Faster cognitive decline in elders without dementia and decreased risk of cancer mortality

NEDICES Study

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ABSTRACT

Objective: To assess whether faster cognitive decline in elders without dementia is associated with decreased risk of cancer mortality.

Methods: In this population-based, prospective study of 2,627 people without dementia aged 65 years and older (Neurological Disorders in Central Spain), a 37-item version of the Mini-Mental State Examination (37-MMSE) was administered at 2 visits (baseline and follow-up, approximately 3 years later). We divided change in 37-MMSE into tertiles (lower tertile ≥2 point improvement in score, higher tertile ≥2 point decline in score). Community-dwelling elders were followed for a median of 12.9 years, after which the death certificates of those who died were examined.

Results: A total of 1,003 (38.2%) died, including 339 (33.8%) deaths among participants who were in the higher tertile of 37-MMSE change and 664 (66.2%) deaths among those in the remaining tertiles. Cancer was reported significantly less often in those in the higher tertile of MMSE change (20.6%) than in those in the remaining tertiles (28.6%): in an unadjusted Cox model, hazard ratio for cancer mortality in participants within the higher tertile = 0.75 ($p = 0.04$) compared with the participants within the remaining tertiles. In a Cox model that adjusted for a variety of demographic factors and comorbidities, hazard ratio for cancer mortality in participants within the higher tertile = 0.70 ($p = 0.01$).

Conclusion: In this population-based, prospective study of community-dwelling elders without dementia, faster cognitive decline was associated with a decreased risk of cancer mortality. Further studies are required to elucidate this inverse association in elders without dementia. ***Neurology*®** **2014;82:1441–1448**

GLOSSARY

AD = Alzheimer disease; **CI** = confidence interval; ***DSM-IV*** = *Diagnostic and Statistical Manual of Mental Disorders,* 4th edition; **HR** = hazard ratio; ***ICD-9*** = *International Classification of Diseases,* ninth revision; **MMSE** = Mini-Mental State Examination; **37-MMSE** = 37-item Mini-Mental State Examination; **NEDICES** = Neurological Disorders in Central Spain.

A series of prospective studies has shown that Alzheimer disease (AD) is associated with a reduced risk of cancer.[1–3] However, the mechanisms underlying this association remain unknown. The cholinergic system deficit that occurs in patients with AD may explain, at least in part, the decreased risk of cancer.[4] Because acetylcholine stimulates cell proliferation, the association suggests that the degeneration of acetylcholine-secreting cells may have a protective role on cancer onset, as this neurotransmitter would be less available to stimulate cell proliferation.[5] Second, in many observational studies and animal models, inflammation is associated with AD and vascular disease,[6,7] and subsequent studies have documented that inflammation driven by tumor-specific Th1 may prevent some types of cancer.[8] Furthermore, a cytotoxic action has been proposed for β-amyloid (i.e., to eradicate cancer cells in an analogous manner to that performed by host defense peptides).[9,10]

Whereas cancer has been reported to occur less often in patients with AD, a study to determine whether there is an association between cancer and faster cognitive decline in elders without dementia has not been conducted. It has been suggested that a major problem with epidemiologic studies that have reported an inverse association between AD and cancer is the very likely underdiagnosis of

Supplemental data at Neurology.org

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cancer once dementia has been diagnosed.[11] We therefore tested the hypothesis that older persons without dementia who experienced faster decline in cognition would have decreased risk of cancer mortality. To address this question, we utilized data from the Neurological Disorders in Central Spain (NEDICES) Study, in which participants were prospectively evaluated at 2 time points separated by 3 years and followed for a median of 12.9 years, after which the death certificates of those who died were examined.

