer: $\beta = 0.033$, HR = 1.034, 95%CI = 0.211–5.056, $p = 0.96$; With Cancer: $\beta = -0.294$, HR = 0.744, 95%CI = 0.226–2.444, $p = 0.62$; see Supplementary Figure 1).

Furthermore, the high frequency of low mortality rate Cancers (non-melanoma skin Cancer and prostate Cancer, $n = 22$, 44.9%) in our cohort present additional evidence against a potential issue of sample selection on mortality (Supplementary Table 1).

DISCUSSION

In summary, our results support the existence of at least two different profiles of memory decline in a cohort of patients with early amnestic cognitive impairment. We detected one group, named Fast Progressors, with faster memory decline (around 1.6 points out of 15 of MoCA-MIS per year), and another group named Slow Progressors, with slower memory decay (around 0.22 points on MoCA-MIS per year). The two groups showed a similar behavior when measuring total MoCA scores (around 2 and 1.4 points loss in total MoCA per year, respectively) (Table 2 and Fig. 2).

In addition, Fast Progressors showed better baseline cognitive status than Slow Progressors. Besides these cognitive baseline differences there were no evident difference in age, sex, or education between these two groups. Interestingly, Fast Progressors had higher prevalence of depression, better overall functioning and were taking less anti-dementia medications than Slow Progressors (Table 3).

Interestingly, in the group of Fast Progressors we found that the presence of a history of Cancer was associated with a slower decline of their memory and global cognition, as measured by the scores in MoCA-MIS and total MoCA (Table 2 and Fig. 2). The contribution of different types of Cancer (Skin or Non-Skin) seems to contribute similarly but given the small number of patients with Skin Cancer, this was not a conclusive result.

Different trajectories of cognitive decline in patients with amnestic cognitive impairment

One explanation for the two different trajectories (Fast and Slow subgroups) described in this study might be due to their different underlying neuropathological mechanisms. The existence of different subtypes of AD has been proposed based on neuropathology and imaging studies, describing four subtypes of AD: typical, limbic predominant, minimal atrophy, and hippocampal sparing AD (the latter mostly related to atypical AD, such as posterior cortical atrophy, logopenic progressive aphasia, or frontal AD). Of these subtypes, the hippocampal-sparing group has the fastest cognitive decline while the typical AD and limbic predominant forms are the slowest ones [35]. The selection of patients in our study excluded patients with non-amnestic cognitive impairment (Fig. 1), therefore hippocampal sparing and atypical forms of AD were not included in this study and could not account for the Faster decline in the Fast Progression subgroup. Besides, our groups did not differ in cardiovascular comorbidities (HBP, DM2, and hypercholesterolemia) hindering a role of vascular neuropathology in these differences. So, it is possible that these findings are due to other subtle neuropathological characteristics like those found by Wingo et al. (2019), that correlated a faster cognitive decline with increased expression of inflammation, myelination and apoptotic proteins and decreased expression of mitochondrial and synaptic proteins [49].

An alternative interpretation of our results is that Fast and Slow Progressors groups could represent different moments in the illness history. Herein, Fast Progressors would represent an initial stage of the illness and Slow Progressors a later one, explaining why Slow Progressors had lower baseline scores and smaller slopes, in addition to their greater clinical severity (in terms of CDR, CDR-SOB, and AD8 scores) and more use of combined anti-dementia medications. Moreover, Fast Progressors had significantly more depressive symptoms at study entry than the Slow progression group (Table 3). This finding is interesting, since it has been suggested that a first depressive episode in older adults without a history of mood disorders could be an early sentinel event of cognitive decline [50], which might be explained by the important role of the hippocampus not only in memory but also in mood and stress related functions [51].

However, for this last interpretation, one would also expect that Slow Progressors were also older and lived shorter, but our groups did not show any differences in age nor mortality rates (Fig. 3). On the other hand, age has been associated in several studies with Slower cognitive decline [33, 34], which we could not replicate in this study.

