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REVIEW ARTICLE

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

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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-designed perspective studies with strict control of confounding factors are needed to clarify the association between AD and cancer.

Keywords Alzheimer's disease · Cancer · Meta-analysis

Introduction

Alzheimer's disease (AD), which is prevalent in the elderly, more than 65 years old, is one of the most common neurodegenerative disorders. In addition to genetic mutation [including amyloid precursor protein (APP), presenilin 1 (PSEN1) and presenilin 2 (PSEN2)] [1], factors of aging, apolipoprotein Eε4 (APOEε4) carrier, and poor education may also contribute to the development of AD [2]. But the molecular and cellular mechanisms underlying AD are unknown so far [3].

Cancer is another disorder prevalent in the elderly. Cancer is characterized by uncontrolled cell proliferation, which is a mechanism different from that underlying AD. Previous original studies and meta-analysis have reported that negative associations may exist between cancer and neurodegenerative disorders such as Parkinson disease [4, 5]. This may be due to abnormality in gene expression or signaling pathways shared by cancer and neurodegenerative disorders, which may be up-regulated in central nervous system disorders and down-regulated in cancers or vice versa [6]. Some epidemiological data have reported the association between cancer and AD [7–14]. However, the results of previous studies are still inconsistent [7, 13, 15]. In the present meta-analysis, we will investigate the association between AD and cancer by conducting a meta-analysis.

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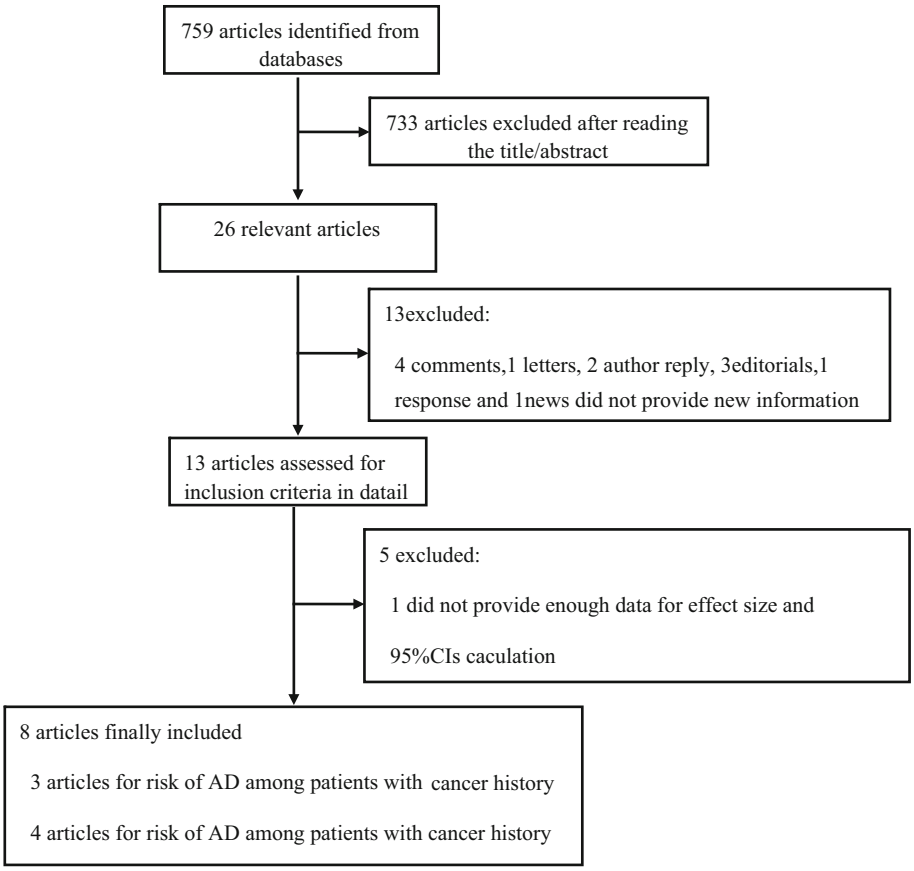