METHODS

Study population. Data for these analyses were derived from the NEDICES Study, a longitudinal, population-based survey of the prevalence, incidence, mortality, and determinants of major age-associated conditions of the elderly, including Parkinson disease, essential tremor, stroke, and dementia.[12–20] Detailed accounts of the study population and sampling methods have been published.[21–23]

The survey area consisted of 3 communities: (1) Las Margaritas (approximately 14,800 inhabitants), a working-class neighborhood in Getafe (Greater Madrid); (2) Lista (approximately 150,000 inhabitants), a professional-class neighborhood in Salamanca district (Central Madrid), and (3) Arévalo (approximately 9,000 inhabitants), the agricultural zone of Arévalo County (125 km northwest of Madrid). Up-to-date lists of residents were generated from population registers. In each community, survey eligibility was restricted to residents aged 65 years or older who were present there on December 31, 1993, or during 6 or more months of 1993. Eligible persons who had moved away from the survey area were not traced. In Margaritas and Arévalo, every eligible subject was to be screened. However, because of the large number of elderly residents in Lista, proportionate stratified random sampling was used to select subjects for screening.

Study evaluation. Briefly, at the time of their baseline assessment (1994–1995), 5,278 elderly subjects were interviewed using a 500-item screening questionnaire that assessed demographic factors and medical conditions. During the face-to-face interview, data were collected on demographics, current medications, and medical conditions. Subjects were asked to bring all medications taken in the past 1 week to the clinic where the interviewer recorded the name and the dose of each one. We assessed depressive symptoms by self-report, using a single screening question ("Do you suffer from depression?"). The same approach has similarly been utilized in previous population studies of depression.[24,25] We also assessed the use of antidepressant medications, a marker that may be less prone to biases than a simple screening question.[26]

A short form of the questionnaire was mailed to subjects who declined or were unavailable for face-to-face interview, or telephone screening. This form assessed demographic characteristics, several neurologic disorders (essential tremor, stroke, dementia, and parkinsonism), current medications, and the name of their family doctor.

As described,[21–23] a 37-item Mini-Mental State Examination (37-MMSE) was administered at both the baseline assessment (1994–1995) and the follow-up assessment (1997–1998).[27–32] This was a Spanish adaptation of the standard MMSE.[27–32] It included all of the standard MMSE items and 3 additional items: (1) an attention task, i.e., "say 1, 3, 5, 7, 9 backward," (2) a visual order, i.e., a man raising his arms, and (3) a simple construction task, i.e., copying 2 overlapping circles.[27–32]

Ten percent of our sample was illiterate, although only a small proportion was completely illiterate and many could read or write a simple phrase. If the participant was completely illiterate, then the one 37-MMSE reading item and the one 37-MMSE writing item were assigned the value 0. The diagnosis of dementia was assigned using *DSM-IV* criteria[33] and required evidence of cognitive impairment (based on a neuropsychological test battery and a clinical mental status examination) as well as impairment in social or occupational function.

During the second (i.e., follow-up) evaluation (1997–1998), the same methods were used. Follow-up data on death were collected until May 1, 2007. The date of death was obtained from the National Population Register of Spain (Instituto Nacional de Estadística). In Spain, a death certificate is completed by a doctor for all deceased individuals at the time of death. The certificate is then sent to the local authority in the municipality where the person had been living, and the information is collected in the National Register. The cause of death (using the *ICD-9* for deaths occurring prior to 1999 [http://www.cdc.gov/nchs/icd/icd9.htm] and the *ICD-10* [http://www.cdc.gov/nchs/icd/icd10.htm] for deaths occurring thereafter) was divided into 6 main categories: dementia, cerebrovascular disorders, cardiovascular disorders (pulmonary embolism, congestive heart failure, myocardial infarction, heart or aortic rupture, and asystole), respiratory diseases, cancer, and other causes (infections, trauma, and genitourinary or gastrointestinal disorders). In accordance with the recommendations of the World Health Organization, the classification of causes of death is based on the basic cause of death (http://www.who.int/topics/mortality/en/). This is defined as the illness or injury that started the chain of pathologic events which directly led to death (http://www.who.int/topics/mortality/en/).

Final selection of participants. Of the 5,278 participants evaluated at baseline, we excluded 467 participants with dementia, including 306 with dementia diagnosed at baseline evaluation (1994–1995) (i.e., prevalent cases), and 161 who developed dementia by the follow-up evaluation (1997–1998) (i.e., incident cases). We further excluded 2,184 participants who were evaluated at baseline because they declined a follow-up assessment or had incomplete follow-up assessments, had died or were unreachable (n = 1,278), or had incomplete 37-MMSE examinations (n = 906) (figure e-1 on the *Neurology*® Web site at Neurology.org).