Cancer effect on cognition

Patients with non-central nervous system Cancers usually report impairments of short-term and working memory, attention, executive functions and/or processing speed after chemotherapy; however, it remains unclear whether the cognitive deficits are due to the biological effects of the treatment, the Cancer itself and/or stress-related psychological factors [52]. In the cohort of non-demented individuals of Ospina-Romero et al. (2019), a new Cancer diagnosis was associated with a short-term decline, but the rate of cognitive decline recovered after diagnosis and in all

was Slower in individuals with Cancer compared to those without [32].

In this work, the presence of a history of Cancer was associated with a slower decline of memory and global cognition in the group of Fast Progressors (Table 2 and Fig. 2). This was also suggested when separating the type of Cancer in Skin and Non-Skin Cancer, although the number of patients in the groups was too small to be conclusive (Table 4 and Fig. 2D). The absence of the protective effect of Cancer in the Slow Progression group could be due to the fact that the slope is already too low to detect a change. It also suggests that the major effect of Cancer might be on the memory domain.

As mentioned above, it is known that treatments for malignancies affect cognition; however, the Cancers in this study were diagnosed a mean of 6.8 years before the diagnosis of cognitive impairment, therefore the types of treatment for cancer would not have had a relevant effect on the cognitive performance during the study.

Even though this is an observational study subject to many threats to causality, we provide results that make a spurious correlation less likely, such as an analysis between high and low mortality types of Cancer (e.g., Skin versus Non-Skin Cancer) and a sensitivity analysis to hidden bias. Even though these robustness checks do not eliminate all possible unobserved confounders, they do provide a specific bound for the magnitude of confounding. This means that any potential confounder should be sizable enough and, most likely, more evident in order to explain our findings.

Possible survival biases

The results obtained were not likely explained by early mortality of the individuals since no differences were found in survival analysis for Cancer versus Non-Cancer and Fast versus Slow Progression groups (Fig. 3), nor when the sample was divided by sex, considering that women could survive longer than men (Supplementary Figure 1).

Another argument in favor of the absence of survival bias is the cancer profile of our subjects. As stated above, we present a high proportion of low mortality Cancers (skin and prostate Cancers), and other more aggressive Cancers do not differ significantly from the general population (except for the absence of lung Cancer in our study) (Supplementary Table 1). Furthermore, the analysis of the Skin Cancer group, which is generally not lethal, also shows a slower cognitive decline (Table 4 and Fig. 2D).

However, considering that older adults are more exposed to severe neoplastic diseases and that this segment will never be evaluated in this kind of studies for early mortality, there is still room for mortality bias in the inverse relationship between the severity of the neoplastic phenomenon and amnestic cognitive impairment.

Relationships between cancer biology and amnestic cognitive impairment

Although in this work we support the idea that there is a possible causality in the temporal, biological, and statistical association of Cancer history and the rate of amnesic deterioration in Fast Progressors, it remains a complex causal inference. Both cancer and AD are polygenic disorders and have important environmental variables in their development, which makes the specificity of the results difficult.

In this study, we support the hypothesis that Cancer and AD are inversely associated, with Cancer having a protective effect on cognition. We and others have proposed that Cancer and AD may share common biological mechanisms inversely deregulated in opposite directions; Cancer is characterized by cell proliferation whereas AD is distinguished by neuronal loss [24–27]. The fact that this inverse association is observed between a neurodegenerative disease and cancers of almost all types suggests there might be some sort of communication between cancer cells and the neurodegenerative process in the brain. An immune factor might be a good candidate. We have proposed that individuals who survived cancer are left with an immune system of diminished tolerance or a beneficial proinflammatory systemic milieu that grants them protection from developing AD [53]. Accordingly, we have reported that lymphocytes of patients with AD have a higher susceptibility to oxidative death and those of patients with a history of cancer are more resistant to this treatment. Moreover, we showed that this H_2O_2-induced death of lymphocytes was dependent on p53. Interestingly, we found that lymphocytes from patients with a history of cancer that later developed AD—as the cancer group in this study—had a susceptibility to cell death similar to patients with a history of cancer without cognitive impairment, which was protected by 53 inhibition, suggesting that Cancer might leave a trace that protects from AD [54–56]. Hippocampal regions in the brain could be specifically sensitive to

this pathogenic effect due to its important plasticity and regeneration capacity [51]. In sum, the results of this study suggest that the protection given by Cancer could apply not only to decrease the chance of developing AD, but also to Slow down the progression of the disease when cognitive deterioration is already present.

