UNIVERSIDAD COMPLUTENSE DE MADRID
FACULTAD DE MEDICINA
DEPARTAMENTO DE PSIQUIATRÍA

TESIS DOCTORAL

Causas de mortalidad en la cohorte Nedices.

Riesgo inverso entre demencia y cáncer

MEMORIA PARA OPTAR AL GRADO DE DOCTOR
PRESENTADA POR

Juan Pablo Romero Muñoz

Directores

Félix Bermejo Pareja
Julián Benito León

Madrid, 2014

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Dr. Julián Benito León

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A mi familia y a mis amigos.

Agradecimientos

Soy un hombre afortunado. He logrado mucho de lo que siempre soñé. Esta tesis es uno más de esos sueños. Pero no he actuado solo, toda mi energía viene del amor que me ha sido dado con gratuidad absoluta. Todo se lo debo a los que han dejado su huella en mi vida. Gracias.

A mis padres Rolando y Paulina que supieron siempre ir más allá de las expectativas. Me dieron el ejemplo de hacer mucho más de lo que se espera de mí y hacerlo con alegría. Tuvieron la bondad de criarme rodeado de amor, invertir en mi educación y de darme una vida en la que mis sueños no conocieron límites.

A mis hermanos Andres, Paulina y Carla que fueron mis primeros maestros en generosidad y en amor. Son la evidencia de que la distancia y el tiempo no pueden jamás con el amor verdadero.

A mis abuelos Ligia y Pepe cuyo cariño endulzó tantos veranos en la infancia y cuyos cuentos despertaron mi imaginación y a mis abuelos José y Olga a quienes amo aun sin haberles conocido.

A mis profesores de la Universidad Central del Ecuador, porque hicieron lo imposible para enseñarme a ser un buen médico con lo poco o mucho que tenían a su alcance y porque son ellos con sus palabras de aliento los que me enseñaron que mi propio trabajo y esfuerzo me llevarán a donde deba llegar.

A mis compañeros y maestros del Hospital Universitario 12 de Octubre porque de ellos aprendo cada día. Con ellos crecí como quien crece en una familia, mi cariño hacia ellos es indeleble como lo es su marca en mi forma de hacer mi profesión.

Al personal de enfermería y secretaría del hospital y la fundación de investigación 12 de Octubre porque sin su ayuda mi día a día sería un caos, gracias sobre todo por su paciencia.

A mis pacientes, porque son ellos el libro en el que más aprendo, y son sus sonrisas y su gratitud el mejor pago a mi trabajo. Especialmente a aquellos

pacientes más humildes y desfavorecidos del Ecuador porque algunas de sus caras de dolor o de alegría las llevo grabadas para siempre. Ellos me ayudaron siempre más de lo que imaginaron.

A mis amigos y a mis compañeros, sin los momentos de felicidad que compartimos no me imagino la vida. En especial a Frank, Edu, Jaime, Laura y Esther porque que cada uno en su momento han sido mi apoyo y refugio.

Finalmente agradezco enormemente a mis directores de tesis Félix Bermejo Pareja, ejemplo y modelo de un investigador consagrado y a Julián Benito León, un gran científico que ha sido un apoyo incondicional en los momentos más inciertos de mi profesión. Sin la ayuda, la generosidad y la guía de estos doctores, esta tesis seguiría siendo solo un proyecto. Son para mí un ejemplo a seguir.

INDICE GENERAL

ACRONIMOS

ACL: Alteración Cognitiva Leve.

ACVA: Accidente Cerebro Vascular Agudo.

AD: Alzheimer´s Disease.

AIVD: Actividades Instrumentales de la Vida Diaria.

CDR: Clinical Dementia Rating.

EA: Enfermedad de Alzheimer.

EC: Enfermedades Crónicas.

DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders, Third Edition III. Revised.

DSM-IV : Diagnostic and Statistical Manual of Mental Disorders, fourth Edition.

ENC: Enfermedades Neurológicas Crónicas.

EP: Enfermedad de Parkinson.

EPOC: enfermedad pulmonar obstructiva crónica.

FR: Factor de riesgo.

FRCV: Factores de riesgo cardiovascular.

HR: Hazard Ratio.

HTA: hipertensión arterial.

IC: Intervalo de confianza.

ICE: Clasificación Internacional de Enfermedades de la Organización Mundial de la Salud.

IM: Infarto de Miocardio.

INE: Instituto Nacional de Estadística.

MMSE: Mini Mental Status Exam.

MMSE-37: Versión 37 puntos de MMSE.

NEDICES: Neurological Disorders in Central Spain.

NINDS-ADRDA: National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer´s Disease and Related Disorders Association.

OMS: Organización Mundial de la Salud.

OR: Odds Ratio.

RR: Relative Risk.

SEN: Sociedad Española de Neurología.

SNC: Sistema nervioso central.

SNS: Sistema Nacional de Salud.

WHO: World Heath Organization

I. RESUMEN (INGLES)

INTRODUCTION

Multiple studies worldwide show a rapid increase in the prevalence of dementia that is parallel to the alarming aging population of the developed countries. It is estimated that in 2030 there will be 67.5 million demented people in the world.

The relevance of mortality attributed to nervous system diseases (including Alzheimer's disease) has increased in recent years to the point that they are the fourth leading cause of death in Spain behind cardio circulatory diseases, tumors and respiratory diseases.

Mortality data in dementia are mainly obtained from death certificates; however there are several publications that warn about low coding of this diagnosis in clinically demented patients.

It has been reported that chronic diseases such as cardio vascular and respiratory diseases are commonly recorded on death certificates of deceased old people with and without dementia. However cancer, even if it is also a disease commonly associated with aging occurs less frequently in demented people when compared with those without dementia

OBJECTIVES

This thesis seeks to know if in Spain there is an infra codification of dementia in death certificates as reported in other countries and whether the presence of dementia on death certificates is inversely correlated with coding of

cancer.

Finally we seek if this correlation persists in patients who have not yet developed symptoms of dementia but have an initial decline in MMSE-37 scores.

METHODS

This study is based in a prospective population-based study (NEDICES) involving 5,278 elderly people. All the participants were screened for symptoms of dementia with a validated instrument and confirm any suspected dementia patients with a clinical examination (i.e., a two-phase investigation method). A 37-item version of the Mini-Mental State Examination (MMSE) was administered at 2 visits (baseline and follow-up, approximately 3 years later)

We divided change in 37-MMSE, in non-demented people aged 65 years and older in this cohort (2,627), into tertiles (lower tertile ≥ 2 point improvement in score, higher tertile ≥ 2 point decline in score). Community-dwelling subjects with and without dementia were identified and followed for a median of 12.5 years, after which the death certificates of those who deceased were examined to estimate the proportion of reporting of dementia and if the cancer-specific mortality is associated with the cognitive decline in non-demented subjects or AD and other types of dementia.

RESULTS

A total of 1,976 (47.1%) died, including 277 who had possible or probable AD and 126 with non-AD dementia.

Dementia was rarely reported as the primary cause of death, even in known cases of dementia (20.8%). Indeed it was reported in only 13.3% of those with mild dementia and 24.3% of those with moderate or severe dementia; in 24.9% of those with possible or probable Alzheimer's disease; and in 11.9% of those with non-Alzheimer dementia. In a stepwise multiple logistic regression analysis with the dependent variable being presence or absence of dementia on the death certificate, the significant associated independent variables were age at death, severity of dementia, and etiology of dementia

Cancer was reported significantly less often in those with possible or probable AD (5.8%) or non-AD dementia (6.3%) than in those without dementia (26.5%). In an unadjusted Cox model, relative risk (RR) of cancer-specific mortality in participants with AD = 0.45 (p = 0.002) and RR in participants with non-AD dementia = 0.62 (p = 0.179) when compared to the non-demented group. In a Cox model that adjusted for a variety of demographic factors and co-morbidities, RRs of cancer-specific mortality in participants with AD = 0.50 (p = 0.028) and 0.97 (p = 0.942) in non-AD dementia.

Finally cancer was also reported significantly less often in those non demented subjects in the higher tertile of MMSE change (20.6%) than in those in the remaining tertiles (28.6%): in an unadjusted Cox model, relative risk (RR) of cancer mortality in participants within the higher tertile= 0.75 (p = 0.04) when compared to the participants within the remaining tertiles. In a Cox model that adjusted for a variety of demographic factors and co-morbidities, RRs of cancer-specific mortality in participants within the higher tertile was 0.70 (p = 0.02)

CONCLUSIONS

Dementia is infra coded on death certificates, similar to worldwide reports, probably due to a number of circumstances among which are the insufficient training of medical staff and the miss conception of dementia as a non- fatal disease. This infra coding should increase the awareness about the reliability of dementia mortality data in Spain and worldwide.

The diagnosis of dementia is inversely related with coding of cancer in death certificates in NEDICES cohort which is consistent with previous publications that establish the same correlation in other countries. The deterioration in scores on cognitive tests (MMSE-37), although not reaching criteria for dementia, also correlates with a lower incidence of cancer according to the coding of the death certificate, which suggests that there is an interaction between oncogenic and neurodegenerative pathways even in preclinical stages. This interaction has not been successfully described yet and may be on a molecular level.

II. INTRODUCCION

En una época donde la sociedad debe responder de manera adecuada a una demanda cada vez mayor de recursos sanitarios, inevitablemente deben reexaminarse continuamente las políticas de salud local y global. Esta planificación debe basarse en las necesidades del sistema sanitario y la carga comparativa que representan las diferentes enfermedades en el grueso de la población. La manera en la que se afronta esta necesidad de información viene de fuentes que muchas veces son contradictorias. La fiabilidad de los datos recogidos es de crucial importancia.

El envejecimiento de la población constituye un elemento primordial a la hora de establecer objetivos y prioridades socio sanitarias, lo cual se ve reflejado en actividades a nivel global para estudiar una actitud conjunta que permita al mundo prepararse para afrontar la potencial discapacidad de los 115 millones de dementes que vivirán a nivel mundial en el año 2050.(The Lancet Neurology 2014)

Los estudios epidemiológicos en ancianos están adquiriendo importancia creciente por el rápido envejecimiento de la población, las características peculiares de la salud de los ancianos y la dificultad de su preciso conocimiento por los sistemas sanitarios y la discapacidad crónica de alto coste sanitario y social.

La frecuencia de la demencia está íntimamente relacionada con el envejecimiento. Un estudio de Lobo muestra que la prevalencia de demencia es del 6,4% en personas mayores de 65 años, con una diferencia notable entre

el 0,8% en el grupo de edad de 65 a 69 años, y el 28,5% en los mayores de 90 años en varios estudios europeos (Lobo et al. 2000)

Múltiples estudios a nivel mundial muestran un rápido incremento en la prevalencia de la demencia que es paralela al alarmante envejecimiento de la población de los países más desarrollados. Se estima que en 2030 habrá 67,5 millones de dementes a nivel mundial. (Gulland 2012)

En España la prevalencia atribuida a la demencia varia en diversos estudios españoles encontrándose valores que varían entre 3,5 y 17,2%.(de Pedro-Cuesta et al. 2009) En un estudio poblacional en mayores de 65 años se estima que es de 5,8%. (Bermejo-Pareja et al. 2008)

Se estima que la enfermedad de Alzheimer es responsable de un 4,9% de muertes en mayores de 65 años, riesgo que aumenta considerablemente con la edad, alcanzando un 30% en varones mayores de 85 años, y un 50% en mujeres de la misma edad. (Aevarsson, Svanborg, and Skoog 1998)

La demencia ha sido ampliamente reconocida como un factor que aumenta el riesgo de muerte en los sujetos afectados.(Todd et al. 2013) Este riesgo se incrementa proporcionalmente a la gravedad de la demencia y la edad, siendo la causa de muerte atribuible de casi un tercio de los sujetos mayores de 85 años.(Villarejo et al. 2011). Aunque se ha considerado que hay diferencias en cuanto a la prevalencia de esta enfermedad según el desarrollo socio económico de los países, estas diferencias se deben probablemente a la baja detección de casos leves o una menor sobrevida. (Ferri et al. 2005) Según

un meta análisis reciente los datos de mortalidad de los sujetos dementes probablemente sean similares tanto en países desarrollados como en vías de desarrollo.(Prince et al. 2012)

En cuanto a la mortalidad atribuida a las enfermedades del sistema nervioso (incluyendo a la enfermedad de Alzheimer), su importancia ha aumentado en los últimos años al punto de ubicarse como la cuarta causa de muerte en España por detrás de las enfermedades circulatorias, tumores y respiratorias, según informe del INE. La principal enfermedad de este grupo fue la EA que ha sido la causa atribuida a 11.907 muertes, más del doble de lo registrado en el año 2000.(INE 2014). En un estudio andaluz se notifica un incremento anual de la mortalidad de la demencia del 4,2% y 3,8% en hombres y mujeres respectivamente.(Ruiz Ramos 2012)

Esta tendencia al incremento de la mortalidad atribuida a la demencia también se ha registrado en Francia con un 11,3% más de mortalidad entre los años 2000 y 2006 (Brosselin, Duport, and Bloch 2010)

Los datos de mortalidad en la demencia se obtienen principalmente de los certificados de defunción, sin embargo hay varias publicaciones que alertan acerca de la baja codificación de este diagnóstico en los certificados de sujetos clínicamente dementes.(Morgan and Clarke 1995; M Ganguli and Rodriguez 1999; Mary Ganguli et al. 2005; Ostbye, Hill, and Steenhuis 1999; Chamandy and Wolfson 2005; Nitrini et al. 2005) Esto significa que aun cuando se menciona un aumento de la mortalidad por la enfermedad en varias partes del

mundo, estos datos podrían subestimar la realidad por el bajo registro de la demencia como causa de muerte.

En la población de ancianos, es de esperar la acumulación de la incidencia de diversas enfermedades crónicas y asociadas al envejecimiento como son: las enfermedades cardiovasculares, hipertensión arterial (HTA), Accidente Cerebro Vascular Agudo (ACVA), diabetes, cáncer, enfermedad pulmonar obstructiva crónica (EPOC), enfermedades musculo esqueléticas (artritis, artrosis), enfermedades mentales (demencia, depresión) y déficit sensoriales (alteraciones visuales, y presbiacusia).

Se ha notificado que enfermedades crónicas como las cardio vasculares y respiratorias son causas de muerte comúnmente registradas en los certificados de defunción de los ancianos con y sin demencia (Villarejo et al. 2011), sin embargo el cáncer, aun cuando también es una enfermedad comúnmente asociada con el envejecimiento se presenta con menor frecuencia en los ancianos dementes cuando se comparan con aquellos no dementes.(Villarejo et al. 2011; Musicco et al. 2013; Driver et al. 2012).

Dicha correlación inversa se ha demostrado también en el caso de otras enfermedades del SNC (Sistema Nervioso Central) como la enfermedad de Huntington, enfermedad de Parkinson y Esclerosis Múltiple. (Catalá-López et al. 2014)

Esta llamativa correlación entre la incidencia de cáncer y enfermedades neurodegenerativas ha generado diversas hipótesis que tratan de explicar estos hallazgos.

Se han propuesto factores ambientales y tóxicos (consumo de alcohol y tabaco), efectos secundarios de medicación crónica, estilo de vida asociado a ciertas patologías (sedentarismo asociado a la discapacidad), menor acceso a atención sanitaria (acceso a programas de cribado de cáncer), estatus socio económico, etc.

Desde el punto de vista molecular y biológico las teorías propuestas son también diversas (Behrens, Lendon, and Roe 2009) y se enfocan a nivel genómico (L. G. T. Morris, Veeriah, and Chan 2010; Martin 2008), inmunológico (Glass et al. 2010), oxidativo (Underwood et al. 2010) y otras.

Esta situación hace necesaria una teoría integradora que explique esta dicotomía que parece existir entre neurodegeneración y cáncer, la cual probablemente está presente y actuando desde etapas preclínicas de la neurodegeneración. Este conocimiento será de gran relevancia para la investigación de la neurodegeneración y la oncogénesis permitiendo inferir cuales son los mecanismos que llevan a los tejidos a tomar uno u otro camino y en el futuro probablemente nos permitan regular esta decisión.

Esta tesis responde a la necesidad de conocer la fiabilidad de los datos epidemiológicos extraídos de los certificados de defunción en España debido a la implicación antes mencionada de estos datos en las políticas de salud.

También se busca proporcionar evidencia de calidad de la existencia o no de una correlación inversa de la demencia y el cáncer en la población estudiada en la cohorte NEDICES.

Finalmente se busca aportar al conocimiento global de un tema de tanto interés y significancia analizando cual es la situación de esta correlación en sujetos que aún no han desarrollado síntomas de demencia pero en quienes se han puesto ya en marcha probablemente mecanismos neurodegenerativos lo cual podría estar reflejado por un declive cognitivo leve inicial.

III. HIPOTESIS

1. Los certificados de defunción en la población española subestiman la mortalidad por demencia.

2. Existe un riesgo inverso entre el fallecimiento por enfermedad de Alzheimer y riesgo de muerte por cáncer

3. Existe un riesgo inverso entre el fallecimiento por cáncer y el declive cognitivo leve.

IV. OBJETIVOS

1. Los datos epidemiológicos obtenidos de la codificación de la demencia en los certificados de defunción en diferentes partes del mundo subestiman el impacto de esta enfermedad en la población como se intentará demostrar con una revisión de la literatura.

2. En España se reproduce una infra codificación de la demencia en los certificados de defunción tal como se ha comprobado en otros estudios en otros países.

3. La presencia de demencia en los certificados de defunción se correlaciona inversamente con la codificación de mortalidad por cáncer en el estudio poblacional NEDICES

4. El declive cognitivo en sujetos no dementes está asociado con una disminución del riesgo de fallecimiento por cáncer.

V. METODOS

Los datos usados para este trabajo se han obtenido en su integridad de los producidos por el estudio NEDICES (*Neurological Diseases in Central Spain*). El valor de este estudio epidemiológico en la población anciana ha sido ratificado en numerosas publicaciones previas pero cabe resaltar que en los estudios poblacionales de enfermedades neurológicas crónicas existe una dificultad añadida de índole práctica, la participación suele disminuir en los muy ancianos en los que las enfermedades neurológicas crónicas siguen aumentando. El aislamiento, cambio de domicilio, la fragilidad o muerte (a veces lejos del domicilio habitual) son frecuentes en ellos (Matthews et al. 2004). El coste de estos estudios (necesidad de expertos y de seguimiento riguroso, incluida mortalidad) suele ser elevado.

El estudio NEDICES y sus métodos han sido ya ampliamente publicados en la literatura médica nacional e internacional(Bermejo-Pareja et al. 2008), por lo que a continuación se hará una descripción breve de las líneas metodológicas generales del estudio y los datos que conciernen particularmente a la evaluación del deterioro cognitivo y la demencia que son los temas que aquí nos ocupan.

OBJETIVOS DEL ESTUDIO NEDICES:

El estudio NEDICES (acrónimo en inglés de *Neurological Disorders in Central Spain)* es un estudio poblacional longitudinal, que incluye sujetos de 65 y más años. Tiene dos tipos de objetivos: generales y neurológicos.

Sus objetivos generales son el estudio del estado de salud, estilo de vida, FRCV y su evolución (en el tiempo de seguimiento de la cohorte) y su repercusión en la mortalidad de la misma.

Como objetivos neurológicos se plantea analizar diversos aspectos epidemiológicos (prevalencia, incidencia y FR) de varias enfermedades neurológicas crónicas (ENC): demencia y enfermedad de Alzheimer, alteración cognitiva, Parkinson y parkinsonismos, ACVA o ictus e isquemia transitoria, y temblor esencial.

POBLACIÓN DE ESTUDIO

El cálculo del tamaño mínimo muestral se hizo considerando la enfermedad con menos incidencia (Enfermedad de Parkinson) con los intervalos de confianza usuales (95%) y una disminución calculada de la cohorte del 15-20% anual. La muestra calculada fue superior a 1.500 participantes.

Se incluyeron sujetos provenientes de tres zonas de la región central de España. Estas zonas son: Margaritas, Getafe en la periferia de Madrid; barrio de Salamanca en el centro de Madrid; y 38 aldeas de la zona rural de Arévalo, Ávila) (Bermejo et al. 2001)(Morales et al. 2004)

Estas tres zonas fueron elegidas de acuerdo con los siguientes criterios:

a) Población censal de alrededor de 2.000 mayores. Tamaño adecuado para poder evaluar prevalencia (e incidencia a tres años) de las enfermedades neurológicas investigadas por área.

b) Existencia de registros informáticos con datos médicos de atención primaria en el área de salud.

c) Acceso a registros sanitarios que permitieran completar la información con datos médicos en los casos de rechazo.

d) Poblaciones de diferentes estratos socio económicos que permitiera obtener una población total de estructura social, nivel educativo y socioeconómico, *hábitat,* y estilo de vida variado que permitiera contar con una mezcla de población anciana con diferentes estilos de vida y factores de riesgo.

e) Poblaciones que pudieran ser atendidas por un único equipo neurológico (H. Universitario “12 de Octubre”) para disponer así de criterios diagnósticos más uniformes

La base de donde se obtuvo la población del estudio fue la lista de todos los residentes a fecha del 31 de diciembre de 1993 sacada del censo del Ayuntamiento en las áreas de Margaritas y Arévalo. En el barrio de Lista, se realizó un muestreo *inicial* de unas 2.000 personas, obtenido por grupos de 5 años y por edad y sexo, de modo que fueran representativas del total de la población de Lista. En las otras dos áreas todas las personas de 65 y más años del censo fueron consideradas elegibles. Las condiciones precisas de elegibilidad de la población en las tres zonas para el estudio fueron:

- residencia censal en las áreas a 31-12-1993
- residencia real durante seis o más meses en 1993

Se incluyeron como elegibles a los mayores de 65 años que vivían en su domicilio o en instituciones (si el asilamiento estaba ubicado en el barrio o cerca de él, excluyendo a los empadronados en el barrio pero institucionalizados fuera de él por razones de factibilidad de la investigación).

La investigación obtuvo datos de la familia y allegados, si estaban encargados del cuidado de las personas elegibles, en las tres comunidades (Morales et al. 2004; Bermejo et al. 2001).

METODOLOGÍA GENERAL DEL ESTUDIO

Se realizó un estudio puerta a puerta ya que muchos de los ancianos no acuden a los servicios sanitarios (Ross et al. 1997; Benito-León, Porta-Etessam, and Bermejo 1998; Bermejo-Pareja 2003). Con esta metodología se investiga a toda la población seleccionada o elegible y de esta forma se determina el número de participantes en un determinado momento (día de prevalencia).