The final sample of 2,627 was similar to the base sample of 5,278 participants in sex (1,509 [57.4%] vs 3,040 [57.6%] women, $\chi^2 = 0.02$, $p = 0.89$). However, they were more educated (268 [10.2%] vs 711 [13.6%] were illiterate, $\chi^2 = 18.71$, $p < 0.001$) and, on average, 1.6 years younger (72.7 ± 5.9 vs 74.3 ± 7.0 years, $t = 11.0$, $p < 0.001$).

Standard protocol approvals, registrations, and patient consents. All procedures were approved by the ethical standards committees on human experimentation at the University Hospitals 12 de Octubre (Madrid) and La Princesa (Madrid). Written (signed) informed consent was obtained from all enrollees.

Statistical analyses. Data analyses were performed in SPSS version 20.0 (SPSS, Inc., Chicago, IL). None of the continuous variables (i.e., age, 37-MMSE score, and change in 37-MMSE score) was normally distributed (Kolmogorov-Smirnov, $p < 0.001$), even after log-transformation. Therefore, baseline characteristic scores were compared using Mann-Whitney test; χ^2 tests were applied to determine associations between categorical variables.

Change in 37-MMSE was divided into tertiles (lower tertile ≥2-point improvement in score, higher tertile ≥2-point decline in score). For the current analyses, we dichotomized this variable into higher vs middle and lower tertiles. We determined the proportion of cases in which a diagnosis of cancer

was listed on the death certificate in the higher tertile (i.e., those with faster cognitive decline) vs the proportion in the remaining tertiles.

We used Cox proportional-hazards models to estimate hazard ratios (HRs) for cancer-specific mortality; this also generated 95% confidence intervals (CIs). The time variable was the years from the date of the first evaluation (1994–1995) to the date of death in subjects who had died. The dependent (outcome) variable was presence of a cancer condition on the death certificate, with the remaining causes of death serving as the reference group. We began with an unadjusted model. Then, in adjusted models, we first considered baseline variables that in univariate analyses were associated at the $p \leq 0.30$ level with both the exposure (higher tertile of 37-MMSE change vs the remaining tertiles [the reference category]) and the outcome (cancer-related mortality) (model 1 [more restrictive criteria for confounding]), and then considered baseline variables that in univariate analyses were associated at the $p \leq 0.30$ level with either the exposure or the outcome (model 2 [less restrictive criteria for confounding]). A value of $p \leq 0.30$ rather than $p < 0.05$ was conservatively chosen to allow us to more carefully include any possible source of confounding. Variables assessed at baseline that we considered included age in years, sex, educational level (illiterate, can read and write, primary studies, secondary and higher studies), geographical area (Las Margaritas, Lista, and Arévalo), living area during childhood/adolescence (rural vs urban area), self-rated

Table 1 Baseline (1994–1995) demographic and clinical characteristics of deceased participants within the higher tertile of 37-MMSE change vs those within the remaining tertiles (n = 1,003)