To our understanding, this is the first article showing Cancer as a modifying factor in the rate of cognitive decline in amnestic cognitively impaired patients. Also, based on our novel statistical analyzes, we added a finer clinical description of the group of patients presenting this effect of Cancer, which gives rise to a more specific study of the underlying neuropathology in these subjects. Finally, understanding the neurobiology of the interaction between Cancer and AD might lead to the development of more adequate treatments for these two diseases of older adults.

Limitations

The main limitations of this study are the small number of subjects and the retrospective methodology based on clinical records and patient interviews, which could have biases in data collection or memory of the subjects' informant. Therefore, it is desirable to support the results of this study in a prospective study with a greater number of subjects.

Another limitation of this study is the high- and middle-income socioeconomic status of our subjects and thus the relatively high educational training presented in our sample, which is not very representative of the Chilean population where MoCA scales were validated. However, this pitfall gives more homogeneity and comparability to the sample for further interpretation of results.

In addition, it is not clear whether there is a linear relationship between the severity of the neoplastic phenomenon and its impact on amnestic cognitive impairment, possibly due to the poor survival of the elderly with severe Cancers. So, even though we tried to rule out survival biases, it cannot conclusively be excluded as the explanation of an inverse association between AD and Cancer.

Finally, a last limitation of the study is the lack of biomarkers for the diagnosis of amnestic cognitive impairment as a complementary measure of the speed of cognitive decline. Although an attempt was made to relate family history of AD and family history of Cancer with Cancer, no significant association was obtained.

CONCLUSION

In summary, we identified two different types of memory decline, a Fast and a Slow one, in an amnestic cognitively impaired cohort of patients, that could be derived from different underlying neuropathological mechanisms or different clinical stages. Interestingly, in the subgroup of Fast Progressors the presence of a history of Cancer was associated with a slowdown in the rate of progression of memory decline, supporting the hypothesis of an inverse biological association between AD and Cancer.

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SUPPLEMENTARY MATERIAL

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REFERENCES

[1] Crome L (1963) Mental Illness and the Ageing Brain. By J. A. Corsellis. Oxford University Press. 1962. Pp. viii+76. Price 30 s. *Br J Psychiatry* **109**, 322-323.

[2] DeSouky AL (1992) The relationship between cancer and Alzheimer's disease. *J Am Geriatr Soc* **40**, 1075.

[3] Yamada M, Sasaki H, Mimori Y, Kasagi F, Sudoh S, Ikeda J, Hosoda Y, Nakamura S, Kodama K (1999) Prevalence and risks of dementia in the Japanese population: RERF's Adult Health Study Hiroshima Subjects. *J Am Geriatr Soc* **47**, 189-195.

[4] Roe CM, Behrens MI, Xiong C, Miller JP, Morris JC (2005) Alzheimer disease and cancer. *Neurology* **64**, 895-898.

[5] Roe CM, Fitzpatrick AL, Xiong C, Sieh W, Kuller L, Miller JP, Williams MM, Kopan R, Behrens MI, Morris JC (2010) Cancer linked to Alzheimer disease but not vascular dementia. *Neurology* **74**, 106-112.

[6] Attner B, Lithman T, Noreen D, Olsson H (2010) Low cancer rates among patients with dementia in a population-based register study in Sweden. *Dement Geriatr Cogn Disord* **30**, 39-42.

[7] Realmuto S, Cinturino A, Arnao V, Mazzola MA, Cupidi C, Aridon P, Ragonese P, Savettieri G, D'Amelio M (2012) Tumor diagnosis preceding Alzheimer's disease onset: Is there a link between cancer and Alzheimer's disease? *J*

Alzheimers Dis **31**, 177-182.

