RAPPORTO TRA CANCEROGENESI E NEURODEGENERAZIONE: QUALI IMPLICAZIONI PER LA RICERCA IN SANITÀ PUBBLICA

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1. LE EVIDENZE EPIDEMIOLOGICHE
DEMENZA E TUMORI

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REVIEW ARTICLE

Inverse relationship between cancer and Alzheimer's disease: a systemic review meta-analysis

Qinghua Zhang[1] · Shougang Guo[1] · Xiao Zhang[1] · Shi Tang[1] · Wen Shao[1] · Xiaojuan Han[1] · Lu Wang[1] · Yifeng Du[1]

Abstract Alzheimer's disease (AD) and cancer are both prevalent in the elderly. Some epidemiological researches have reported the negative association between AD and cancer, but the results are controversial. The present meta-analysis is aimed to clarify the association between cancer and AD. PubMed, Web of knowledge and the Cochrane library databases were searched for eligible publications. The analysis indicated that history of cancer was associated with a reduced risk of AD (ES 0.62, 95 % CIs 0.53–0.74; $p < 0.001$), with no significance between-study heterogeneity and publication bias. Similar results were found in subgroup analysis by stratifying variables with education and APOEε4 carriers, years of follow-up and sample size of cases. The negative association was also found in analysis of risk of cancer among patients with AD (ES 0.59, 95 % CIs 0.42–0.82; $p = 0.002$), but with evidence of between-study heterogeneity and publication bias. In order to identify sources of the heterogeneity, subgroup analysis was performed by stratifying variable with or without education adjusted, sample size of cases and years of follow-up. Negative association was found in all subgroup analysis except in studies with less than 5-year follow-up and with heterogeneity disappeared only in the subgroup analysis stratified with sample size of cases. Our results in the present meta-analysis support the negative association between AD and cancer. But further well-

Search strategy

We performed a comprehensive electronic searches on the database of PubMed, Web of knowledge and the Cochrane library to identify eligible studies published before January 2014. The words including "Alzheimer's disease", "dementia", "AD", "cancer", "neoplasm", "carcinoma" and "tumor" were used as both medical subject heading (Mesh) terms and abstracts/title text with restriction of English publication. Reference lists of located articles were searched to find additional relevant studies.

Study selection

We included studies if they met the following criteria: (1) studies that examine the association between cancer and AD; (2) case–control, cross-sectional or cohort study design; (3) clear diagnosis criteria for AD and cancer; and (4) providing RR, OR, HR or SIR and 95 % confidence intervals or enough data to calculate these numbers. We excluded studies that did not discriminate AD from other causes of dementia and articles that did not provide original data such as reviews, editorials and letters.

Fig. 1 Flowchart of study selection process

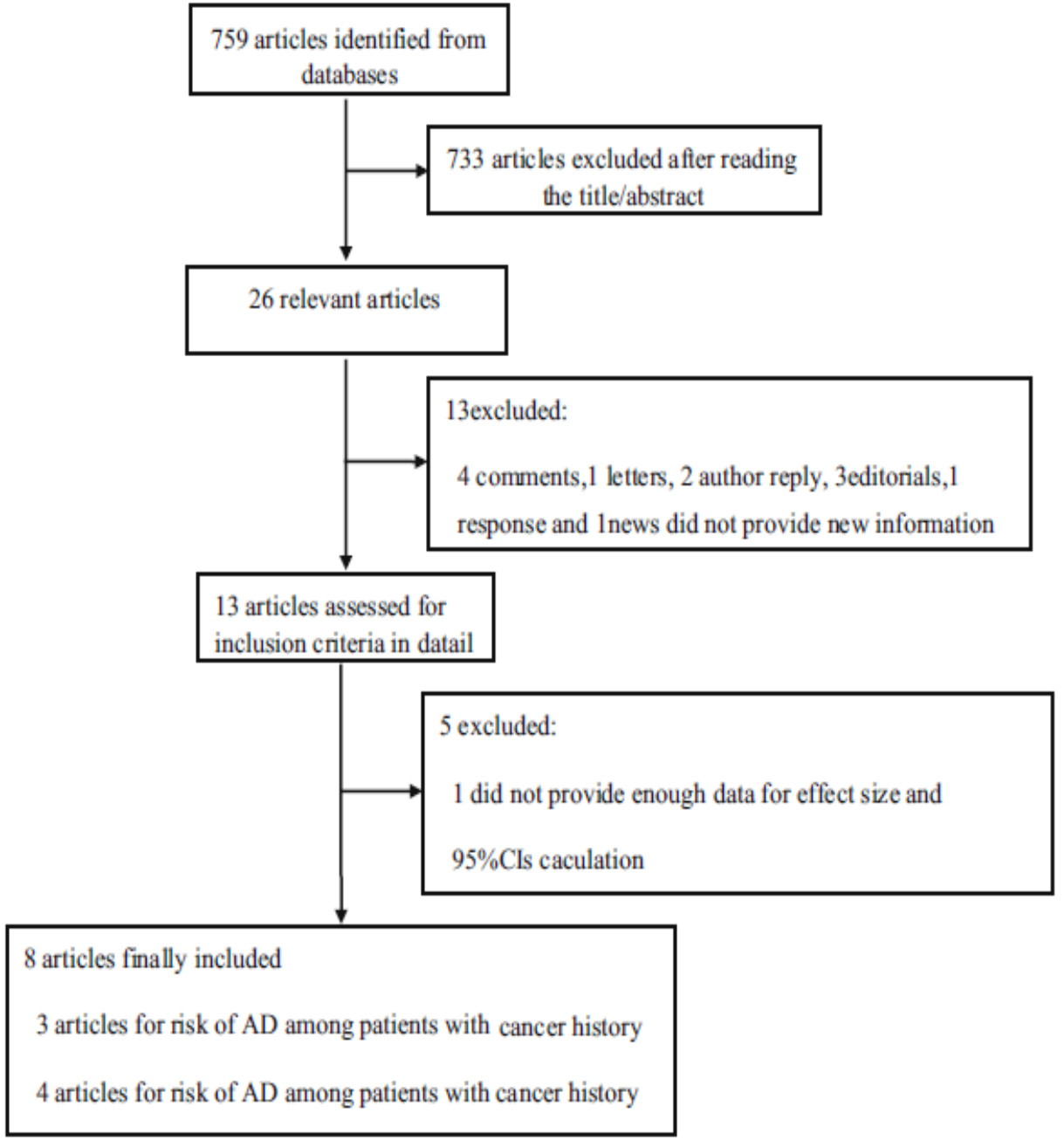


Table 1 Characteristics of included studies analyzing risk of AD among patients with cancer history

References	Study design sample source Country	Number of cases	Number of control	Criteria for AD diagnosis	Criteria for cancer diagnosis	Age (years)	Years of follow-up (mean)	ES (95 % CIs)	Factors adjusted
Yamada et al. [14]	Cohort study community-based Japan	230	1992	NINCDS/ADRDA	Clinical examination	≥60	4	OR 0.30 (0.05–0.98)	No
Roe et al. [13]	Cohort study volunteer-based America	50	199	Clinical diagnosis, histopathology confirmed	Self-report	≥54	4.2	HR 0.40 (0.12–1.13)	Sex, age at first assessment, education
Roe et al. [12]	Cohort study population-based America	390	1761	NINCDS-ADRDA	Cancer hospitalization records	≥65	5.4	HR 0.57 (0.36–0.90)	Sex, age, education, income, number of ApoEε4 alleles, hypertension, race, diabetes, coronary heart disease
Driver et al. [11]	Cohort study community-based America	423	851	NINCDS-ADRDA	Chart review	≥65	10	HR 067 (0.47–0.97)	Sex, age, smoking, incident cancer
Lai et al. [7]	Case–control population-based Taiwan	3281	13,124	NINCDS-ADRDA	Chart review	≥65	10	HR 0.51 (0.19–1.42)	Diabetes, cirrhosis, alcoholic liver damage, other chronic hepatitis
Musicco et al. [10]	Cohort study population-based Northern Italy	21,451	–	Clinical history	Cancer registry	≥60	5	RR 0.64 (0.50–0.81)	Age, sex
White et al. [8]	Cohort study community-based America	1134[a] (total)		NINCDS-ADRDA	Self-report	≥68	3.7	HR 0.69 (0.39–1.23)	Sex, education, occupation, diabetes, coronary heart disease, hypertension

[a] The cases and controls were not separately reported in this article

Table 2 Characteristics of included studies analyzing risk of cancer among patients with AD

References	Study design sample source country	Number of cases	Number of controls	Criteria for AD diagnosis	Criteria for cancer diagnosis	Age (years)	Years of follow-up (mean)	ES (95 % CIs)	Factors adjusted
Ou et al. [9]	Cohort study population-based Taiwan	6960	–	Registry of catastrophic illness	Not mentioned	≥40	4.25	SIR 0.88 (0.80–0.97)	No
Musicco et al. [10]	Cohort study population-based Northern Italy	2832	–	Medical records	Cancer registry	≥60	5	RR 0.79 (0.64–0.97)	Sex, age
Driver et al. [11]	Nested case–control community-based America	327	981	NINCDS-ADRDA	Chart review confirmed by pathology report	≥65	10	HR 0.39 (0.26–0.58)	Age, sex
Roe et al. [12]	Cohort study population-based America	71	2107	NINCDS-ADRDA	Cancer hospitalization records	≥65	8.3	HR 0.31 (0.12–0.86)	Sex, age, education, income, smoking, race etc.
Roe et al. [13]	Cohort study volunteer-based America	395	199	Clinical diagnosis histopathology confirmed	Self-report	≥47	3.57	HR 0.39 (0.21–0.74)	Sex, age at first assessment, education

Fig. 2 Forest plot of studies analyzing risk of AD among patients with cancer history

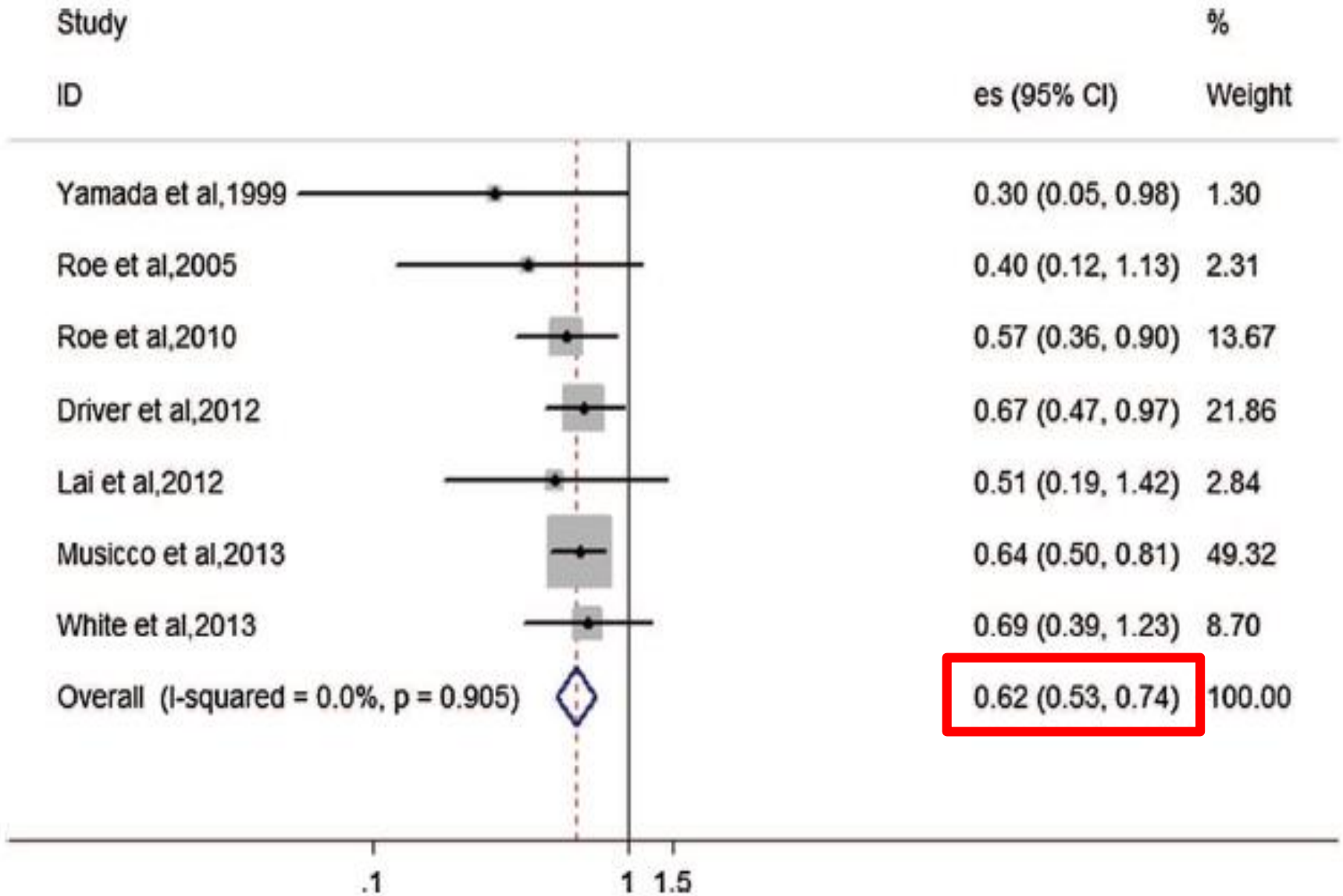
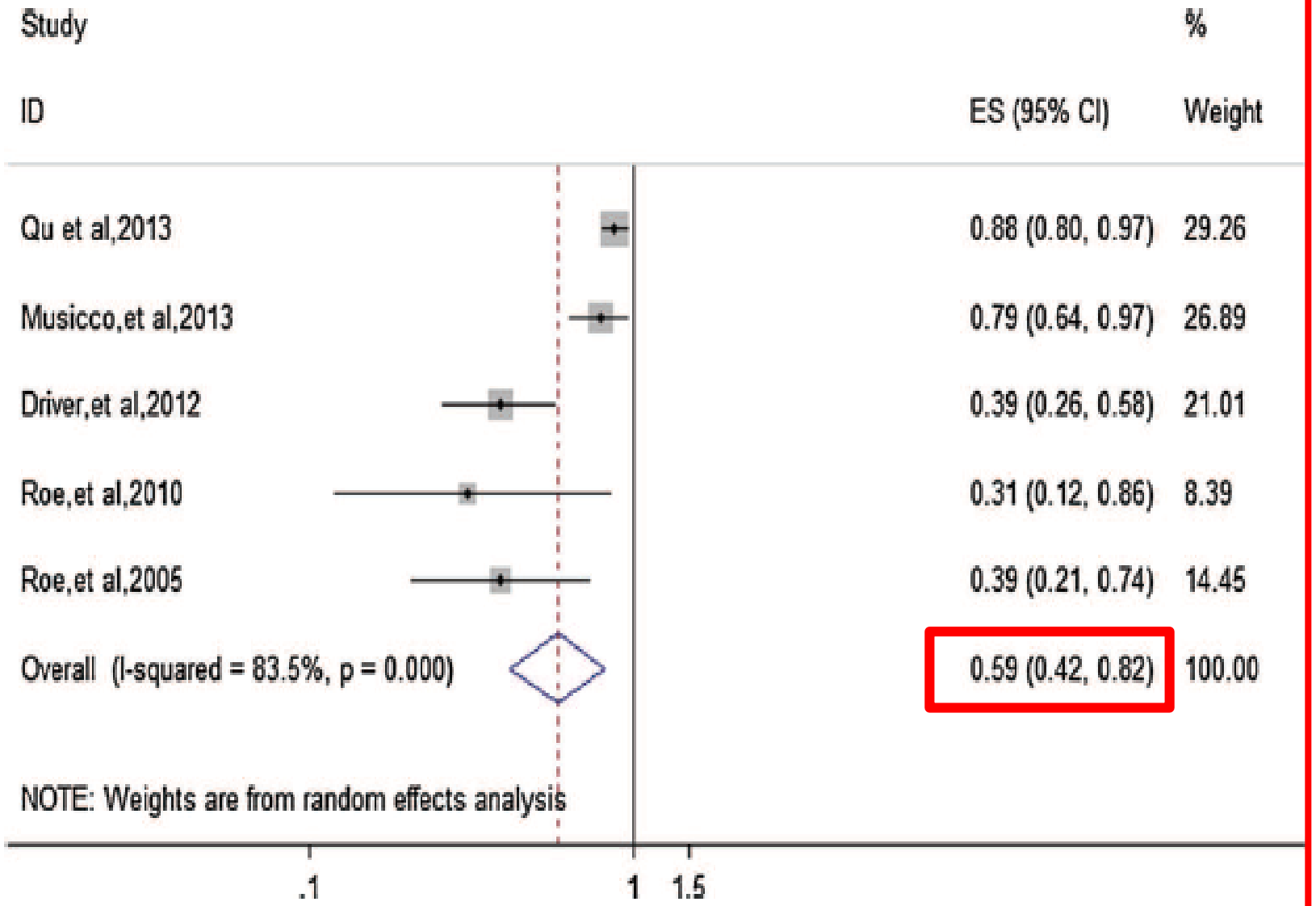


Fig. 3 Forest plot of studies analyzing risk of cancer among patients with AD



Inverse occurrence of cancer and Alzheimer disease

A population-based incidence study

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ABSTRACT

Objective: To evaluate the incidence of cancer in persons with Alzheimer disease (AD) and the incidence of AD dementia in persons with cancer.