Fig. 1 Flowchart of study selection process

Results

Characteristics of studies included

As shown in Fig. 1, 759 articles were identified from primary databases research. Of them, 733 articles were excluded after title/abstract screening. Then, after full text review, 12 articles including comment, response, reply and letters with no additional new information were excluded. Another one was excluded since we did not find the full text [16]. Furthermore, according to the inclusion criteria, three papers were excluded due to not distinguishing AD from other causes of dementia [17–19]. And one was excluded as we cannot obtain data to calculate the effect size and 95 % CIs [20] and another due to selection bias in which only AD patients with reports of autopsy were included [21]. Finally, three studies analyzing risk of AD among patients with history of cancer [7, 8, 14], one study analyzing risk of cancer among patients with AD [9] and four studies analyzing both risk of AD among patients with history of cancer and risk of cancer among patients with AD [10–13] were included. Characteristics of the selected studies analyzing risk of AD among patients with a history of cancer and risk of cancer among patients with AD are summarized in Tables 1 and 2, respectively.

Risk of AD among patients with cancer history

As shown in Fig. 2, seven studies including more than 21,648 cancer patients were included in the meta-analysis. The overall results showed that history of cancer was associated with a reduced risk of AD (ES 0.62, 95 % CIs 0.52–0.74; $p < 0.001$), with no significance between-study heterogeneity ($I^2 = 0.00$ %, $p = 0.814$) and publication bias (Egger's test: $p = 0.104$). As shown in Table 3, similar results were found in subgroup analysis by stratifying variables with or without education adjusted (ES 0.59, 95 % CIs 0.42–0.83, $p = 0.002$ vs ES 0.63, 95 % CIs 0.52–0.77, $p < 0.001$), with or without APOEε4 carriers adjusted (ES 0.57, 95 % CIs 0.36–0.90, $p = 0.016$ vs ES 0.63, 95 % CIs 0.53–0.76, $p < 0.001$), years of follow-up (ES 0.56, 95 % CIs 0.36–0.86, $p = 0.009$ for studies with less than 5-year follow-up vs ES 0.63, 95 % CIs 0.47–0.84, $p = 0.001$ for studies with more than 5-year follow-up) and sample size of cases (ES 0.59, 95 % CIs 0.46–0.77, $p < 0.001$ for studies with less than 1000 AD cases vs ES 0.64, 95 % CIs 0.50–0.81, $p < 0.001$ for studies with more than 1000 AD cases). The sensitivity analysis by excluding one study at a time confirmed the negative association between risk of AD and cancer history [ES with 95 % CIs ranging from 0.62 (0.51–0.75) to 0.66 (0.54–0.79)].

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 controls	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

Risk of cancer among patients with AD

As shown in Fig. 3, five studies including 10,585 AD patients were included in the meta-analysis. The overall results showed that risk of cancer was significantly reduced among patients with AD (ES 0.59, 95 % CIs 0.42–0.82, $p = 0.002$), but with evidence of between-study heterogeneity ($I^2 = 83.5$ %, $p < 0.001$) and publication bias (Egger's test: $p = 0.025$). The sensitivity analysis by excluding one study at a time confirmed the negative association between risk of cancer and AD [ES with 95 % CIs ranging from 0.48 (0.29–0.79) to 0.70 (0.53–0.93)]. Significant negative association were found in further subgroup analysis stratified by variable with or without education adjusted (ES 0.37, 95 % CIs 0.21–0.62, $p < 0.001$ vs ES 0.69, 95 % CIs 0.49–0.96, $p = 0.028$), sample size of cases (ES 0.38, 95 % CIs 0.28–0.52, $p < 0.001$ for studies with less than 1000 AD cases vs ES 0.86, 95 % CIs 0.79–0.94, $p = 0.001$ for studies with more than 1000 AD cases) and studies with more than 5-year follow-up (ES 0.38, 95 % CIs 0.26–0.55, $p < 0.001$),but not in studies with less than 5-year follow-up (ES 0.63, 95 % CIs 0.29–1.37, $p = 0.241$) (Table 3). In addition, the between-study heterogeneity was disappeared within groups stratified by sample size of cases.