	Higher tertile of 37-MMSE change (n = 339)	Middle and lower tertiles of 37-MMSE change (n = 664)	*p* Value
Age, y	76.3 ± 6.9	74.9 ± 6.2	0.002[a]
Sex, female	158 (46.6)	302 (45.5)	0.735[b]
Education			0.10[b]
Illiterate	44 (13.0)	62 (9.3)	
Can read and write	151 (44.5)	274 (41.3)	
Primary studies	93 (27.4)	224 (33.7)	
≥Secondary studies	51 (15.0)	104 (15.7)	
Geographical area			0.131[b]
Las Margaritas	84 (24.8)	165 (24.8)	
Lista	108 (31.9)	250 (37.7)	
Arévalo	147 (43.4)	249 (37.5)	
Living area during childhood/adolescence[c]			0.023[b]
Rural	91 (27.1)	225 (34.2)	
Urban	245 (72.9)	433 (65.8)	
Self-rated health[c]			0.371[b]
Good/very good	191 (57.0)	374 (56.6)	
So-so	96 (28.7)	210 (31.8)	
Bad/very bad	48 (14.3)	77 (11.6)	
Ever smoker (ex-smoker/current smoker)	153 (45.1)	320 (48.2)	0.358[b]
Ever drinker (ex-drinker/current drinker)[c]	197 (58.3)	405 (61.2)	0.376[b]
Cancer[c]	18 (5.6)	44 (6.8)	0.465[b]
Arterial hypertension	142 (41.9)	299 (45.0)	0.343[b]
Diabetes mellitus	53 (15.6)	140 (21.1)	0.038[b]
Heart diseases[c]	55 (16.3)	80 (12.0)	0.064[b]
Chronic obstructive pulmonary disease[c]	59 (17.5)	144 (22.0)	0.10[b]
Osteoporosis[c]	59 (17.9)	91 (13.9)	0.10[b]
Stroke	18 (5.3)	28 (4.2)	0.434[b]
Depressive symptoms or antidepressant use[c]	86 (25.6)	161 (24.4)	0.678[b]
37-MMSE total score	30.1 ± 4.9	28.9 ± 5.3	<0.001[a]

Abbreviation: 37-MMSE = 37-item Mini-Mental State Examination.
Mean ± SD and frequency (%) are reported.
[a] Mann-Whitney *U* test.
[b] χ^2 test.
[c] Data on some participants were missing.

health (good/very good, so-so, and bad/very bad), smoker (ever vs never), drinker (ever vs never), cancer, arterial hypertension, diabetes mellitus, heart diseases, osteoporosis, chronic obstructive pulmonary disease, stroke, depressive symptoms ("do you suffer from depression?") or antidepressant use, and the 37-MMSE score. Finally, for completeness, we adjusted for all the potential confounders, independent of their statistical significance (i.e., even if they were not associated with either the exposure or the outcome) (model 3).

Kaplan-Meier survival curves for subjects within the higher tertile of change vs those within the middle and lower tertiles were assessed; the log-rank test was used to compare the differences between the 3 curves.

Table 2 Baseline (1994–1995) demographic and clinical characteristics of deceased participants who died of cancer vs other causes (n = 1,003)

	Cancer (n = 260)	Other causes (n = 743)	*p* Value
Age, y	73.6 ± 5.9	75.9 ± 6.5	<0.001[a]
Sex, female	90 (34.6)	370 (49.8)	<0.001[b]
Education[c]			0.139[b]
Illiterate	25 (9.6)	81 (10.9)	
Can read and write	97 (37.3)	328 (44.1)	
Primary studies	90 (34.6)	227 (30.6)	
≥Secondary studies	48 (18.5)	107 (14.4)	
Geographical area			0.768[b]
Las Margaritas	66 (25.4)	183 (24.6)	
Lista	88 (33.8)	270 (36.3)	
Arévalo	106 (40.8)	290 (39.0)	
Living area during childhood/adolescence[c]			0.464[b]
Rural	77 (30.0)	239 (32.4)	
Urban	180 (70.0)	498 (67.6)	
Self-rated health[c]			<0.001[b]
Good/very good	169 (65.5)	396 (53.7)	
So-so	73 (28.3)	233 (31.6)	
Bad/very bad	16 (6.2)	109 (14.8)	
Ever smoker (ex-smoker/current smoker)	152 (58.5)	321 (43.2)	<0.001[b]
Ever drinker (ex-drinker/current drinker)[c]	175 (67.3)	427 (57.7)	0.006[b]
Cancer[c]	23 (8.9)	39 (5.5)	0.052[b]
Arterial hypertension	104 (40.0)	337 (45.4)	0.134[b]
Diabetes mellitus	43 (16.5)	150 (20.2)	0.199[b]
Heart diseases[c]	33 (12.7)	102 (13.7)	0.668[b]
Chronic obstructive pulmonary disease[c]	46 (17.8)	157 (21.4)	0.213[b]
Osteoporosis[c]	29 (11.3)	121 (16.6)	0.041[b]
Stroke	2 (0.8)	44 (5.9)	0.001[b]
Depressive symptoms or antidepressant use[c]	59 (22.8)	188 (25.5)	0.382[b]
37-MMSE total score	30.4 ± 4.7	28.9 ± 5.3	<0.001[a]

Abbreviation: 37-MMSE = 37-item Mini-Mental State Examination.
Mean ± SD and frequency (%) are reported.
[a] Mann-Whitney *U* test.
[b] Fisher exact test or χ^2 test.
[c] Data on some participants were missing.