Methods: This was a cohort study in Northern Italy on more than 1 million residents. Cancer incidence was derived from the local health authority (ASL-Mi1) tumor registry and AD dementia incidence from registries of drug prescriptions, hospitalizations, and payment exemptions. Expected cases of AD dementia were calculated by applying the age-, sex-, and calendar year-specific incidence rates observed in the whole population to the subgroup constituted of persons with newly diagnosed cancers during the observation period (2004–2009). The same calculations were carried out for cancers in patients with AD dementia. Separate analyses were carried out for the time period preceding or following the index diagnosis for survivors and nonsurvivors until the end of 2009 and for different types and sites of cancer.

Results: The risk of cancer in patients with AD dementia was halved, and the risk of AD dementia in patients with cancer was 35% reduced. This relationship was observed in almost all subgroup analyses, suggesting that some anticipated potential confounding factors did not significantly influence the results.

Conclusions: The occurrence of both cancer and AD dementia increases exponentially with age, but with an inverse relationship; older persons with cancer have a reduced risk of AD dementia and vice versa. As AD dementia and cancer are negative hallmarks of aging and senescence, we suggest that AD dementia, cancer, and senescence could be manifestations of a unique phenomenon related to human aging. *Neurology*® 2013;81:322-328

Table 1 Incidence rates, age, sex, and person-years of observation before and after the diagnosis and within survivors and nonsurvivors of the 2 cohorts of people with cancers or Alzheimer disease dementia

	Alzheimer dementia cohort (n = 2,832)	Cancer cohort (n = 21,451)
Men/women, n	947/1,885	12,225/9,226
Age, y, mean ± SD	78.1 ± 6.8	72.4 ± 7.8
Person-years		
Total	15,063.0	101,317.9
Before the diagnosis	8,674.5	60,023.0
After the diagnosis	6,388.5	41,294.9
Survivors	9,877.7	55,642.5
Nonsurvivors	5,185.3	45,675.4
IR (95% CI)[a]	22.1 (21.9–22.4)	175.1 (174.4–175.8)

CONTROLLO DI POSSIBILE CONFONDENTE NELLA RELAZIONE AD-CANCER E VICEVERSA

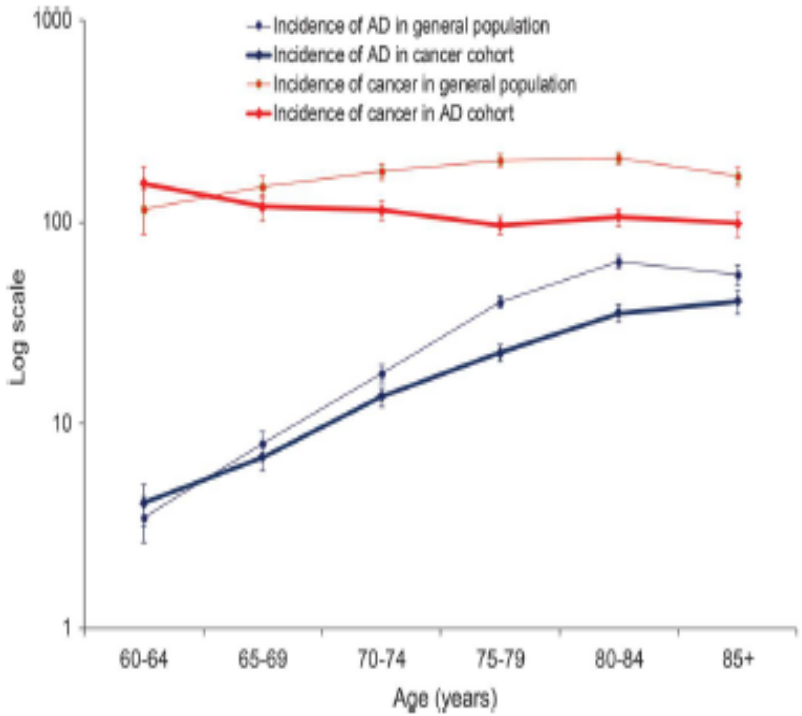
other neurodegenerative disorders, such as Parkinson disease.[7] Issues of confounding might underlie the observed lower occurrence of cancer in patients with dementia and vice versa.[8] First, both cancer and AD dementia limit life expectancy of affected persons and thus reduce the available lifetime for occurrence of other diseases. Second, the presence of one disease might obscure the diagnosis of other disorders, because any new occurring symptoms in patients with AD dementia or cancer might be interpreted as a consequence of the already diagnosed primary disease. Finally, cognitive decline due to AD neurodegeneration may be falsely interpreted as an undesired chemotherapy side effect in patients with cancer.[9]

Table 2 Observed and expected cases and relative risk of occurrence of Alzheimer disease dementia in the cohort of persons with cancer and of cancers in the cohort of persons with AD dementia[a]

	Cancers in AD dementia cohort		AD dementia in cancer cohort	
	Obs/exp[b]	RR (95% CI)	Obs/exp[b]	RR (95% CI)
Total	161/281.2	0.57 (0.49–0.67)	161/246.0	0.65 (0.56–0.76)
Before the diagnosis	69/163.4	0.42 (0.32–0.53)	93/140.1	0.66 (0.54–0.81)
After the diagnosis	93/117.8	0.79 (0.64–0.97)	68/105.9	0.64 (0.50–0.81)
In survivors	78/184.4	0.42 (0.33–0.53)	78/135.1	0.58 (0.46–0.72)
In nonsurvivors	83/96.8	0.86 (0.69–1.06)	83/110.9	0.75 (0.60–0.93)
Cancer type				
Epithelial	132/219.9	0.60 (0.50–0.71)	132/200.2	0.66 (0.55–0.78)
Mesenchymal	3/5.2	0.58 (0.12–1.70)	3/4.4	0.69 (0.14–2.00)
Blood	9/19.1	0.47 (0.21–0.89)	9/16.3	0.55 (0.25–1.05)
Nervous system	3/4.3	0.70 (0.14–2.05)	3/2.6	1.17 (0.23–3.41)
Unspecified	14/32.8	0.43 (0.23–0.72)	14/22.5	0.62 (0.34–1.04)
Cancer site				
Breast	26/37.0	0.70 (0.46–1.03)	26/38.1	0.68 (0.45–1.00)
Lung	16/26.6	0.60 (0.34–0.98)	16/18.7	0.85 (0.49–1.39)
Bladder	18/22.4	0.81 (0.48–1.27)	18/22.9	0.79 (0.47–1.24)
Prostate	19/20.3	0.94 (0.56–1.46)	19/22.0	0.87 (0.52–1.35)
Colorectal	13/30.0	0.43 (0.23–0.74)	13/29.5	0.44 (0.23–0.75)
Other	69/145.0	0.48 (0.37–0.60)	69/114.8	0.60 (0.47–0.76)

Abbreviations: AD = Alzheimer disease; CI = confidence interval; RR = relative risk.
[a] Expectations are calculated with reference to the general population of the same sex, age, and calendar year of follow-up.
[b] Observed vs expected values.

Figure 1 Age-specific incidence rates of cancers and Alzheimer disease dementia



Age-specific incidence rates of cancers in the general population and in the cohort of persons with Alzheimer disease (AD) dementia, and age-specific incidence rates of AD dementia in the general population and in the cohort of persons with cancers, ×10,000 person-years.

Neurol Sci (2015) 36:1987–1994
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REVIEW ARTICLE

Inverse relationship between cancer and Alzheimer's disease: a systemic review meta-analysis

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

AMSTAR – a measurement tool to assess the methodological quality of systematic reviews.

1. Was an 'a priori' design provided?

The research question and inclusion criteria should be established before the conduct of the review.

- ☐ Yes
- ☐ No
- ☐ Can't answer
- ☐ Not applicable

Note: Need to refer to a protocol, ethics approval, or pre-determined/a priori published research objectives to score a "yes."

4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?

The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.

- ☐ Yes
- ☐ No
- ☐ Can't answer
- ☐ Not applicable

Note: If review indicates that there was a search for "grey literature" or "unpublished literature," indicate "yes." SIGLE database, dissertations, conference proceedings, and trial registries are all considered grey for this purpose. If searching a source that contains both grey and non-grey, must specify that they were searching for grey/unpublished lit.

7. Was the scientific quality of the included studies assessed and documented?

'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.

Note: Can include use of a quality scoring tool or checklist, e.g., Jadad scale, risk of bias, sensitivity analysis, etc., or a description of quality items, with some kind of result for EACH study ("low" or "high" is fine, as long as it is clear which studies scored "low" and which scored "high"; a summary score/range for all studies is not acceptable).

- ☐ Yes
- ☐ No
- ☐ Can't answer
- ☐ Not applicable

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8. Was the scientific quality of the included studies used appropriately in formulating conclusions?

The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.

Note: Might say something such as "the results should be interpreted with caution due to poor quality of included studies." Cannot score "yes" for this question if scored "no" for question 7.

- ☐ Yes
- ☐ No
- ☐ Can't answer
- ☐ Not applicable

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2. LE EVIDENZE EPIDEMIOLOGICHE
PARKINSON E TUMORI

Cancer Causes Control (2010) 21:697–707
DOI 10.1007/s10552-009-9497-6

ORIGINAL PAPER

Parkinson's disease and cancer risk: a systematic review and meta-analysis

Archna Bajaj · Jane A. Driver · Eva S. Schernhammer

Abstract

Objective To appraise the existing literature on cancer risk among patients with Parkinson's disease (PD), determine the overall cancer risk ratio among patients with PD, explore reasons for variations in study results, and assess the potential for publication bias.

Methods Studies reporting cancer risk in patients with PD were identified by searching electronic databases through 18 November 2009 using the terms PARKINSON DISEASE, NEOPLASM, and CANCER. Reviewers individually performed data extraction and scored each study using a quality assessment instrument. Cancer risk in all patients with PD was calculated overall, and after excluding melanoma and other skin cancers. We tested for heterogeneity and publication bias, and stratified for gender, smoking-related versus non-smoking-related cancers, and study quality. We pooled effect sizes using fixed-effects and random-effects models.

Results We included 29 studies in the overall analysis for a total of 107,598 patients with PD. Compared to controls, the aggregate risk for cancer in patients with PD was 0.73 (95% confidence interval [CI], 0.63–0.83), and after excluding skin tumors, 0.69 (95% CI, 0.62–0.78). These risks varied by gender (males, RR = 0.71, 95% CI, 0.57–0.88; females, RR = 0.82; 95% CI, 0.68–0.98). After strictly excluding skin tumors, both smoking-related (RR = 0.61; 95% CI, 0.58–0.65) and non-smoking-related cancer rates (RR = 0.76; 95% CI, 0.65–0.89) were significantly lower among patients with PD .

Conclusions Studies on cancer risk among patients with PD collectively show significantly reduced cancer risk ratios. Further research to explain the biological mechanisms, particularly for the association with non-smoking-related cancers, appears warranted.

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Search strategy

We aimed to identify all studies reporting rates of cancer among individuals with PD. We conducted electronic searches of MEDLINE (from 1966 to 18 November 2009), EMBASE (from 1974 to 18 November 2009), and ISI Web of Science (from 1900 to 18 November 2009), with the aid of a reference librarian at Countway library (Boston, MA). PARKINSON DISEASE, NEOPLASM, and CANCER were entered as medical subject heading terms and text words and then connected through Boolean operators. We restricted the search to studies including human study participants. We also manually searched the reference list of all studies retrieved for detailed evaluation and of any relevant review articles and contacted experts in the field to locate additional publications and any unpublished data. We placed no constraints on the language in which the studies were written, the region of residence, or age group of study subjects. We were careful, however, to minimize overlapping data sets among the included studies to avoid duplicate counting of events and the bias this can introduce into a quantitative summary of the evidence.

We conducted and reported this analysis in accordance with MOOSE guidelines for meta-analysis of observational studies in epidemiology [9].

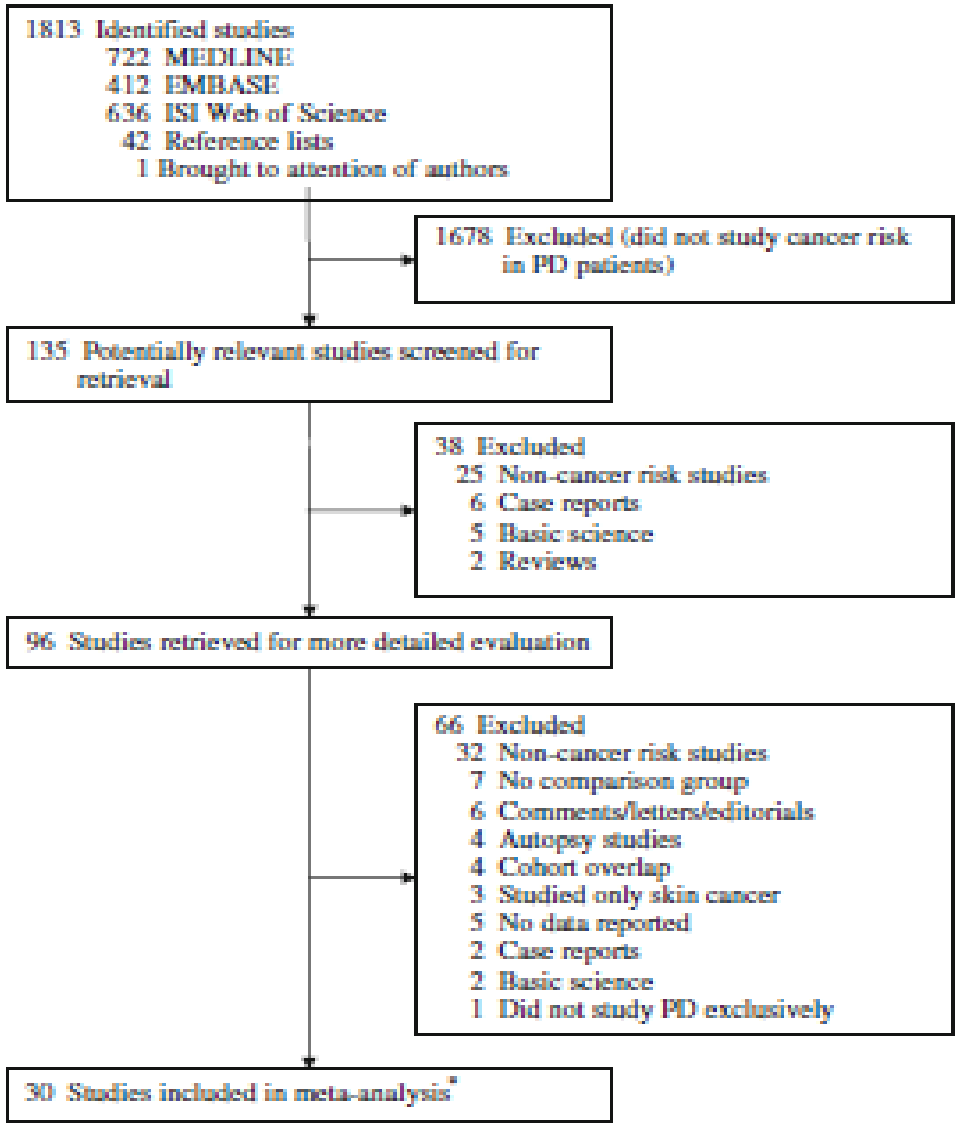

Fig. 1 Flow diagram: patients with PD and cancer risk. * However, only 29 studies were included in overall analysis, see explanation in "Methods"