ESTUDIO EN DOS FASES

La metodología del estudio NEDICES se realiza en dos fases: una fase I de recolección de datos demográficos, de salud, estilo de vida y otros, y de

detección de casos posibles de las ENC investigadas, y una fase II de estudio detenido de los casos posibles (con cribado positivo) por neurólogos en un centro sanitario (ambulatorio del SNS) o, en algunos casos, de sujetos impedidos o que no quieren asistir al Centro de Salud o ambulatorio del SNS, en su propio domicilio (sólo se debía atender en hospitales del SNS, los casos de difícil diagnóstico).

PRIMER CORTE (1-5-1994)

Se utilizó la prevalencia puntual como medida de frecuencia más útil en enfermedades crónicas irreversibles y se estableció el 1/05/94 como día de prevalencia puntual. Esto es, la presencia de parkinsonismo, temblor, demencia e ictus debería estar presente o no el día de prevalencia para considerar al participante del estudio afecto o no de la misma.

Fase I. Instrumentos de cribado

La evaluación inicial se realizó entre 1994 y 1995. Se administraron dos tipos de cuestionario, uno largo y uno corto.

El largo se realizó cara a cara o por teléfono, y consistía en 500 ítems que recogían datos demográficos, estado de salud (incluyendo enfermedades médicas, neurológicas y psiquiátricas), factores de riesgo para enfermedades neurológicas, fármacos y preguntas sobre el estilo de vida, incluyendo hábitos como el consumo de tabaco o alcohol.

El cuestionario corto se envió por correo a los sujetos que rehusaron participar o a los que no se pudo contactar telefónicamente o cara a cara. Este cuestionario incluía sólo la información demográfica, las enfermedades neurológicas objeto de estudio (demencia, ictus, temblor esencial y parkinsonismo), medicación y el nombre del médico de Atención Primaria(Bermejo-Pareja et al. 2008). Familiares y cuidadores rellenaron los cuestionarios en los casos de personas analfabetas.

Los instrumentos de cribado para la demencia fueron las versiones en español del MMSE de Folstein (versión modificada y extendida de 37 preguntas) y de la escala funcional “Cuestionario de Actividades Funcionales” (FAQ) de Pfeffer. Este protocolo de cribado se utilizó en el proyecto de la Organización Mundial de la Salud (OMS) de Demencias Asociadas al Envejecimiento (WHO (World Health Organization) 1990);(Amaducci et al. 1991), y se ha validado en estudios realizados en España(Villanueva-Iza et al. 2003), con una sensibilidad cercana al 95%. Se ha realizado también un estudio de la concordancia inter observador de este protocolo para el diagnóstico de demencia(Baldereschi et al. 1994) Sus dos componentes se resumen a continuación:

1) MMSE-37 (Adaptación del MMSE de Folstein; Se trata de una adaptación del MMSE de Folstein (Folstein, Folstein, and McHugh 1975) modificada y ampliada para hispanoparlantes y con algunas preguntas especialmente adaptadas para los participantes analfabetos, diseñadas por un estudio OMS

(Baldereschi M, Meneghini F, and Quiroga P 1994). Contiene 37 ítems e incluye tareas de orientación temporal y espacial, memoria, atención, cálculo, lenguaje, reconocimiento de objetos, órdenes elementales y capacidad visuo constructiva.

2) Cuestionario de Actividades Funcionales (FAQ – Functional Activities Questionnaire) de Pfeffer (Pfeffer et al. 1982). Es un cuestionario adaptado al español y ligeramente modificado del original (Bermejo et al, 2008c), que evalúa 11 actividades instrumentales de la vida diaria (AIVD). El FAQ de Pfeffer fue diseñada fundamentalmente para detectar la incapacidad funcional asociada a la alteración cognitiva y la demencia(Pfeffer et al. 1982; Pfeffer et al. 1981). La versión en castellano, fue preparada por un equipo de la OMS, y cuenta con una validación española para su uso en la Demencia (Villanueva-Iza et al. 2003; Olazarán, Mouronte, and Bermejo 2005)

Fase II. Diagnóstico clínico

En esta fase se realizó la evaluación, por parte de neurólogos, de aquellos participantes que habían resultados positivos en el cribado de demencia realizado en la fase I. Se consideró positivo el cribado de demencia si el sujeto cumplía alguno de los siguientes requisitos:

- Puntuación en el MMSE-37 menor o igual a 23.
- Puntuación en la escala FAQ de Pfeffer mayor de 5.

- Quejas en los cuestionarios o por parte del Médico de Familia sobre pérdida de memoria, deterioro cognitivo o demencia.

También fueron evaluados por un neurólogo los participantes que:

- Daban alguna respuesta positiva en los cuestionarios de cribado en ictus, parkinsonismo o temblor.

- Tenían un cuestionario de cribado incompleto.

- Existía alguna información contradictoria sobre los datos del cribado (cribado dudoso).

La fase II se realizó preferentemente en ambulatorios o consultorios del Sistema Nacional de Salud (SNS) u Hospitales (H. U. “12 de Octubre”, y H. U. “de la Princesa”), aunque muchos ciudadanos, sobre todo incapacitados o en cama, fueron visitados en sus domicilios. Se procuró que el neurólogo efectuara la entrevista cara a cara con el paciente. La evaluación incluía una anamnesis semiestructurada, una exploración neurológica y un examen del estado mental, a menudo con un nuevo MMSE-37.

Todos los casos de demencia fueron evaluados al menos por uno de los neurólogos participantes. Si este neurólogo tenía alguna duda respecto al diagnóstico, el paciente era valorado de nuevo por un neurólogo diferente. Además, todos los participantes podían ser remitidos al servicio de Neurología del Hospital Universitario “Doce de Octubre”, si se consideraba que requerían un estudio en profundidad. Las historias clínicas de los participantes que

recibieron el diagnóstico de demencia fueron revisadas por un neurólogo especializado en enfermedades neurodegenerativas (F. Bermejo), con la ayuda de un geriatra (S. Vega) y un psicólogo (F. Sánchez-Sánchez).

Si persistía alguna duda sobre algún aspecto del diagnóstico, se obtenía información adicional, fundamentalmente del médico de familia a cargo del sujeto.

Criterios diagnósticos

Para el diagnóstico de demencia, se aplicaron los criterios del DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, fourth Edition)(American Psychiatric Association 1994). La gravedad de la demencia se clasificó en leve, moderada y grave siguiendo el DSM-III-R (Diagnostic and Statistical Manual of Mental Disorders, Third Edition III. revised) (American Psychiatric Association 1987).

Se estableció una categoría de demencia cuestionable, análoga a la puntuación de 0,5 en el CDR (Clinical Dementia Rating) (J. C. Morris 1993), y que ya había sido utilizada en un estudio sobre envejecimiento de la OMS(Baldereschi et al. 1994). De acuerdo con estos criterios, se clasificaba a los participantes como cognitivamente sanos, con demencia cuestionable o con demencia, que a su vez se dividía en leve, moderada o grave. Desde el punto de vista etiológico, los criterios utilizados para las principales causas de demencia fueron:

a) Enfermedad de Alzheimer: criterios del National Institute of Neurological and Communicative Diseases and Stroke-Alzheimer´s Disease and Related Disorders Association (NINDS-ADRDA)(McKhann et al. 1984).

b) Demencia vascular: criterios del DSM-IV(American Psychiatric Association 1994), utilizando la escala de Hachinski como soporte.(Hachinski, Lassen, and Marshall 1974)

c) Demencia mixta (Vascular y EA), de acuerdo con criterios del DSM-IV (American Psychiatric Association 1994).

d) Demencia con parkinsonismo, categoría que incluía la demencia asociada a la enfermedad de Parkinson y la que aparecía en pacientes con otros tipos de parkinsonismo de más de un año de evolución.

e) Demencia secundaria, cuando una causa específica se consideraba la causante de la demencia.

f) Demencia indeterminada, en aquellos casos en que la información disponible era insuficiente para definir una etiología.

SEGUNDO CORTE (1-5-1997)

Se efectuó con un día de prevalencia puntual (1 de Mayo de 1997), tres años después del corte basal. En líneas generales, la metodología del segundo corte fue similar a la del primero: estudio en dos fases en las tres áreas del

corte basal, a la misma población cribada en el primer corte (5.278 mayores) y con la análoga metodología general de estudio en dos fases.

Modificaciones del Protocolo del primer corte.

Se mantuvieron los mismos instrumentos de cribado para las enfermedades neurológicas investigadas del primer corte. Asimismo, se incluyó un cuestionario específico con varias preguntas sobre cada enfermedad neurológica investigada (ictus, demencia y deterioro cognitivo, parkinsonismo y temblor) por si un médico u hospital hubiera diagnosticado al participante en el período de tres años alguno de los mencionados trastornos. También se precisaron y aumentaron la información de las personas que rechazaron la participación, recogiéndose una hoja con abundante información en el caso de fallecimiento del sujeto (día de fallecimiento, causas, lugar, información de los allegados, del médico de cabecera u hospital y del certificado de defunción) y preguntas sobre si el participante había padecido demencia, infarto de miocardio (IM), temblor, ictus, parkinsonismo.

En lo que concierne al diagnóstico de la demencia en este segundo corte se incluyó una batería psicométrica elemental con la intención precisar mejor el diagnóstico psicométrico de la ACL (alteración cognitiva leve) (Bermejo FP. 1998; Petersen et al. 2001)

Se incluyeron pruebas neuropsicológicas de las que existían una amplia experiencia en estudios neurológicos multicéntricos de la Sociedad Española

de Neurología (SEN) (Bermejo et al. 1994; Peña-Casanova J., Gramunt NF, and Gich JF 2004) o con validación en estudios previos:

a) Prueba de inteligencia verbal. El test de acentuación de palabras (Del Ser et al. 1997). Consiste en que el participante lea 30 palabras inhabituales que se le muestran sin tildes y cuya acentuación ha de hacer correctamente. Este test es una prueba de inteligencia verbal

b) Pruebas de memoria. Una prueba de memoria verbal lógica (episódica), adaptada de la batería de memoria de Wechsler (Wechler D 1987) y las láminas de reconocimiento y memoria de la SEN (Bermejo et al. 1994)

c) Pruebas de fluidez del lenguaje (lenguaje categorial). Se anotó el número de frutas en treinta segundos y en un minuto que podía recordar el participante(Bermejo FP., Porta-Etessam J., and Díaz JG. 2001)

d) La versión española y abreviada del test del informador o Informant Questionnaire on Cognitive Decline in the Elderly, (Del-Ser et al. 1997; Bermejo FP., Porta-Etessam J., and Díaz JG. 2001)

INFORMACION DE MORTALIDAD (1-5-2007)

Se estudió la mortalidad general de toda la cohorte con un período de seguimiento de 13 años, determinando el status vida / muerte y fecha de fallecimiento de todos los casos, tomando como fecha inicial la fecha de cribado, y como fecha de análisis de mortalidad el 1 de Mayo de 2007. Las defunciones ocurridas desde el reclutamiento de la cohorte se obtuvieron a partir de las historias clínicas y mediante el cruce de la base de datos del estudio NEDICES con el Registro Nacional de Defunciones proporcionado por el Instituto Nacional de Estadística (INE). El cruce se realizó mediante la detección de concordancia de sexo, fecha de nacimiento y apellidos (por este orden). En caso de discrepancia en cuanto a fecha de defunción se tomó como correcta la fecha reflejada en el certificado de defunción.

La variable tiempo fue calculada como personas-año desde la fecha de cribado hasta la fecha de defunción en el caso de los participantes fallecidos (evento a estudio), o hasta el 1 de Mayo de 2007 en los participantes vivos (casos censurados). En el caso de los 50 sujetos fallecidos desde su selección en el censo, pero antes del inicio del estudio, y que habían sido estudiados a través de un familiar, el tiempo de evaluación se computó como 0,5 meses.

Las causas de muerte se han analizado mediante el "Fichero Nacional Básico de Defunciones según Causa de Muerte" del Instituto Nacional de Estadística, tras obtener los permisos pertinentes. Este registro se realiza con los datos de cada Boletín Estadístico de Defunción, que los médicos rellenan junto con el Certificado de Defunción. Recoge la causa básica o fundamental

de muerte, de acuerdo con la Clasificación Internacional de Enfermedades de la Organización Mundial de la Salud, la ICE-9 desde 1980 hasta 1999, y la ICE-10 desde esa fecha.

PARTICIPACIÓN EN EL ESTUDIO

Ver Tabla 1 y Figura1 respecto al primer corte

Ver Tabla 2 y Figura 2 respecto al segundo corte

VI. RESULTADOS

A continuación se resumen los principales resultados del análisis de las bases de datos de la cohorte NEDICES que se han hecho para responder los objetivos de esta tesis. Los detalles del análisis de datos se pueden encontrar en cada una de las publicaciones que forman parte de la tesis y que están anexas a ella. (ANEXO 1.1, 1.2, 1.3 y 1.4)

1.) Revisión de la Literatura: Codificación de la demencia en los certificados de defunción.

Se realizó una búsqueda sistemática de la literatura para identificar la información más actualizada respecto a la codificación de la demencia en los certificados de defunción.

En la búsqueda se identificaron 170 artículos de los cuales solo 7 cumplían los criterios de inclusión de nuestro estudio (Estudios poblacionales donde todos los sujetos hayan sido cribados para demencia y aquellos positivos hayan sido examinados y diagnosticados clínicamente).

Los estudios investigados tenían una muestra que variaba entre los 527 y 10,263 participantes y el rango de notificación de la demencia en todos ellos solo alcanzaba del 7.2 al 34%. Las causas de muerte más notificadas entre los sujetos dementes fueron las respiratorias y cardio o cerebro vasculares. (Ver tabla 1 en anexo 1.1)

En cuanto a la correlación con otras variables que pudieran influir en la codificación de la demencia encontramos diversos análisis entre los cuales destacan:

- Tanto el género como la edad o lugar de muerte (casa o institucionalizado) no se correlacionan significativamente con la tasa de notificación de demencia en uno de los estudios ingleses incluidos (Morgan and Clarke 1995). Sin embargo respecto al género hay dos artículos contradictorios si incluimos artículos excluidos del análisis pero que igualmente dan estos resultados como significativos estadísticamente. (Raiford et al. 1994; Newens, Forster, and Kay 1993)
- Variación temporal de la codificación en el mismo estudio: Morgan y Clarke hace una comparación en la tasa de codificación entre los períodos de 1985-1990 y 1990-1994 pero no encuentra diferencias. (Morgan and Clarke 1995)
- En el estudio de Ganguli se asocia una mayor codificación con una mayor severidad de la demencia, que la demencia sea del tipo Alzheimer o que la muerte se produzca en una institución de cuidados crónicos. (M Ganguli and Rodriguez 1999)
- En una publicación basada en el estudio canadiense de salud y envejecimiento también se aportan datos acerca de la infra codificación que también se extiende a otros tipos de demencia como es el caso de la demencia vascular en la que tan solo el 23,3% de los sujetos constan como dementes en alguna parte del certificado.(Ostbye, Hill, and Steenhuis 1999).

En cuanto a la calidad de los artículos se observó que todos los artículos incluidos satisfacían por lo menos un 83% de los criterios de STROBE para evaluación de estudios observacionales.(Malta et al. 2010)

2.) Codificación de la demencia en los certificados de defunción de sujetos clínicamente dementes del Estudio NEDICES

En la cohorte se incluyeron 5278 sujetos, de los cuales en 4197 (incluyendo 467 dementes) se hizo un seguimiento medio de 10.1 años (media 12,5 años rango 0,03-13,5 años) (ver fig. 1 en anexo 1.2)

Entre los 467 dementes habían 321 (68,7%) diagnosticados de Alzheimer y 146 (31.3%) dementes no Alzheimer.

Cuando se hizo una comparación entre el grupo de dementes y no dementes se constató que estos primeros eran significativamente mayores y con un menor nivel de educación que los no dementes. Además había diferencias significativas en género, educación, consumo de alcohol y tabaco además de síntomas depresivos y uso de antidepresivos.

Al final del seguimiento (promedio 7.1 años (0.03-13.3 años)) habían fallecido 1,976 sujetos, incluyendo 403 (86,3%) entre los 467 dementes y 1,573 (42,2%) entre los 3,730 no dementes. De los 403 participantes con demencia fallecidos, 277 tenían posible o probable EA y 126 tenían demencia No EA

El principal hallazgo fue que únicamente el 20,8% de los sujetos clínicamente diagnosticados como dementes tenían la demencia registrada como una causa primaria de muerte en sus certificados de defunción.

Las variables que se asociaron en con el registro de demencia en el certificado de defunción este estudio son las siguientes:

- Los sujetos <85 años tienen un OR 2.33 (IC 1.33-4.10. P=0.003) de tener la demencia como causa primaria de defunción en sus certificados de muerte.
- Aquellos sujetos moderada o severamente dementes tienen un OR 2.15 (IC 1.16 – 3.97. P=0.015) de tener codificada la demencia en sus certificados.
- Los sujetos con diagnóstico de posible o probable enfermedad de Alzheimer tienen un OR 2.88 (IC 1.34-6.17. P=0.007) de tener la demencia codificada en sus certificados en comparación con aquellos diagnosticados de demencia de otro tipo (No Alzheimer)
- No hay diferencias significativas cuando se compara la codificación de la demencia en los certificados de defunción de los sujetos dementes fallecidos entre 1994-2001 con aquellos fallecidos entre 2001-2007.

Las causas de muerte más comúnmente referidas, entre los grupos de sujetos dementes y no dementes, de manera similar a lo descrito en los artículos de la revisión sistemática, fueron las enfermedades cardiovasculares (27,5% y 28,4% respectivamente) y enfermedades respiratorias (14,4% y 14,3% respectivamente) sin diferencias estadísticamente significativas entre los grupos. Por otro lado sí se vieron sorprendentemente diferencias

estadísticamente significativas en la notificación de cáncer en los certificados de muerte siendo de 6% entre los dementes y de 26,5% en los no dementes (p<0,001).

3.) Mortalidad por cáncer entre los sujetos dementes de la cohorte NEDICES.

En un modelo de Cox ajustado para edad, genero, nivel educativo, consumo de tabaco y alcohol, síntomas depresivos y uso de antidepresivos el riesgo de mortalidad por cáncer en los sujetos con Enfermedad de Alzheimer es RR=0.53 (IC 95% 0.29-0.95. P=0.034)

Los sujetos que murieron por cáncer comparados con los que no, tenían un 37-MMSE más alto, tomaban menos medicación, consideraban que su estado de salud era bueno o muy bueno, era más probable que hayan fumado o consumido alcohol en su vida y era menos probable que fueran hipertensos, osteoporóticos o que hayan sufrido un ictus.

La causa de muerte en los certificados de defunción difería significativamente según el grado de severidad de la demencia. El cáncer era codificado con menor frecuencia en aquellos sujetos con posible o probable Enfermedad de Alzheimer (5.8%) o demencia no Alzheimer (6.3%) en comparación con aquellos sujetos no dementes (26.5%)

El cáncer estaba presente en similar proporción de sujetos con demencia en un estadio leve (6.4%) en comparación con aquellos en un estadio moderado o severo (4.8%) (Chi cuadrado= 0.288, p=0.591).

4.) Velocidad de declive cognitivo y su relación con la mortalidad por cáncer en la cohorte NEDICES

Se incluyeron 2715 sujetos de la cohorte original. (Ver fig. 1 en anexo 1.4) Cuando se comparó este grupo con la cohorte original se vio que aunque eran similares en relación al género, eran significativamente diferentes en cuanto a la edad, siendo 1.6 años más jóvenes (72.7 ± 5.9 vs. 74.3 ± 7.0 años, t = 11.0, p < 0.001). y mejor educados (268 [10.2%] vs. 711 [13.6%] eran analfabetos, chi^2 = 18.71, p < 0.001). Se separó la muestra en tertiles según el cambio que habían tenido en el MMS entre el primer y segundo corte. (Ver análisis estadístico en artículo de referencia). 1003 (38,2%) de los 2715 murieron durante el seguimiento, de los cuales 339 (33.8%) estaban en el tertil más alto (aquellos con declive cognitivo más rápido) y 664 (66.2%) en el tertil medio y bajo.

Las diferencias encontradas entre el tertil más alto y los inferiores fueron las siguientes:

- Hay diferencias significativas en cuanto a la edad de base (76.3 ± 6.9 vs. 74.9 ± 6.2 años, p = 0.002) la incidencia de diabetes (15.8% vs 21.6%. p=0.029), y el 37-MMSE total (30.1±4.9 vs 28.9±5.3 p=<0.001)
- El cáncer fue codificado con menor frecuencia en el certificado de defunción en el tertil más alto. (20.6% vs 28.6%. p=0.01)
- La demencia fue más frecuente en los certificados de defunción del tertil más alto (7.1% vs 3.6% p=0.01)
- Los tipos de canceres no variaban significativamente entre tertiles

- Las enfermedades cardiovasculares eran más frecuentes en los tertiles más altos (33.3% vs 26.2% p=0.02)

La mortalidad atribuible al cáncer era menor en el tertil superior comparado con el resto de tertiles en 3 modelos de cox ajustados para diferentes variables. (Ver artículo de referencia)

VII. DISCUSION

Existen tres Fuentes de información de mortalidad a nivel poblacional: Los registros civiles y los sistemas de estadística vital oficiales; las encuestas y los censos poblacionales.(“Approaches to the Collection of Mortality Data in the Context of Data Needs.” 2014) Los registros civiles son considerados de mayor calidad ya que los datos que se registran tienen validez legal y tienen una función administrativa. Los certificados de defunción son la base de estos documentos oficiales de registro de mortalidad, se usan para la realización de estudios regionales y locales de estadísticas de mortalidad y son usados para justificar la solicitud de fondos para investigación, para orientar políticas de salud pública y para estudiar el efecto de medidas preventivas.(Byass 2007) Adicionalmente, los certificados de defunción, por su carácter oficial y administrativo, son un documento indispensable para permitir la inhumación de los cadáveres y a su vez permitir a los familiares realizar trámites de seguros, propiedades y herencias.(Huffman 1997)

La preocupación por la exactitud de los certificados de defunción y su utilidad para determinar variables epidemiológicas ha sido ampliamente publicada (Cendales and Pardo 2011)

Sin embargo, hay muy pocos artículos de calidad que documenten la falta de concordancia en el registro de demencia en los certificados de defunción. En los artículos analizados en la revisión sistemática hecha en este trabajo, todos ellos coinciden en señalar que la demencia se codifica en menos de un tercio de sujetos dementes fallecidos.