Discussion

Results in the present meta-analysis demonstrated the negative association between cancer and AD. The stability of the sensitivity analysis confirmed the conclusion. Similar results were found in subgroup analysis stratified by APOEε4 and with or without education adjusted, and years of follow-up in studies analyzing risk of AD among patients with history of cancer. Although significant negative association between risk of cancer and AD were found in subgroup analysis stratified with or without education adjusted, year of follow-up and sample size of cases, except studies with less than 5 years follow-up, the differences of pooled effect size between groups is significant. In addition, our subgroup analysis indicates that researches without education or APOEε4 adjusted may underestimate or overstate the effect, as well as periods of follow-up and sample size. And studies with small sample size may contribute to the between-study heterogeneity in studies analyzing risk of cancer among patients with AD.

The negative association between AD and risk of cancer was previously reported in one meta-analysis, but only three researches with 895 AD patients were included [4]. Our results in the present meta-analysis including 10,585 AD patients and more than 21,648 cancer patients were more credible. However, there are several limitations in

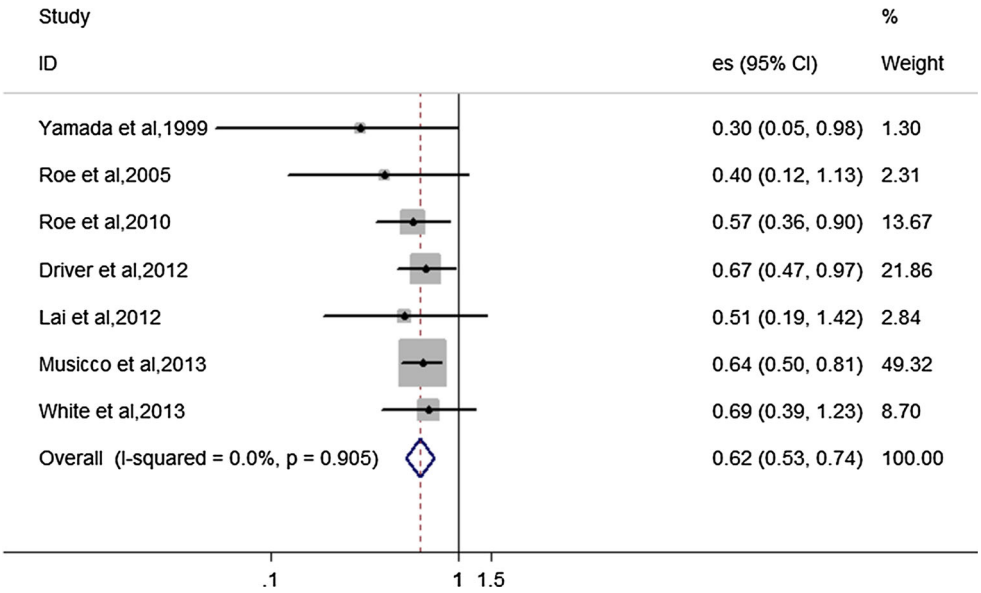

Fig. 2 Forest plot of studies analyzing risk of AD among patients with cancer history

Table 3 Subgroup meta-analysis of the association between AD and cancer

	Studies included	ES (95 % CIs)	p_z	Statistic model	I^2 (%)	p
Risk of AD						
Education adjusted						
Yes	3	0.59 (0.42–0.83)	0.002	Fixed	0.00	0.679
No	4	0.63 (0.52–0.77)	<0.001	Fixed	0.00	0.742
ApoEε4 alleles adjusted						
Yes	1	0.57 (0.36–0.90)	0.016	Fixed	–	–
No	6	0.63 (0.53–0.76)	<0.001	Fixed	0.00	0.851
Years of follow-up						
<5 years	4	0.56 (0.36–0.86)	0.009	Fixed	0.00	0.667
≥5 years	2	0.63 (0.47–0.84)	0.001	Fixed	0.00	0.588
Sample size of cases						
<1000	5	0.59 (0.46–0.77)	<0.001	Fixed	0.00	0.766
≥1000	1	0.64 (0.50–0.81)	<0.001	Fixed	–	–
Risk of cancer						
Education adjusted						
Yes	2	0.37 (0.21–0.62)	<0.001	Random	0.00	0.698
No	3	0.69 (0.49–0.96)	0.028	Random	86.90	<0.001
Years of follow-up (years)						
<5	2	0.63 (0.29–1.37)	0.241	Random	83.60	0.013
≥5	2	0.38 (0.26–0.55)	<0.001	Random	0.00	0.672
Sample size of cases						
<1000	3	0.38 (0.28–0.52)	<0.001	Fixed	0.00	0.910
≥1000	2	0.86 (0.79–0.94)	0.001	Fixed	0.00	0.356

p_z, p value for z test

our meta-analysis. First, the diagnosis criteria for AD and cancer were inconsistent. Cancer was ascertained by self-report in several studies, but previous study found that the overall rate of false-negative reporting in self-report was 39.2 % [22]. Second, the conduction of incident cancer after enrollment was different between studies. For example, participants without a prevalent cancer history, but who later had an incident cancer hospitalization, were