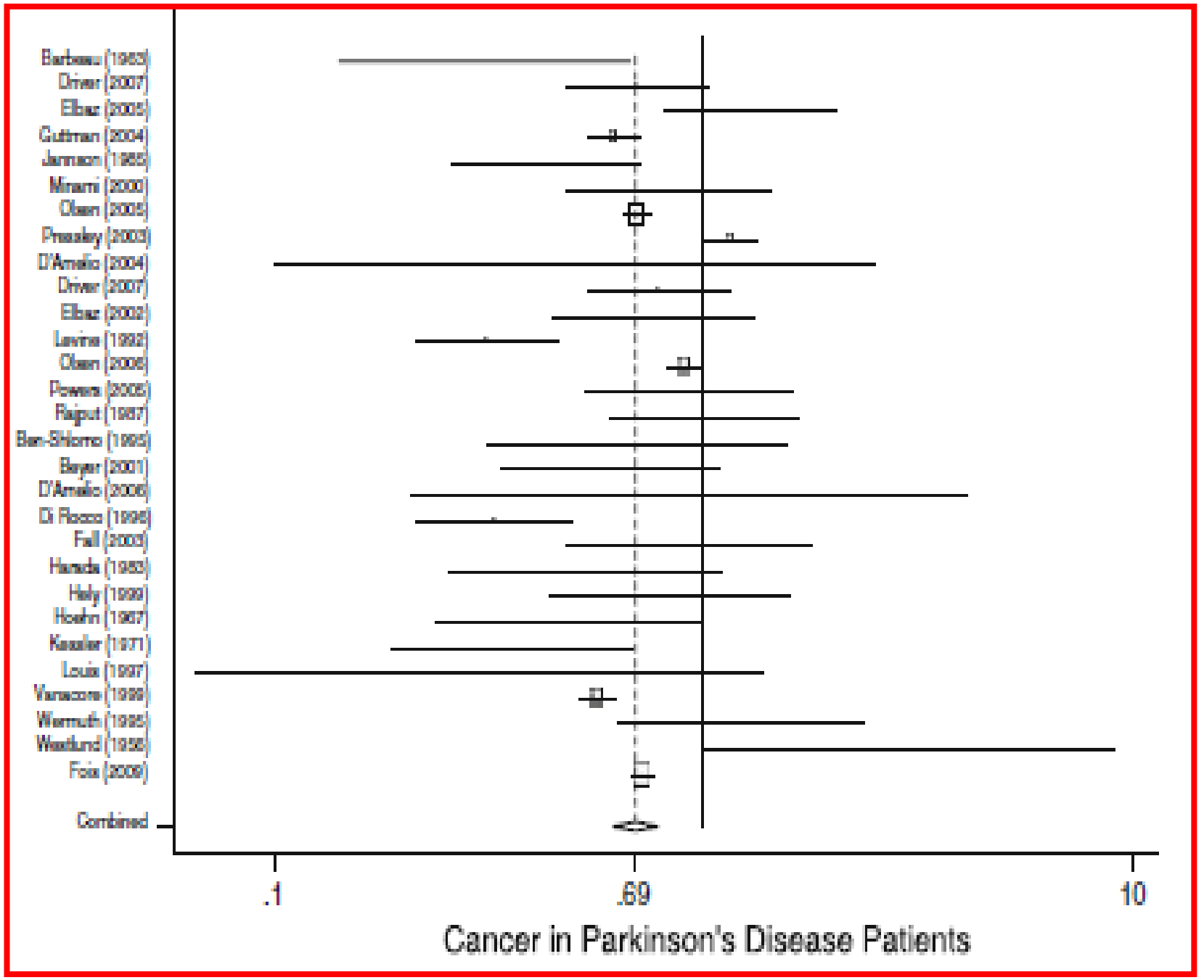
Barbeau (1963)
Driver (2007)
Elbaz (2005)
Guttman (2004)
Jamison (1985)
Minami (2000)
Olsen (2005)
Pressley (2003)
D'Amelio (2004)
Driver (2007)
Elbaz (2002)
Levine (1992)
Olsen (2005)
Powers (2005)
Rajput (1987)
Ben-Shlomo (1995)
Beyer (2001)
D'Amelio (2006)
Di Rocco (1998)
Fall (2003)
Hamada (1983)
Hely (1999)
Hoehn (1967)
Kessler (1971)
Louis (1997)
Vanacore (1999)
Wermuth (1995)
Westlund (1956)
Foix (2009)
Combined
.1
.69
10
Cancer in Parkinson's Disease Patients

Table 2 Association between PD and site-specific cancers

	No. of studies	RR (95% CI)[a]		Ri statistic	*Q* test (*p* value)
		Fixed effects	Random effects		
Site-specific cancers					
Melanoma	8[b]	1.56 (1.27–1.91)	1.41 (0.90–2.19)	0.17	0.02
Other skin cancers	8	0.94 (0.87–1.02)	0.79 (0.46–1.36)	0.54	<0.001
Breast	7	1.00 (0.90–1.11)	0.96 (0.75–1.21)	0.06	<0.01
Colorectal	9	0.77 (0.71–0.83)	0.76 (0.65–0.89)	0.05	<0.001
Prostate	9	0.80 (0.72–0.88)	0.80 (0.72–0.88)	<0.01	0.41
Leukaemias and lymphomas	6	0.76 (0.64–0.89)	0.76 (0.64–0.89)	<0.001	0.66
Lung	10	0.46 (0.41–0.51)	0.46 (0.41–0.51)	<0.001	0.70

[a] Risk ratio and 95% confidence interval

[b] Note that this is a small subset of the available literature on the association between melanoma and PD

UNA COORTE DI 10322 PAZIENTI PARKINSONIANI RESIDENTI NELLA PROVINCIA DI ROMA

Mortality cancer risk in parkinsonian patients: A population-based study

Article abstract—Cancer mortality in a population-based cohort of 10,322 parkinsonian patients (448 deaths observed during 1987 to 1994) was compared with that of the Italian province of Rome using the standardized mortality ratio (SMR). The overall cancer mortality risk was lower in this cohort than in the reference population (SMR, 56; 95% CI, 51 to 61). This reduction included most cancer sites as well as both smoking-related (SMR, 51; 95% CI, 42 to 60) and nonsmoking-related cancers (SMR, 58; 95% CI, 52 to 65). The observed reduction in cancer mortality risk in this cohort cannot be explained entirely by the hypothesis that smokers are less likely to develop PD.

NEUROLOGY 1999;52:395–398

Nicola Vanacore, MD; Stefania Spila-Alegiani, MSc; Roberto Raschetti, MSc; and Giuseppe Meco, MD

	Parkinsonian men			Parkinsonian women			Parkinsonian total			Rome province total*		
	No. of deaths			No. of deaths			No. of deaths			No. of deaths		
Age, y	All causes	All cancer	Person-years	All causes	All cancer	Person-years	All causes	All cancer	Person-years	All causes	All cancer	No. of subjects
25–44	4	0	356	3	0	410	7	0	765	1,228	332	1,108,243
45–49	4	1	243	0	0	265	4	1	509	646	299	255,248
50–54	3	1	528	6	1	436	9	2	964	1,030	500	254,760
55–59	18	3	963	11	1	840	29	4	1,802	1,647	809	235,194
60–64	51	6	1,955	40	9	1,850	91	15	3,805	2,587	1,185	213,558
65–69	176	12	3,505	97	16	3,426	273	28	6,931	3,428	1,430	177,596
70–74	300	46	4,771	198	12	5,186	498	58	9,956	3,659	1,270	117,941
75–79	560	76	6,099	523	65	8,380	1,083	141	14,479	5,320	1,509	103,859
80–84	622	68	4,625	657	54	7,757	1,279	122	12,382	5,315	1,080	61,008
>85	435	35	2,556	620	42	4,944	1,055	77	7,500	6,198	740	34,497
Total	2,173	248	25,601	2,155	200	33,493	4,328	448	59,094	31,058	9,154	2,561,904

* The number of deaths and people are reported as average annual figures.

ICD IX	Sites	Obs	Exp	SMR	95% CI
140–208	Malignant neoplasm	448	802.8	56	51–61
*140–149	Lip, oral cavity, and pharynx	4	9.4	43	12–109
141	Tongue	1	2.3	44	1–245
146	Oropharynx	1	1.1	95	2–527
149	Other and ill-defined sites	2	1.2	169	20–610
150–159	Digestive organs and peritoneum	173	312.6	55	47–64
*150	Esophagus	5	9.0	55	18–129
151	Stomach	43	77.7	55	40–74
152–154	Intestine, colon, and rectum	65	101.9	64	49–81
155	Liver and intrahepatic bile ducts	15	47.7	31	17–51
156	Gallbladder	8	19.0	42	18–83
*157	Pancreas	22	33.0	67	41–100
158	Retroperitoneum and peritoneum	2	2.6	76	9–274
159	Other and ill-defined sites	13	21.6	60	32–103
160–165	Respiratory and intrathoracic organs	81	170.3	48	38–59
161	Larynx	8	10.9	73	32–144
*162	Trachea, bronchus, and lung	69	154.5	45	35–56
164	Thymus, heart, and mediastinum	3	1.6	187	39–546
165	Other and ill-defined sites	1	0.6	174	4–971
170–175	Bone, connective tissue, skin, and breast	35	61.3	57	39–79
170	Bone and articular cartilage	2	3.6	56	7–202
174–175	Female and male breast	29	47.8	61	40–87
173	Others of skin	1	3.8	26	1–145
172	Melanoma of skin	3	4.3	70	14–204
179–184	Female genital organs	20	30.1	66	40–102
179	Uterus, unspecified	6	11.9	50	18–110
*180	Cervix uteri	2	1.6	125	15–452
182	Body of uterus	1	1.9	53	1–296
183	Ovary and other uterine adnexa	9	10.0	90	41–171
184	Others and unspecified	2	4.7	43	5–154

ICD IX	Sites	Obs	Exp	SMR	95% CI
185–187	Male genital organs	34	54.9	62	42–86
185	Prostate	33	53.8	61	42–86
187	Other male genital organs	1	0.7	135	3–753
188–189	Urinary organs	31	54.3	57	38–81
*188	Bladder	22	40.6	54	33–81
*1890	Kidney	8	12.7	63	27–124
1892	Ureter	1	0.2	546	14–3041
190–199	Other and unspecified sites	28	50.6	55	36–79
200–208	Lymphatic and hematopoietic tissue	42	59.3	71	51–95
201	Hodgkin's disease	2	1.9	105	13–379
202	Others of lymphoid and histiocytic tissue	5	15.2	33	11–77
203	Multiple myeloma	15	11.8	127	69–208
204	Lymphoid leukemia	7	10.1	69	28–143
205	Myeloid leukemia	5	9.9	51	16–118
206	Monocytic leukemia	1	0.4	255	6–1421
208	Leukemia, unspecified cell type	7	8.8	80	32–164

* Smoking-related cancer deaths.[1]

715 CASI INCIDENTI DI PARKINSON IN UNA COORTE DI 220494 PERSONE

IJEA

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Original article

Original article

Exploring causality of the association between smoking and Parkinson's disease

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Background: The aim of this paper is to investigate the causality of the inverse association between cigarette smoking and Parkinson's disease (PD). The main suggested alternatives include a delaying effect of smoking, reverse causality or an unmeasured confounding related to a low-risk-taking personality trait.

Methods: A total of 715 incident PD cases were ascertained in a cohort of 220 494 individuals from NeuroEPIC4PD, a prospective European population-based cohort study including 13 centres in eight countries. Smoking habits were recorded at recruitment. We analysed smoking status, duration, and intensity and exposure to passive smoking in relation to PD onset.

Results: Former smokers had a 20% decreased risk and current smokers a halved risk of developing PD compared with never smokers. Strong dose–response relationships with smoking intensity and duration were found. Hazard ratios (HRs) for smoking <20 years were 0.84 [95% confidence interval (CI) 0.67–1.07], 20–29 years 0.73 (95% CI 0.56–0.96) and >30 years 0.54 (95% CI 0.43–0.36) compared with never smokers. The proportional hazard assumption was verified, showing no change of risk over time, arguing against a delaying effect. Reverse causality was disproved by the consistency of dose–response relationships among former and current smokers. The inverse association between passive smoking and PD, HR 0.70 (95% CI 0.49–0.99) ruled out the effect of unmeasured confounding.

Conclusions: These results are highly suggestive of a true causal link between smoking and PD, although it is not clear which is the chemical compound in cigarette smoking responsible for the biological effect.

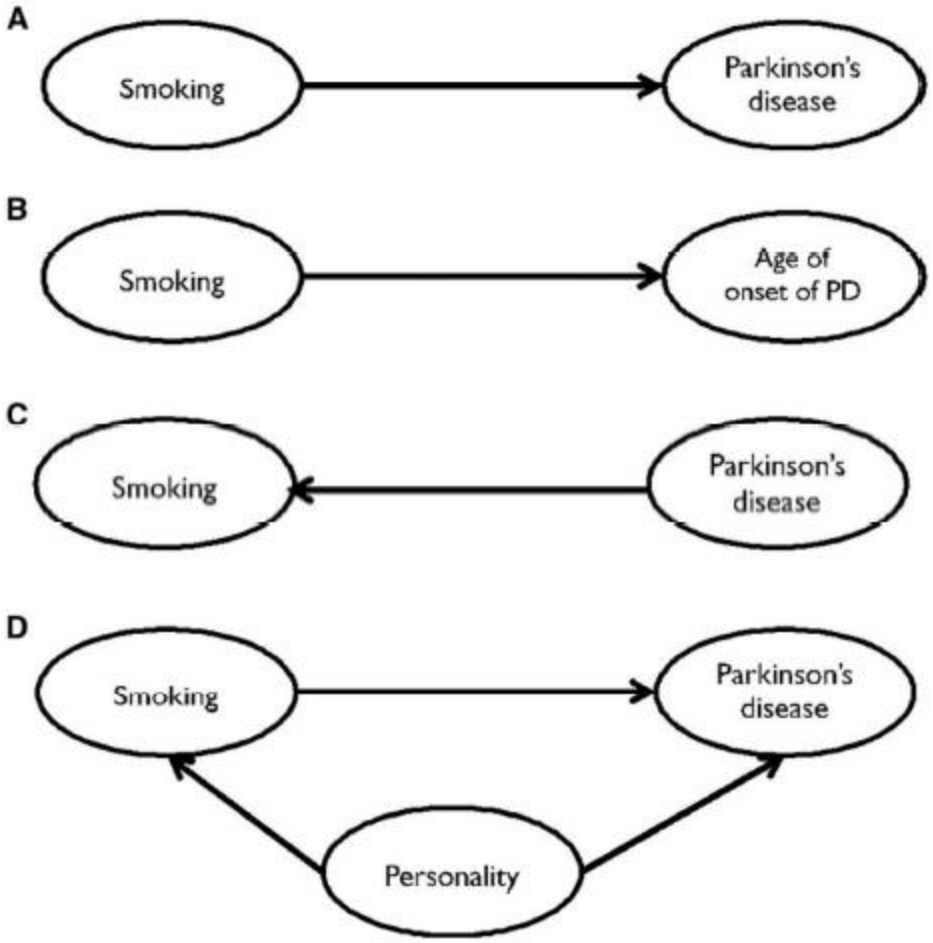

Figure 1. Direct Acyclic Graphs (DAGs) showing the hypotheses on the observed association between cigarette smoking and Parkinson's disease. (**A**) Smoking protects against PD (causal effect); (**B**) smoking delays PD onset; (**C**) subjects with a specific personality trait are both less likely to smoke and more susceptible to PD (confounding effect); (**D**) subtle dopaminergic changes before disease onset make quitting smoking easier (reverse causality).