La codificación de la demencia parece estar relacionada con el tipo de demencia, ya que se halla con más frecuencia en los certificados de los sujetos con demencia de tipo Alzheimer que en aquellos con otros tipos de demencia. (Romero et al. 2013; M Ganguli and Rodriguez 1999; Mölsä, Marttila, and Rinne 1986; Macera et al. 1992; Thomas, Starr, and Whalley 1997)

Otro factor identificado en una publicación es la mayor codificación de la demencia en los certificados de defunción cuando la muerte se produce en instituciones de cuidados crónicos.(M Ganguli and Rodriguez 1999) lo cual se debe a que probablemente en estos centros hay sujetos con una demencia más grave.(Olichney et al. 1995)

En cuanto a la edad al momento de la muerte hay resultados inconsistentes ya que en el estudio CERAD (Raiford et al. 1994) no hay una relación significativa, sin embargo en uno de nuestros estudios aquellos más jóvenes al momento de la muerte tienen un mayor índice de notificación de la demencia. (Romero et al. 2013) Esto podría indicar que la demencia en edades avanzadas es considerada parte del envejecimiento normal y por tanto es probablemente infra notificada. Esto está en línea con el hallazgo de que la gravedad de la demencia esta también correlacionada con un mayor registro en los certificados de defunción (M Ganguli and Rodriguez 1999; Romero et al. 2013; Kukull et al. 1994) ya que cuando la demencia es leve el medico suele infra estimar su peso en la mortalidad del paciente (Newens, Forster, and Kay 1993) aun cuando la demencia es una causa reconocida de un incremento de la mortalidad (Villarejo et al. 2011).

La demencia es causa frecuente de varias complicaciones entre las que están la inmovilidad, alteraciones de deglución, incontinencia y malnutrición que a su vez pueden llevar a la muerte, sin embargo aunque estas complicaciones subyazcan a otras causas más inmediatas de muerte como la neumonía (Chamandy and Wolfson 2005; Mölsä, Marttila, and Rinne 1986; Thomas, Starr, and Whalley 1997; Burns et al. 1990) y otras enfermedades respiratorias o enfermedades cardiovasculares son estas últimas las codificadas en detrimento de la demencia que es realmente la causa de muerte fundamental.

Los certificados de defunción son normalmente completados por personal médico cualificado en la mayoría de países desarrollados. Sin embargo se ha estimado en un análisis internacional que solo 31 de 192 países a nivel mundial producen datos de mortalidad de alta calidad, entre los cuales los certificados de defunción elaborados en España han experimentado una sustancial mejoría en su calidad en los últimos 50 años y actualmente tienen una calidad media a alta con la recopilación del 70 al 100% de los datos requeridos. (Mahapatra et al. 2007)

Vista la infra codificación de la demencia en varios estudios poblacionales (2 canadienses, 2 norte americanos, 1 brasileño y 1 inglés) y ante la inexistencia de un estudio español se revisó la base NEDICES para comparar los hallazgos en este estudio poblacional español, el primero en su clase.

Los resultados muestran que efectivamente, al igual que en el resto de estudios referidos (0,8-78%) (Morgan and Clarke 1995; M Ganguli and Rodriguez 1999; Ostbye, Hill, and Steenhuis 1999; Chamandy and Wolfson 2005; Mary Ganguli et al. 2005; Nitrini et al. 2005), la notificación de la demencia en los certificados de defunción de los sujetos clínicamente dementes es también muy baja en España (20.8%).

Por otro lado, al igual que en otros trabajos, el diagnóstico es significativamente más probable en aquellos sujetos que son más jóvenes y en aquellos con un estado más severo de la enfermedad.

Probablemente la capacitación que tenga el personal médico para completar correctamente formato de los certificados de defunción y el conocimiento adecuado de la clasificación usada para codificar las muertes en cada país tiene importancia en la codificación de estos datos. El cambio de ICD 9 a ICD 10 se ha reflejado en España con una disminución del 3.2% de la mortalidad de la demencia probablemente como consecuencia del solo hecho del cambiar de sistema de codificación.(Cano-Serral, Perez, and Borrell 2006)

Varios estudios publicados coinciden en que la principal razón para esta inexacta codificación de los certificados de defunción es la falta de capacitación del personal médico al respecto.(Hoel et al. 1993; Jiménez-Cruz, Leyva-Pacheco, and Bacardi-Gascón 1993; Smith Sehdev and Hutchins 2001)

En respuesta a este evidente problema, múltiples instituciones y países han elaborado programas educativos específicos para personal sanitario

basados en material impreso, videos, auditorias de la certificación, entre otras políticas.(Aung, Rao, and Walker 2010) siendo los más efectivos aquellos programas más pragmáticos e interactivos.

Hay datos de incremento de la prevalencia y mortalidad atribuida a demencia a nivel mundial, visto que muchos de estos datos se obtienen de certificados de defunción es difícil estimar si este aumento de prevalencia se debe a un real aumento del número de casos o simplemente al aumento de su registro. En todo caso sea cual sea el escenario se podría asumir que hay una infra estimación de la mortalidad atribuida a la demencia.

En varias publicaciones a nivel mundial se habla de una disminución de la incidencia de cáncer entre los sujetos dementes y viceversa, lo cual ha generado numerosas hipótesis de esta curiosa relación causal. (Musicco et al. 2013; C M Roe et al. 2010)

En la cohorte NEDICES el riesgo de muerte por una neoplasia entre los sujetos dementes es casi la mitad, estos resultados concuerdan con varios estudios ya publicados al respecto (Chamandy and Wolfson 2005; Mary Ganguli et al. 2005; C M Roe et al. 2010; Driver et al. 2012)

Esta asociación no se da en sujetos con demencia vascular(C M Roe et al. 2010) sin embargo en aquellos sujetos con demencia mixta (vascular y EA) si se demuestra esta asociación inversa (HR= 0.41, 95%IC=0.20-0.84), aunque sigue siendo más fuerte en el caso de sujetos con EA pura (HR=0.31, 95%IC=0.12-0.86).

Los mecanismos que justifican esta asociación son desconocidos y probablemente estén a nivel molecular.

Entre las teorías que se han enunciado para explicar esta asociación están:

- Déficit colinérgico: Se conoce que en los cerebros de los sujetos con EA hay un déficit colinérgico (Francis et al. 1999), dado que la acetilcolina ha sido reconocida como un factor que promueve la mitosis y oncogénesis (Peng et al. 2013; Hua et al. 2012; Greig, Reale, and Tata 2013) El déficit de este sistema podría explicar la reducción de la incidencia de cáncer. A este respecto no hay estudios que demuestren el efecto en esta relación del uso de medicamentos anti colinesterásicos comúnmente usados en el tratamiento sintomático de la enfermedad de Alzheimer.

- Existen varios estudios que plantean que en la Enfermedad de Alzheimer hay una respuesta inflamatoria particular que la acompaña (Jones 2001; Engelhart et al. 2004; Akiyama 1994) y hay reciente evidencia de que algunos tipos de inflamación podrían controlar fenómenos oncogénicos. (Haabeth et al. 2011). En concordancia con estos hallazgos se ha descrito también una posible función citotoxica de la proteína amiloide (actuando como un péptido de defensa del huésped) sobre las células cancerígenas (Kinnunen 2010; 2009). El mecanismo propuesto es la permeabilización de las membranas celulares por medio de estas proteínas formadas a partir del amiloide que por otro lado

podrían también actuar potenciando la muerte celular y neuro degeneración.(Harris, Dennison, and Phoenix 2012)

- Finalmente se ha demostrado una sobre expresión de genes de supresión de tumores en muestras de tejido nervioso de sujetos afectados por la enfermedad de Alzheimer. (Blalock et al. 2004) y más recientemente en un estudio genético a gran escala se observó superposición de varios genes sobre expresados en enfermedades neurodegenerativas (Alzhiemer y Parkinson) que a la vez están suprimidos en el cáncer.(Ibáñez et al. 2014)

Se ha visto también una asociación inversa similar en el caso de otras enfermedades neurodegenerativas como el Parkinson y la enfermedad de Huntington. (Vanacore et al. 1999; Sørensen, Fenger, and Olsen 1999)

En el estudio Framingham se demuestra que también se da una asociación inversa cuando se estudia aquellos pacientes supervivientes de cáncer y la incidencia de Alzheimer en estos (HR=0.67, 95% IC=0.47-0.97) y que este riesgo es aún menor en aquellos pacientes supervivientes a canceres relacionados con el tabaco (HR=0,26, 95% IC 0.08-0.82) en comparación con otros tipos de cáncer (HR=0.82, 95% IC=0.57-1.19)

En este último caso, Driver propone que un factor de confusión importante puede ser la sobrevida de los pacientes con cáncer que impide que desarrollen demencia pero Ganguli llama la atención de las limitaciones de los estudios observacionales para hacer este tipo de inferencia y señala que aunque se demuestre la asociación de un factor con un cambio en la

probabilidad de desarrollar una enfermedad, puede no ser parte de su patogenia sino un factor mediador o modificador de otro factor inadvertido que sea el causante real de la asociación entre neurodegeneración y oncogénesis. (Mary Ganguli 2012)

También se enuncia la posibilidad de que en los pacientes con enfermedad de Alzheimer debido a sus características como falta de queja de síntomas, menos seguimiento por parte del médico generalista, etc. se lleven a cabo con menos rigor los programas de cribado del cáncer (Bennett and Leurgans 2010; Catherine M Roe and Behrens 2013). Sin embargo uno de nuestros estudios demuestra que los sujetos no dementes con un declive cognitivo más rápido también muestran una menor incidencia de cáncer.

De acuerdo a los resultados de nuestra cohorte aquellos sujetos con un declive cognitivo más rápido (sin estar dementes) tienen un riesgo relativo un 30% menor de desarrollar cáncer comparado con menores cambios en el 37-MMSE

Esto indica que probablemente estos sujetos tienen un nivel de neurodegeneración subclínica en la cual ya se nota la correlación descrita. Se ha descrito previamente que los sujetos con un declive cognitivo leve dentro de rangos normales podrían tener ya datos subclínicos de cambios neurodegenerativos con acumulación de beta amiloide como uno de los procesos más precoces.(Oh et al. 2012; Mormino et al. 2009).

En el contexto de esta tesis quedan pendientes varias preguntas que podrían ser respondidas por futuros estudios. Tal vez una de las más

relevantes sea demostrar si el uso de fármacos anti colinesterásicos, cuyo uso se ha generalizado en los últimos años en el tratamiento sintomático de las demencias, varía la asociación inversa descrita entre demencia y cáncer.

VIII. LIMITACIONES Y FORTALEZAS

La revisión de la literatura puede haber estado limitada por los criterios de exclusión del protocolo de búsqueda bibliográfica lo cual puede haber excluido importantes estudios no publicados en las bases de datos utilizadas, sin embargo esto es bastante improbable.

En cuanto a los datos de mortalidad no se recogieron los datos de lugar de muerte ni comorbilidad (causas de muerte secundarias) en el momento de la muerte o la especialidad del profesional que firma el certificado (médico general, neurólogo, geriatra, etc.). La correlación de estos datos con las tasas de codificación de la demencia aportaría datos seguramente interesantes ya que es lógico pensar que dependiendo del grado de sensibilización ante la demencia como causa de muerte, o el lugar de defunción la codificación pueda variar.

En el caso del estudio del riesgo de mortalidad por cáncer entre los dementes se ajustó el riesgo para un número importante de factores de confusión pero la evaluación de la depresión en la cohorte era limitada y se puede haber infra diagnosticado casos de depresión entre los participantes.

Se ha asociado la depresión con el riesgo incrementado de demencia (Jorm 2000)y a la vez con un riesgo aumentado de mortalidad por cáncer(Satin, Linden, and Phillips 2009). Sin embargo esto es improbable ya que el cribado realizado en el estudio NEDICES tiene una alta concordancia con los datos resultantes de una entrevista psiquiátrica reglada tal como se muestra en un estudio de validación hecho al respecto.(Louis et al. 2007)

Para estudiar la mortalidad por cáncer usamos la información de los certificados de defunción. Sin embargo aun cuando en España se ha mostrado que la exactitud de su notificación en los certificados de defunción es adecuada, la certificación de algunos tipos de cáncer es baja.(Pérez-Gómez et al. 2006)

El riesgo competitivo es una extensión del análisis de supervivencia que debe considerarse cuando un sujeto es susceptible de sufrir más de un evento mutuamente excluyente, tal como la muerte por diferentes causas, la ocurrencia de uno de ellos previene que el otro llegue a suceder. (Koller et al. 2012) Este es un tema que ha sido señalado con frecuencia en otros estudios que correlacionan el cáncer y la demencia.(Mary Ganguli 2012) Los ancianos saludables que no mueren por cáncer tienen el riesgo de desarrollar enfermedades neurodegenerativas que incluyen la demencia y a su vez aquellos que mueren de cáncer al no llegar a la vejez más avanzada no han podido desarrollar demencia.

Entre las fortalezas de los estudios está el contar con una base de datos con un gran número de participantes y que al ser un estudio poblacional permite detectar casos de demencia no diagnosticados previamente y a su vez permite la evaluación y seguimiento de un grupo de población no demente que no tienen el sesgo de ser seleccionados por tratamiento. La evaluación de los sujetos se hizo siempre de una manera prospectiva y estandarizada.

Finalmente, el diseño del estudio nos permitió ajustar el análisis para un importante número de factores de confusión potenciales.

IX. CONCLUSIONES

Los estudios epidemiológicos en neurología son fundamentales para obtener datos fiables acerca de la incidencia, prevalencia y mortalidad de las enfermedades neurológicas crónicas, por la discapacidad que conllevan y sus implicaciones socio sanitarias.

Los estudios epidemiológicos en la población anciana son de gran dificultad por las características propias de este grupo de la población que llevan a una infra codificación de enfermedades y poca predisposición para participar en estudios, sin embargo su importancia es evidente como herramienta para inferir importantes correlaciones o interacciones con otras patologías crónicas que pueden afectar a grupos más jóvenes de la población de manera sub clínica.

Los trabajos que se presentan en esta tesis cumplen los objetivos planteados en el marco de las hipótesis de trabajo y han permitido la generación de las siguientes conclusiones específicas:

1. La demencia esta infra codificada en los certificados de defunción probablemente debido a una serie de circunstancias entre las cuales están la infra capacitación para el cumplimentado de estos documentos y la concepción de la demencia como una enfermedad no mortal.
2. La infra codificación de la demencia es similar a nivel mundial, generalizando de esta manera la dificultad para tener datos de la mortalidad de la enfermedad que sean altamente fiables.

3. El diagnóstico de demencia está relacionado inversamente con codificación de cáncer en los certificados de defunción del estudio poblacional NEDICES lo cual concuerda con publicaciones previas que establecen la misma correlación en otros países.

4. El deterioro en la puntuación en pruebas cognitivas (MMSE-37) aun cuando no alcance criterios de demencia se correlaciona con una menor incidencia de cáncer según la codificación del certificado de defunción, lo cual respalda (más allá del sesgo que puede producir el infra reporte de la demencia) la asociación inversa de la neurodegeneración y cáncer aun en etapas preclínicas.

X. ESTUDIO NEDICES

En estas líneas finales cabe recalcar la validez e importancia del Estudio NEDICES en la neuroepidemiología española. Gracias a su diseño poblacional prospectivo, único en su clase, ha permitido realizar más de medio centenar de publicaciones de gran relevancia.

Como se ha dicho previamente, los estudios epidemiológicos en los ancianos son de gran dificultad ya que este grupo de la población suele tener poca predisposición para participar en estudios, sin embargo son de gran importancia para obtener datos fiables acerca de la incidencia, prevalencia y mortalidad de las enfermedades neurológicas crónicas, por la discapacidad que conllevan y sus implicaciones socio sanitarias.

Como se ha demostrado ya en el estudio NEDICES los estudios poblacionales permiten un cribado exhaustivo de los sujetos incluidos evitando el infra diagnóstico de varias enfermedades que se asumen como consecuencia normal del envejecimiento, entre ellas la demencia.

Ya que el estudio NEDICES aborda varias enfermedades neurodegenerativas asociadas al envejecimiento tales como el temblor esencial, la demencia y la enfermedad de Parkinson, en un futuro próximo será interesante analizar si se da esta correlación inversa descrita entre el cáncer y otras enfermedades neurodegenerativas en esta cohorte.

XI. TABLAS Y FIGURAS

TABLA1

Población del corte basal en el estudio NEDICES (tres áreas)

(Clasificada según su tipo de evaluación en el estudio)

GRUPO DE EDAD	POBLACIÓN CENSAL		POBLACIÓN ELEGIBLE		POBLACIÓN CRIBADA	
	6,395		5,941		5,278	
	HOMBRES	MUJERES	HOMBRES	MUJERES	HOMBRES	MUJERES
65-69	853 (32,3)	1,072 (28,6)	808 (33,0)	1,009 (29,1)	736 (32,9)	911 (30,0)
70-74	701 (26,5)	945 (25,2)	673 (27,5)	889 (25,6)	623 (27,8)	788 (25,9)
75-79	480 (18,2)	688 (18,3)	437 (17,9)	641 (18,5)	404 (18,1)	555 (18,3)
80-84	342 (12,9)	582 (15,5)	305 (12,5)	533 (15,4)	279 (12,5)	460 (15,1)
85-89	195 (7,4)	329 (8,8)	165 (6,7)	283 (8,2)	151 (6,7)	236 (7,8)
90 Y MÁS	72 (2,7)	135 (3,6)	58 (2,4)	113 (3,3)	45 (2,0)	90 (3,0)
TOTAL	2,643(41,3)	3,752 (58,7)	2,446 (41,3)	3,468 (58,6)	2,238 (42,4)	3,040 (57,6)
	6,395 (100,0%)		5,914 (92,5%)		5,278 (82,5%)	

* PRIMER CORTE AÑO 1994

TOMADO DE *Cohorte de ancianos NEDICES*. Madrid: EDIMSA, 2007.

TABLA2

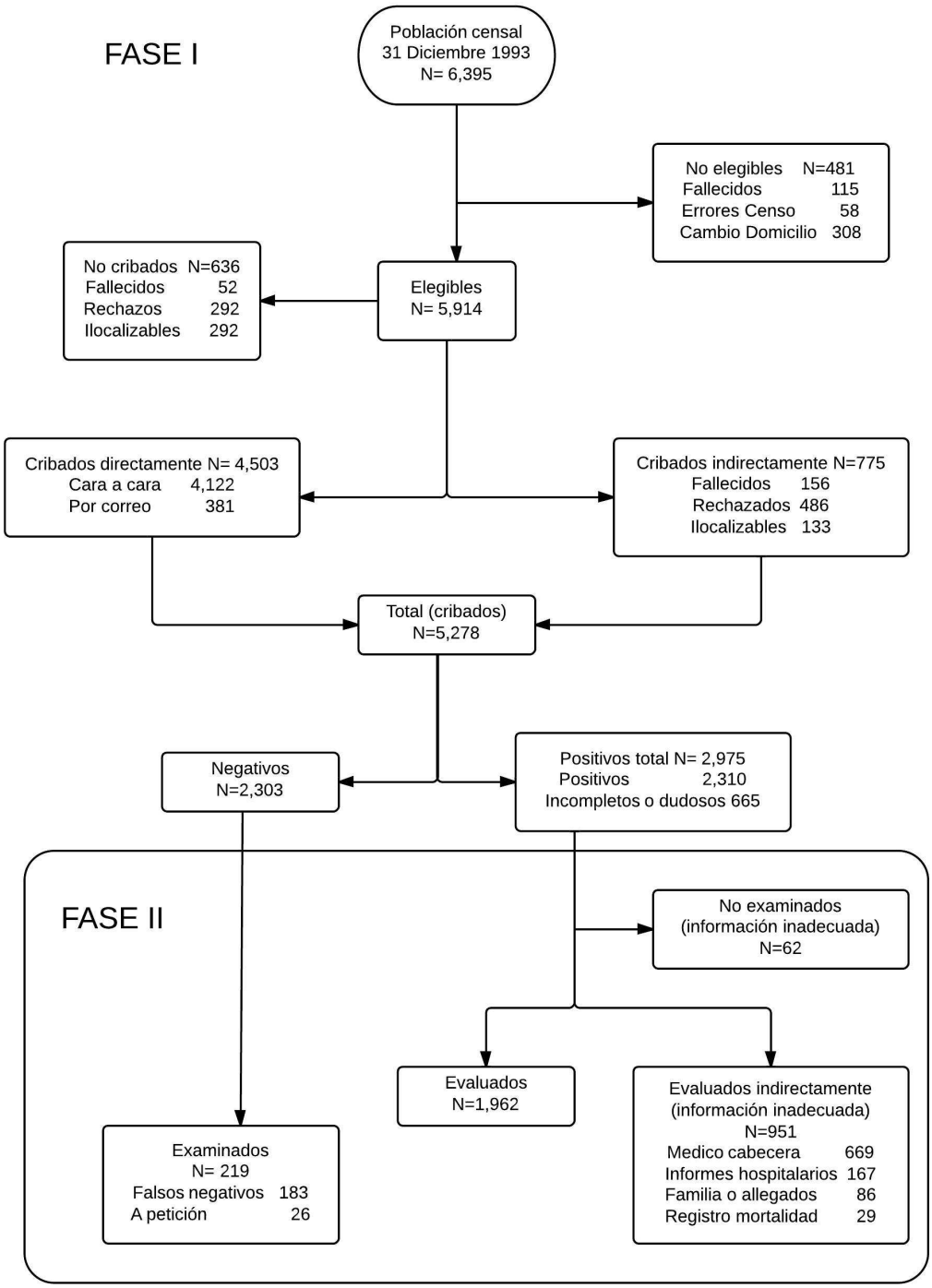
Evolución de la Población cribada del corte basal (n=5278). Situación en el segundo corte.