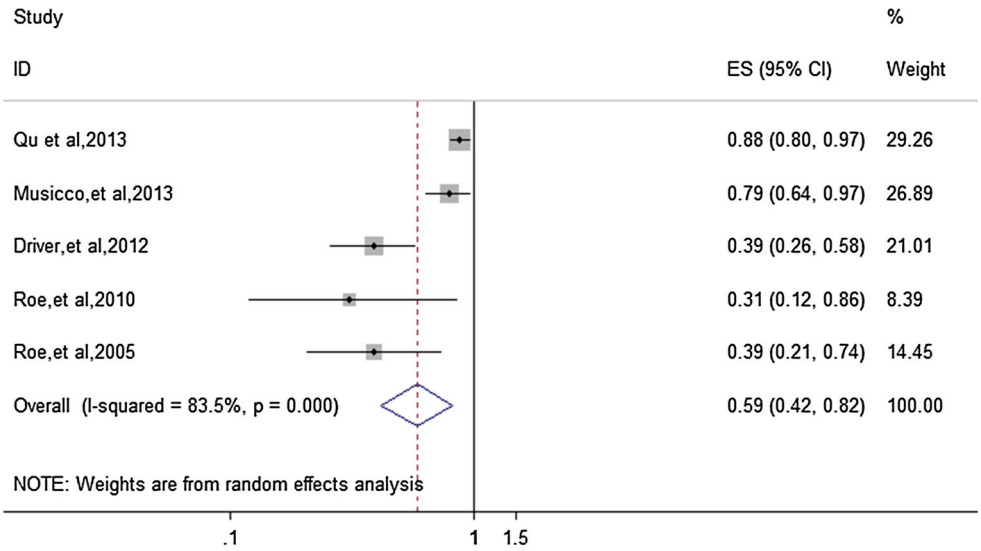

Fig. 3 Forest plot of studies analyzing risk of cancer among patients with AD

included in the baseline "no cancer history" group in one study [12], but they were included in the cancer history group in another study [11]. These findings may underestimate the association between cancer and AD. Third, the source of patients may affect the results, since the patients with dementia who later developed cancer may not be hospitalized as frequently for cancer as those without dementia and vice versa. What's more, both cancer and dementia would increase the risk of death, so the short survive of patients with cancer and dementia may reduce the likelihood of all late-onset diseases including dementia and cancer. Fourth, some researches indicated that the negative association may be appointed to special type of cancer and AD. But in the present study, the type of cancer was not taken into account. Fifth, previous studies suggest that cognitive impairment is a complication of cancer therapy, for example, survivors of breast cancer who received adjuvant chemotherapy is more likely to develop dementia [23], and cranial irradiation can induce neuronal damage and neuron loss [24]. However, the affect of cancer therapy on cognition was not taken into account in all of these included studies. Sixth, most of the studies were conducted in America. These findings may not be extended to other populations. Seventh, the publication bias was significant in studies analyzing risk of cancer among patients with AD. In addition, the confounding factors were not adequately controlled, such as education and alleles of APOE. A meta-analysis based on 13 cohort and 6 case–control studies found that the RR for low vs high education level was 1.80 (95 % CI 1.43–2.27) for AD [25]. And previous studies also found that individuals with higher levels of education are better able to cope with AD brain pathology without observable deficits in cognition [26]. APOEε4 allele is the first gene found to be definitely associated with increased risk of sporadic AD. And risk of AD increased 2–4 times in APOEε4 allele carriers [27]. Therefore, it is important to fully adjust APOEε4 allele and education for the study of causal inference of AD.