[8] Driver JA, Beiser A, Au R, Kreger BE, Splansky GL, Kurth T, Kiel DP, Lu KP, Seshadri S, Wolf PA (2012) Inverse association between cancer and Alzheimer's disease: Results from the Framingham Heart Study. *BMJ* **344**, e1442.

[9] Musicco M, Adorni F, di Santo S, Prinelli F, Pettenati C, Caltagirone C, Palmer K, Russo A (2013) Inverse occurrence of cancer and Alzheimer disease: A population-based incidence study. *Neurology* **81**, 322-328.

[10] Nudelman KNH, Risacher SL, West JD, McDonald BC, Gao S, Saykin AJ (2014) Association of cancer history with Alzheimer's disease onset and structural brain changes. *Front Physiol* **5**, 423.

[11] Benito-Leon J, Romero JP, Louis ED, Bermejo-Pareja F (2014) Faster cognitive decline in elders without dementia and decreased risk of cancer mortality: NEDICES Study. *Neurology* **82**, 1441-1448.

[12] Frain L, Swanson D, Cho K, Gagnon D, Lu KP, Betensky RA, Driver J (2017) Association of cancer and Alzheimer's disease risk in a national cohort of veterans. *Alzheimers Dement* **13**, 1364-1370.

[13] Sánchez-Valle J, Tejero H, Ibáñez K, Portero JL, Krallinger M, Al-Shahrour F, Tabarés-Seisdedos R, Baudot A, Valencia A (2017) A molecular hypothesis to explain direct and inverse co-morbidities between Alzheimer's disease, glioblastoma and lung cancer. *Sci Rep* **7**, 4474.

[14] Seddighi S, Houck AL, Rowe JB, Pharoah PDP (2019) Evidence of a causal association between cancer and Alzheimer's disease: A Mendelian randomization analysis. *Sci Rep* **9**, 13548.

[15] Gupta A, Preis SR, Beiser AS, Splansky GL, DeCarli CS, Au R, Driver JA (2019) Relationship of cancer to brain aging markers of Alzheimer's disease: The Framingham Heart Study. *Adv Geriatr Med Res* **1**, e190006.

[16] Sun M, Wang Y, Sundquist J, Sundquist K, Ji J (2020) The association between cancer and dementia: A national cohort study in Sweden. *Front Oncol* **10**, 73.

[17] Ma L-L, Yu J-T, Wang H-F, Meng X-F, Tan C-C, Wang C, Tan L (2014) Association between cancer and Alzheimer's disease: Systematic review and meta-analysis. *J Alzheimers Dis* **42**, 565-573.

[18] Zhang Q, Guo S, Zhang X, Tang S, Shao W, Han X, Wang L, Du Y (2015) Inverse relationship between cancer and Alzheimer's disease: A systemic review meta-analysis. *Neurol Sci* **36**, 1987-1994.

[19] Catalá-López F, Suárez-Pinilla M, Suárez-Pinilla P, Valderas JM, Gómez-Beneyto M, Martinez S, Balanzá-Martínez V, Climent J, Valencia A, McGrath J, Crespo-Facorro B, Sanchez-Moreno J, Vieta E, Tabarés-Seisdedos R (2014) Inverse and direct cancer comorbidity in people with central nervous system disorders: A meta-analysis of cancer incidence in 577,013 participants of 50 observational studies. *Psychother Psychosomatics* **83**, 89-105.

[20] Ospina-Romero M, Glymour MM, Hayes-Larson E, Mayeda ER, Graff RE, Brenowitz WD, Ackley SF, Witte JS, Kobayashi LC (2020) Association between Alzheimer disease and cancer with evaluation of study biases. *JAMA Network Open* **3**, e2025515.

[21] Freedman DM, Wu J, Chen H, Kuncl RW, Enewold LR, Engels EA, Freedman ND, Pfeiffer RM (2016) Associations between cancer and Alzheimer's disease in a U.S. Medicare population. *Cancer Med* **5**, 2965-2976.

[22] Hanson HA, Horn KP, Rasmussen KM, Hoffman JM, Smith KR (2016) Is cancer protective for subsequent Alzheimer's disease risk? Evidence from the Utah Population Database. *J Gerontol B Psychol Sci Soc Sci* **72**, 1032-1043.