PARTICIPANTES	NÚMERO	PORCENTAJE
No cribados por cambio de domicilio (no elegibles)	185	3,5
No cribados por fallecimiento (sin información)	510	9,7
No cribados por no localizados	294	5,6
No cribados por rechazo	112	2,1
Cribado directo cara a cara	3,015	57,1
Cribado por correo	144	2,7
Cribado por teléfono	388	7,4
Cribados información indirecta	630	11,9
- A través de médico de familia	-148	-2,8
- Informe Hospitalario	-101	-1,9
- Fallecidos durante período de incidencia con información	-381	-7,2
Total	5,278	100,0

TOMADO DE *Cohorte de ancianos NEDICES*. Madrid: EDIMSA, 2007.

FIGURA 1

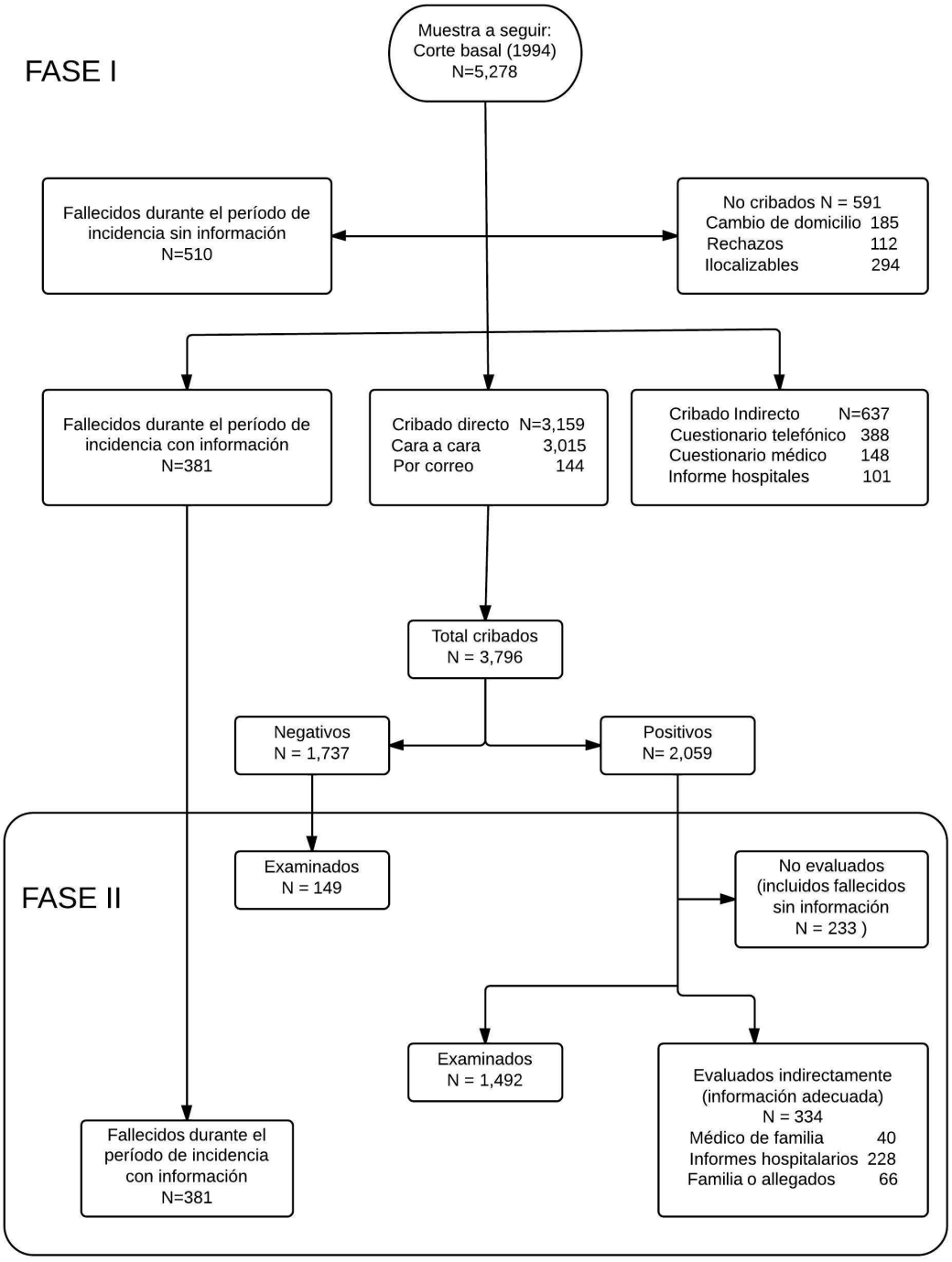
Diagrama de flujo del corte basal (1994)



TOMADO DE *Cohorte de ancianos NEDICES*. Madrid: EDIMSA, 2007.

FIGURA 2

Diagrama del flujo del segundo corte



TOMADO DE *Cohorte de ancianos NEDICES*. Madrid: EDIMSA, 2007.

XII. ANEXOS

CARTA DE LOS DIRECTORES DE TESIS

A la atención del órgano responsable
Departamento de Psiquiatría
(Doctorado en Neurociencias)
Facultad de Medicina
Universidad Complutense de Madrid

Nosotros, Julián Benito León (DNI 07510142K, Hospital Universitario 12 de Octubre) y Félix Bermejo Pareja (DNI 02168665H, Hospital Universitario 12 de Octubre). Codirectores de la Tesis Doctoral (Titulo: CAUSAS DE MORTALIDAD EN LA COHORTE NEDICES. RIESGO INVERSO ENTRE DEMENCIA Y CANCER.) de Juan Pablo Romero Muñoz con DNI 51708678D alumno del programa de Doctorado de Neurociencias del Departamento de Psiquiatría de la Facultad de Medicina de la UCM y neurólogo del Hospital Universitario 12 de Octubre certificamos que:

Este doctorando hace bajo nuestra dirección su tesis y se ha decidido la realización bajo la modalidad de recopilación de publicaciones. Su participación como autor de los cuatro artículos incluidos en esta tesis ha involucrado la creación, escritura, análisis y revisión de los resultados de cada uno de los trabajos incluidos. Todos estos trabajos son de gran calidad, responden a los objetivos planteados en la elaboración de la tesis y a fecha de este certificado han sido aceptados para su publicación en revistas internacionales que son de gran renombre dentro de la especialidad.

Los editores del Journal of Alzheimer Disease han seleccionado dos de estas publicaciones (1y2) para un "press release" lo cual denota su gran calidad y relevancia.

A continuación se listan las publicaciones antes mencionadas.

1. *Under Reporting of Dementia Deaths on Death Certificates: A Systematic Review of Population-based Cohort Studies* **Juan Pablo Romero MD**; Julián Benito-León MD, PhD; Elan D. Louis, MD, MSc; Félix Bermejo Pareja MD, PhD Publicado el 28 de febrero de 2014 en **Journal of Alzheimers Disease** DOI: 10.3233/JAD-132765
2. *Under Reporting of Dementia Deaths on Death Certificates using Data from A Population-Based Study (NEDICES)* **Juan Pablo Romero**, Julián Benito-León, Alex J. Mitchell, Rocío Trincado, Félix Bermejo-Pareja Publicado el 19 de Noviembre de 2013 en **Journal of Alzheimers Disease** DOI: 10.3233/JAD-131622
3. *Alzheimer's Disease is associated with Decreased Risk of Cancer-Specific Mortality: A Prospective Study (NEDICES)* **Juan Pablo Romero MD**; Julián Benito-León MD, PhD; Elan D. Louis, MD, MSc Publicado el 21 de enero de 2014 en **Journal of Alzheimers Disease** DOI:10.3233/JAD-132048
4. *Faster cognitive decline in non-demented elders and decreased risk of cancer mortality (NEDICES)* Julian Benito-Leon, **Juan Pablo Romero**, Elan Louis, and Félix Bermejo-Pareja Aceptado en **NEUROLOGY** para publicación con la referencia: NEUROLOGY/2013/561845 el 15 de Enero de 2014.

Factor de Impacto (Journal Citation Reports, 2012):

- **JAD tiene un factor de impacto de 4.17**
- **NEUROLOGY tiene un factor de impacto de 8.25**

Madrid, 20 de Marzo de 2014

Julián Benito León

Félix Bermejo Pareja

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A continuación se adjuntan los correos electrónicos de las editoriales de las revistas aprobando el uso de los artículos incluidos en esta tesis y su publicación como parte de la misma.

1. JOURNAL OF ALZHEIMERS DISEASE

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Enviado el: jueves, 06 de febrero de 2014 14:41
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To: 'Carry Koolbergen' <c.koolbergen@iospress.nl>, <publisher@iospress.nl>, <editorial@j-alz.com>

CC: 'Julián Benito' <jbenitol@meditex.es>

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List of mentioned publications.

1. Alzheimer's Disease is associated with Decreased Risk of Cancer-Specific Mortality: A Prospective Study (NEDICES) Juan Pablo Romero MD; Julián Benito-León MD, PhD; Elan D. Louis, MD, MSc; Félix Bermejo Pareja MD, PhD (JAD13-2048), scheduled for Volume 40, issue 2 (April 2014)

2. Under Reporting of Dementia Deaths on Death Certificates using Data from A Population-Based Study (NEDICES) Juan Pablo Romero, Julián Benito-León, Alex J. Mitchell, Rocío Trincado, Félix Bermejo-Pareja DOI: 10.3233/JAD-131622

3. Under Reporting of Dementia Deaths on Death Certificates: A Systematic Review of Population-based Cohort Studies Juan Pablo Romero MD; Julián Benito-León MD, PhD; Elan D. Louis, MD, MSc, Felix Bermejo pareja MD, PhD. JAD 13-2765R1

Greetings

Juan Pablo Romero Muñoz

Neurologo

Proyecto Neurotremor

Hospital Universitario 12 de Octubre

Madrid

2. NEUROLOGY

-----Mensaje original-----

De: Rachel Seroka [mailto:RSeroka@aan.com] Enviado el: martes, 28 de enero de 2014 18:05
Para: Juan Pablo Romero; 'Julian Benito-Leon'
CC: Angela Babb; Michelle Uher
Asunto: RE: Special Request NEUROLOGY MS ID# NEUROLOGY/2013/561845

Dear Dr. Romero,

Thank you very much for your inquiry. The journal is willing to allow this, as long as the research is not published in any other way.

Kindest regards,

Rachel L. Seroka
Manager, Media and Public Relations
American Academy of Neurology
201 Chicago Avenue
Minneapolis, MN 55415

Ph: 612-928-6129 Mobile: 612-807-6968 Fax: 612-454-2744
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-----Original Message-----

From: Juan Pablo Romero [mailto:j.romero.neuro@hotmail.com]
Sent: Wednesday, January 22, 2014 7:34 AM
To: 'Julian Benito-Leon'; Rachel Seroka
Subject: Special Request NEUROLOGY MS ID# NEUROLOGY/2013/561845

Dear Rachel Seroka,
Neurology.

I am Juan Pablo Romero, a co-author of the following article:
NEUROLOGY MS ID#: NEUROLOGY/2013/561845
MS TITLE: Faster cognitive decline in non-demented elders and decreased risk of cancer mortality (NEDICES) Julian Benito-Leon, Juan Pablo Romero, Elan Louis, and Félix Bermejo-Pareja

This publications has been accepted to be published by your journal. This publication is part of my PHD thesis work, so I would like to include it as an annex document on my PHD Thesis.
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Thank you in advance

Greetings. Feel free for any questions about this.

Juan Pablo Romero Muñoz
Hospital Universitario 12 de Octubre

ANEXO 1.

ANEXO 1.1 REVISIÓN SISTEMÁTICA DEL INFRA REPORTE DE LA DEMENCIA EN LOS CERTIFICADOS DE MUERTE EN ESTUDIOS POBLACIONALES DE COHORTE. (TÍTULO ORIGINAL: UNDER REPORTING OF DEMENTIA DEATHS ON DEATH CERTIFICATES: A SYSTEMATIC REVIEW OF POPULATION-BASED COHORT STUDIES)

Publicado el 28 de febrero de 2014 en **Journal of Alzheimers Disease** DOI: 10.3233/JAD-132765. Pub Med ID: 24583403

Resumen:

El propósito de esta revisión es evaluar el grado en que la demencia se omite como causa de la muerte en los certificados de defunción de los pacientes con demencia. Se realizó una búsqueda sistemática de la literatura para identificar estudios de cohortes de base poblacional en el todos los participantes hayan sido examinados buscando síntomas de demencia haciendo uso de instrumentos validados y confirmados mediante examen clínico de los casos sospechosos (investigación en dos fases). Se extrajeron los datos de manera estandarizada y evaluados a través de herramienta propuesta por Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) initiative.

Siete estudios cumplieron los criterios de selección. Estos eran de América (5 artículos, de los cuales 2 de Canadá, 2 de los Estados Unidos , y el 1 de Brasil) , y Europa (2 artículos, de los cuales 1 en Reino Unido y 1 de España) .

Todos los artículos cumplen al menos el 83% de los criterios de STROBE. La notificación de la demencia en los certificados de defunción era baja en todos los 7 estudios, que van desde el 7,2 % al 34 %. El uso de los certificados de defunción para el estudio de las variables epidemiológicas de la demencia subestima en gran medida el impacto de esta enfermedad en la población. El informe deficiente de la demencia en estos certificados sugiere una falta de conciencia entre el personal médico sobre la importancia de la demencia como causa de muerte. Hay una necesidad urgente de proporcionar una mejor educación sobre la importancia de la codificación de la demencia en los certificados de defunción, a fin de minimizar los errores en los estudios epidemiológicos sobre la demencia.

Under Reporting of Dementia Deaths on Death Certificates: A Systematic Review of Population-based Cohort Studies

Juan Pablo Romero MD;[1] Julián Benito-León MD, PhD;[1,2,3]

Elan D. Louis, MD, MSc; [4, 5, 6, 7] Félix Bermejo Pareja MD, PhD;[1,2,3]

From the Department of Neurology,[1] University Hospital "12 de Octubre", Madrid,Spain;

Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas

(CIBERNED),[2] Spain; Department of Medicine,[3] Complutense University, Madrid,

Spain; G.H. Sergievsky Center,[4] College of Physicians and Surgeons, Columbia University, New York, NY, USA; Department of Neurology,[5] College of Physicians and

Surgeons, Columbia University, New York, NY, USA; Taub Institute for Research on

Alzheimer's Disease and the Aging Brain,[6] College of Physicians and Surgeons, Columbia University, New York, NY, USA; Department of Epidemiology,[7] Mailman

School of Public Health, Columbia; University, New York, NY, USA

Abstract. The purpose of this review is to assess the extent to which dementia is omitted as a cause of death from the death certificates of patients with

dementia. A systematic literature search was performed to identify population-based cohort studies in which all participants were examined or screened for symptoms of dementia with a validated instrument followed by confirmation of any suspected cases with a clinical examination (two-phase investigation). Data were extracted in a standardized manner and assessed through the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) initiative. Seven studies met the selection criteria. These were from America (5 articles, including 2 from Canada, 2 from the United States, and 1 from Brazil), and Europe (2 articles, including 1 from the United Kingdom, and 1 from Spain). Each met at least 83% of the STROBE criteria. The reporting of dementia on death certificates was poor in these 7 studies, ranging from 7.2% - 34%. Respiratory or circulatory-related problems were the most frequently reported causes of death among people who were demented but who were not reported as demented on death certificates. The use of death certificates for studying dementia grossly underestimates the occurrence of dementia in the population. The poor reporting of dementia on these certificates suggests a lack of awareness of the importance of dementia as a cause of death among medical personnel. There is an urgent need to provide better education on the importance of codification of dementia on death certificates in order to minimize errors in epidemiological studies on dementia.

INTRODUCTION

Since the early 12th century, death certificates have been an important source of information on population health.[1] Today, nearly 900 years after the

introduction of the death certificate, death certificate data continue to be immensely important in shaping our understanding of the health of a population.[1] Death certification, and the specification of the underlying cause of death, has been used to map the geographical distribution of multiple diseases. For example, dementia has been studied in this way. Death certificates have been used as a data source to address both the prevalence and incidence of dementia[2] as well as the causes of death associated with dementia. In both of these areas, however, the utility of death certificate data may be limited.[3]

In view of the importance of the subject matter, and the absence of a comprehensive review of the validity of death certificates with respect to dementia, we undertook a systematic review with the aim to determine the extent to which dementia is omitted as a cause of death from the death certificate in patients with known dementia. We included population-based cohort studies in which (i) all participants had been examined to detect dementia cases or (ii) in which participants had been screened for symptoms of dementia with a validated instrument and subsequent confirmation of any suspected dementia cases with a clinical examination (two-phase investigation).

MATERIAL AND METHODS

Search Strategy and Information Sources

Searches were performed in December 2013 using PUBMED/MEDLINE and Google Scholar. The keywords were different combinations of “dementia”,

"death certificates", and "Alzheimer's disease". In addition, our own extensive files were searched. Original articles were obtained, and all reference lists were scanned for further relevant articles. No time limit was applied in our search strategy. The final list was reviewed by two authors (J.P.R. and J.B.-L.) to identify additional studies or unpublished data.

Inclusion and Exclusion Criteria

We included population-based cohort studies in which (i) all participants had been examined to detect dementia cases or (ii) in which participants had been screened for symptoms of dementia with a validated instrument and subsequent confirmation of any suspected dementia cases with a clinical examination (two-phase investigation). We excluded studies based on inpatient databases or clinical series. No language restrictions were applied.

Data Extraction

Two investigators (J.P.R. and J.B.-L.) independently reviewed the title and abstract of all citations identified by the initial search and excluded citations that clearly did not meet the inclusion criteria. We retrieved the full text of the remaining studies and both investigators reviewed each study to assess whether it met the inclusion criteria. All differences were settled by discussion. For each study, data were abstracted on the design, population size, and clinical diagnostic methods. The outcome of this systematic review was the concordance of cause of death codification (as coded on the death certificate) with clinical diagnosis of dementia; this concordance was expressed as a percentage.

The selected articles were also evaluated to assess whether they conformed to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations, which seek to assess clarity in the description of epidemiological studies.[4] The STROBE includes 22 items that are related to the information that must be present in the title, abstract, introduction, methods, results, and discussion of scientific articles describing observational studies.[4]

Statistical analysis

For the evaluation of article selection criteria and study quality among reviewers, the kappa-measured agreement was based on the specifications of the specialized literature: $k < 0.10$, no agreement; $k < 0.40$, weak agreement; $0.40 < k < 0.75$, good agreement; $k > 0.75$, excellent agreement.[5]

RESULTS

The electronic search identified a total of 170 articles, of which 7 articles met our inclusion criteria.[6-12] Because the independent selection of articles for inclusion in this review showed excellent agreement (k = 0.970), the intervention of a third researcher was not required. Figure 1 shows the progressive selection procedure and the number of articles at each step.

Description of studies

The seven articles that met the specific inclusion criteria at the end of the selection procedure included five from America (2 from Canada, 2 from the

United States, and 1 from Brazil), and two from Europe (1 from the United Kingdom, and 1 from Spain). The sample size of the studies ranged from 527 to 10,263 participants. Overall, the reporting of dementia on death certificates in these 7 studies was poor, ranging from 7.2 to 34% (Table 1). Four articles reported results from two cohorts (the Monongahela Valley Independent Elders Survey [MoVIES] and the Canadian Study of Health and Aging).[7-10] Table 1 summarizes the diagnostic criteria used for dementia as well as the causes of death among those who were demented but who were not reported as demented on death certificates. Respiratory or circulatory-related problems were the most frequently reported causes of death in these people.

Of 1,042 elderly people, randomly selected by Morgan and Clarke,[6] there were 512 deaths in the period from 1985–1994, with 44 of these deaths occurring among respondents who, at clinical interview, met Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition—Revised (DSM-III-R) criteria for dementia.[13] The presence of dementia, however, was recorded on only 15 (34%) of the 44 death certificates.[6] This low level of recording was not significantly related to the patient's gender, age, or place of death (i.e., at a private home vs. at an institution). Also, earlier (1985–1990) and later (1990–1994) certificates showed similar levels of non-recording.[6]

Ganguli and Rodríguez[9] used a prospective epidemiological study in which community-dwelling elderly subjects with and without dementia (N = 1,422, the MoVIES study) were identified and followed until death, after which their death certificates were examined.[9] The cohort was established between 1987 and 1989, and mortality data were reported as of December 31, 1996.[9]

Death certificates were examined for a total of 527 deceased participants, including 172 individuals to whom research diagnoses of dementia had been assigned during life applying DSM-III-R criteria.[9] Of these 172 deceased subjects, conditions indicating or suggesting dementia were reported in 23.8% of death certificates.[9] In a multiple logistic regression model, variables associated independently with the reporting of dementia in demented individuals were: greater severity of dementia, likely etiology of dementia (probable Alzheimer's disease more frequently reported), and dying in a long-term care institution.[9]

Østbye et al.[7], using data from the Canadian Study of Health and Aging, compared 5-year overall mortality and causes of death in elderly with and without dementia. The cohort consisted of 2,923 people who underwent a clinical examination and 7,340 people who screened negative for cognitive impairment and did not undergo a clinical examination.[7] Among patients clinically diagnosed with Alzheimer's disease, only 14.3% had any dementing illness recorded as the underlying cause of death; 41.8% had any dementing illness recorded anywhere on the death certificate.[7] For vascular dementia, the corresponding numbers were 5.8% and 23.3%.[7]

Chamandy and Wolfson [10] also examined the associations between clinical dementia and underlying cause of death in the Canadian Study of Health and Aging. However, the methods were slightly different from the paper by Østbye et al.[7] who previously examined cause of death in the cohort, but in the context of a larger analysis and a coarser partition of causes of death (e.g., pneumonia was not differentiated from chronic respiratory conditions). Cause-of

death data were obtained via death certificates for 2,924 of 2,982 deceased subjects. Among 754 demented, 7.2% were coded as Alzheimer's disease in death certificates.[10]

Ganguli et al.,[8] examined mortality rates, duration of survival, causes of death, and the contribution of Alzheimer's disease to the risk of mortality in the MoVIES study, a community-based cohort of 1,670 elderly adults (1,422 randomly selected from voter registration lists and an additional 259 volunteers from the same area).[8] Mortality data were reported as of December 31, 2002. Only 29 (12.3%) of the 236 participants with Alzheimer's disease had this condition reported in their death certificate.[8]

Nitrini et al.,[11] studied a cohort of 1,656 elderly individuals who were screened for dementia at their homes in 1997. The same population was re-evaluated in 2000, and information on deaths was obtained from relatives and from the municipal obituary service.[11] As of 1997, the number of deaths was 58 (51.3%) among the patients with dementia and 163 (12.7%) among those without dementia. Dementia and/or Alzheimer's disease were mentioned in only 12.5% of the death certificates of individuals with dementia.[11]

Finally, Romero at al.,[12] in a prospective population-based study (NEDICES), using a two-phase approach involving 4,197 community-dwelling elderly subjects with and without dementia followed during a median of 12.5 years, examined the death certificates of those who died (1,976 [47.1%], including 403 subjects with dementia). Dementia was rarely reported as the primary cause of death, even in known cases of dementia (20.8%).[12] Specifically, it was reported in only 13.3% of those with mild dementia and

24.3% of those with moderate or severe dementia; in 24.9% of those with possible or probable Alzheimer's disease; and in 11.9% of those with non-Alzheimer dementia.[12] In a stepwise multiple logistic regression analysis with the dependent variable being presence or absence of dementia on the death certificate, age at death, severity of dementia, and etiology of dementia were the significantly associated independent variables.[12]

Quality of studies

The evaluation of agreement between the evaluators (J.P.R. and J.B.-L.) in the classification of articles, according to the STROBE criteria showed excellent agreement (k = 0.758). All articles met at least 83% of the STROBE criteria (Table 2). All of them stated the specific objectives. In addition, the key elements of the study design and main results were presented in all seven articles (Table 2).