RESULTS The 2,627 participants had a mean duration of follow-up of 11.2 years (median 12.9 years, range 2.7–14.1 years). One thousand three (38.2%) of 2,627 participants died over a median follow-up of 8.7 years (range 2.7–13.2 years), including 339 (33.8%) deaths among participants who were in the higher tertile of 37-MMSE change and 664 (66.2%) deaths among those in the middle and lower tertiles. There were significant differences in baseline age, diabetes mellitus, and the MMSE total score when participants within the higher tertile of 37-MMSE change and within the remaining tertiles were compared (table 1). In addition, the percentage of those living in urban areas during childhood/adolescence was significantly higher than in the remaining tertiles.

Baseline characteristics of the participants who died of cancer vs those who died of other causes are shown in table 2. At baseline, those who died of cancer were younger, scored higher in the 37-MMSE, and were more likely to be male and to have ever smoked and ever drunk, and to have rated their health as good/very good. In addition, they were less likely to have osteoporosis and stroke.

Cause of death noted on the death certificates differed significantly by tertiles of 37-MMSE change (table 3). Cancer was reported significantly less often in those in the higher tertile of MMSE change than in those in the remaining tertiles (table 3). However, as expected, dementia was reported significantly more often in those in the higher tertile of MMSE change than in those in the remaining tertiles (table 3). In addition, cardiovascular diseases were reported significantly more often in those in the higher tertile of MMSE change than in those in the remaining tertiles (table 3). Types of cancers listed on the death certificates did not differ significantly by tertiles of 37-MMSE change (table 4).

In an unadjusted Cox model, risk of cancer-specific mortality was decreased in participants within the higher tertile of 37-MMSE change vs those within the remaining tertiles (reference group) (table 5). In a Cox model that adjusted for baseline age, educational level, diabetes mellitus, chronic obstructive pulmonary disease, osteoporosis, and the 37-MMSE score (i.e., variables that were associated with both 37-MMSE change tertiles and cancer-specific mortality), the risk of mortality remained decreased in participants within the higher tertile of 37-MMSE change (model 1 in table 5). The results did not change in a Cox model that adjusted for variables that were associated with either 37-MMSE change tertile or cancer-specific mortality (i.e., baseline age, sex, educational level, geographical area, living area during childhood/adolescence, self-rated health, ever smoker [ex-smoker/current smoker], ever drinker

Table 3 Primary cause of death by tertiles of 37-MMSE change

	Higher tertile of 37-MMSE change	Middle and lower tertiles of 37-MMSE change	*p* Value[a]
Dementia	24 (7.1)	24 (3.6)	0.01
Cerebrovascular disorders	28 (8.3)	51 (7.7)	0.75
Cardiovascular diseases	113 (33.3)	174 (26.2)	0.02
Respiratory diseases	44 (13.0)	108 (16.3)	0.17
Cancer	70 (20.6)	190 (28.6)	0.01
Other causes	60 (17.7)	117 (17.6)	0.97
Total	339 (100)	664 (100)	—

Abbreviation: 37-MMSE = 37-item Mini-Mental State Examination.
Data are n (%).
[a] χ^2 test.