[23] Roderburg C, Loosen SH, Kunstein A, Mohr R, Jördens MS, Luedde M, Kostev K, Luedde T (2021) Cancer patients have an increased incidence of dementia: A retrospective cohort study of 185,736 outpatients in Germany. *Cancers (Basel)* **13**, 2027.

[24] Tabarés-Seisdedos R, Rubenstein JL (2013) Inverse cancer comorbidity: A serendipitous opportunity to gain insight into CNS disorders. *Nat Rev Neurosci* **14**, 293-304.

[25] Driver JA, Zhou XZ, Lu KP (2015) Pin1 dysregulation helps to explain the inverse association between cancer and Alzheimer's disease. *Biochim Biophys Acta* **1850**, 2069-2076.

[26] Nudelman KNH, McDonald BC, Lahiri DK, Saykin AJ (2019) Biological hallmarks of cancer in Alzheimer's disease. *Mol Neurobiol* **56**, 7173-7187.

[27] Behrens M, Lendon C, Roe C (2009) A common biological mechanism in cancer and Alzheimer's disease? *Curr Alzheimer Res* **6**, 196-204.

[28] Forés-Martos J, Boullosa C, Rodrigo-Domínguez D, Sánchez-Valle J, Suay-García B, Climent J, Falcó A, Valencia A, Puig-Butillé JA, Puig S, Tabarés-Seisdedos R (2021) Transcriptomic and genetic associations between Alzheimer's disease, Parkinson's disease, and cancer. *Cancers (Basel)* **13**, 2990.

[29] Sherzai AZ, Parasram M, Haider JM, Sherzai D (2020) Alzheimer disease and cancer. *Alzheimer Dis Assoc Disord* **34**, 122-127.

[30] van der Willik KD, Schagen SB, Ikram MA (2018) Cancer and dementia: Two sides of the same coin? *Eur J Clin Invest* **48**, e13019.

[31] van der Willik KD, Schagen SB, Ikram MA (2020) Association between the tumor marker carcinoembryonic antigen and the risk of dementia. *J Alzheimers Dis* **76**, 845-851.

[32] Ospina-Romero M, Abdiwahab E, Kobayashi L, Filshtein T, Brenowitz WD, Mayeda ER, Glymour MM (2019) Rate of memory change before and after cancer diagnosis. *JAMA Network Open* **2**, e196160.

[33] Bernick C, Cummings J, Raman R, Sun X, Aisen P (2012) Age and rate of cognitive decline in Alzheimer disease: Implications for clinical trials. *Arch Neurol* **69**, 901-905.

[34] Stanley K, Whitfield T, Kuchenbaecker K, Sanders O, Stevens T, Walker Z (2019) Rate of cognitive decline in Alzheimer's disease stratified by age. *J Alzheimers Dis* **69**, 1153-1160.

[35] Ferreira D, Nordberg A, Westman E (2020) Biological subtypes of Alzheimer disease. *Neurology* **94**, 436-448.

[36] McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, Mohs RC, Morris JC, Rossor MN, Scheltens P, Carrillo MC, Thies B, Weintraub S, Phelps CH (2011) The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* **7**, 263-269.

[37] Nasreddine ZS, Phillips NA, BédirianV, Charbonneau S, Whitehead V, Collin I, Cummings JL, Chertkow H (2005) The Montreal Cognitive Assessment, MoCA: A brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* **53**, 695-699.

[38] Delgado C, Araneda A, Behrens MI (2017) Validation of the Spanish-language version of the Montreal Cognitive Assessment test in adults older than 60 years. *Neurologia (Engl Ed)* **34**, 376-385.

[39] Julayanont P, Brousseau M, Chertkow H, Phillips N, Nasreddine ZS (2014) Montreal Cognitive Assessment Memory Index Score (MoCA-MIS) as a predictor of conversion from mild cognitive impairment to Alzheimer's disease. *J Am Geriatr Soc* **62**, 679-684.

[40] First MB (1997) *Structured clinical interview for DSM-IV axis I disorders: SCID-I/P, version 2.0.* Biometrics Research Department, New York State Psychiatric Institute, New York.