DISCUSSION

In this review of population-based studies published up to December 2013 in PubMed/Medline and Google Scholar databases, we tried to elucidate the extent to which dementia is omitted as a cause of death from death certificates. We restricted our analysis to population-based cohort studies in which all participants were examined or in which all participants were screened for symptoms of dementia with a validated instrument followed by a confirmation of any suspected cases with a clinical examination (two-phase

investigation). We focused on these types of studies because, unlike clinical series or hospital registries, these tended to include even those with previously undiagnosed dementia residing in the population.

Our conclusions are as follows. First, there are very few studies (seven in total) meeting these criteria. Second, all studies we included met the majority of required items from the STROBE guidelines. Finally, dementia was reported in fewer than one third of the deaths of community-dwelling demented individuals.

Three of the studies assessed whether a broad range of variables was correlated with the reporting of dementia on death certificates.[6, 9, 12] Dementia was significantly more likely to be reported in more advanced dementia, those with probable Alzheimer's disease, younger patients, and those who die in nursing homes. However, gender does not appear to influence this reporting. In a British series of death certificates of early onset-cases from hospital-case records, Newens et al.,[14] found that dementia was more likely to be underreported in men; by contrast, in other clinical series, such as CERAD, dementia was significantly less likely to be certified in women who had been diagnosed as having Alzheimer's disease.[15]

With respect to age at death, the results are not consistent. In the NEDICES study, among those died before 85 years, compared to those aged 85 and over, the odds that dementia was reported on death certificates was 2.33, 95%, confidence interval (1.33–4.10), p = 0.003. This suggests that physicians may consider cognitive disorders to be a function of normal ageing

and not diagnose dementia in their oldest patients. In CERAD, age at death was not related to under reporting of dementia on death certificates.[15]

All of the included cohorts were ethnically homogeneous.[6-12] This did not allow us to analyse the impact of race on reporting; however, in clinical series, dementia was significantly less likely to be certified in blacks.[15]

Dementia seems more likely to be listed on death certificates of individuals who had been clinically diagnosed with Alzheimer's disease or probable Alzheimer's disease than those diagnosed as other non- Alzheimer's disease dementias.[9, 12] This is in line with the results from other dementia registries.[16-18] This may reflect a lack of recognition of dementia in the context of stroke or a displacement of dementia from the death certificate by the underlying vascular causes of both death and dementia, mainly cerebrovascular diseases. With respect to severity of dementia, higher severity of dementia was associated with higher odds of reporting dementia in the death certificates,[9, 12] similar to clinical series.[19] The certifying physician might be less likely to have documented dementia when the disorder is mild.[14] In other words, mild dementia may be less likely to be listed on death certificates because its presence is less evident to the certifying physician. It is widely known that severe dementia increases the mortality risk through immobility, swallowing disorders, incontinence, and malnutrition.[9, 20] However, physicians may not report dementia, even when they are aware of the severity of dementia, if they do not feel to be underlying or contributing to the patient's death.[9] The aforementioned complications of severe dementia, in turn, underlie more

immediate causes of death, including pneumonia.[10, 16, 18, 21] Further, common comorbid disorders in the elderly, such as heart disease, stroke, hip fractures, and chronic obstructive lung disease are in general better accepted as causes of death. In other reported conditions, such as Parkinson's disease, cognitive problems, including dementia, are often observed.[22, 23] If death certificates data are to be used to estimate mortality from dementing disorders, it may be useful to simultaneously search for documentation of other reported central nervous system conditions likely to be associated with dementia.[9]

Dementia is more often reported for the demented who die in psychiatric and geriatric facilities.[9] It seems logical that nursing homes have more patients with more severe and full-blown dementia and therefore physicians attending those centers are more likely to report dementia on death certificates.[24]

Although regional or national differences in diagnostic accuracy of conditions reported on death certificates have been suggested, with European rates higher than rates in the USA,[16, 18, 21] the rates of the present review are similar. Thus, in the MoVIES study, conducted in the USA, conditions indicating or suggesting dementia was reported in 23.8% of death certificates vs. 20.8% in the Spanish NEDICES study.[9, 12]

In the last years, dementia awareness has increased among both physicians and the public, in general. Previous surveys have found that the frequency with which dementia was recorded on death certificates increased

significantly over the years of their study.[14, 15] However, the period during which death certificates were completed did not influence the rate of reporting in the MoVIES and NEDICES studies,[9, 12] or in Morgan and Clarke's study,[6].

Increased awareness of medical staff regarding the mortality and morbidity associated with dementia could lessen the degree of under reporting. For example, in the CERAD study, in the first wave, only 49% endorsed dementia versus 65% in the second wave ($p < 0.025$),[15] suggesting that greater awareness among the medical staff could result in increased coding of dementia as a cause of death. Of interest, none of the studies assessed who signed the death certificate (i.e., general physician versus neurologist or geriatrician). It is logical to assume that the level of expertise of the physician who signed the death certificate might predict the level of accuracy of that certificate.

This study had potential limitations. Database restriction and the search strategy may have excluded important studies that were not published in the data sources we searched, although we used multiple overlapping study identification methods, so this is not likely.

In closing, the use of death certificates for studying dementia grossly underestimates the occurrence of dementia in the population. The poor reporting of dementia on these certificates suggests a lack of awareness of the importance of dementia as a cause of death among medical personnel. There is an urgent need to provide better education on the importance of codification of

dementia on death certificates in order to minimize errors in epidemiological studies on dementia.

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Table 1: Main characteristics of the selected studies

Reference	Diagnostic criteria for dementia	Reporting of dementia on death certificates	Causes of death in those who were demented but who were not reported as demented on death certificates
Morgan and Clarke., 1995	DSM-III-R	34% (as an associated underlying condition)	Broncho-pneumonia (72.1%); cerebrovascular disease (11.6%); heart disease (9.1%); cancer (4.6%); sepsis (2.3%)
Ganguli and Rodríguez., 1999	DSM-III-R	23.8%	Not reported
Østbye et al., 1999	DSM-III-R	41.8% of Alzheimer's disease patients. 23.3% of vascular dementia patients	Most deaths in people with dementia were due to diseases of the respiratory or circulatory systems (yet percentages were not reported)
Chamandy and Wolfson., 2005	DSM-III-R	7.2% (Alzheimer's disease)	Ischemic heart disease (19.2%); other heart/circulatory system disease (13.3%); cerebrovascular disease (13.1%); pneumonia (12.3%); cancer (10.7%); chronic respiratory disease (4.2%)
Ganguli et al., 2005	DSM-III-R	12.3% of Alzheimer's disease patients	Cardiovascular (47.5%); respiratory (22.5%); cancer (12.3%); other brain disorder (5.5%); genitourinary (5.5%); gastrointestinal (4.7%); unknown "natural causes" (2.1%); miscellaneous (10.2%)
Nitrini et al., 2005	DSM-IV	12.5%	Pneumonia (40.0%); respiratory failure (27.5%); heart failure (20.0%); sepsis (20.0%); stroke (20.0%); cancer (17.5%); cardiorespiratory arrest (15%); renal failure (12.5%); arrhythmia (10%); pulmonary embolism (7.5%); acute myocardial infarction (5.0%); coronary artery disease (5.0%)
Romero et al., 2013	DSM-IV	20.8%	Cerebrovascular disorders (13.4%); cardiovascular diseases (27.5%); respiratory diseases (14.4%); cancer (6.0%); other causes (17.9%)

Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition—Revised (DSM-III-R)

Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV)

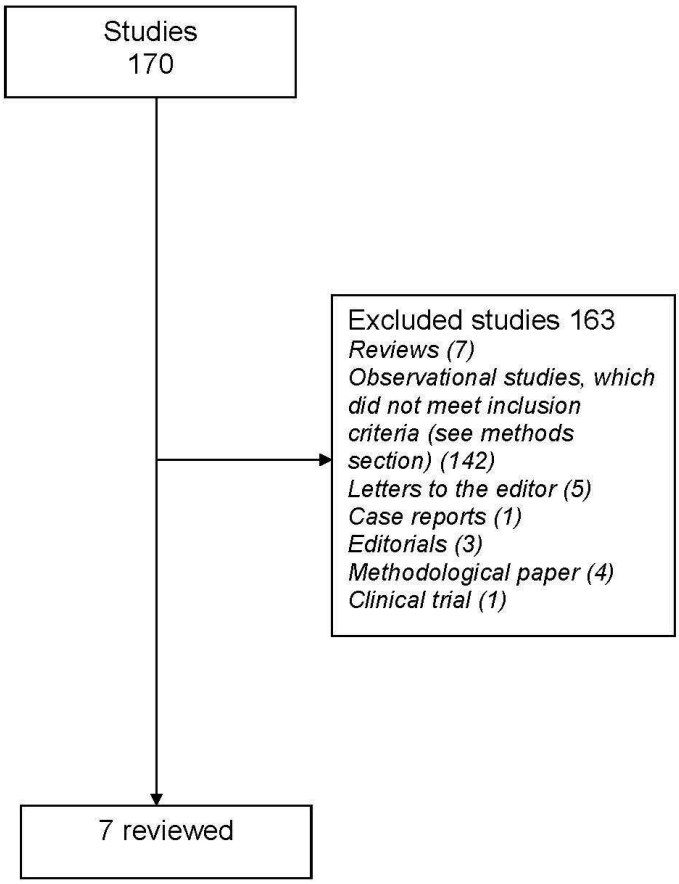
Table 2: Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations and reported percentages of observational studies.

		Recommendation	**Morgan and Clarke, 1995**	**Ganguli and Rodriguez, 1999**	**Ostbye, et al., 1999**	**Chamandy and Wolfson, 2005**	**Ganguli et al., 2005**	**Nitrini et al., 2005**	**Romero et al., 2013**	**Reported percentage (Number reported/possible)**
Title and abstract	Title and abstract	(a) Indicate the study's design with a commonly used term in the title or the abstract	X	X	X	X	X	X	X	7/7(100%)
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	X	X	X	X	X	X	X	7/7(100%)
Introduction	Background/rationale	Explain the scientific background and rationale for the investigation being reported	X	X	X	X	X	X	X	7/7(100%)
	Objectives	State specific objectives, including any prespecified hypotheses	X	X	X	X	X	X	X	7/7(100%)
Methods	Study design	Present key elements of study design early in the paper	X	X	X	X	X	X	X	7/7(100%)
	Setting	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	X	X	X	X	X	X	X	7/7(100%)
	Participants	Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	X	X	X	X	X	X	X	7/7(100%)
	Variables	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	X	X	X	X	X	X	X	7/7(100%)
	Data sources/ measurement	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	X	X	X	X	X	X	X	7/7(100%)
	Bias	Describe any efforts to address potential sources of bias	X	X	X	X	X	X	X	7/7(100%)
	Study size	Explain how the study size was arrived at	X	X	X	X	X	X	X	7/7(100%)
	Quantitative variables	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	X	X	X	X	X	X	X	7/7(100%)
	Statistical methods	(a) Describe all statistical methods, including those used to control for confounding	X	X	X	X	X	X	X	7/7(100%)
		(b) Describe any methods used to examine subgroups and interactions	X	X	X	X	X	X	X	7/7(100%)
		(c) Explain how missing data were addressed	X	X	X	X	X	X	X	7/7(100%)
		(d) If applicable, explain how loss to follow-up was addressed	X	X	X	X	X	X	X	7/7(100%)

Results	Participants	(a) Report numbers of individuals at each stage of study—e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	X	X	X	X	X	X	X	7/7(100%)
		(b) Give reasons for non-participation at each stage	0	0	0	0	0	0	0	0/7 (0%)
		(c) Consider use of a flow diagram	0	0	0	X	0	0	X	2/7(28.5%)
	Descriptive data	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders	0	0	0	X	0	X	X	3/7(42.8%)
		(b) Indicate number of participants with missing data for each variable of interest	0	0	0	0	0	0	0	0/7 (0%)
		(c) Summarise follow-up time (e.g., average and total amount)	X	X	X	X	X	X	X	7/7(100%)
	Outcome data	Report numbers of outcome events or summary measures over time	X	X	X	X	X	X	X	7/7(100%)
	Main results	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included	X	X	X	X	X	X	X	7/7(100%)
	Other analyses	Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses	0	X	X	X	X	X	X	6/7(85.7%)
Discussion	Key results	Summarise key results with reference to study objectives	X	X	X	X	X	X	X	7/7(100%)
	Limitations	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	X	0	0	X	0	X	X	4/7(57.1%)
	Interpretation	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	X	X	X	X	X	X	X	7/7(100%)
	Generalizability	Discuss the generalizability (external validity) of the study results	X	X	X	X	X	X	X	7/7(100%)
Other Information	Funding	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	X	X	X	X	X	X	X	7/7(100%)
STROBE fulfilment percentage			83.3%	83.3%	83.3%	93.3%	83.3%	90%	93.3%	

Information on the STROBE Initiative is available at http://www.strobe-statement.org.

Figure 1: Identification of studies in the systematic review.



ANEXO 2.2 INFRA REPORTE DE LA DEMENCIA EN LOS CERTIFICADOS DE DEFUNCIÓN. DATOS DE UN ESTUDIO POBLACIONAL (NEDICES). (TÍTULO ORIGINAL: UNDER REPORTING OF DEMENTIA DEATHS ON DEATH CERTIFICATES USING DATA FROM A POPULATION-BASED STUDY (NEDICES))

Publicado el 19 de Noviembre de 2013 en **Journal of Alzheimers Disease** DOI: 10.3233/JAD-131622 Pub Med ID: 24254704

Resumen:

Estudios previos han demostrado que la demencia se omite con frecuencia como causa de muerte en el certificado de defunción en sujetos con demencia de larga evolución. Sin embargo, la mayoría de los estudios no consideran sujetos dementes de la población que no han sido diagnosticados. Con el fin de superar este problema, es necesario hacer un cribado de deterioro cognitivo en la población y confirmar el diagnóstico con un examen clínico (aproximación en dos fases). Hemos utilizado esta metodología para estimar la proporción de codificación de la demencia en los certificados de defunción en un estudio poblacional prospectivo (NEDICES) que incluyo a 4.197 ancianos, siguiendo una aproximación en dos fases. Se identificaron los sujetos con y sin demencia en la población estudiada y fueron seguidos durante una media de 12,5 años, después de lo cual se examinaron los certificados de defunción de los que fallecieron. Un total de 1976 (47,1 %) fallecieron (403 sujetos con demencia). La demencia raramente se reportó como la primera causa de muerte, incluso en los casos conocidos de demencia (20,8 %). De hecho, se informó en sólo el 13,3 % de las personas con demencia leve y el 24,3 % de las personas con demencia moderada o grave, y en el 24,9 % de las personas con la

enfermedad de Alzheimer posible o probable, y en el 11,9 % de los sujetos con una demencia distinta del Alzheimer. En un análisis de regresión logística múltiple escalonada, siendo la variable dependiente la presencia o ausencia de demencia en el certificado de defunción, las variables independientes asociadas significativas fueron la edad, la gravedad de la demencia, y la etiología de la demencia. Llegamos a la conclusión de que la codificación de la demencia en los certificados de defunción sigue siendo pobre. Esto sugiere una falta de conciencia de la importancia de la demencia como causa de muerte.

Under reporting of dementia deaths on death certificates using data from a population-based study (NEDICES)

Juan Pablo Romero MD;[1] Julián Benito-León MD, PhD;[1,2,3]

Alex J. Mitchell MD;[4] Rocío Trincado MA;[1,2]

Félix Bermejo-Pareja MD, PhD;[1,2,3]

From the Department of Neurology,[1] University Hospital "12 de Octubre", Madrid, Spain; Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas (CIBERNED),[2] Spain; Department of Medicine,[3] Complutense University, Madrid, Spain; and the Department of Psycho-oncology,[4] Leicestershire Partnership Trust and University of Leicester, Leicester, UK

Abstract. Previous studies have shown that dementia is frequently omitted as a cause of death from the death certificate in patients with long-standing dementia. However, most studies exclude those undiagnosed dementia sufferers in the population. In order to overcome this problem is necessary to screen the population for symptoms of dementia and confirm the diagnosis with a clinical examination (two-phase approach). We used this methodology to estimate the proportion of reporting of dementia on death certificates in a prospective population-based study (NEDICES), using a two-phase approach involving 4,197 elderly people. Community-dwelling subjects with and without dementia were identified and followed during a median of 12.5 years, after which the death certificates of those who deceased were examined. A total of 1,976 (47.1%) died (403 subjects with

dementia). Dementia was rarely reported as the primary cause of death, even in known cases of dementia (20.8%). Indeed it was reported in only 13.3% of those with mild dementia and 24.3% of those with moderate or severe dementia; in 25.2% of those with possible or probable Alzheimer's disease (AD) and 11.6% of those with non-AD dementia. In a stepwise multiple logistic regression analysis with the dependent variable being presence or absence of dementia on the death certificate, the significant associated independent variables were age at death, severity of dementia, and etiology of dementia. We conclude that reporting of dementia on death certificates remains poor. This suggests a lack of awareness of the importance of dementia as a cause of death.

INTRODUCTION

The burden of neurodegenerative diseases in high income countries is increasing as the mean age of population also increases. Alzheimer´s disease and other types of dementias occupy the fourth place in the top 10 leading causes of disability according to 2001 WHO data[1] and are among the top 10 most frequent causes of death.[2]. With the increase in the prevalence of older people observed during recent decades, knowledge of epidemiological information on dementia remains essential.[3] Mortality rate and the causes of death are two of the most relevant public health indicators.. Death certificates have been used as a data source to address both the epdemilogy of dementia[4] as well as the causes of death associated with dementia.[5] In both of these areas, however, the utility of such data may be limited. Often, death certificates do not accurately reflect mortality of dementia Previous studies have shown that dementia is frequently omitted from the death certificate in patients even in cases with clear and long-standing dementia.[6-

16] Most of these studies that have analyzed the under-reporting of dementia on death certificates have recruited their study subjects from treatment settings (i.e., service-based studies) or have used a records linkage system (i.e., medical records of patients evaluated at a clinic or hospital). [6-8, 10-12, 15, 16] These studies may be subject to bias since they exclude a significant proportion of undiagnosed dementia sufferers in the population. The only way to overcome this problem is to screen the population for symptoms of dementia with a validated instrument and confirm any suspected patients with a clinical examination (two-phase investigation method). This type of approach has been rarely performed in order to determine the extent to which dementia is reported by certifying physicians.[9, 13, 14] The scarcity of this type of survey in the literature encouraged us to estimate the reporting of dementia on death certificates in a prospective population-based study in central Spain using a two-phase investigation method.

METHODS

Study population

Data for these analyses were derived from the Neurological Diseases in Central Spain (NEDICES) study, a longitudinal, population-based survey of the prevalence, incidence, and determinants of major age-associated conditions of the elderly, including Parkinson's disease, essential tremor, stroke, and dementia.[17-25] Detailed accounts of the study population and sampling methods have been published.[26-28]

The survey area consisted of three communities: Margaritas (approximately 14,800 inhabitants), a working-class neighborhood in Getafe (Greater Madrid); Lista (approximately 150,000 inhabitants), a professional-class neighborhood in Salamanca

(Central Madrid), and 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, in Lista, proportionate stratified random sampling was used to select subjects for screening because of the large number of elderly residents. 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.

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. The face-to-face interview included data collection on demographics, current medications (including drugs that affect the central nervous system), and medical conditions.

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 neurological disorders (essential tremor, stroke, dementia, and parkinsonism), current medications, and the name of their family doctor.

The screening protocol for dementia included a 37-item version of the Mini-Mental State Examination [37-MMSE])[23, 24, 29-33] and an 11-item version of the

Pfeffer Functional Activities Questionnaire (FAQ).[34] Every person completed an initial screening for cognitive impairment and for those who tested positive at step one (37-MMSE < 24 and FAQ > 5 points)[23, 24] they then had a neurological examination which comprised a clinical history, a general neurological exam and a mental status interview. The second step assessment was at conducted at National Health Service clinics or at home, The diagnosis of dementia was done following the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM)–IV[35] 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. Severity of dementia was established by the DSM-III-R criteria according to daily function.[36] Mild dementia was defined when impairment for work and social activities with the capacity for independent living remaining largely intact; moderate dementia defined when independent living was hazardous and the person required some degree of supervision; and severe dementia was defined by impaired activities of daily living such that continual supervision is required. Medical records were available for all of these participants, including those from their general practitioners, from in-patient hospitalizations, and from neurological specialists (if they had visited one).

For this study we categorized the different types of dementia into possible or probable Alzheimer's disease (AD) according to the NINCDS-ADRDA criteria)[37] and other types of dementia (non-AD dementia).

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, all deceased individuals receive a death certificate, completed by a doctor, at the time of death. The certificate is then sent to the local police authority in the municipality where the person had been living, and the information is collected in the National Register. Causes of death in the dementia and control group were compared. The cause of death (using the International Classification of Diseases - ICD- 9th Revision for deaths occurred prior to 1999, [http://www.cdc.gov/nchs/icd/icd9.htm], and the ICD 10th Revision [http://www.cdc.gov/nchs/icd/icd10.htm], for deaths occurring thereafter) was classified into 6 main categories: dementia, cerebrovascular disorders, other cardiovascular disorders (pulmonary embolism, congestive heart failure, myocardial infarction, heart or aortic rupture, and asystole), respiratory diseases, cancer, and other causes (infections, trauma, genitourinary or gastrointestinal disorders). In accordance with the recommendations of the World Health Organization, the classification of causes of death was investigated and tabulated depending of the basic cause of death (http://www.who.int/topics/mortality/en/). This is defined as the illness or injury which started the chain of pathological events which directly led to death (http://www.who.int/topics/mortality/en/).