Table 3. Hazard ratios (HRs) and relative 95% confidence intervals (CIs) from Cox-regression models investigating smoking variables in relation to PD onset in men and women separately and sensitivity analysis including only definite and very likely PD cases

	Men		Women		All	
	PD cases	HR (95% CI)[a]	PD cases	HR (95% CI)[a]	Definite and very likely PD cases	HR (95% CI)[a]
Smoking status at recruitment						
Never smokers	149	1.00	253	1.00	228	1.00
Former smokers	165	0.77 (0.62–0.97)	67	0.80 (0.60–1.07)	121	0.85 (0.66–1.08)
Current smokers	52	0.49 (0.35–0.67)	29	0.46 (0.31–0.69)	40	0.42 (0.29–0.59)
Duration of smoking						
Never smokers	149	1.00	253	1.00	228	1.00
<20 years	57	0.83 (0.61–1.14)	35	0.83 (0.58–1.21)	55	0.98 (0.72–1.34)
20–29 years	47	0.76 (0.54–1.06)	22	0.68 (0.43–1.07)	33	0.64 (0.44–0.94)
30+ years	95	0.55 (0.42–0.72)	28	0.45 (0.30–0.67)	64	0.52 (0.39–0.70)
	Trend	<0.001	Trend	<0.001	Trend	228
Smoking intensity[b]						
Never smokers	149	1.00	253	1.00	228	1.00
<12 cigarettes/day	56	0.79 (0.57–1.10)	35	0.83 (0.58–1.25)	51	0.85 (0.61–1.19)
12+ cigarettes/day	79	0.56 (0.42–0.76)	11	0.53 (0.28–0.99)	46	0.47 (0.33–0.68)
	Trend	<0.001	Trend	0.043	Trend	<0.001
Time since quitting smoking						
Never smoker	149	1.00	253	1.00	228	1.00
19+ years	82	0.89 (0.67–1.18)	28	0.79 (0.53–1.19)	58	1.05 (0.77–1.44)
9–18 years	40	0.68 (0.48–0.97)	18	0.78 (0.48–1.27)	28	0.67 (0.45–1.01)
<9 years	33	0.66 (0.45–0.97)	16	0.73 (0.44–1.23)	30	0.75 (0.50–1.11)
	Trend	0.008	Trend	0.106	Trend	0.046
Age when quitting smoking						
Never smoker	149	1.00	253	1.00	228	1.00
<33 years	44	1.10 (0.78–1.55)	10	0.56 (0.29–1.07)	36	1.25 (0.86–1.80)
34–43 years	33	0.60 (0.41–0.88)	20	0.96 (0.60–1.53)	28	0.74 (0.49–1.11)
44+ years	78	0.72 (0.54–0.97)	32	0.77 (0.52–1.12)	52	0.73 (0.53–1.01)
	Trend	0.006	Trend	0.164	Trend	0.032
Age when started smoking						
Never smoker	149	1.00	253	1.00	228	1.00
20+ years	75	0.71 (0.53–0.94)	61	0.77 (0.57–1.04)	67	0.70 (0.52–0.93)
17–19 years	61	0.70 (0.51–0.95)	13	0.36 (0.20–0.64)	38	0.58 (0.41–0.84)
<16 years	72	0.63 (0.47–0.84)	14	0.58 (0.33–1.02)	52	0.73 (0.53–1.01)
	Trend	0.001	Trend	<0.001		Trend
Passive smoking in childhood	53	1.25 (0.70–2.24)	103	0.88 (0.60–1.32)		
Passive smoking at home/work	54	0.71 (0.40–1.23)	84	0.68 (0.43–1.08)		

[a]Models adjusted for educational level and sex (where appropriated) and stratified by centre and age at recruitment.
[b]Excluding Sweden ($N = 53\,291$) and missing for 10 876 subjects who were excluded from this model.

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Original article

Neurological Disorders and Cancer

Associations between cancer and Parkinson's disease in U.S. elderly adults

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Background: Several studies suggest that cancer is reduced before and after a Parkinson's disease (PD) diagnosis. However, determining relationships among diseases of ageing is challenging due to possible biases in ascertaining disease. This study evaluates the PD and cancer relationship, addressing potential biases.

Methods: Using Surveillance, Epidemiology, and End Results-Medicare linked data (1992–2005) of adults ≥ 65 years, we assessed PD risk after cancer comparing PD in 743 779 cancer patients with PD in a non-cancer group ($n = 419\,432$) in prospective cohort analyses. We also conducted a case-control study of 836 947 cancer cases and 142 869 controls to assess cancer following PD. We applied Cox proportional hazards models to estimate hazards ratios (HRs) for PD after cancer and unconditional logistic regression to estimate odds ratios (ORs) for PD preceding cancer, controlling for physician visits and other factors. To explore biases in ascertaining cancer, we examined relationships between cancer and automobile accident injuries, which we expected to be null.

Results: No association was observed between cancer and subsequent PD [HR = 0.97; 95% confidence interval (CI) = 0.92-1.01] nor between cancer and subsequent automobile injuries (HR = 1.03; 95% CI = 0.98-1.07). One site, lung cancer, was associated with subsequent reduced PD, which may reflect confounding by smoking. In the case-control analysis, PD was associated with reduced subsequent cancer, overall (OR = 0.77; 95% CI = 0.71-0.82) and for several cancer sites. However, the automobile injury/ subsequent cancer association was similar (OR = 0.83; 95% CI = 0.78-0.88), suggesting a cancer detection bias after serious health outcomes.

Conclusions: In totality, our data do not support a biological relationship between PD and cancer.

Cancer Causes Control (2010) 21:697–707
DOI 10.1007/s10552-009-9497-6

ORIGINAL PAPER

Parkinson's disease and cancer risk: a systematic review and meta-analysis

Archna Bajaj · Jane A. Driver · Eva S. Schernhammer

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

AMSTAR – a measurement tool to assess the methodological quality of systematic reviews.

1. Was an 'a priori' design provided?

The research question and inclusion criteria should be established before the conduct of the review.

Note: Need to refer to a protocol, ethics approval, or pre-determined/a priori published research objectives to score a "yes."

- ☐ Yes
- ☐ No
- ☐ Can't answer
- ☐ Not applicable

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4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?

The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.

Note: If review indicates that there was a search for "grey literature" or "unpublished literature," indicate "yes." SIGLE database, dissertations, conference proceedings, and trial registries are all considered grey for this purpose. If searching a source that contains both grey and non-grey, must specify that they were searching for grey/unpublished lit.

- ☐ Yes
- ☐ No
- ☐ Can't answer
- ☐ Not applicable

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5. Was a list of studies (included and excluded) provided?

A list of included and excluded studies should be provided.

Note: Acceptable if the excluded studies are referenced. If there is an electronic link to the list but the link is dead, select "no."

- ☐ Yes
- ☐ No
- ☐ Can't answer
- ☐ Not applicable

3. IL PARADIGMA DELLA COMPLESSITA' DELLA NEURODEGENERAZIONE E DELLA CANCEROGENESI

ELSEVIER

Alzheimer's & Dementia 13 (2017) 267-273

Alzheimer's & Dementia

Review Article

Exploring the nexus of Alzheimer's disease and related dementias with cancer and cancer therapies: A convening of the Alzheimer's Association & Alzheimer's Drug Discovery Foundation

Heather M. Snyder[a,*], Tim Ahles[b], Stuart Calderwood[c], Maria C. Carrillo[a], Honglei Chen[d], Chung-Chou H. Chang[e,f,g,h], Suzanne Craft[i], Philip De Jager[j], Jane A. Driver[k,l], Howard Fillit[m], David Knopman[n], Michael Lotze[o,1], Mary C. Tierney[p], Suzana Petanceska[q], Andrew Saykin[r], Sudha Seshadri[s], Diana Shineman[m], Mary Ganguli[t]

Recent population studies suggest an intriguing inverse relationship between several types of cancer and neurodegenerative diseases, including Alzheimer's disease. Understanding the intersection of the underlying biology for these two distinct families of diseases with one another may offer novel approaches to identify new therapeutic approaches and possible opportunities to repurpose existing drug candidates. The Alzheimer's Association and the Alzheimer's Drug Discovery Foundation convened a one-day workshop to delve into this discussion. Workshop participants outlined research focus areas, potential collaborations, and partnerships for future action.

3. Mechanistic links between cancer and AD

Neoplasia and neurodegeneration share many genes and biological pathways, although they are often regulated in different directions [17,18]. The common pathways implicated in both cancer and neurodegenerative diseases include those that have an age-related change in regulation: cellular metabolism, inflammation, immunosenescence, oxidative stress, angiogenesis, DNA repair, apoptotic cell death and removal of effete proteins and organelles, and cell cycle entry. Aging is also associated with alterations in chaperone-mediated protein folding and protein degradation. In support of the hypothesis that cellular molecular processes are dysregulated in opposite directions, Ibanez et al. conducted transcriptome meta-analyses of microarray gene expression data from three neurodegenerative diseases and three cancers, examining pathways that were downregulated in central nervous system disorders and upregulated in cancer, and vice versa. Metabolism and genetic information-processing pathways were most significantly downregulated in central nervous system disorders and upregulated in cancer [19]. Holohan et al. [18] reviewed differential pathway

4. Genetic links between cancer and AD

Genes that are implicated in both cancer and neurodegenerative disease may provide clues about pathogenic mechanisms as well as point to potential therapeutic targets. For example, the breast and ovarian cancer type 1 susceptibility gene (*BRCA1*) encodes a DNA repair protein, BRCA1. BRCA1 is expressed at reduced levels in the brains of individuals with AD and in animal models of AD. Aβ oligomers reduce BRCA1 levels in neuronal cultures, and BRCA1 depletion in mice is associated with impaired cognitive function [52]. It is not yet known whether mutations in *BRCA1* would change its function in the brain. In addition, the apolipoprotein E (*APOE*) ε2 allele, which reduces risk of AD, may increase risk and aggressiveness of some cancers [64].

APOE ε4 is the strongest genetic risk factor for late onset AD [53]. The presence of the ε4 haplotype is also associated with poor cognitive function after chemotherapy, possibly because of impaired neural repair mechanisms [54]. Recently, bexarotene, a drug developed to treat skin cancer that targets the expression of *APOE*, has shown promise in AD mouse models, both clearing Aβ and reversing cognitive, social, and olfactory deficits [55]. A proof of concept phase 2 clinical trial of this drug did not suggest a benefit of the drug compared with placebo and highlighted potential cardiovascular adverse events [56].

Other genes that have been linked to both cancer and AD include tumor suppressor genes, including *BIN1* [57], the transmembrane receptor gene expressed on myeloid cells *TREM2* [58], and genes involved in cell cycle and angiogenesis transcriptional signaling, pathways [59]. A mutation in the gene *LRRK2*, which is associated with increased PD susceptibility, has also been shown to increase the risk of certain cancers [60].

Identified research priorities include the following:

(1) Explore existing cancer cohort studies with AD biomarker studies including genetics and genomics, blood and cerebrospinal fluid analytes, and advanced neuroimaging. Conversely, new studies could include more comprehensive assessment of cancer data in cohorts addressing aging-related cognition and magnetic resonance imaging outcomes.

(2) Develop systematic, longitudinal immunoprofiling of the human peripheral and resident immune system in subjects with deep phenotypic characterization relevant to AD pathology and cancer, to understand how systemic and brain immune functions affect one another in making someone susceptible to AD and cancer.

(3) Develop longitudinal characterization of immunosenescence to understand immune system dynamics and identify biomarkers with which to measure innate immune function that is relevant to cancer and AD.

(4) Invest in large-scale functional and compound screening of novel human in vitro systems to understand and perturb the functional consequences of genetic and other AD risk factors in immune cells.

(5) Develop comprehensive phenotyping across multiple domains of available cohorts through collaborations between National Cancer Institute, National Institute on Aging, and other agencies.

(6) Identify well-characterized cohorts of young adults and following them through late adulthood with a life course approach to simultaneously identify and track the development of both cancer and neurodegeneration, including their risk factors and preclinical marker.

(7) Identify common or variant biomarkers that reflect the two diseases.

Biogerontology (2014) 15:547–557
DOI 10.1007/s10522-014-9523-2

REVIEW ARTICLE

Inverse association between cancer and neurodegenerative disease: review of the epidemiologic and biological evidence

Jane A. Driver

Received: 12 May 2014 / Accepted: 23 July 2014 / Published online: 12 August 2014

Abstract Growing evidence suggests an unusual epidemiologic association between cancer and certain neurological conditions, particularly age-related neurodegenerative diseases. Cancer survivors have a 20–50 % lower risk of developing Parkinson's and Alzheimer's disease, and patients with these neurodegenerative conditions have a substantially lower incidence of cancer. We review the epidemiologic evidence for this inverse co-morbidity and show that it is not simply an artifact of survival bias or under-diagnosis. We then review the potential biological explanations for this association, which is intimately linked to the very different nature of dividing cells and neurons. The known genetic and metabolic connections between cancer and neurodegeneration generally fall within two categories. The first includes shared genes and pathways such as Pin1 and the ubiquitin proteasome system that are dysregulated in different directions to cause one disease or the other. The second includes common pathophysiological mechanisms such as mitochondrial dysfunction, oxidative stress and DNA damage that drive both conditions, but with different cellular fates. We discuss examples of these biological links and their implications for developing new approaches to prevention and treatment of both diseases.

Keywords Cancer · Neurodegeneration · Alzheimer's disease · Parkinson's disease · Epidemiology

Table 1 Comparison of dividing cells and neurons

Characteristic	Dividing cell	Neuron
Function	Various functions Cells of the same type can be replaced	Information processing, communication with other neurons The individual cell is irreplaceable
Tissue survival	Interval mitosis renews cell population Response to growth and mitotic factors regulated carefully	Individual cell must survive as long as the organism Unable to complete mitosis Normally unresponsive to mitogens
DNA repair	Ongoing focal repair Careful checking and repair of entire genome during cell cycle	Ongoing focal repair of necessary genes only No cell cycle
Energy production	Can meet its own needs Normal mode is oxidative phosphorylation but also uses glycolysis during hypoxia and proliferation	Dependent on astrocytes for glycolysis and antioxidant production Neuron uses oxidative phosphorylation almost exclusively

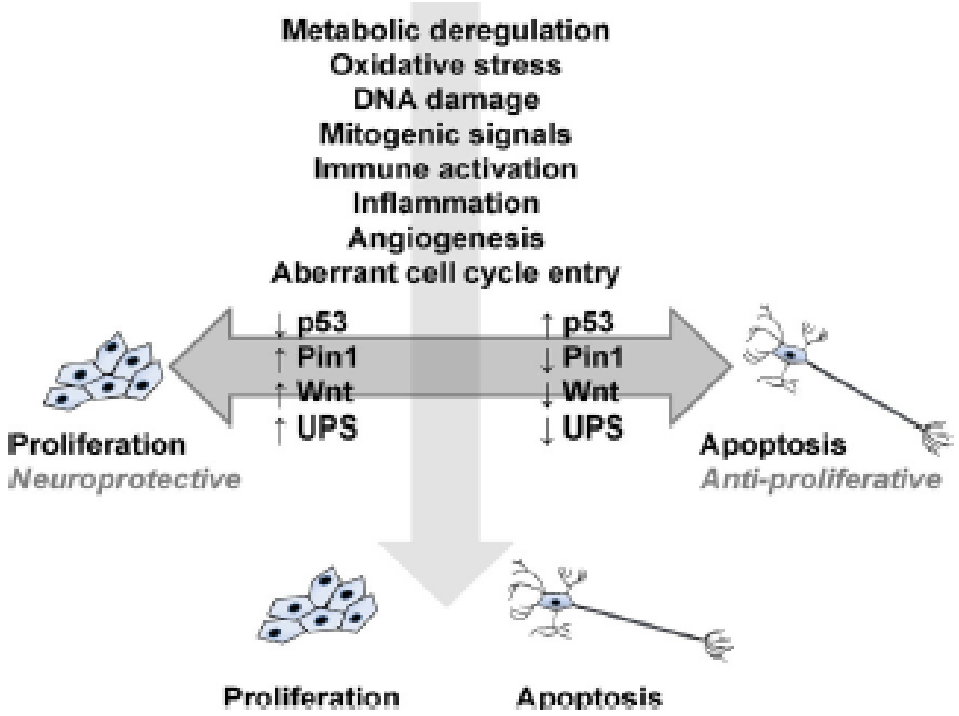

Fig. 1 Cancer and AD/PD can be seen as extremes along the same axis (horizontal axis). If proliferative pathways (e.g. Pin1 and the ubiquitin proteasome system (UPS) are upregulated they may promote cancer but provide neuroprotection. If p53 function is upregulated, it will promote apoptosis but protect against cancer. Cancer and neurodegenerative disease also share many pathophysiological features in common (*vertical* axis). Due to the very different nature of the two cell types, these forces promote cancer in the peripheral cell but apoptosis in the neuron. Age-related metabolic deregulation and metabolic reprogramming may be an initiating event for both carcinogenesis and neurodegeneration

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A common biological mechanism in cancer and Alzheimer's disease?