[ex-drinker/current drinker], cancer, arterial hypertension, diabetes mellitus, heart diseases, chronic obstructive pulmonary disease, osteoporosis, stroke, and the 37-MMSE total score) (model 2 in table 5). Furthermore, in a model that adjusted for baseline age, sex, educational level, living area during childhood/adolescence, self-rated health, geographical area (Las Margaritas, Lista, and Arévalo), ever smoker (ex-smoker/current smoker), ever drinker (ex-drinker/current drinker), cancer, arterial hypertension, diabetes mellitus, heart diseases, osteoporosis, chronic obstructive pulmonary disease, stroke, depressive symptoms ("do you suffer from depression?") or antidepressant use, and the 37-MMSE score (i.e., all potential confounders independent of their statistical significance) (model 3 in table 5), the results remained unchanged.

In a final analysis, we excluded all participants (n = 21) in which a diagnosis of AD was listed on the death certificate. In these analyses, the results were similar (model 1: HR = 0.74, 95% CI = 0.56–0.99, $p = 0.04$; model 2: HR = 0.74, 95% CI = 0.55–0.99, $p = 0.04$; and model 3: HR = 0.73, 95% CI = 0.55–0.98, $p = 0.04$).

The Kaplan-Meier curve for overall survival (figure e-2) showed that those in the higher tertile of 37-MMSE were not at increased risk of death vs those in the middle or lower tertiles (log-rank $p = 0.64$).

DISCUSSION The results of the current study suggest that elderly people without dementia with faster cognitive decline are at reduced risk of mortality from malignant neoplasm. Relative to those in the middle and lower tertiles, the HR of neoplasms as underlying cause of death was 30% lower in subjects who were within the higher tertile of 37-MMSE change (i.e., faster cognitive decline). We acknowledge that some participants with faster cognitive decline would finally developed AD. However, after excluding those who died with AD, the results were similar.

The mechanisms underlying this association remain unknown. This inverse association has also been reported in several neurodegenerative processes, including AD, Parkinson disease, and Huntington disease.[1–3,34,35] As yet undiscovered mechanisms may either promote a neurodegenerative process (uncontrolled cellular destruction) or annul other conditions, namely, cancer (uncontrolled cellular proliferation). Both cancer and neurodegenerative disorders are characterized by a disarrangement of cell-regulation mechanisms, with increased cell survival and proliferation in the former and with increased cell death in the latter process.

Cognitively healthy elderly people who are experiencing subtle cognitive decline within the normal range may be undergoing a clinically silent pathologic cascade of brain changes, during this phase, with β-amyloid deposition as the primary event in this cascade.[36,37] Neural cells may become vulnerable to cytotoxicity by amyloid-forming peptides, such as β-amyloid,[9] which shares the same mechanism of toxicity with host defense peptides, components of innate immune response, whose mission is to eradicate a broad range of microbes and cancer cells.[9] It appears that this activity is mediated by the ability of these peptides to permeabilize cell membranes via the formation of amyloid-associated structures.[9,10] Augmented cell death due to oxidative stress caused by cytotoxic amyloid-forming peptides and host

Table 4 Types of cancers listed on the death certificate by tertiles of 37-MMSE change

	Higher tertile of 37-MMSE change	Middle and lower tertiles of 37-MMSE change	*p* Value[a]
Malignant neoplasm of digestive organs and peritoneum	22 (31.4)	67 (35.3)	0.56
Malignant neoplasm of respiratory and intrathoracic organs	14 (20.0)	28 (14.7)	0.31
Malignant neoplasm of lymphatic and hematopoietic tissue	7 (10.0)	26 (13.7)	0.43
Malignant neoplasm of genitourinary organs	16 (22.9)	36 (18.9)	0.48
Other types of cancers	11 (15.7)	33 (17.4)	0.75
Total	70 (100)	190 (100)	—

Abbreviation: 37-MMSE = 37-item Mini-Mental State Examination.
Data are n (%).
[a] χ^2 test.

Table 5 HRs of cancer-specific mortality in participants who were within the higher 37-MMSE change tertile vs those within the middle and lower tertiles (reference group)

	Unadjusted			Model 1[a]			Model 2[b]			Model 3[c]		
	HR	95% CI	*p* Value	HR	95% CI	*p* Value	HR	95% CI	*p* Value	HR	95% CI	*p* Value
Higher tertile (faster cognitive decline) (n = 339)	0.75	0.57–0.99	0.04	0.69	0.52–0.92	0.01	0.70	0.52–0.93	0.01	0.70	0.52–0.93	0.02
Middle and lower tertiles (n = 664) (reference category)	1.00	—		1.00	—		1.00	—				

Abbreviations: CI = confidence interval; HR = hazard ratio; 37-MMSE = 37-item Mini-Mental State Examination.