Final selection of participants

Of the 5,278 participants screened for neurological disorders at baseline (1994-1995), we detected 306 prevalent dementia cases, leaving 4,972 participants without baseline dementia (Figure). Of these 4,972, 555 were lost to the follow-up evaluation (1997–1998) (Figure). Of the remaining participants, sufficient data were available on 3,891 (including 161 incident cases of dementia) who completed the follow-up

evaluation (1997–1998), which consisted of a screening questionnaire and a neurological examination (Figure).[23, 24]

To maximize the number of clinically diagnosed dementia cases, we used data from the baseline (1994–1995) and the second evaluation (1997–1998) (i.e., we included all available prevalent [N = 306] as well as incident cases of dementia [N = 161] [Figure]).[23, 24]

The final sample of 4,197, including 467 dementia cases and 3,730 non-dementia participants at the second evaluation (1997–1998), was similar to the base sample of 5,278 participants in terms of gender (2,435 [58.0%] vs. 3,040 [57.6%] women, chi-square = 0.17, p = 0.68) and education (564 [13.5%] vs. 711 [13.6%] were illiterate, chi-square = 3.20, p = 0.36), but it was, on average, 0.4 years younger (73.9 ± 6.9 vs. 74.3 ± 7.0 years, t = - 2.86, p = 0.004).

Statistical analyses

Data analyses were performed in SPSS Version 20.0 (SPSS, Inc., Chicago, IL). Unadjusted (bivariate) analyses were performed using the *t* test to compare mean ages and chi-square tests to determine associations between categorical variables.

We determined the overall proportion of cases of clinically diagnosed dementia in which a diagnosis of dementia (a dementia condition) was listed on the death certificates. To further determine whether a dementia condition was more likely to be certified in distinct subgroups of individuals with dementia, we characterized the sample in several ways: by age, gender, severity of dementia, and by likely etiology (probable or possible AD vs. other types of dementia).

To identify those subjects' characteristics associated independently with having a dementia condition reported on death certificates, we performed a stepwise multiple logistic regression model with the dependent (outcome) variable being presence or absence of a dementia condition on the death certificate. Independent (predictor) variables eligible for inclusion in the model were age at death (≥ 85 years vs. < 85 years), gender (women vs. men), year of death (May 1, 1994 to April 30, 2001 vs. May 1, 2001 to May 1, 2007), severity of dementia (moderate and severe vs. mild), and subtype of dementia (possible or probable AD vs. non-AD dementia. These analyses generated odds ratios (OR) with 95% confidence intervals (CI).

RESULTS

The 4,197 participants had a mean duration of follow-up of 10.1 years (median = 12.5 years; range = 0.03 - 13.5 years). Four hundred sixty-seven (11.1%) of 4,197 participants were diagnosed with dementia by the time of baseline (N = 306) and second evaluation (N = 161). 317 (67.9%) had AD and 150 (32.1%) non-AD dementia. Baseline demographic characteristics are shown in Table 1. Subjects with dementia were significantly older and had a lower level of education. In addition, there were a higher proportion of women and a higher proportion of the dementia cases living in Las Margaritas (blue collar area) (Table 1).

1,976 (47.1%) of 4,197 participants died over a median follow-up of 7.1 years (range 0.03–13.3 years), including 403 (86.3%) deaths among 467 participants with dementia and 1,573 (42.2%) deaths among 3,730 participants without dementia.

Cause of death noted on the death certificates differed significantly by dementia status (table 2). Dementia was only rarely reported as the primary cause of death, even in the participants with dementia (20.8%). In both groups, cardiovascular disease was the most frequent reported cause of death, but stroke was more frequent in dementia participants. Cancer was listed significantly less often in those with dementia (6.0%) than in those without dementia (26.5%).

Among participants with dementia in whom a dementia condition was reported (N = 84) were, on average, 2.1 years younger than in those in whom it was not (N = 319) (80.6 ± 7.4 vs. 82.7 ± 6.9 years, t = - 2.37, p = 0.018). The proportions of women (N = 57, 67.9%) and men (N = 207, 64.9%) with certification of dementia conditions were not significantly different (chi-square = 0.259, p = 0.611).

Of the 403 demented participants who died, 350 (86.8%) had information on severity of dementia. Dementia conditions were listed in a significantly (chi-square = 6.123, p = 0.013) smaller proportion of those with milder stage (17, 13.3%) than of those with moderate or severe dementia stage (54, 24.3%).

Dementia was listed on the death certificates in 69 (25.2%) of those with possible or probable AD and in 15 (11.6%) of those with non-AD dementia. These proportions were significantly different (chi-square = 9.767, p = 0.002).

Of the 128 individuals with mild dementia who died, 93 (72.7%) were diagnosed as possible or probable AD, and 35 (27.3%) as non-AD dementia. Of the 222 individuals with moderate and severe dementia who died, 164 (73.9%) were diagnosed as possible or probable AD, and 58 (26.1%) as non-AD dementia. Proportions of deceased subjects with possible or probable AD, and non-AD

dementia were not significantly different with respect to severity of dementia, i.e., there was no association between stage and likely etiology of dementia (chi-square = 0.062, p = 0.804).

We compared the periods before and after April 30, 2001. As the cohort ages over time, the rate of subjects dying every year increases. Therefore, we categorized our study period into two unequal intervals, May 1, 1994 to April 30, 2001 and May 1, 2001 to May 1, 2007, to provide a more uniform distribution of deaths (959 and 1,017, respectively). In the larger sample of all deceased subjects (N = 1,976), the proportion of those with reported dementia in the later period (N = 76, 51.4%) was similar than that of those who died in the earlier period (N = 72, 48.6%) (chi-square = 0.001, p = 0.977). Again, when restricting the analyses to deceased subjects with clinical diagnoses of dementia (N = 403), there was no significant difference in proportions of those with reported dementia among those who died between May 1, 1994 to April 30, 2001 (N = 72, 48.6%) and those who died between May 1, 2001 to May 1, 2007 (N = 76, 51.4%) (chi-square = 1.248, p = 0.264).

Predictors of reporting dementia on death certificates in the present study are shown in table 3. The significantly associated independent variables in the model were age at death, severity of dementia, and likely etiology of dementia. There was no evidence of lack of fit in the final model according to the Hosmer-Lemeshow goodness-of-fit statistic (p = 0.734).

DISCUSSION

This is the first study in Spain to investigate the association of possible determinants of dementia reporting on death certificates using a population-based

approach. Dementia was reported in less than one-quarter (20.8%) of the deaths examined, but it was significantly more likely to be reported in more advanced cases of dementia, those with possible or probable AD, and those who died younger. Both gender and the period during which the study was conducted (i.e., 1994 to 2007) did not appear to influence the likelihood that an existing dementia would be reported in some form on the death certificates. This level of under-reporting is at the lower end of the range from other studies worldwide that have examined the frequency of mentioning dementia on death certificates in known cases of dementia (0.8–78%).[6-16]

Our results are in agreement with prior community or population-based surveys that have analyzed the proportion of reporting of dementia on death certificates, using a two-phase investigation method, thus permitting to prevent the selection bias.[9, 13, 14] In the Nottingham Longitudinal Study of Activity and Ageing cohort of 1,042 randomly sampled elderly people (aged >65), 48% of those for whom there was evidence of dementia and who had subsequently died, had this information recorded on their death certificates.[9] In a prospective community-based study of 1,422 people age 65 or older study, dementia was only reported in 23.8% on death certificates in the population but significantly more likely to be noted in more advanced cases of dementia, those with probable AD, and those who died in nursing homes.[13] Age and gender did not appear to influence the likelihood that an existing dementia would be reported in some form on the death certificates.[13] There was a nonsignificant trend towards dementia was more likely to be recorded on the death certificates of individuals with greater comorbidity (as implied by total number of conditions listed on the death certificate) and in recent years compared

with previous years.[13] Finally, for people who underwent a clinical examination (n = 2,923) from the national Canadian Study of Health and Aging (CSHA), it was determined how frequently dementia was recorded on the death certificate.[14] Among patients clinically diagnosed with AD, only 14.3% had any dementia related illness recorded as the underlying cause of death; 41.8% had any dementia related illness recorded anywhere on the death certificate.[14]

Other circumstances requiring future analyses are the limitations of the format of the death certificates of each country, the variations of encrypting and dissemination of these changes in health care workers as well as expected changes in diagnostic accuracy due to the advance of diagnostic techniques available.[38] In Spain, for example, the change from International Classification of Diseases (ICD)-9th revision to the ICD-10th revision has meant a declined by 3.2% under the latter, which alerts about the reliability to be given to the data obtained purely with this methodology.[39]

Probably, increased awareness of medical staff regarding the mortality and morbidity associated with dementia could change the codification. This was found in death certificates of CERAD American study, in which during the first wave, only 49% notified the existence of the disease vs. 65% in the second wave ($p < 0.025$),[8] concluding that greater awareness of the medical staff could influence on the increased dementia coding as a cause of death. In the NEDICES study, there were no differences on the codification of dementia in death certificates according to the year of death (May 1, 1994 to April 30, 2001 vs. May 1, 2001 to May 1, 2007).

It is beyond the scope of this article to determine if the trend of increasing prevalence of dementia in different publications and studies based on death certificates is due to a real increase in the prevalence or purely reflects an increase in the registration of the disease in death certificates. In any case we could assume that even in the most optimistic case these new data underestimate the true mortality attributed to dementia.

The observation that cancer was listed significantly less often in those individuals with dementia is of interest and is in line with the possible and inverse occurrence of cancer and AD.[40] Indeed, older persons with cancer have a reduced risk of AD dementia and vice versa.[40]

Our study has limitations. Specifically we did not collect the place of death and comorbidity at death, as well as who signed the death certificate (general physician vs. neurologist 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. This study also has several strengths, including the large number of participants and that it was population-based, allowing us to assess a group of people with dementia unselected.

In conclusion, the results of the NEDICES study not only support the previous findings of previous studies,[6-16] but also reflect the need for a greater understanding and awareness by physicians, public health authorities, and other health management organs that dementia should be considered as an important risk factor for increased mortality in older population.

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Table 1: Baseline (1994–1995) demographic and clinical characteristics of participants with (or who subsequently developed incident dementia) vs. without dementia.

Characteristics at Baseline Assessment	**Participants with or who subsequently developed dementia** **(N = 467)**	**Participants without dementia** **(N = 3,730)**	***p* value**
Age in years	81.5 ± 7.2	72.9 ± 6.2	<0.001[a]
Female gender	312 (66.8%)	2,123 (56.9%)	<0.001[b]
Geographical area			0.018[b]
Arévalo county (rural area)	154 (33.0%)	1,273 (34.1%)	
Las Margaritas (blue collar area)	197 (42.2%)	1,343 (36.0%)	
Lista (white collar area)	116 (24.8%)	1,114 (29.9%)	
Education *			<0.001[b]
Illiterate	144 (31.4%)	420 (11.3%)	
Can read and write	170 (37.0%)	1,556 (41.9%)	
Primary studies	102 (22.2%)	1,203 (32.4%)	
≥Secondary studies	43 (9.4%)	538 (14.5%)	

[a] Student t test.

[b] Chi-square test.

*Data on some participants were missing.
Mean ± standard deviation and frequency (%) are reported.

Table 2 Primary cause of death (IDC 9th) by diagnostic groups.

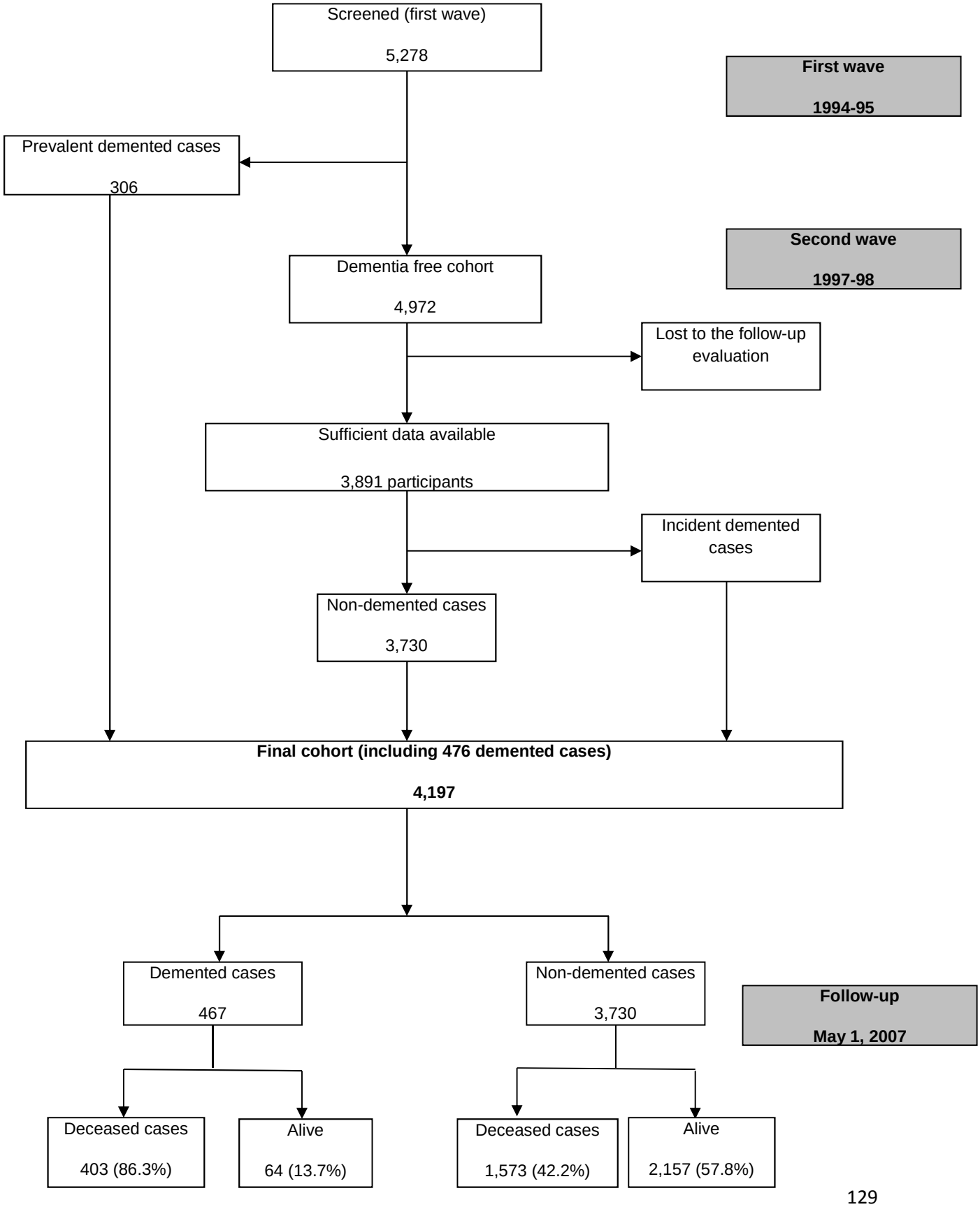
	Dementia N (%)	**No dementia N (%)**	***p* Value ***
Dementia	84 (20.8%)	64 (4.1%)	<0.001
Cerebrovascular disorders	54 (13.4%)	123 (7.8%)	0.026
Cardiovascular diseases	111 (27.5%)	447 (28.4%)	0.136
Respiratory diseases	58 (14.4%)	225 (14.3%)	0.404
Cancer	24 (6.0%)	417 (26.5%)	<0.001
Other	72 (17.9%)	297 (18.9%)	0.174
Total	403 (100%)	1,573 (100%)	

* Chi-square test.

Table 3 Predictors of reporting dementia on death certificates in the deceased participants with clinically diagnosed dementia (N = 403) from the NEDICES study.

	Odds ratio	**95% Confidence Interval**	**p value**
Age at death			
< 85 years	2.24	1.28-3.90	0.004
≥ 85 years (reference)	1	-	-
Severity of dementia			
Moderate and severe	2.04	1.11-3.74	0.022
Mild (reference)	1	-	-
Subtype of dementia			
Possible or probable Alzheimer's disease	3.30	1.54-7.05	0.002
Non-Alzheimer's disease dementia (reference)	1	-	-

Figure 1 : Flow chart of the study



ANEXO 1.3 LA ENFERMEDAD DE ALZHEIMER ESTÁ ASOCIADA CON UN RIESGO DISMINUIDO DE MORTALIDAD POR CÁNCER: UN ESTUDIO PROSPECTIVO (NEDICES) (TÍTULO ORIGINAL: "ALZHEIMER'S DISEASE IS ASSOCIATED WITH DECREASED RISK OF CANCER-SPECIFIC MORTALITY: A PROSPECTIVE STUDY (NEDICES)")

Publicado el 21 de enero de 2014 en **Journal of Alzheimers Disease**

DOI:10.3233/JAD-132048 Pub Med ID: 24448786

Resumen:

Estudios previos han demostrado que la enfermedad de Alzheimer (EA) se asocia con un riesgo reducido de cáncer. Sin embargo, la mayoría de los estudios no incluyen aquellos sujetos dementes que no han sido diagnosticados. La única manera de superar este problema metodológico es examinar a todos los participantes o hacer un cribado de la población con un instrumento validado y confirmar cualquier sospecha de demencia con un examen clínico. (Siguiendo un método de investigación en dos fases). Hemos utilizado esta metodología para estimar si la mortalidad específica por cáncer se asocia con EA y otros tipos de demencia en un estudio poblacional prospectivo (NEDICES) que implica 5.278 personas mayores. Se identificaron los sujetos que viven en comunidad con y sin demencia y fueron seguidos durante una media de 12,5 años, después de lo cual se examinaron los certificados de defunción de los que fallecieron. Un total de 1976 (47,1 %) murieron, incluyendo 277 que tenían posible o probable EA y 126 con demencia no Alzheimer. El cáncer se informó significativamente menos frecuentemente en aquellos con posible o probable EA (5,8 %) o demencia no EA (

6,3 %) que en aquellos sin demencia (26,5 %). En un modelo de Cox no ajustado, el riesgo relativo (RR) de mortalidad específica por cáncer en los participantes con EA = 0,45 (p = 0,002) y RR en participantes con demencia no EA = 0,62 (p = 0,179) en comparación con el grupo de no dementes. En un modelo de Cox ajustado para varios factores demográficos y comorbilidades, los RR de la mortalidad específica por cáncer en los participantes con EA = 0,50 (p = 0,028) y 0,97 (p = 0,942) en la demencia no Alzheimer. Este estudio proporciona más evidencia de una asociación inversa entre el cáncer y el Alzheimer.

Alzheimer's disease is associated with decreased risk of cancer-specific mortality: A prospective study (NEDICES)

Juan Pablo Romero MD;[1] Julián Benito-León MD, PhD;[1,2,3]

Elan D. Louis, MD, MSc;[4, 5, 6, 7]Félix Bermejo-Pareja MD, PhD;[1,2,3]

From the Department of Neurology,[1] University Hospital "12 de Octubre", Madrid,Spain;

Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas

(CIBERNED),[2] Spain; Department of Medicine,[3] Complutense University, Madrid, Spain;

G.H. Sergievsky Center,[4] College of Physicians and Surgeons, Columbia University, New York, NY, USA; Department of Neurology,[5] College of Physicians and Surgeons, Columbia University, New York, NY, USA; Taub Institute for Research on Alzheimer's Disease and the Aging Brain,[6] College of Physicians and Surgeons, Columbia University, New York, NY, USA; Department of Epidemiology,[7] Mailman School of Public Health, Columbia; University, New York, NY, USA

Abstract. Previous studies have shown that Alzheimer disease (AD) is associated with a reduced risk of cancer. However, most studies exclude those with undiagnosed dementia. The only way to overcome this methodological issue is to examine all the participants or to screen the population for symptoms of dementia with a validated instrument and confirm any suspected dementia patients with a

clinical examination (i.e., a two-phase investigation method). We used this methodology to estimate whether cancer-specific mortality is associated with AD and other types of dementia in a prospective population-based study (NEDICES) involving 5,278 elderly people. Community-dwelling subjects with and without dementia were identified and followed for a median of 12.5 years, after which the death certificates of those who deceased were examined. A total of 1,976 (47.1%) died, including 277 who had possible or probable AD and 126 with non-AD dementia. Cancer was reported significantly less often in those with possible or probable AD (5.8%) or non-AD dementia (6.3%) than in those without dementia (26.5%). In an unadjusted Cox model, relative risk (RR) of cancer-specific mortality in participants with AD = 0.45 (p = 0.002) and RR in participants with non-AD dementia = 0.62 (p = 0.179) when compared to the non-demented group. In a Cox model that adjusted for a variety of demographic factors and co-morbidities, RRs of cancer-specific mortality in participants with AD = 0.50 (p = 0.028) and 0.97 (p = 0.942) in non-AD dementia. This study provides further evidence of an inverse association between cancer and AD.

INTRODUCTION

The burden of neurodegenerative diseases and cancer in high income countries is increasing as a consequence of ageing. Dementia, including Alzheimer´s disease (AD) and other types of dementias, and cancer occupy the fourth and fifth places, respectively, in the top 10 leading causes of disability according to 2001 WHO data[1] and are among the top 10 most frequent causes of death.[2, 3] Therefore, the probability of co-occurrence of both dementia and cancer in the same patient would be expected to rise with increasing age. However, a handful of

prospective studies have shown that AD is associated with a reduced risk of cancer.[4-10] Some of these studies may be subject to bias since they exclude a significant proportion of undiagnosed dementia sufferers in the population. [4, 5, 9] The only way to overcome this methodological issue is to examine all participants or to screen the population for symptoms of dementia with a validated instrument and confirm any suspected patients with a clinical examination (two-phase investigation method).[6-8, 10] These types of approaches have rarely been performed in order to determine the extent to which AD is associated with a decreased risk of cancer.[6-8, 10] The scarcity of this type of survey encouraged us to estimate whether AD and other types of dementia are associated with a reduced risk of cancer-specific mortality in a prospective population-based study, using a two-phase approach, involving 5,278 elderly people.