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Abstract

Cancer and Alzheimer's disease (AD) are two common disorders for which the final pathophysiological mechanism is not yet clearly defined. In a prospective longitudinal study we have previously shown an inverse association between AD and cancer, such that the rate of developing cancer in general with time was significantly slower in participants with AD, while participants with a history of cancer had a slower rate of developing AD. In cancer, cell regulation mechanisms are disrupted with augmentation of cell survival and/or proliferation, whereas conversely, AD is associated with increased neuronal death, either caused by, or concomitant with, beta amyloid (Aβ) and tau deposition. The possibility that perturbations of mechanisms involved in cell survival/death regulation could be involved in both disorders is discussed. Genetic polymorphisms, DNA methylation or other mechanisms that induce changes in activity of molecules with key roles in determining the decision to "repair and live"- or "die" could be involved in the pathogenesis of the two disorders. As examples, the role of p53, Pin1 and the Wnt signaling pathway are discussed as potential candidates that, speculatively, may explain inverse associations between AD and cancer.

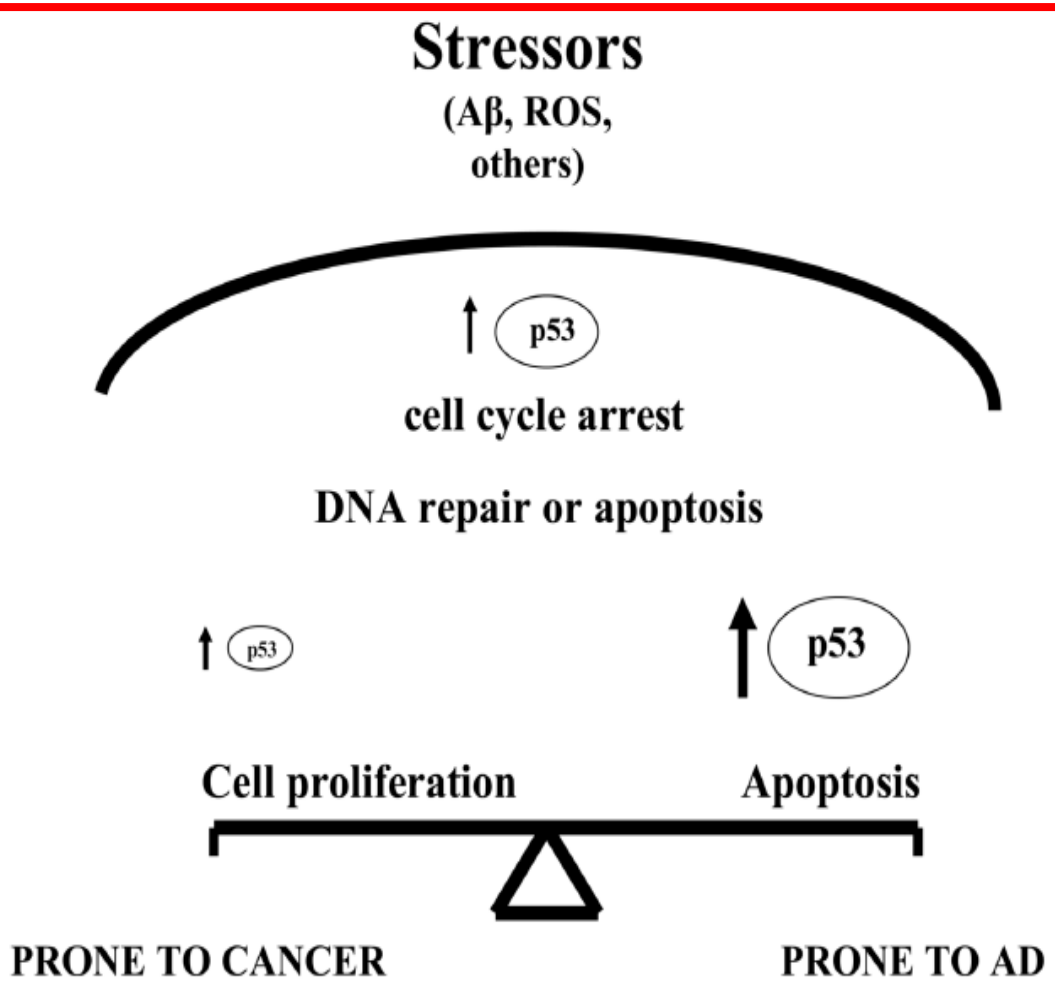

Figure 1.
Role of p53 in cancer and AD. In response to toxic or stress signals, p53 is activated through a number of post-translational modifications and induces cell cycle arrest among other functions. The decision is made whether to induce DNA repair or apoptosis of damaged cells to maintain genomic stability. If the cell machinery in the whole organism were shifted to high p53 in response to stressors, the cells would be more prone to cell death and AD could develop. If, on the contrary, the cell machinery were shifted to low or no p53, the cells would be more prone to develop a cancer. ROS, reactive oxygen species.

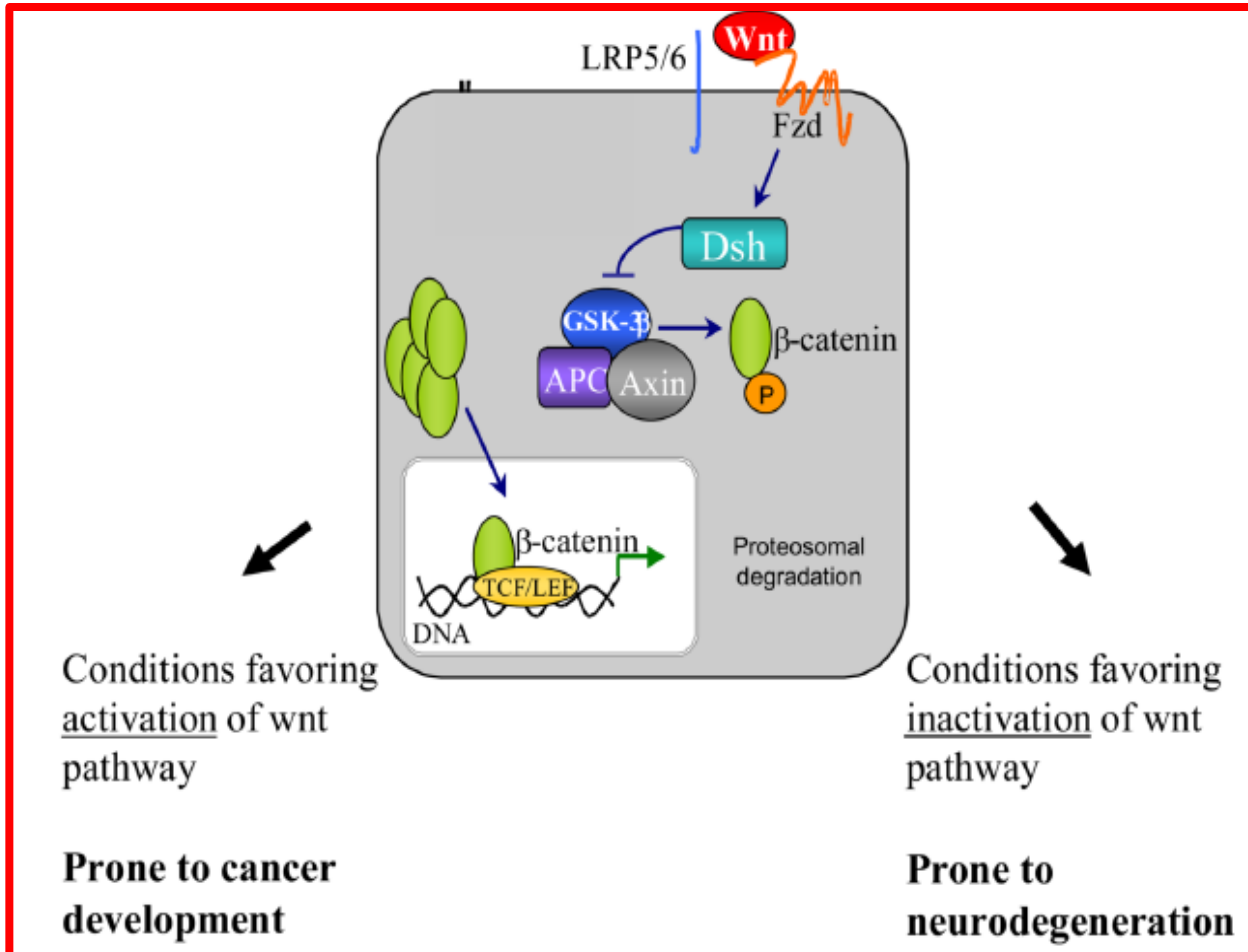

Figure 2.
The wnt signaling pathway involvement in cancer and neurodegeneration. When wnt binds to the LRP-frizzled receptor in the surface of the cell,β-catenin is stabilized promoting expression of wnt target genes and proliferation. Subtle disequilibrium in any step of the pathway in a manner that determines activation of the pathway, such as increased expression or polimorphisms that induce activation of wnt or β-catenin would favor cancer development, preventing neurodegeneration. On the contrary, conditions that induce inactivation of the pathway would favor the development of Alzheimer's disease or other degenerative disorder, and as a consequence protect from cancer development.

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Pin1 dysregulation helps to explain the inverse association between cancer and Alzheimer's disease

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Abstract

BACKGROUND—Pin1 is an intracellular signaling molecule which plays a critical but opposite role in the pathogenesis of Alzheimer's disease (AD) and many human cancers.

SCOPE OF REVIEW—We review the structure and function of the Pin1 enzyme, the diverse roles it plays in cycling cells and neurons, the epidemiologic evidence for the inverse association between cancer and AD, and the potential therapeutic implications of Pin1-based therapies.

MAJOR CONCLUSIONS—Pin1 is a unique enzyme that has effects the function of target proteins by "twisting" them into different shapes. Cycling cells use Pin1 to help coordinate cell division. It is over-expressed and/or activated by multiple mechanisms in many common human cancers, and acts on multiple signal pathways to promote tumorigenesis. Inhibition of Pin1 in animal models has profound anti-tumor effects. In contrast, Pin1 is down-regulated or inactivated by multiple mechanisms in AD brains. The absence of Pin1 impairs tau function and amyloid precursor protein processing, leading to tangle- and amyloid-related pathologies and neurodegeneration in an age-dependent manner, resembling human AD. We have developed cis and trans conformation-specific antibodies to provide the first direct evidence that tau exists in distinct cis and trans conformations and that Pin1 accelerates its cis to trans conversion, thereby protecting against tangle formation in AD.

GENERAL SIGNIFICANCE—Available studies on Pin1 suggest that cancer and AD may share biological pathways that are deregulated in different directions. Pin1 biology opens exciting preventive and therapeutic horizons for both cancer and neurodegeneration.

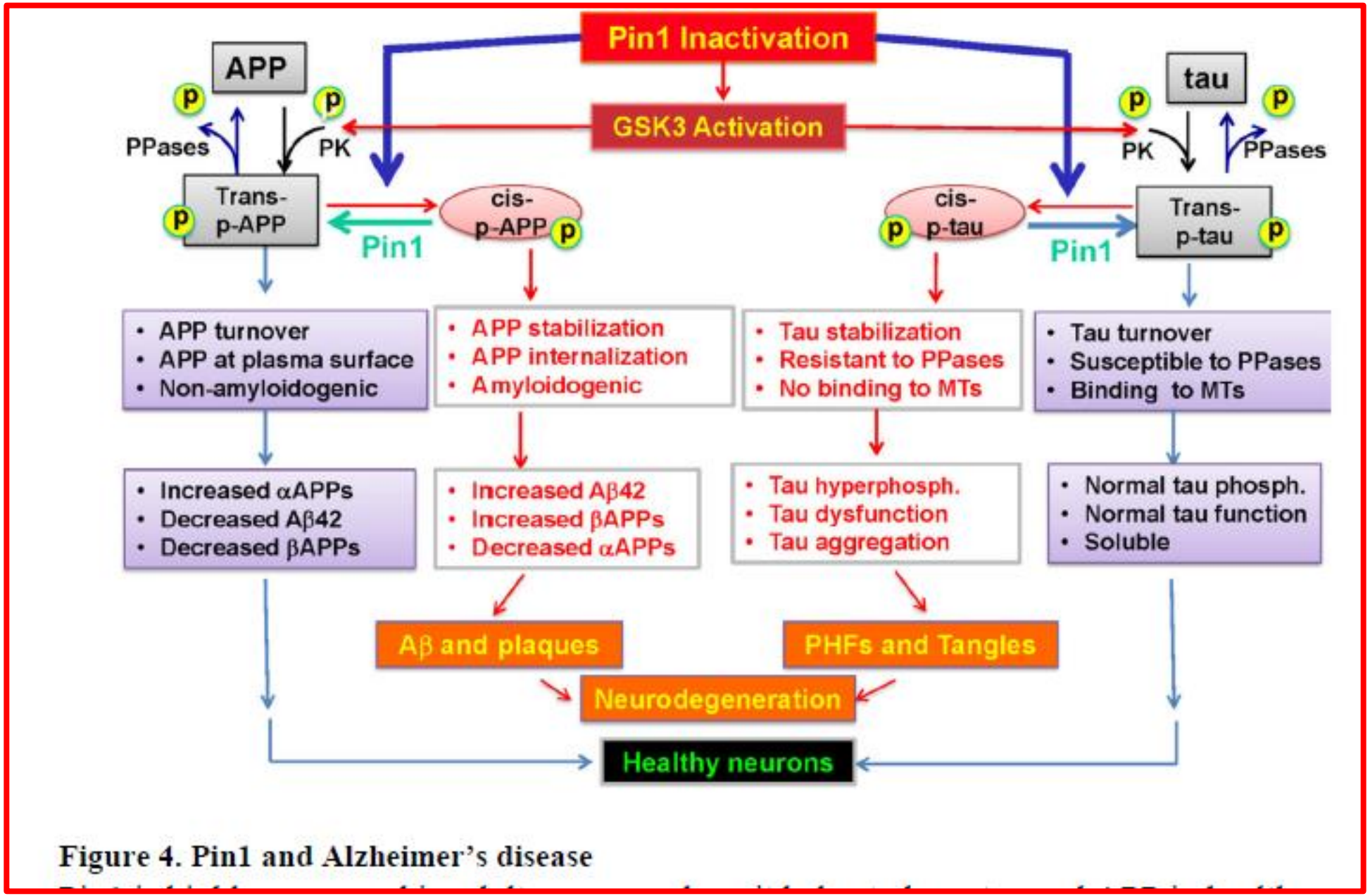

Figure 4. Pin1 and Alzheimer's disease

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ORIGINAL INVESTIGATION

Investigating the genetic relationship between Alzheimer's disease and cancer using GWAS summary statistics

Yen-Chen Anne Feng[1] · Kelly Cho[4,5] · Sara Lindstrom[1,3] · Peter Kraft[1,2] · Jean Cormack[4] · IGAP Consortium, Colorectal Transdisciplinary Study (CORECT) · Discovery, Biology, and Risk of Inherited Variants in Breast Cancer (DRIVE) · Elucidating Loci Involved in Prostate Cancer Susceptibility (ELLIPSE) · Transdisciplinary Research in Cancer of the Lung (TRICL) · Liming Liang[1,2] · Jane A. Driver[4,5]

Abstract Growing evidence from both epidemiology and basic science suggest an inverse association between Alzheimer's disease (AD) and cancer. We examined the genetic relationship between AD and various cancer types using GWAS summary statistics from the IGAP and GAME-ON consortia. Sample size ranged from 9931 to 54,162; SNPs were imputed to the 1000 Genomes European panel. Our results based on cross-trait LD Score regression showed a significant positive genetic correlation between AD and five cancers combined (colon, breast, prostate, ovarian, lung; $r_g = 0.17$, $P = 0.04$), and specifically with breast cancer (ER-negative and overall; $r_g = 0.21$ and 0.18, $P = 0.035$ and 0.034) and lung cancer (adenocarcinoma, squamous cell carcinoma and overall; $r_g = 0.31$, 0.38 and 0.30, $P = 0.029$, 0.016, and 0.006). Estimating the genetic correlation in specific functional categories revealed mixed positive and negative signals, notably stronger at annotations associated with increased enhancer activity. This suggests a role of gene expression regulators in the shared genetic etiology between AD and cancer, and that some shared variants modulate disease risk concordantly while others have effects in opposite directions. Due to power issues, we did not detect cross-phenotype associations at individual SNPs. This genetic overlap is not likely driven by a handful of major loci. Our study is the first to examine the co-heritability of AD and cancer leveraging large-scale GWAS results. The functional categories highlighted in this study need further investigation to illustrate the details of the genetic sharing and to bridge between different levels of associations.