[41] Powell MJD (2009) *The BOBYQA algorithm for bound constrained optimization without derivatives.* Cambridge NA Report NA2009/06, University of Cambridge.

[42] Johnson PCD (2014) Extension of Nakagawa & Schielzeth's R^2_{GLMM} to random slopes models. *Methods Ecol Evol* **5**, 944-946.

[43] Nakagawa S, Schielzeth H (2013) A general and simple method for obtaining R^2 from generalized linear mixed-effects models. *Methods Ecol Evol* **4**, 133-142.

[44] Nakagawa S, Johnson PCD, Schielzeth H (2017) The coefficient of determination R^2 and intra-class correlation coefficient from generalized linear mixed-effects models revisited and expanded. *J R Soc Interface* **14**, 20170213.

[45] Rubin DB (1974) Estimating causal effects of treatments in randomized and nonrandomized studies. *J Educ Psychol* **66**, 688-701.

[46] Frank KA, Maroulis SJ, Duong MQ, Kelcey BM (2013) What would it take to change an inference? Using Rubin's causal model to interpret the robustness of causal inferences. *Educ Eval Policy Anal* **35**, 437-460.

[47] White RS, Lipton RB, Hall CB, Steinerman JR (2013) Non-melanoma skin cancer is associated with reduced Alzheimer disease risk. *Neurology* **80**, 1966-1972.

[48] Leiter U, Eigentler T, Garbe C (2014) Epidemiology of skin cancer. In *Sunlight, Vitamin D and Skin Cancer*, Springer New York, NY, pp. 120-140.

[49] Wingo AP, Dammer EB, Breen MS, Logsdon BA, Duong DM, Troncosco JC, Thambisetty M, Beach TG, Serrano GE, Reiman EM, Caselli RJ, Lah JJ, Seyfried NT, Levey AI, Wingo TS (2019) Large-scale proteomic analysis of human brain identifies proteins associated with cognitive trajectory in advanced age. *Nat Commun* **10**, 1619.

[50] Almeida OP, Hankey GJ, Yeap BB, Golledge J, Flicker L (2017) Depression as a modifiable factor to decrease the risk of dementia. *Transl Psychiatry* **7**, e1117.

[51] Toda T, Parylak SL, Linker SB, Gage FH (2019) The role of adult hippocampal neurogenesis in brain health and disease. *Mol Psychiatry* **24**, 67-87.

[52] Lange M, Joly F, Vardy J, Ahles T, Dubois M, Tron L, Winocur G, de Ruiter MB, Castel H (2019) Cancer-related cognitive impairment: An update on state of the art, detection, and management strategies in cancer survivors. *Ann Oncol* **30**, 1925-1940.

[53] Rogers NK, Romero C, SanMartín CD, Ponce DP, Salech F, López MN, Gleisner A, Tempio F, Behrens MI (2020) Inverse relationship between Alzheimer's disease and cancer: How immune checkpoints might explain the mechanisms underlying age-related diseases. *J Alzheimers Dis* **73**, 443-454.

[54] Salech F, Ponce DP, SanMartín CD, Rogers NK, Henríquez M, Behrens MI (2018) Cancer imprints an increased PARP-1 and p53-dependent resistance to oxidative stress on lymphocytes of patients that later develop Alzheimer's disease. *Front Neurosci* **12**, 58.

[55] Behrens MI, Silva M, Salech F, Ponce DP, Merino D, Sinning M, Xiong C, Roe CM, Quest AFG (2012) Inverse susceptibility to oxidative death of lymphocytes obtained from Alzheimer's patients and skin cancer survivors: Increased apoptosis in Alzheimer's and reduced necrosis in cancer. *J Gerontol A Biol Sci Med Sci* **67**, 1036-1040.

[56] Ponce D, Salech F, Martin C, Silva M, Xiong C, Roe C, Henriquez M, Quest F, Behrens I (2014) Increased susceptibility to oxidative death of lymphocytes from Alzheimer patients correlates with dementia severity. *Curr Alzheimer Res* **11**, 892-898.