METHODS

Study population

Data for these analyses were derived from the Neurological Diseases in Central Spain (NEDICES) study, a longitudinal, population-based survey of the prevalence, incidence, and determinants of major age-associated conditions of the elderly, including Parkinson's disease, essential tremor, stroke, and dementia.[11-19] Detailed accounts of the study population and sampling methods have been published.[20-22]

The survey area consisted of three communities: Margaritas (approximately 14,800 inhabitants), a working-class neighborhood in Getafe (Greater Madrid); Lista (approximately 150,000 inhabitants), a professional-class neighborhood in Salamanca (Central Madrid), and 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. 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.

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, medical conditions, depressive symptoms (the question, “do you suffer from depression?”), and life style questions.

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 neurological disorders (essential tremor, stroke, dementia, and parkinsonism), current medications, and the name of their family doctor.

The screening protocol for dementia included a 37-item version of the Mini-Mental State Examination [37-MMSE])[17, 18, 23-27] and an 11-item version of the

Pfeffer Functional Activities Questionnaire (FAQ).[28] Every person completed an initial screening for cognitive impairment, and those who tested positive at step one (37-MMSE < 24 and FAQ > 5 points)[17, 18] then had a neurological evaluation, which comprised a clinical history, a general neurological exam and a mental status interview. The second step of the assessment was conducted at National Health Service clinics or at home. The diagnosis of dementia was assigned using Diagnostic and Statistical Manual of Mental Disorders (DSM)–IV criteria [29] 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.

Severity of dementia was established by the DSM-III-R criteria according to daily function.[30] Mild dementia was when there was impairment at work and social activities, but the capacity for independent living remaining largely intact; moderate dementia was when independent living was hazardous and the person required some degree of supervision; and severe dementia was defined by impaired activities of daily living such that continual supervision is required. Medical records were available for all participants, including records from their general practitioners, from in-patient hospitalizations, and from neurological specialists (if they had visited one).

For this study we categorized the different types of dementia into possible or probable Alzheimer's disease (AD) according to the NINCDS-ADRDA criteria)[31], and other types of dementia (non-AD dementia).

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, all deceased individuals receive a death certificate, completed by a doctor, at the time of death. The certificate is then sent to the local police authority in the municipality where the person had been living, and the information is collected in the National Register. Causes of death in the dementia and control group were compared. The cause of death (using the International Classification of Diseases - ICD- 9th Revision for deaths occurred prior to 1999, [http://www.cdc.gov/nchs/icd/icd9.htm], and the ICD 10th Revision [http://www.cdc.gov/nchs/icd/icd10.htm], for deaths occurring thereafter) was classified into 6 main categories: dementia, cerebrovascular disorders, other cardiovascular disorders (pulmonary embolism, congestive heart failure, myocardial infarction, heart or aortic rupture, and asystole), respiratory diseases, cancer, and other causes (infections, trauma, genitourinary or gastrointestinal disorders). In accordance with the recommendations of the World Health Organization, the classification of causes of death was investigated and tabulated depending on the basic cause of death (http://www.who.int/topics/mortality/en/). This was defined as the illness or injury that started the chain of pathological events which directly led to death (http://www.who.int/topics/mortality/en/).

Final selection of participants

Of the 5,278 participants screened for neurological disorders at baseline (1994-1995), we detected 306 prevalent dementia cases, leaving 4,972 participants without baseline dementia (Figure). Of these 4,972, 555 were lost to the follow-up evaluation (1997–1998) (Figure). Of the remaining participants, sufficient data were available on 3,891 (including 161 incident cases of dementia) who completed the follow-up

evaluation (1997–1998), which consisted of a screening questionnaire and a neurological examination (Figure).[17, 18]

To maximize the number of clinically diagnosed dementia cases, we used data from the baseline (1994–1995) and the second evaluation (1997–1998) (i.e., we included all available prevalent [N = 306] as well as incident cases of dementia [N = 161] [Figure]).[17, 18]

The final sample of 4,197, including 467 dementia cases and 3,730 non-dementia participants at the second evaluation (1997–1998), was similar to the base sample of 5,278 participants in terms of gender (2,435 [58.0%] vs. 3,040 [57.6%] women, chi-square = 0.17, p = 0.68) and education (564 [13.5%] vs. 711 [13.6%] were illiterate, chi-square = 3.20, p = 0.36), but it was, on average, 0.4 years younger (73.9 ± 6.9 vs. 74.3 ± 7.0 years, t = - 2.86, p = 0.004).

Statistical analyses

Data analyses were performed in SPSS Version 20.0 (SPSS, Inc., Chicago, IL). Unadjusted (bivariate) analyses were performed using the *t* test or analysis of variance (ANOVA) test to compare mean ages, and chi-square tests to determine associations between categorical variables.

We determined the overall proportion of cases of clinically diagnosed dementia in which a diagnosis of cancer was listed on the death certificate.

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 to 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 were associated with both the exposure (subtype of dementia [possible or probable AD vs. other types of dementia vs. non-demented participants [the reference category]) and the outcome (cancer-related mortality) ("Model 1" [more restrictive criteria for confounding]) and then considered baseline variables that were associated with either subtype of dementia or cancer-related mortality ("Model 2" [less restrictive criteria for confounding]). Variables assessed at baseline that we considered included age in years, gender, educational level (illiterate, can read and write, primary studies, secondary and higher studies), hypertension, diabetes mellitus, heart diseases, current smoker, current drinker, and depressive symptoms ("do you suffer from depression?") or antidepressant use.

RESULTS

The 4,197 participants had a mean duration of follow-up of 10.1 years (median = 12.5 years; range = 0.03 - 13.5 years). Four hundred sixty-seven (11.1%) of 4,197 participants were diagnosed with dementia by the time of the baseline (N = 306) and second evaluations (N = 161). 321 (68.7%) had AD and 146 (31.3%) non-AD dementia. Baseline demographic characteristics are shown in Table 1. Subjects with dementia were significantly older and had a lower level of education. In addition, there were a higher proportion of women and a higher proportion of the dementia cases living in Las Margaritas (blue collar area) (Table 1).

1,976 (47.1%) of 4,197 participants died over a median follow-up of 7.1 years (range 0.03–13.3 years), including 403 (86.3%) deaths among 467 participants with

dementia and 1,573 (42.2%) deaths among 3,730 participants without dementia. Of the 403 participants with dementia, 277 had possible or probable AD and 126 non-AD dementia. There were significant differences in age, gender, education, drinking and smoking status, as well as depressive symptoms or antidepressant use when dementia and non-dementia participants were compared (Table 2).

Baseline characteristics of the participants who died of cancer versus who died of other causes are shown (Table 3). At baseline, those who died of cancer were more frequently men, younger and more educated. In addition, they were less likely to have hypertension, diabetes mellitus, and depressive symptoms/or antidepressant use; a higher proportion drank and smoked (Table 3).

Cause of death noted on the death certificates differed significantly by dementia status (Table 4). Cancer was reported significantly less often in those with possible or probable AD (5.8%) or non-AD dementia (6.3%) than in those without dementia (26.5%). In the three groups, cardiovascular disease was the most frequent reported cause of death, but stroke was more frequent in non-AD dementia participants.

In an unadjusted Cox model, risk of cancer-specific mortality was decreased in participants with AD (RR = 0.45, 95% CI = 0.27 – 0.74, p = 0.002) vs. those with other non-AD dementia (RR = 0.62, 95% CI = 0.31 – 1.25, p = 0.179) and those ones without dementia (reference group). In a Cox model that adjusted for age, gender, educational level, current smoker, current drinker, and depressive symptoms or antidepressant use (i.e., variables that were associated with both dementia status and cancer-specific mortality), the risk of mortality remained decreased in

participants with AD (RR = 0.53, 95% CI = 0.29 – 0.95, p = 0.034, Model 1 in Table 3). The results did not change in a Cox model that adjusted for variables that were associated with either dementia status or cancer-specific mortality (age, gender, educational level, current smoker, current drinker, depressive symptoms or antidepressant use, hypertension, and diabetes mellitus) (Model 2 in Table 3).

Of the 277 participants with AD who died, 260 (93.9%) had information on severity of dementia. Cancer conditions were listed in a similar proportion of those with milder stage (6, 6.4%) than of those with moderate or severe dementia stage (8, 4.8%) (chi-square = 0.288, p = 0.591).

DISCUSSION

The results of the current study support the view that people with AD are at reduced risk of mortality from malignant neoplasm. Relative to the non-demented, the hazard ratios of neoplasms as underlying cause of death were half in subjects with an AD diagnosis.

Our results are in agreement with prior prospective community or population-based surveys that have analyzed the proportion of reporting of cancer on death certificates among demented patients, using a two-phase investigation method or that have examined all the participants, thus permitting the minimization of selection bias.[6-8, 10] The national Canadian Study of Health and Aging (CSHA) determined how frequently cancer was recorded on the death certificates of 823 clinically demented and 670 clinically non-demented participants.[6] Among patients clinically diagnosed with AD, the odds of neoplasm as the underlying cause of death was less than half that of the reference group.[6] In a prospective community-based study of

1,670 people age 65 or older study, cancer was only reported in 12.3% on death certificates of demented subjects vs. 26.2% in those without dementia.[7] Participants in the Cardiovascular Health Study–Cognition Substudy, a prospective cohort study, aged 65 years or older (N = 3,020) were followed a mean of 5.4 years for dementia and 8.3 years for cancer.[8] The presence of any AD (pure AD plus mixed AD/vascular dementia; HR = 0.41, 95% CI = 0.20–0.84) and pure AD (HR = 0.31, 95% CI = 0.12–0.86) was associated with a reduced risk of future cancer hospitalization, adjusted for demographic factors, smoking, obesity, and physical activity.[8] No significant associations were found between dementia at baseline and rate of cancer hospitalizations for participants with diagnoses of vascular dementia.[8] Finally, in the Framingham Heart Study, cancer survivors from 1,278 participants with and without a history of cancer who were aged 65 or more and free of dementia at baseline (1986-90), had a lower risk of probable AD (HR = 0.67, 95% CI = 0.47–0.97), adjusted for age, gender, and smoking.[10] The risk was even lower among survivors of smoking related cancers (HR = 0.26, 95% CI = 0.08–0.82) than among survivors of non-smoking related cancers (HR = 0.82, 95% CI = 0.57–1.19).[10] In the nested case-control analysis, participants with probable AD had a lower risk of subsequent cancer (HR = 0.39, 95% CI = 0.26–0.58) than reference participants, as did participants with any AD (HR = 0.38, CI = 0.25–0.56) and any dementia (HR = 0.44, CI = 0.32–0.61).[10]

Although the current and previous findings suggest that AD is associated with decreased cancer-specific mortality,[6-8, 10] the mechanisms underlying this association remain unknown. The cholinergic system deficit seen in AD patients may be an explanation for the decreased risk for cancer.[32] Since acetylcholine (Ach)

stimulates cell proliferation, the association suggests that the degeneration of ACh-secreting cells plays a protective role on cancer onset as this neurotransmitter would be less available to stimulate cell proliferation.[33] Second, direct evidence for an innate inflammatory response in AD was described nearly 20 years ago,[34] and subsequent studies have documented that in AD there is an up-regulation of many tumor suppression genes.[35] In this sense, inflammation may prevent some types of cancer.[36] In line with this, a cytotoxic action has been proposed for amyloid (i.e., to eradicate cancer cells in an analogous manner to that performed by host defense peptides).[37] Currently, however, we know of no proven physiologic explanation for such a cause-and-effect relationship.

Our study has 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 adjusted the risk for a number of important confounders but our evaluation of depression was limited and we may have under-ascertained depression, resulting in residual confounding. Depression may be associated with increased risk of dementia[38] and depression may be also associated with an increased risk of cancer-mortality.[39] Nevertheless, a validation study showed a high level of agreement between the data generated from the screening question we used and a more detailed in-person psychiatric assessment, suggesting that such residual confounding is likely to have been low.[40]

This study also had several strengths. First, the study was population-based, allowing us to assess a group of people with dementia who were unselected.

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 AD, but not other types of dementia, was associated with decreased risk of cancer-specific mortality. This study provides further evidence of the inverse association between cancer and AD.

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Table 1: Baseline (1994–1995) demographic and clinical characteristics of participants with (or who subsequently developed incident dementia) vs. without dementia.

Characteristics at Baseline Assessment	**Participants with or who subsequently developed dementia** **(N = 467)**	**Participants without dementia** **(N = 3,730)**	***p* value**
Age in years	81.5 ± 7.2	72.9 ± 6.2	<0.001[a]
Female gender	312 (66.8%)	2,123 (56.9%)	<0.001[b]
Geographical area			0.018[b]
Arévalo county (rural area)	154 (33.0%)	1,273 (34.1%)	
Las Margaritas (blue collar area)	197 (42.2%)	1,343 (36.0%)	
Lista (white collar area)	116 (24.8%)	1,114 (29.9%)	
Education *			<0.001[b]
Illiterate	144 (31.4%)	420 (11.3%)	
Can read and write	170 (37.0%)	1,556 (41.9%)	
Primary studies	102 (22.2%)	1,203 (32.4%)	
≥Secondary studies	43 (9.4%)	538 (14.5%)	

[a] Student t test.

[b] Chi-square test.

*Data on some participants were missing.
Mean ± standard deviation and frequency (%) are reported.

Table 2 Baseline (1994–1995) demographic and clinical characteristics of deceased participants with (or who subsequently developed incident dementia) vs. without dementia (N = 1,976).

	Possible or probable AD (N = 277)	**Non-AD dementia (N = 126)**	**No dementia (N = 1,573)**	***p* Value**
Age in years	82.7 ± 6.9	81.3 ± 7.2	75.6 ± 6.7	<0.001 [a]
Female gender	190 (68.6%)	74 (58.7%)	740 (47.0%)	<0.001 [b]
Education *				
Illiterate	82 (30.1%)	35 (28.2%)	186 (11.9%)	<0.001 [b]
Can read and write	103 (37.9%)	46 (37.1%)	661 (42.3%)	
Primary studies	66 (24.3%)	23 (18.5%)	479 (30.7%)	
≥Secondary studies	21 (7.7%)	20 (16.1%)	236 (15.1%)	
Hypertension *	136 (53.1%)	63 (53.4%)	855 (55.7%)	0.685 [b]
Diabetes mellitus *	47 (18.7%)	21 (17.8%)	317 (20.7%)	0.589 [b]
Heart diseases *	31 (12.2%)	12 (10.3%)	216 (13.9%)	0.438 [b]
Current smoker *	11 (5.3%)	8 (8.1%)	182 (13.8%)	0.001 [b]
Current drinker *	39 (18.8%)	18 (18.2%)	460 (35.1%)	<0.001 [b]
Depressive symptoms or antidepressant use *	72 (30.6%)	40 (36.4%)	354 (25.1%)	0.011 [b]

[a] ANOVA test; [b] Chi-square test.
*Data on some participants were missing.
Mean ± standard deviation and frequency (%) are reported.

Table 3 Baseline (1994–1995) demographic and clinical characteristics of deceased participants who died of cancer vs. other causes.

	Cancer (N = 441)	**Other causes (N = 1,535)**	***p* Value**
Age in years	74.3 ± 6.6	77.7 ± 7.3	<0.001
Female gender	157 (35.6%)	847 (55.2%)	<0.001
Education *			
Illiterate	50 (11.4%)	253 (16.6%)	0.009
Can read and write	174 (39.7%)	636 (41.8%)	
Primary studies	138 (31.5%)	430 (28.3%)	
≥Secondary studies	76 (17.4%)	201 (13.2%)	
Hypertension *	192 (44.5%)	862 (58.3%)	<0.001
Diabetes mellitus *	67 (15.7%)	318 (21.6%)	0.007
Heart diseases *	49 (11.2%)	210 (14.2%)	0.125
Current smoker *	80 (21.6%)	121 (9.7%)	<0.001
Current drinker *	152 (41.1%)	365 (29.2%)	<0.001
Depressive symptoms or antidepressant use	91 (22.6%)	375 (27.7%)	0.040

[a] ANOVA test; [b] Chi-square test.
*Data on some participants were missing.
Mean ± standard deviation and frequency (%) are reported.

Table 4 Primary cause of death (IDC 9th) by diagnostic groups.

	Possible or probable AD N (%)	**Non-AD dementia N (%)**	**No dementia N (%)**	***p* Value ***
Dementia	69 (24.9%)	15 (11.9%)	64 (4.1%)	<0.001
Cerebrovascular disorders	26 (9.4%)	28 (22.2%)	123 (7.8%)	<0.001
Cardiovascular diseases	79 (28.5%)	32 (25.4%)	447 (28.4%)	0.771
Respiratory diseases	40 (14.4%)	18 (14.3%)	225 (14.3%)	0.998
Cancer	16 (5.8%)	8 (6.3%)	417 (26.5%)	<0.001
Other	47 (17.0%)	25 (19.8%)	297 (18.9%)	0.709
Total	277 (100%)	126 (100%)	1,573 (100%)	-

* Chi-square test.

Table 5: Relative risks of cancer-specific mortality in participants who had Alzheimer's disease and other types of dementia vs. non-demented participants (reference group).

	Unadjusted			**Model 1**			**Model 2**		
	Relative risk	95% CI	*p* value	Relative risk	95% CI	*p* value	Relative risk	95% CI	*p* value
Possible or probable AD N = 277	0.45	0.27-0.74	0.002	0.53 *	0.29-0.95	0.034	0.50	0.27-0.93	0.028
Non-AD dementia N = 126	0.62	0.31-1.25	0.179	0.97	0.48-1.98	0.937	0.97	0.48-1.99	0.942
No dementia N = 1,573 (reference category)	1.00	_		1.00	_		1.00	_	

Model 1: Adjusted for age, gender, educational level, current smoker, current drinker, and depressive symptoms or antidepressant use (variable associated with both dementia status and cancer-specific mortality).

Model 2: Adjusted for age, gender, educational level, current smoker, current drinker, depressive symptoms or antidepressant use, hypertension, and diabetes mellitus (variables associated with either dementia status or cancer-specific mortality).

Figure 1 : Flow chart of the study

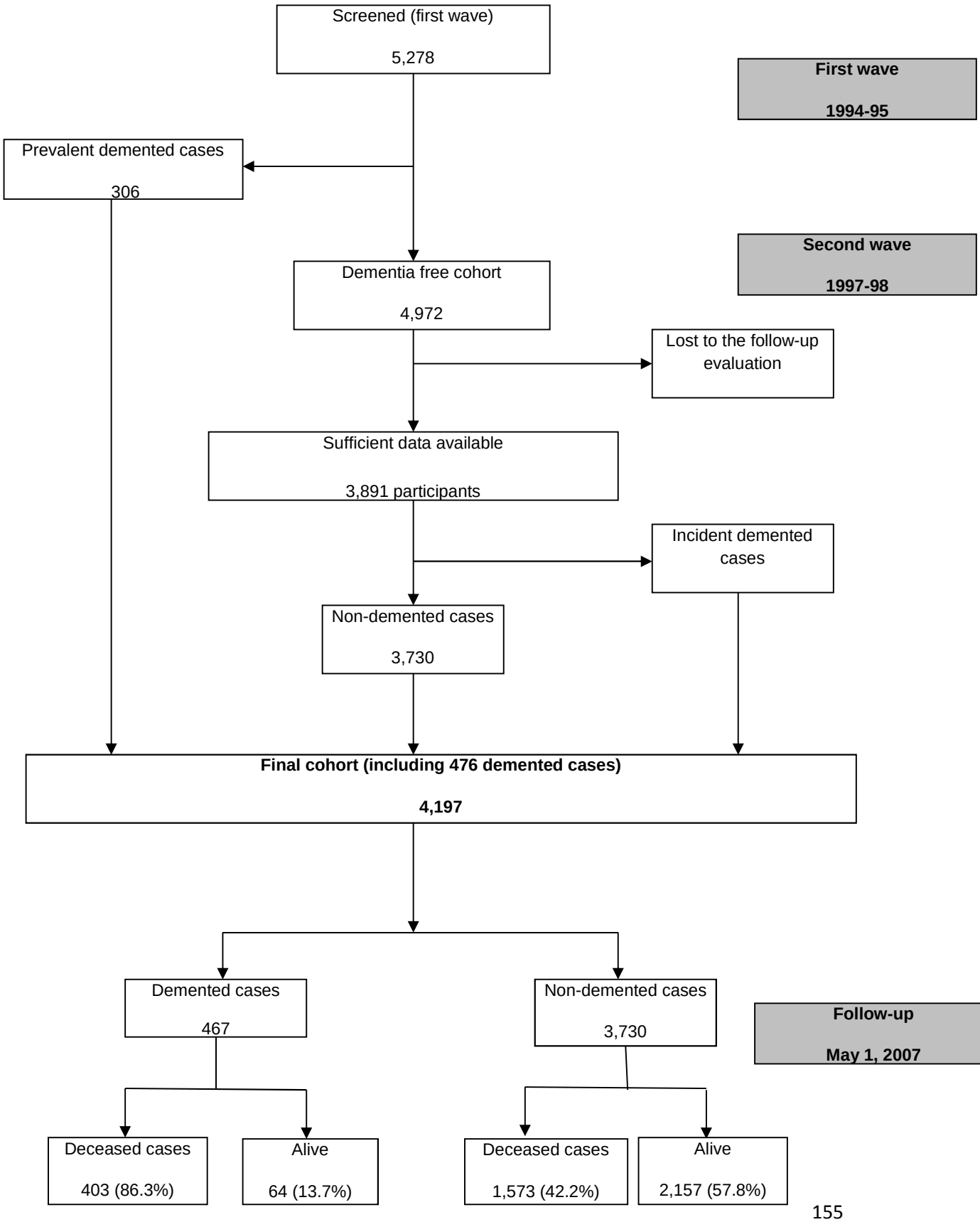
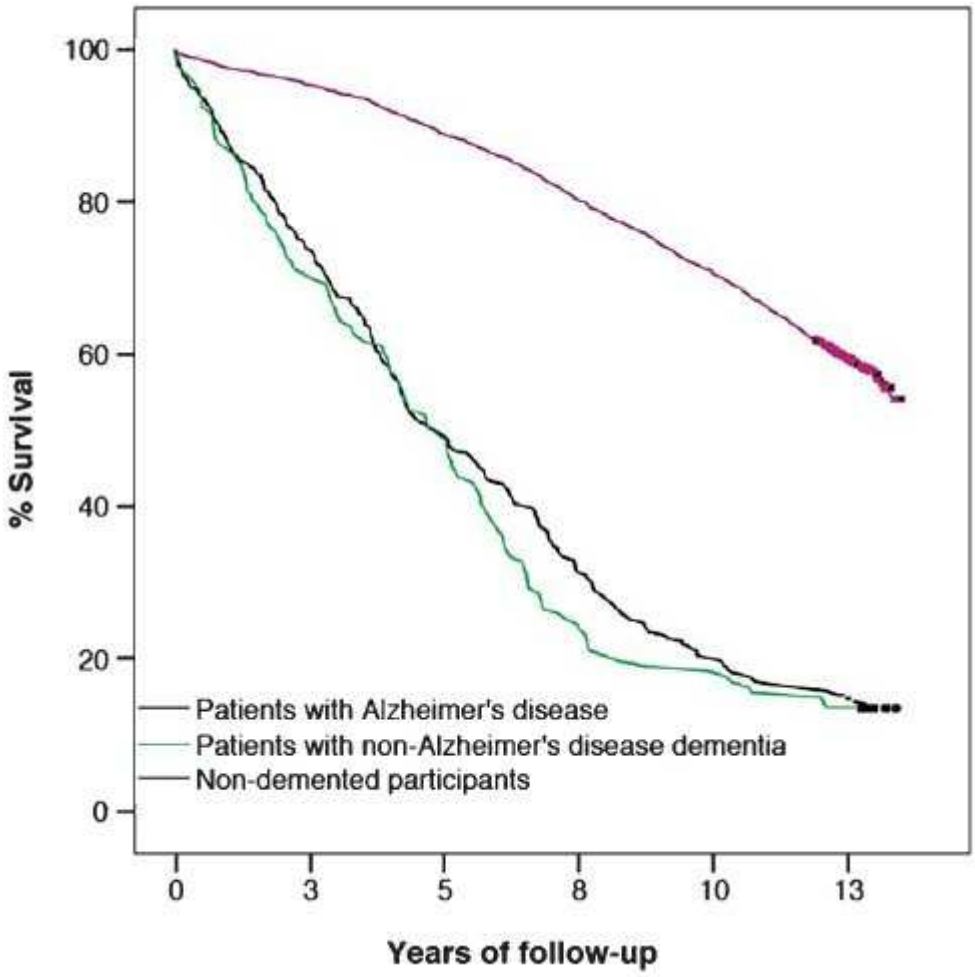


Fig. 2. Kaplan-Meier curves of percent survival for subjects with and without dementia (log-rank $p < 0.001$).