The members of the IGAP Consortium, Colorectal Transdisciplinary Study (CORECT), Discovery, Biology, and Risk of Inherited Variants in Breast Cancer (DRIVE), Elucidating Loci Involved in Prostate Cancer Susceptibility (ELLIPSE), Transdisciplinary Research in Cancer of the Lung (TRICL) teams are provided in the Acknowledgements section.

Electronic supplementary material The online version of this

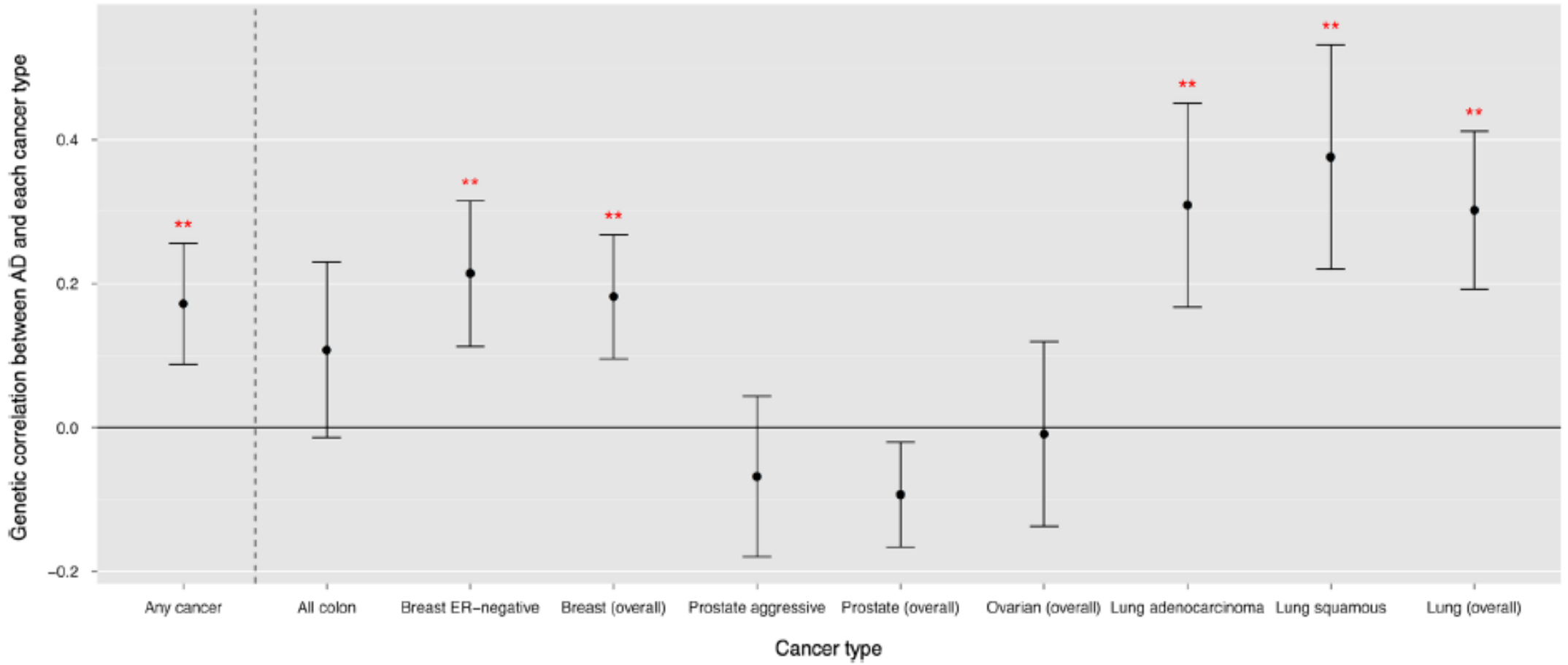
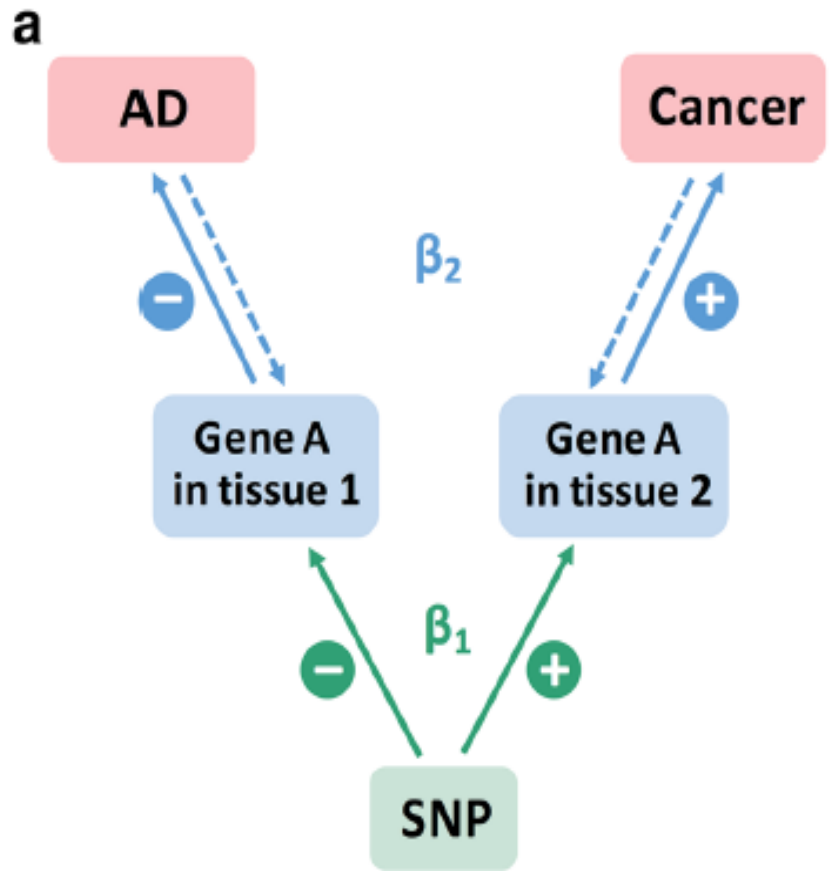


Fig. 1 Genetic correlation between AD and each cancer type, estimated by cross-trait LD score regression. *Error bars* are displayed as point estimate ± SE; ***p* value for genetic correlation <0.05; "any cancer" category includes all colon cancer, breast cancer (overall), prostate cancer (overall), ovarian cancer (overall), and lung cancer (overall)



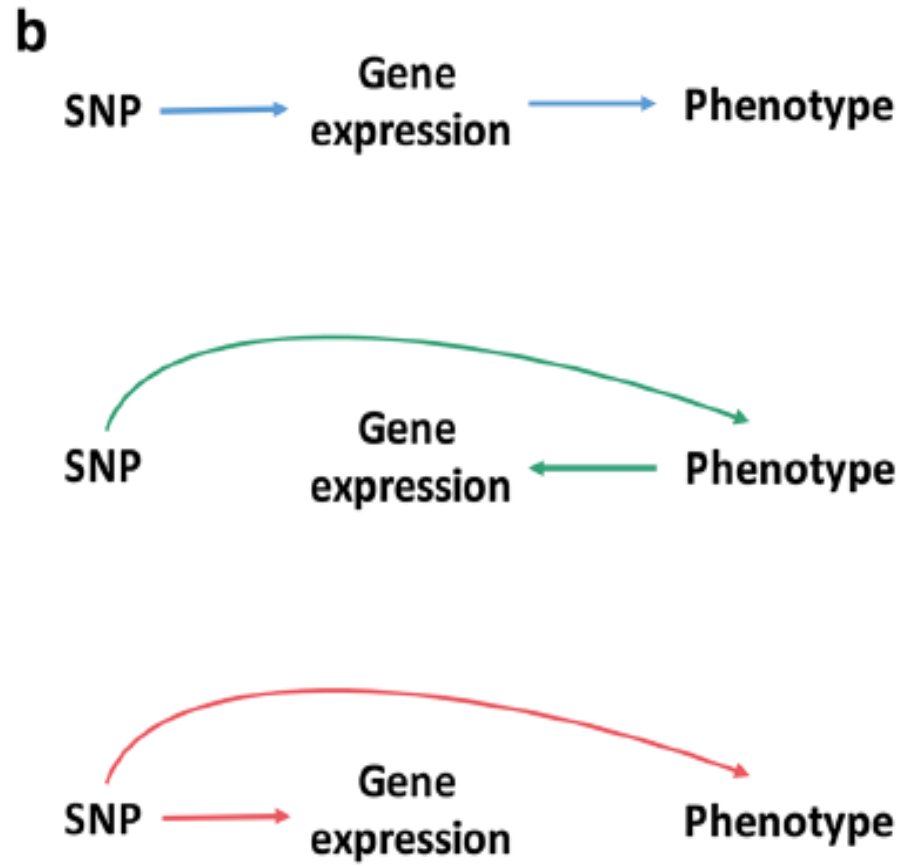


Fig. 3 Relationship between SNP, gene expression, and observed phenotype(s). **a** A possible scenario where an inverse correlation of gene expression effects (Ibanez et al. 2014) and a positive correlation of SNP effects between AD and cancer can be observed. **b** Possible causal pathways for the relationship between the three components if correlation exists between either two components. From up to down: causal effect of SNP on phenotype mediated through gene expression; gene expression reacts to phenotypic change due to SNP effect; pleiotropic effect of SNP on both gene expression and phenotype

Association of Cancer History with Alzheimer's Disease Dementia and Neuropathology

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Abstract

Background—Cancer and Alzheimer's disease (AD) are common diseases of aging and share many risk factors. Surprisingly, however, epidemiologic data from several recent independent cohort studies suggest that there may be an inverse association between these diseases.

Objective—To determine the relationship between history of cancer and odds of dementia proximate to death and neuropathological indices of AD.

Methods—Using data from two separate clinical-pathologic cohort studies of aging and AD, the Religious Orders Study (ROS) and the Rush Memory and Aging Project (MAP), we compared odds of AD dementia proximate to death among participants with and without a history of cancer. We then examined the relation of history of cancer with measures of AD pathology at autopsy, i.e., paired helical filament tau (PHFtau) neurofibrillary tangles and amyloid-β load.

Results—Participants reporting a history of cancer had significantly lower odds of AD (OR 0.70 [0.55–0.89], $p = 0.0040$) proximate to death as compared to participants reporting no prior history of cancer. The results remained significant after adjusting for multiple risk factors including age, sex, race, education, and presence of an *APOE* ε4 allele. At autopsy, participants with a history of cancer had significantly fewer PHFtau tangles ($p < 0.001$) than participants without a history of cancer, but similar levels of amyloid-β.

Conclusions—Cancer survivors have reduced odds of developing AD and a lower burden of neurofibrillary tangle deposition.

Table 1

Characteristics of the study participants

	No History of Cancer at Baseline	History of Cancer at Baseline	*p* value *p* value
No.	888	401	
Age at death [mean (SD)], y	88.7 (6.6)	88.6 (6.7)	$p = 0.79$
Duration of longitudinal follow up [mean (SD)], y	6.9 (4.7)	6.7 (4.6)	$p = 0.59$
Sex [No. (%)]			$p = 0.99$
Female	580 (65.3%)	262 (65.3%)	
Male	308 (34.7%)	139 (34.5%)	
Years of formal education [mean (SD)], y	16.3 (3.8)	16.5 (3.5)	$p = 0.27$
Race [No. (%)]			$p = 0.09$
Non-Hispanic, White	857 (96.5%)	394 (98.3%)	
Non-white or unknown	31 (3.5%)	7 (1.8%)	
≥1 ApoE4 allele	237 (26.9%)	100 (25.3%)	$p = 0.55$
AD dementia proximate to death	383 (43.9%)	139 (35.5%)	$*p = 0.0053$

Table 3

At brain autopsy, participants with a history of cancer had decreased expression neurofibrillary tangles, but similar rates of amyloid-β. as participants with no history of cancer

	PHF tau tangles	Amyloid-β plaques
Unadjusted analysis	Est = 0.88, StdEr = 0.22, $p < 0.0001$	Est = 0.07, StdEr = 0.12, $p = 0.60$
Model A		
+Age, sex	Est = 0.87, StdEr = 0.22, $p < 0.0001$	Est = 0.06, StdEr = 0.12, $p = 0.65$
Model B		
+education, race, and ApoE4	Est = 0.82, StdEr = 0.22, $p = 0.0002$	Est=0.01, StdEr = 0.12, $p = 0.91$

4. POSSIBILI IMPLICAZIONI PER LA RICERCA IN SANITA' PUBBLICA

Open Access Protocol

BMJ Open

Can commonly prescribed drugs be repurposed for the prevention or treatment of Alzheimer's and other neurodegenerative diseases? Protocol for an observational cohort study in the UK Clinical Practice Research Datalink

Venexia M Walker,[1,2] Neil M Davies,[1,2] Tim Jones,[3] Patrick G Kehoe,[4] Richard M Martin[1,2]

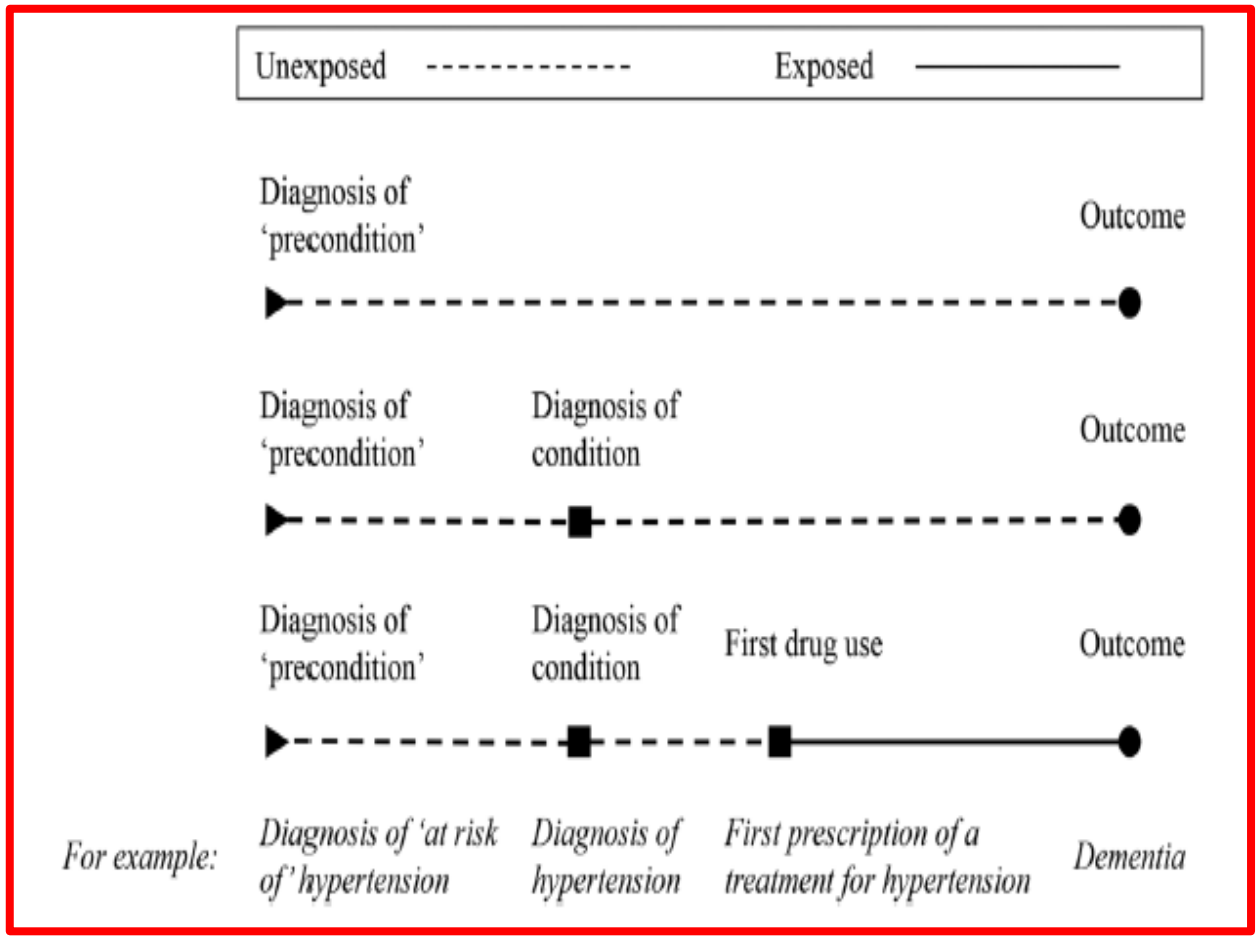
Strengths and limitations of this study

- This study will involve a large sample of data and has considerable power to detect even relatively small effects, even under highly conservative Bonferroni corrections. For example, the sample to assess the progression of dementia contains 105 471 patients and has a minimum detectable HR of 0.931.
- We plan to use four different statistical methods in our analysis, which have different approaches for modelling confounding. By doing this, we will be able to assess the merits of each method in the given situation in order to minimise confounding.
- Dementia is a heterogeneous outcome, and electronic codes used to define cases in primary care may not be as accurate as cases in clinical cohorts. We will undertake sensitivity analyses to explore how this may affect our results.