[a] Model 1: Adjusted for baseline age, educational level, diabetes mellitus, chronic obstructive pulmonary disease, osteoporosis, and the 37-MMSE total score (variables associated with 37-MMSE change tertiles and cancer-specific mortality). Regarding overall model fit, for model 1, $\chi^2 = 24.30$, $p < 0.001$.

[b] Model 2: Adjusted for baseline age, sex, educational level, geographical area, living area during childhood/adolescence, self-rated health, ever smoker (ex-smoker/current smoker), ever drinker (ex-drinker/current drinker), cancer, arterial hypertension, diabetes mellitus, heart diseases, chronic obstructive pulmonary disease, osteoporosis, stroke, and the 37-MMSE total score (variables associated with either 37-MMSE change tertiles or cancer-specific mortality). Regarding overall model fit, for model 2, $\chi^2 = 56.17$, $p < 0.001$.

[c] Model 3: Adjusted for baseline age, sex, educational level, living area during childhood/adolescence, self-rated health, geographical area (Las Margaritas, Lista, and Arévalo), ever smoker (ex-smoker/current smoker), ever drinker (ex-drinker/current drinker), cancer, arterial hypertension, diabetes mellitus, heart diseases, osteoporosis, chronic obstructive pulmonary disease, stroke, depressive symptoms ("do you suffer from depression?") or antidepressant use, and the 37-MMSE score. Regarding overall model fit, for model 3, $\chi^2 = 56.01$, $p < 0.001$.

defense peptides is in agreement with the apparent protective effect of AD and probably age-related cognitive decline, from cancer.[9,10] Furthermore, studies in subjects without dementia have suggested that low-grade peripheral systemic inflammation is associated with increased cognitive decline[38] and reduced hippocampal volume.[39] There is evidence that inflammation driven by tumor-specific Th1 may prevent some types of cancer.[8]

This study had several limitations. First, we did not collect data on comorbidity at death or data on who signed the death certificate (general physician vs neurologist vs oncologist or geriatrician). It is logical to think that the level of expertise of the physician who signed the death certificate may predict the level of accuracy of that certificate. Second, we based the diagnoses of cancer using death certificates. Nevertheless, the accuracy of cancer death certification in Spain has been shown to be high.[40] Third, while the base sample comprised 5,278 participants, because of the many exclusions, the final sample comprised 2,627, and the final sample, although population-based, in some respects resembled a convenience sample. Fourth, competing mortality is an issue to consider—healthy elders who do not die of cancer are at risk of developing neurodegenerative disorders including dementia. Finally, we included participants with cancer at baseline; however, we expect that this would have made it more difficult to detect the observed inverse association because cancer-related or cancer-treatment–related issues might have resulted in more cognitive rather than fewer cognitive issues.

This study also had several strengths. First, the study was population-based, allowing us to assess a group of people without dementia who were unselected for treatment considerations. Second, the assessments were conducted prospectively in a standardized manner. Finally, we were able to adjust for the potential confounding effects of a number of important factors.

Using a prospective, population-based design, we demonstrated that faster cognitive decline in community-dwelling elders without dementia was associated with decreased risk of cancer-specific mortality. This study provides evidence of an inverse association between cancer and cognitive decline. Further studies are required to elucidate this inverse association in community-dwelling elders without dementia.

AUTHOR CONTRIBUTIONS

Dr. Benito-León: conception, organization, and execution of the research project, statistical analysis design, and writing of the manuscript first draft and review and critique of the manuscript. Dr. Romero and Dr. Louis: conception and organization of the research project, and review and critique of the manuscript. Dr. Bermejo-Pareja: conception, organization, and execution of the research project, and review and critique of the manuscript.

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DISCLOSURE

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