ANEXO 1.4 EL DECLIVE COGNITIVO MÁS ACELERADO EN SUJETOS NO DEMENTES REDUCE EL RIESGO DE MORTALIDAD POR CÁNCER. (TÍTULO ORIGINAL: " FASTER COGNITIVE DECLINE IN NON-DEMENTED ELDERS DECREASES THE RISK OF CANCER MORTALITY (NEDICES)")

Aceptado en **NEUROLOGY** para publicación con la referencia:

NEUROLOGY/2013/561845 el 15 de Enero de 2014.

Resumen:

El objetivo de este estudio es evaluar si el declive cognitivo más rápido en ancianos sin demencia se asocia con un menor riesgo de mortalidad por cáncer El estudio está basado en un estudio poblacional prospectivo que incluye a 2.627 personas sin demencia de 65 años y más (NEDICES), una versión de 37 ítems del Mini Examen del Estado Mental (MMSE) se administró en 2 visitas (visita inicial y de seguimiento, aproximadamente 3 años después). Dividimos el cambio de puntuación en el examen de 37 ítems (MMSE) en tertiles (tertil inferior mejoría ≥ 2 puntos en la puntuación, tertil superior descenso ≥ 2 puntos en la puntuación). Los ancianos incluidos en el estudio poblacional fueron seguidos durante una media de 12,9 años, después de lo cual se examinaron los certificados de defunción de los que murieron. 1003 (38.2 %) murieron, incluyendo 339 (33,8%) muertes entre los participantes que estaban en el tertil superior de cambio del puntaje del 37-MMSE y 664 (66.2 %) muertes entre aquellos en los tertiles restantes. El cáncer se informó significativamente menos frecuente en los del tertil más alto de cambio MMSE (20,6 %) que en aquellos en los tertiles restantes (28,6%): en un modelo de Cox no ajustado, el

riesgo relativo (RR) de mortalidad por cáncer en los participantes dentro del tertil superior = 0,75 (p = 0,04) en comparación con los participantes dentro de los tertiles restantes . En un modelo de Cox ajustado para una variedad de factores demográficos y comorbilidades, el RR de la mortalidad específica por cáncer en los participantes en el tertil superior = 0,69 (p = 0,01). En este estudio poblacional prospectivo de ancianos no dementes, un deterioro cognitivo más rápido se asoció con un menor riesgo de mortalidad por cáncer

Correo Electrónico de aceptación de la publicación

De: squimby@neurology.org [mailto:squimby@neurology.org] Enviado el: miércoles, 15 de enero de 2014 21:37

Para: Julian Benito-Leon
CC: Juan Pablo Romero; Elan Louis; Félix Bermejo-Pareja
Asunto: NEUROLOGY MS ID# NEUROLOGY/2013/561845

NEUROLOGY MS ID#: NEUROLOGY/2013/561845
MS TITLE: Faster cognitive decline in non-demented elders and decreased risk of cancer mortality (NEDICES) Julian Benito-Leon, Juan Pablo Romero, Elan Louis, and Félix Bermejo-Pareja

15 January 2014

Dear Dr. Benito-Leon:

We are pleased to accept your paper for publication in NEUROLOGY.

Faster cognitive decline in non-demented elders and decreased risk of cancer mortality (NEDICES)

Julián Benito-León MD, PhD;[1,2,3] Juan Pablo Romero MD;[1]

Elan D. Louis, MD, MSc;[4, 5, 6, 7]Félix Bermejo-Pareja MD, PhD;[1,2,3]

From the Department of Neurology,[1] University Hospital "12 de Octubre", Madrid,Spain;

Centro de Investigación Biomédica en Red sobre Enfermedades Neurodegenerativas

(CIBERNED),[2] Spain; Department of Medicine,[3] Complutense University, Madrid, Spain;

G.H. Sergievsky Center,[4] College of Physicians and Surgeons, Columbia University,

New York, NY, USA; Department of Neurology,[5] College of Physicians and

Surgeons, Columbia University, New York, NY, USA; Taub Institute for Research on

Alzheimer's Disease and the Aging Brain,[6] College of Physicians and Surgeons,

Columbia University, New York, NY, USA; Department of Epidemiology,[7] Mailman

School of Public Health, Columbia; University, New York, NY, USA

Abstract

Objective: To assess whether faster cognitive decline in non-demented elders is associated with decreased risk of cancer mortality.

Methods: In this population-based, prospective study of 2,627 non-demented people aged 65 years and older (Neurological Disorders in Central Spain), a 37-item version of the Mini-Mental State Examination (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: 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, relative risk (RR) of cancer mortality in participants within the higher tertile= 0.75 (p = 0.04) when compared to the participants within the remaining tertiles. In a Cox model that adjusted for a variety of demographic factors and co-morbidities, RRs of cancer-specific mortality in participants within the higher tertile = 0.70 (p = 0.02).

Conclusion: In this population-based, prospective study of non-demented community-dwelling elders, faster cognitive decline was associated with a decreased risk of cancer mortality. Further studies are required to elucidate this inverse association in non-demented elders.

INTRODUCTION

A series of prospective studies has shown that Alzheimer's disease (AD) is associated with a reduced risk of cancer.[1-3] However, the mechanisms underlying this association remain unknown The cholinergic system deficit seen in AD patients may explain, at least in part, the decreased risk for cancer.[4] Since acetylcholine (Ach) stimulates cell proliferation, the association suggests that the degeneration of ACh-secreting cells may play 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 beta-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 non-demented elders has not been conducted. It has been suggested that a major problem with epidemiological studies that have reported an inverse association between AD and cancer, is the very likely under diagnosis of cancer once dementia has been diagnosed.[11] We therefore tested the hypothesis that non-demented older persons 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 two

times points separated by three 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, and determinants of major age-associated conditions of the elderly, including Parkinson's 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 three 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 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 one 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 neurological 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 three additional items: (1) an attention task, i.e., "say 1, 3, 5, 7, 9 backwards", (2) a visual order,

i.e., a man raising his arms, and (3) a simple construction task, i.e., copying two 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 Diagnostic and Statistical Manual of Mental Disorders (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, all deceased individuals receive a death certificate, completed by a doctor, 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 International Classification of Diseases - ICD- 9th Revision for deaths occurred prior to 1999, [http://www.cdc.gov/nchs/icd/icd9.htm], and the ICD 10th Revision [http://www.cdc.gov/nchs/icd/icd10.htm], for deaths occurring thereafter) was classified 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, genitourinary or

gastrointestinal disorders). In accordance with the recommendations of the World Health Organization, the classification of causes of death was investigated and tabulated depending on the basic cause of death (http://www.who.int/topics/mortality/en/). This was defined as the illness or injury that started the chain of pathological 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 with incomplete 37-MMSE examinations (N = 906) (Figure 1; please see the figure in the supplementary data available in Neurology online).

The final sample of 2,627 was similar to the base sample of 5,278 participants in terms of gender (1,509 [57.4%] vs. 3,040 [57.6%] women, chi-square = 0.02, p = 0.89). However, they were more educated (268 [10.2%] vs. 711 [13.6%] were illiterate, chi-square = 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, number of medications, 37-MMSE, and change in 37-MMSE) was normally distributed (Kolmogorov-Smirnov, $p < 0.001$), even after log-transformation. Therefore, baseline characteristics scores were compared using Mann–Whitney test. Chi-square 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 to 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 $p \leq 0.05$ 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, gender, 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 area vs. urban area), self-rated health (good / very good, normal, and bad / very bad), number of medications, smoker (ever vs. never), drinker (ever vs. never), cancer, arterial hypertension, diabetes mellitus, heart diseases, osteoporosis, obstructive pulmonary chronic 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.

RESULTS

The 2,715 participants had a mean duration of follow-up of 11.2 years (median = 12.9 years; range = 2.7 - 14.1 years). 1,003 (38.2%) of 2,715 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 versus who died of other causes are shown in Table 2. At baseline, those who died of cancer were younger, scored higher in 37-MMSE, took fewer medications, and were more likely 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 hypertension, 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). On the other hand, 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, obstructive pulmonary chronic disease, osteoporosis, and the 37-MMSEscore (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, educational level, geographical area, living area during childhood / adolescence, self-rated health, number of medications, ever smoker (exsmoker/current smoker), ever drinker (exdrinker/current drinker), cancer, arterial hypertension, diabetes mellitus, heart diseases, obstructive pulmonary chronic disease, osteoporosis, stroke, and the 37-Mini-Mental State Examination total score) (Model 2 in Table 5). Further, in a model that adjusted for baseline age, gender, educational level, living area during childhood /

adolescence, self-rated health, geographical area (Las Margaritas, Lista, and Arévalo), number of medications, ever smoker (exsmoker/current smoker), ever drinker (exdrinker/current drinker), cancer, arterial hypertension, diabetes mellitus, heart diseases, osteoporosis, obstructive pulmonary chronic 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 (RR = 0.74, 95% CI = 0.56 – 0.99, p = 0.04, Model 1; RR = 0.74, 95% CI = 0.55 – 0.99, p = 0.04, Model 2; and RR = 0.73, 95% CI = 0.54 – 0.98, p = 0.04, Model 3).

The Kaplan-Meier curve for overall survival (Figure 2; please see the figure in the supplementary data available in Neurology online) showed that those in the higher tertile of 37-MMSE not to be 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 non-demented elderly people with faster cognitive decline are at reduced risk of mortality from malignant neoplasm. Relative to those in the middle and lower tertiles, the RR 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's disease, and Huntington disease. [1-3, 34, 35] As yet undiscovered mechanisms may either promote a neurodegenerative process 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 pathological cascade of brain changes, during this phase, with beta-amyloid deposition as the primary event in this cascade.[36, 37] Neural cells may become vulnerable to cytotoxicity by amyloid-forming peptides, such as beta-amyloid.[9] Beta-amyloid 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 defense peptides is in agreement with the apparent protective effect of AD and probably age-related cognitive decline, from cancer.[9, 10] In addition, these mechanisms would also promote cancer by antioxidants, suppressing apoptosis.[13] 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, due to the many exclusions, the final sample comprised 2,627, and the final sample, though population-based, in some respects resembled a convenience sample. Fourth, competing mortality is an issue to consider – healthy elders who do not die from cancer are at risk for the development of 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 non-demented people 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 non-demented community-dwelling elders 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 non-demented community-dwelling elders.

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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 in years	76.3 ± 6.9	74.9 ± 6.2	0.002 [a]
Female gender	203 (59.9%)	386 (58.1%)	0.594 [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 *			0.023 [b]
Rural area	91 (27.1%)	225 (34.2%)	
Urban area	245 (72.9%)	433 (65.8%)	
Self-rated health *			0.371 [b]
Good / very good	191 (57.0%)	374 (56.6%)	
Normal	96 (28.7%)	210 (31.8%)	
Bad / very bad	48 (14.3%)	77 (11.6%)	
Number of medications	2.7 ± 2.0	2.7 ± 2.0	0.682 [a]
Ever smoker (exsmoker/current smoker)	153 (45.1%)	320 (48.2%)	0.358 [b]
Ever drinker (exdrinker/current drinker) *	197 (58.3%)	405 (61.2%)	0.376 [b]
Cancer *	18 (5.6%)	44 (6.8%)	0.465 [b]
Arterial hypertension *	185 (54.6%)	367 (55.4%)	0.794 [b]
Diabetes mellitus *	53 (15.8%)	142 (21.6%)	0.029 [b]
Heart diseases *	55 (16.3%)	80 (12.0%)	0.064 [b]
Obstructive pulmonary chronic disease *	59 (17.5%)	144 (22.0%)	0.10 [b]
Osteoporosis *	59 (17.9%)	91 (13.9%)	0.10 [b]
Stroke	18 (5.3%)	28 (4.2%)	0.434 [b]
Depressive symptoms or antidepressant use *	86 (25.6%)	161 (24.4%)	0.678 [b]
37- MMSE total score	30.1 ± 4.9	28.9 ± 5.3	<0.001 [a]

[a] Mann-Whitney U test; [b] Chi-square test.
*Data on some participants were missing.
Mean ± standard deviation and frequency (%) are reported.
MMSE = Mini-Mental State Examination score.

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 in years	73.6 ± 5.9	75.9 ± 6.5	<0.001 [a]
Female gender	153 (58.8%)	436 (58.7%)	0.963 [b]
Education *			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 *			0.464 [b]
Rural area	77 (30.0%)	239 (32.4%)	
Urban area	180 (70.0%)	498 (67.6%)	
Self-rated health *			<0.001 [b]
Good / very good	169 (65.5%)	396 (53.7%)	
Normal	73 (28.3%)	233 (31.6%)	
Bad / very bad	16 (6.2%)	109 (14.8%)	
Number of medications	2.1 ± 1.8	2.9 ± 2.0	<0.001 [a]
Ever smoker (exsmoker/current smoker)	152 (58.5%)	321 (43.2%)	<0.001 [b]
Ever drinker (exdrinker/current drinker) *	175 (67.3%)	427 (57.7%)	0.006 [b]
Cancer *	23 (8.9%)	39 (5.5%)	0.052 [b]
Arterial hypertension *	118 (45.6%)	434 (58.5%)	<0.001 [b]
Diabetes mellitus *	43 (16.8%)	152 (20.7%)	0.178 [b]
Heart diseases *	33 (12.7%)	102 (13.7%)	0.668 [b]
Obstructive pulmonary chronic disease *	46 (17.8%)	157 (21.4%)	0.213 [b]
Osteoporosis *	29 (11.3%)	121 (16.6%)	0.041 [b]
Stroke	2 (0.8%)	44 (5.9%)	0.001 [b]
Depressive symptoms or antidepressant use *	59 (22.8%)	188 (25.5%)	0.382 [b]
37-MMSE total score	30.4 ± 4.7	28.9 ± 5.3	<0.001 [a]

[a] Mann-Whitney U test; [b] Fisher's exact test or Chi-square test.
* Data on some participants were missing.
Mean ± standard deviation and frequency (%) are reported.
MMSE = Mini-Mental State Examination score.

Table 3 Primary cause of death (IDC 9th) by tertiles of 37-MMSE change

	Higher tertile of 37-MMSE change	**Middle and lower tertiles of 37-MMSE change**	***p* Value ***
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%)	-

* Chi-square test.

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 ***
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%)	-

* Chi-square test.

Table 5 Relative risks 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).

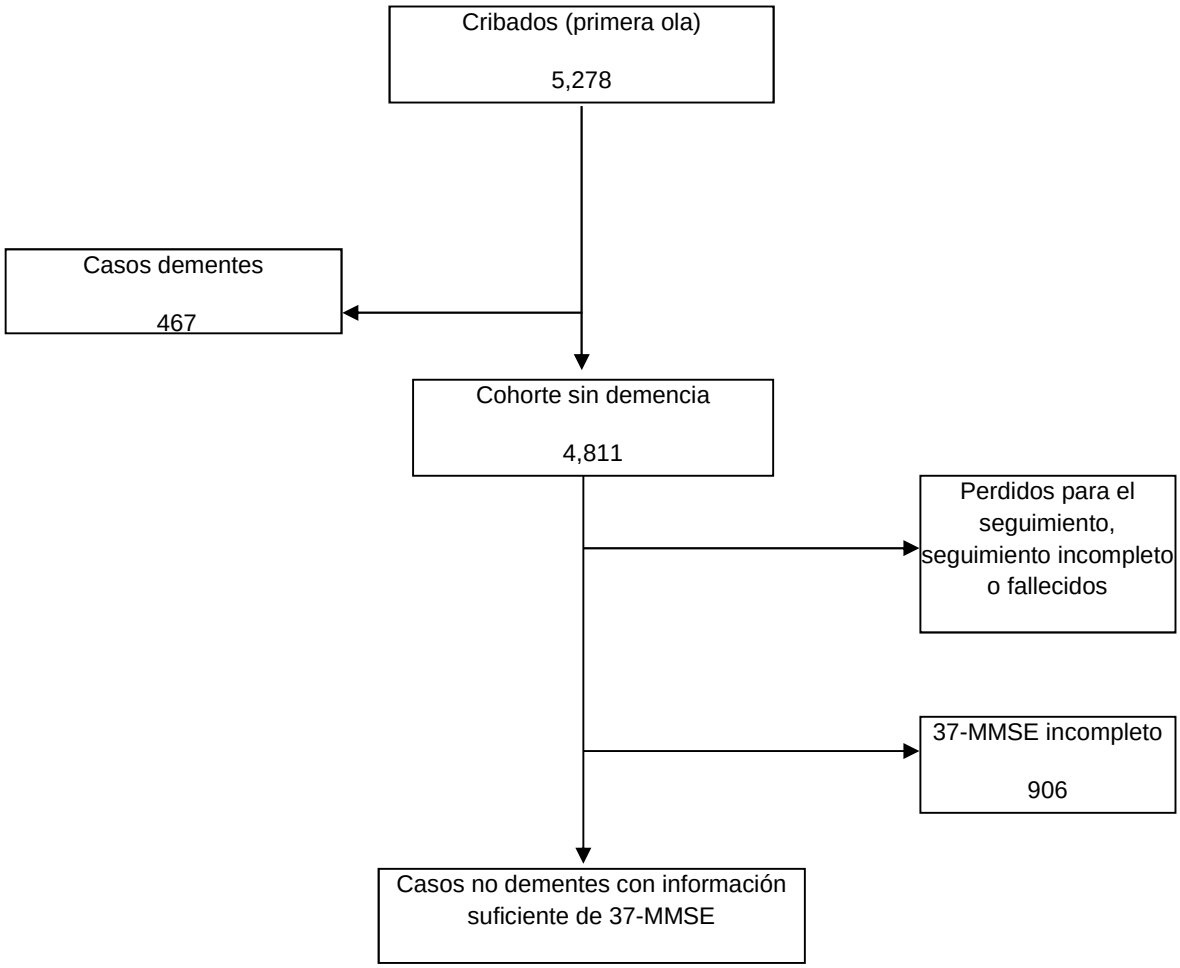
	Unadjusted			**Model 1**			**Model 2**			**Model 3**		
	Relative risk	95% CI	*p* value	Relative risk	95% CI	*p* value	Relative risk	95% CI	*p* value	Relative risk	95% CI	*p* value
Higher tertile (faster cognitive decline) N = 339	0.75	0.57-0.99	0.04	0.69	0.52-0.92	0.01	0.70	0.52-0.93	0.02	0.69	0.51-0.93	0.01
Middle and lower tertiles N = 664 (reference category)	1.00	_		1.00	_		1.00	_				

Model 1: Adjusted for baseline age, educational level, diabetes mellitus, obstructive pulmonary chronic disease, osteoporosis, and the 37-Mini-Mental State Examination total score) (variables associated with 37-Mini-Mental State Examination change tertiles and cancer-specific mortality). In terms of overall model fit, for Model 1, chi-square = 24.30, $p < 0.001$.

Model 2: Adjusted for baseline age, educational level, geographical area, living area during childhood / adolescence, self-rated health, number of medications, ever smoker (exsmoker/current smoker), ever drinker (exdrinker/current drinker), cancer, arterial hypertension, diabetes mellitus, heart diseases, obstructive pulmonary chronic disease, osteoporosis, stroke, and the 37-Mini-Mental State Examination total score (variables associated with either 37-Mini-Mental State Examination change tertiles or cancer-specific mortality). In terms of overall model fit, for Model 2, chi-square = 61.52, $p < 0.001$.

Model 3: Adjusted for baseline age, gender, educational level, living area during childhood / adolescence, self-rated health, geographical area (Las Margaritas, Lista, and Arévalo), number of medications, ever smoker (exsmoker/current smoker), ever drinker (exdrinker/current drinker), cancer, arterial hypertension, diabetes mellitus, heart diseases, osteoporosis, obstructive pulmonary chronic disease, stroke, depressive symptoms (“do you suffer from depression?”) or antidepressant use, and the 37-MMSE score. In terms of overall model fit, for Model 3, chi-square = 61.98, $p < 0.001$.

Figura 1. Diagrama de flujo del estudio



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