Table 1 Comparison of the three cohort types

	Cohort A	Cohort B	Cohort C
Purpose	To investigate incidence by comparing treated and untreated individuals.	To investigate incidence by comparing the different drug subclasses of each treatment.	To investigate progression by comparing treated and untreated individuals.
Number of cohorts required	There will be three cohorts of this type, one for each treatment of interest.	There will be three cohorts of this type, one for each treatment of interest.	There will be three cohorts of this type, one for each of dementia (AD or NADD), PD and ALS.
Exposures	Treatments for hypertension, hypercholesterolaemia and type 2 diabetes.	Treatments for hypertension, hypercholesterolaemia and type 2 diabetes.	Treatments for hypertension, hypercholesterolaemia, and type 2 diabetes.
Start of follow-up (index date)	Date at first risk of the condition the treatment is used for or date of first diagnosis of the condition itself if there was no preceding period 'at risk'.	Date of first prescription of a treatment of interest.	Date of first diagnosis of neurodegenerative disease of interest.
Outcome	Diagnosis of neurodegenerative disease of interest.	Diagnosis of neurodegenerative disease of interest.	Death.
Exclusion criteria	Individuals with <12 consecutive months of records prior to cohort entry.	Individuals prescribed treatment and control medications at the same time or with <12 consecutive months of records prior to cohort entry.	Individuals with <12 consecutive months of records prior to cohort entry.
Statistical analysis	Conventional regression, propensity score regression, instrumental variable analysis and marginal structural models.	Conventional regression, propensity score regression, instrumental variable analysis and marginal structural models.	Conventional regression, propensity score regression and marginal structural models.

AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; NADD, Non-Alzheimer's disease dementias; PD, Parkinson's disease.



Box 1 The drug subclasses of interest for each treatment group with the control treatments indicated

Treatments for hypertension
- Beta-adrenoceptor blocking drugs (control)
- Angiotensin-converting enzyme inhibitors
- Thiazides and related diuretics
- Calcium channel blockers
- Loop diuretics
- Alpha-adrenoceptor blocking drugs
- Centrally acting antihypertensive drugs
- Angiotensin-II receptor antagonists
- Vasodilator antihypertensive drugs
- Potassium-sparing diuretics and aldosterone antagonists

Treatments for hypercholesterolaemia
- Statins (control)
- Fibrates
- Bile acid sequestrants
- Omega-3 fatty acid compounds
- Ezetimibe
- Nicotinic acid group

Treatments for type 2 diabetes
- Biguanides (control)
- Sulphonylureas
- Other antidiabetic drugs

OPINION

Drug repositioning for Alzheimer's disease

Anne Corbett, James Pickett, Alistair Burns, Jonathan Corcoran, Stephen B. Dunnett, Paul Edison, Jim J. Hagan, Clive Holmes, Emma Jones, Cornelius Katona, Ian Kearns, Patrick Kehoe, Amrit Mudher, Anthony Passmore, Nicola Shepherd, Frank Walsh and Clive Ballard

Abstract | Existing drugs for Alzheimer's disease provide symptomatic benefit for up to 12 months, but there are no approved disease-modifying therapies. Given the recent failures of various novel disease-modifying therapies in clinical trials, a complementary strategy based on repositioning drugs that are approved for other indications could be attractive. Indeed, a substantial body of preclinical work indicates that several classes of such drugs have potentially beneficial effects on Alzheimer's-like brain pathology, and for some drugs the evidence is also supported by epidemiological data or preliminary clinical trials. Here, we present a formal consensus evaluation of these opportunities, based on a systematic review of published literature. We highlight several compounds for which sufficient evidence is available to encourage further investigation to clarify an optimal dose and consider progression to clinical trials in patients with Alzheimer's disease.

Table 2 | **Priority candidate drugs for repositioning in Alzheimer's disease**

Drugs (or drug classes)	Proposed candidates	Proposed mechanism of action	Summary of evidence	Remaining work required
Angiotensin receptor blockers (ARBs)	Valsartan	• Inhibition of inflammation, vasoconstriction and mitochondrial dysfunction, and promotion of acetylcholine release • Direct blockade of AT_1 or processing of angiotensin II[28]	• *In vitro* and *in vivo* evidence of reduced Aβ burden and improved cognitive function, and some conflicting outcomes observed with different drugs[30–34] • Established brain penetration[35] • Some epidemiological evidence for reduction of incident dementia[36,37] • Two out of three randomized controlled trials showed some benefit with ARB treatment compared to placebo[38,39]	• Clarification of mechanism of action and the need to distinguish direct effect of treatment from indirect effects on blood pressure and other cardiovascular factors • Clinical work required to link evidence from preclinical work with individual drugs • Clarification of optimal dosage • Confirmation of priority agent • Proof-of-concept study required in patients with Alzheimer's disease
Calcium channel blockers	Nitrendipine, nimodipine and nilvadipine	• Reduction of Aβ production, burden and neurotoxicity[44–48] • Specific mechanism of action unclear but differential effects indicate a novel mechanism independent of antihypertensive properties	• *In vitro* evidence of reduction of Aβ pathology and improved cell survival, with associated cognitive improvement and reduction in disease pathology *in vivo* in rodent and *Drosophila melanogaster* models[44–50] • Established clinical evidence of benefit in patients with dementia, but limited in patients with Alzheimer's disease • Meta-analysis of randomized controlled trials shows clinical benefit on cognition in initial trials[51–53]	• Preclinical work required to refine mechanism of action, obtain further data on the effect on pathology and optimize dose • Clinical work needed to identify effect on Alzheimer's disease pathology in humans • Clarification of optimal dosage • Confirmation of priority agent • Proof-of-concept study in patients with Alzheimer's disease • Further clinical evidence required to support risk reduction for incident Alzheimer's disease[54]

GLP1 analogues	Liraglutide	• Neuroprotective properties involving GSK3β and tau phosphorylation[80,81] • Additional effects on oxidative stress and apoptotic pathways[82]	• Established *in vitro* evidence for reduction of intracellular APP, Aβ and Fe^{2+}-related neurodegeneration[80] • *In vivo* evidence of improved synaptic plasticity and cognitive function, and reduced Alzheimer's disease pathology[82] • Established brain penetration[84,85] • No epidemiological or clinical evidence • Phase II trials underway	• Clinical and/or epidemiological evidence needed • Clarification of optimal dosage • Proof-of-concept study in patients with Alzheimer's disease
Tetracycline antibiotics	Minocycline	• Reduction of Aβ aggregation, promotion of Aβ clearance and reduction of pro-inflammatory markers[89–92] • Specific mechanism of action unclear	• *In vitro* and *in vivo* evidence for effect on Alzheimer's disease pathology and related inflammatory markers, including microglial activation, with some associated benefit to cognitive function, although this is conflicting • Benefit seen only with treatment lasting longer than 28 days[89–92] • No clinical evidence but some promising findings from studies in other neurological conditions[99–101]	• Clinical and/or epidemiological evidence needed • Clarification of optimal dosage • Evidence of safety with long-term use • Proof-of-concept study in patients with Alzheimer's disease
Retinoid therapy	Acitretin	• Direct effect on APP processing mediated by RXR[108] • Upregulation of amyloid-clearing enzymes[109] • Antioxidant regulation[110]	• Established evidence suggesting that impaired retinoic acid signalling may lead to Alzheimer's disease pathology[102–107] • *In vitro* evidence for overall mechanistic effect[107] • *In vivo* evidence for reduction in inflammation, Aβ burden and tau phosphorylation with associated cognitive benefit, although studies are conflicting[110–112] • No clinical data, but Phase II trial is underway • Significant safety concerns	• Further *in vivo* work required to clarify mechanism of action and effect on cognition and behaviour • Clinical evidence • Evidence of safety with long-term use • Clarification of optimal dosage

Aβ, amyloid-β; APP, amyloid precursor protein; AT_1, angiotensin II type 1 receptor; GLP1, glucagon-like peptide 1; GSK3β, glycogen synthase kinase 3β; RXR, retinoid X receptor.

Table 3 | Ongoing trials in Alzheimer's disease related to priority candidates discussed in this article*

Drug	Phase and location	Study description	Status	Estimated completion date	ClinicalTrials.gov identifier
Acitretin	II Germany	28 days of acitretin treatment (30 mg) in patients with mild to moderate Alzheimer's disease; primary objective is to measure the change in APPsα levels in the CSF	Recruiting†	April 2011†	NCT01078168
Exenatide	II United States	Drug administered to patients with early Alzheimer's disease or MCI, with planned follow-up using sum of boxes and ADAS-cog for 36 months following treatment; MRI and CSF biomarkers used as secondary measures	Recruiting	January 2013	NCT01255163
Liraglutide	II Denmark	26 weeks of treatment with liraglutide (intravenously administered) or placebo in patients with mild Alzheimer's disease; primary outcome is amyloid load measured by ^{11}C-PiB–PET imaging	Recruiting	June 2013	NCT01469351
Nilvadipine	III Europe	18-month randomized placebo-controlled trial in 500 patients with Alzheimer's disease across 18 European sites (funded by the European Union)	Finalizing protocol	To be confirmed	To be confirmed

^{11}C-PiB, ^{11}C -labelled Pittsburgh compound B; ADAS-cog, Alzheimer's Disease Assessment Scale-cognitive subscale; APPsα, secreted form of amyloid precursor protein (cleaved by α-secretase); CSF, cerebrospinal fluid; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; PET, positron emission tomography.
*Based on information in the ClinicalTrials.gov database; accessed October 2012. †Last verified in September 2010.

RESEARCH ARTICLE

AlzhCPI: A knowledge base for predicting chemical-protein interactions towards Alzheimer's disease

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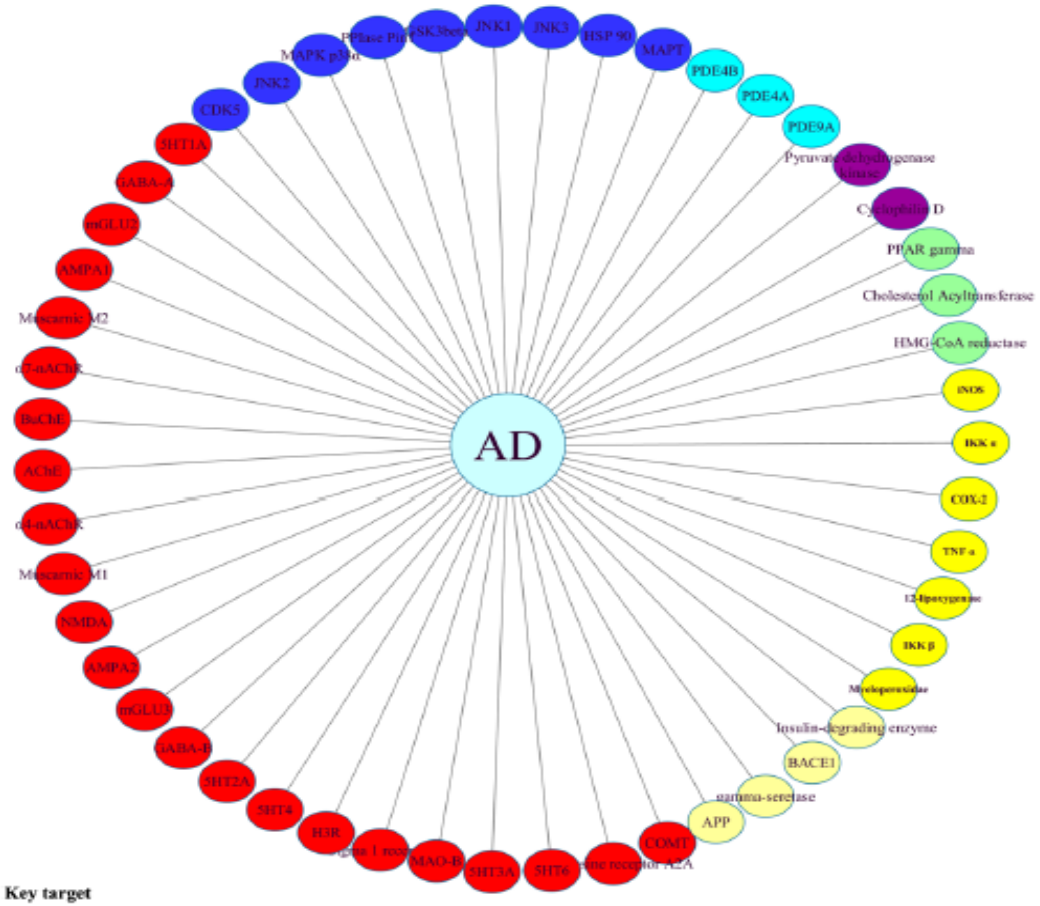
Abstract

Alzheimer's disease (AD) is a complicated progressive neurodegeneration disorder. To confront AD, scientists are searching for multi-target-directed ligands (MTDLs) to delay disease progression. The *in silico* prediction of chemical-protein interactions (CPI) can accelerate target identification and drug discovery. Previously, we developed 100 binary classifiers to predict the CPI for 25 key targets against AD using the multi-target quantitative structure-activity relationship (mt-QSAR) method. In this investigation, we aimed to apply the mt-QSAR method to enlarge the model library to predict CPI towards AD. Another 104 binary classifiers were further constructed to predict the CPI for 26 preclinical AD targets based on the naive Bayesian (NB) and recursive partitioning (RP) algorithms. The internal 5-fold cross-validation and external test set validation were applied to evaluate the performance of the training sets and test set, respectively. The area under the receiver operating characteristic curve (ROC) for the test sets ranged from 0.629 to 1.0, with an average of 0.903. In addition, we developed a web server named AlzhCPI to integrate the comprehensive information of approximately 204 binary classifiers, which has potential applications in network pharmacology and drug repositioning. AlzhCPI is available online at http://rcidm.org/AlzhCPI/index.html. To illustrate the applicability of AlzhCPI, the developed system was employed for the systems pharmacology-based investigation of shichangpu against AD to enhance the understanding of the mechanisms of action of shichangpu from a holistic perspective.



Key target

AChE Acetylcholinesterase; AMPA1 Glutamate receptor ionotropic AMPA1 receptor; AMPA2 Glutamate receptor ionotropic AMPA2 receptor; APP Amyloid beta A4 precursor binding protein; BACE1 Beta-secretase 1; BuChE Butyrylcholinesterase; CDK5 Cyclin-dependent kinase 5; COMT Catechol O-methyltransferase; COX-2 Cyclooxygenase-2; GABA-A Gamma-Aminobutyric acid A receptor; GABA-B Gamma-Aminobutyric acid B receptor; GSK3beta Glycogen syathase kinase 3 beta; H3R Histamine receptor H3; HSP 90 Heat shock protein 90; iNOS Inducible nitric oxide synthase; IKK α Nuclear factor kappa-B kinase alpha; IKK β Nuclear factor kappa-B kinase beta; JNK1 Mitogen-Activated Protein Kinase 8; JNK2 Mitogen-Activated Protein Kinase 9; JNK3 Mitogen-Activated Protein Kinase 10; MAO-B Monoamine Oxidase B; MAPK p38α Mitogen-activated protein kinase 14; MAPT Microtubule-associated protein tau; mGLU2 Metabotropic glutamate receptor 2; mGLU3 Metabotropic glutamate receptor 3; NMDA Glutamate (NMDA) receptor; PDE4A Phosphodiesterase Type 4A; PDE4B Phosphodiesterase Type 4B; PDE9A Phosphodiesterase Type 9A; TNF α Tumor necrosis factor alpha; 5HT1A 5-hydroxytryptamine 1A; 5HT2A 5-hydroxytryptamine 2A; 5HT3A 5-hydroxytryptamine 3A; 5HT4 5-hydroxytryptamine 4; 5HT6 5-hydroxytryptamine 6

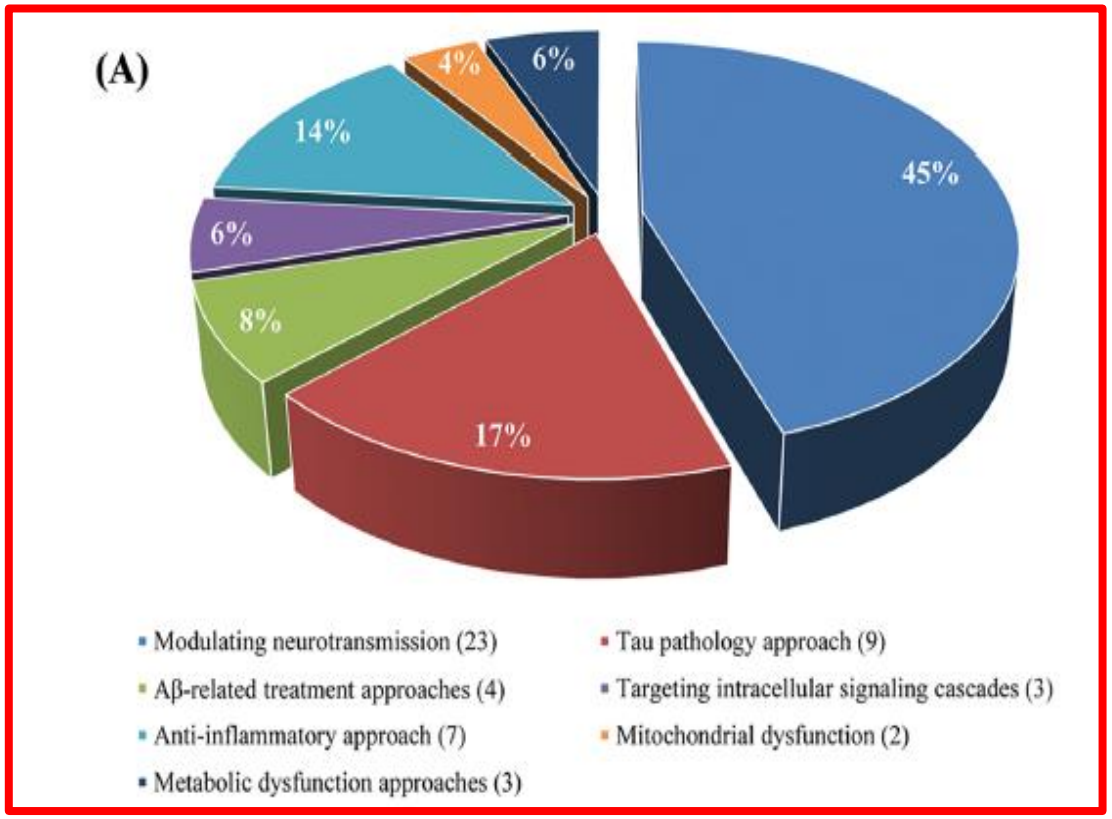
Fig 2. Summary of 51 key targets in AlzhCPI.

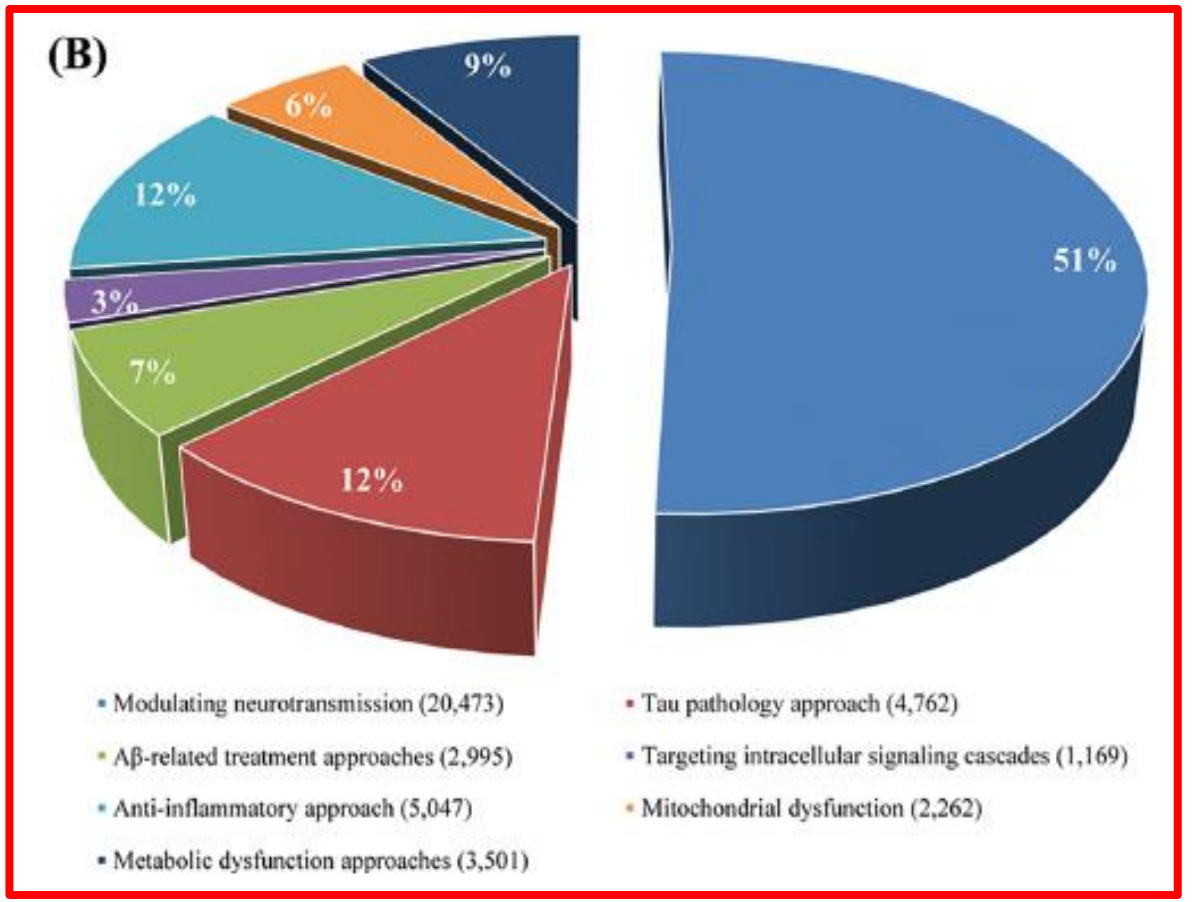
La locuzione latina *in silico*, comparsa di recente in letteratura scientifica, è usata per indicare fenomeni di natura chimico biologica riprodotti in una simulazione matematica al computer, invece che in provetta o in un essere vivente.

Table 1. Detailed statistical description of the entire data set based on the multi-label classification strategy.

Encoding Gene	Training set (ECFP2)				Test set (ECFP2)			
	Inhibitors	decoys	Total	Tanimoto index	Inhibitors	decoys	Total	Tanimoto index
HTR2A	2200	6600	8800	0.288	742	2226	2968	0.198
ADORA2A	2360	7080	9440	0.279	783	2349	3132	0.179
CHRM2	380	1140	1520	0.249	128	384	512	0.15
PDE9A	110	330	440	0.114	33	99	132	0.046
GRM2	310	930	1240	0.28	106	318	424	0.234
GRM3	50	150	200	0.305	16	48	64	0.203
MAPK8	780	2340	3120	0.192	266	798	1064	0.091
MAPK9	330	990	1320	0.13	108	324	432	0.06
MAPK10	510	1530	2040	0.183	174	522	696	0.056
MAPK14	40	120	160	0.181	19	57	76	0.171
HS90AA1	750	2250	3000	0.215	248	744	992	0.1361
PIN1	60	180	240	0.125	23	69	92	0.0544
MAPT	40	120	160	0.1125	12	36	48	0.0209
PTGS2	1760	5280	7040	0.542	583	1749	2332	0.164
NOS2	570	1710	2280	0.33	184	552	736	0.288
MPO	60	180	240	0.338	19	57	76	0.211
CHUK	120	360	480	0.173	41	123	164	0.098
IKBKB	600	1800	2400	0.22	198	594	792	0.123
TNF	560	1680	2240	0.184	192	576	768	0.083
ALOX12	120	360	480	0.2	40	120	160	0.119
CTSD	1250	3750	5000	0.246	423	1269	1692	0.093
PDK1	440	1320	1760	0.261	149	447	596	0.2
HMGCR	600	1800	2400	0.233	199	597	796	0.136
IDE	60	180	240	0.054	20	60	80	0.013
PPARG	1730	5190	6920	0.264	582	1746	2328	0.171
CES1	290	870	1160	0.305	100	300	400	0.27

Fig 3. Targets (A) and active compounds (B) classification within the entire data set in AlzhCPI.





5. CONCLUSIONI

LA NEUROPATOLOGIA DELLE PERSONE ANZIANE SENZA DEMENZA

ANN NEUROL 2013;74:478–489

Much of Late Life Cognitive Decline Is Not due to Common Neurodegenerative Pathologies

Patricia A. Boyle, PhD,[1,2] Robert S. Wilson, PhD,[1,2,3] Lei Yu, PhD,[1,3]
Alasdair M. Barr, PhD,[4] William G. Honer, MD,[5]
Julie A. Schneider, MD,[1,3,6] and David A. Bennett, MD[1,3]

Results: Cognition declined a mean of about 0.11U per year (estimate = −0.109, standard error [SE] = 0.004, $p < 0.001$), with significant individual differences in rates of decline; the variance estimate for the individual slopes was 0.013 (SE = 0.112, $p < 0.001$). In separate analyses, global Alzheimer pathology, amyloid, tangles, macroscopic infarcts, and neocortical Lewy bodies were associated with faster rates of decline and explained 22%, 6%, 34%, 2%, and 8% of the variation in decline, respectively. When analyzed simultaneously, the pathologic indices accounted for a total of 41% of the variation in decline, and the majority remained unexplained. Furthermore, in random change

Participants

Participants came from two clinical-pathologic cohort studies of aging and dementia: the Religious Orders Study and the Memory and Aging Project[14,15]. The Religious Orders Study began in 1994 and involves older Catholic nuns, priests, and monks recruited from more than 40 groups across the United States. The Rush Memory and Aging Project began in 1997 and involves older lay persons recruited from retirement communities, subsidized housing facilities, and social service agencies in the Chicago metropolitan area. Persons in both studies agreed to annual clinical evaluations and brain autopsy at death. Written informed consent was obtained in each study after procedures were fully explained, and both studies were approved by the Institutional Review Board of Rush University Medical Center. The follow up participation rates for both studies exceed 95% of survivors and autopsy rates exceed 80%. At the time of these analyses, data were available from 856 deceased persons with at least 2 cognitive evaluations (mean number of annual evaluations=7.5, SD=3.8, range: 2-18 years); notably, more than 80% of the persons included in these analyses had 4 or more cognitive assessments, about 60% had 5 or more, and about 25% had more than 9 assessments.

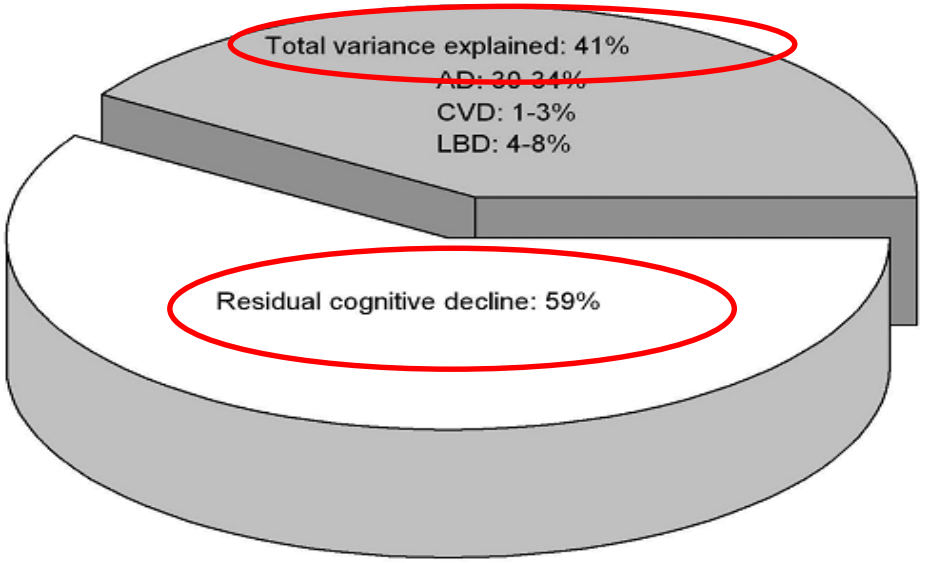


Figure 3.
Variation in cognitive decline explained by the pathologic indices (grey) and the residual, unexplained variation in cognitive decline (white) derived from fully adjusted models.

Agenzia Italiana del Farmaco

AIFA

BANDO AIFA 2017

PER LA RICERCA INDIPENDENTE SUI FARMACI

AGENZIA ITALIANA DEL FARMACO

Assegnazione di finanziamento per la ricerca indipendente sui farmaci ai sensi dell'articolo 48, commi 5, lettera g), e 19 lett b), del decreto-legge 30 settembre 2003, n. 269, convertito nella legge 24 novembre 2003, n. 326.

Finalità e caratteristiche generali

L'Agenzia Italiana del Farmaco, d'ora in poi denominata AIFA, nell'ambito della promozione della ricerca indipendente sui farmaci, finanziata ai sensi dell'art. 48, comma 19, lett.b) della legge n. 326/2003, intende promuovere ricerche volte a generare evidenze nuove, con potenziali ricadute sul sistema sanitario italiano, con riferimento specifico alle seguenti aree tematiche considerate di rilevante interesse:

- **malattie rare;**
- **malattie pediatriche;**
- **medicina di genere;**
- **sicurezza ed efficacia dei farmaci nelle popolazioni anziana e ultra-anziana;**
- **resistenza agli antimicrobici**

Struttura di Missione Temporanea Interdipartimentale

DEMENZA: Prevenzione e percorsi assistenziali, ricerca, diagnosi e terapia

Proponente: Daniela Merlo

Dipartimento di Neuroscienze

Dipartimenti e Centri coinvolti		Direttore	Firma
Dipartimento Neuroscienze	NEURO	Maurizio Pocchiari	
Dipartimento Ambiente e Salute	DAMSA	Eugenia Dogliotti	
Dipartimento sicurezza alimentare, nutrizione e sanità pubblica veterinaria	SANV	Umberto Agrimi	
Centro nazionale ricerca e valutazione preclinica e clinica dei farmaci	CNRVF	Patrizia Popoli	
Centro Nazionale per la prevenzione delle malattie e la promozione della salute	CNAPS	Angela Spinelli	
Centro di Riferimento per la medicina di genere	MEGE	Alessandra Carè	
Centro Nazionale Health Technology Assessment	HTA	Marco Marchetti	
Centro Nazionale per la sperimentazione ed il benessere animale	BENA	Rodolfo Lorenzini	
Servizio grandi strumentazioni e core facilities	FAST	Marco Crescenzi	
Unità di Bioetica	PRE-BIO	Carlo Petrini	

RIORGANIZZAZIONE IN ISS SUL TEMA DELLE DEMENZE

3 Dipartimenti

5 Centri

1 Servizio

1 Unità di Bioetica

PROMUOVERE E SOSTENERE LA RICERCA IN SANITA' PUBBLICA