Although results in the present meta-analysis confirmed the negative association between AD and cancer, the underlying mechanism is still unclear. Several basic researches indicated that neurodegenerative disorders and cancer share several biological pathways which may contribute to this negative association. For example, Pin1, which is down-regulated or inhibited in the brain of AD patients in the early stage, is a unique enzyme playing important role in protein folding and cell cycle control [28–30]. It is important to maintain normal function of tau protein and proper cleavage of APP in the neurons [29]. And deletion or mutation of Pin1 can induce AD-like pathologic changes in mice [30]. However, Pin1 is over-expressed in kinds of human cancers, and Pin1 knockout mice are resistant to breast cancers induced by over-expression of the oncogene Ras or Neu [28]. P53 [31], a major regulator of apoptosis and the Wnt signaling pathway are the other two factors found to be associated with cancer and neurodegenerative disorders (reviewed in [32]). More importantly, results of recent studies found that bexarotene and carmustine, two kinds of cancer chemotherapy drug, could stimulate the clearance of physiological Aβ and restore Aβ induced cognitive deficits in AD mice model [30, 31]. In addition, miRNA may also contribute to the negative association between AD and cancer [33].

In conclusion, results of present meta-analysis confirmed the negative association between cancer and AD. In addition, previous experimental studies also found common biological signal pathways shared by AD and cancer. This may make sense to explore effective treatment and interventions for AD and mechanism research of both AD

and cancer. But further well-designed perspective studies with strict control of confounding factors are needed.

Methods

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.

Data extraction

Data were extracted from the original articles by two investigators independently. Discrepancies were resolved by consensus. The following data was extracted from selected studies: first author, year of publication, study design, country of origin, setting (population-based, volunteer-based or hospital-based), sample size, diagnosis criteria for AD and cancer, age at baseline, years of follow-up, adjusted effect size (HR, RR, OR or SIR) and 95 % CIs and factors adjusted.

Data analysis

We performed the meta-analysis by combining HR, OR, SIR and RR. z test was used to determine the significance of pooled effect size ($p < 0.05$ was considered statistically significance). I^2 statistic was used to quantify the between-study heterogeneity. A fixed-(ManteleHaenszel method) or random-(DerSimoniane-Laird method) effect model was used according to I^2 statistic to calculate the pooled effect size [34]. Publication bias was determined by Egger's regression ($p < 0.10$ as an indication for publication bias) [35]. In addition, we performed subgroup analysis by stratifying variable with APOEε4 carriers and with or without education adjusted, years of follow-up and sample size of cases. Stata version 12 software was used for all statistical analysis.

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Conflict of interest All authors declare no financial competing interests. All authors declare no non-financial competing interests.

References

1. Loy CT, Schofield PR, Turner AM, Kwok JBJ (2014) Genetics of dementia. Lancet 383(9919):828–840. doi:10.1016/s0140-6736(13)60630-3
2. Thies W, Bleiler L (2013) 2013 Alzheimer's disease facts and figures. Alzheimer Dement 9(2):208–245. doi:10.1016/j.jalz.2013.02.003
3. Huang Y, Mucke L (2012) Alzheimer mechanisms and therapeutic strategies. Cell 148(6):1204–1222. doi:10.1016/j.cell.2012.02.040
4. Catala-Lopez F, Suarez-Pinilla M, Suarez-Pinilla P, Valderas JM, Gomez-Beneyto M, Martinez S, Balanza-Martinez V, Climent J, Valencia A, McGrath J, Crespo-Facorro B, Sanchez-Moreno J, Vieta E, Tabares-Seisdedos R (2014) Inverse and direct cancer comorbidity in people with central nervous system disorders: a meta-analysis of cancer incidence in 577,013 participants of 50 observational studies. Psychother Psychosom 83(2):89–105. doi:10.1159/000356498
5. Bajaj A, Driver JA, Schernhammer ES (2010) Parkinson's disease and cancer risk: a systematic review and meta-analysis. Cancer Causes Control 21(5):697–707. doi:10.1007/s10552-009-9497-6
6. Ibanez K, Boullosa C, Tabares-Seisdedos R, Baudot A, Valencia A (2014) Molecular evidence for the inverse comorbidity between central nervous system disorders and cancers detected by transcriptomic meta-analyses. PLoS Genet 10(2):e1004173. doi:10.1371/journal.pgen.1004173
7. Lai SW, Chen HJ, Lin CL, Liao KF (2014) No correlation between Alzheimer's disease and risk of hepatocellular carcinoma in older people: an observation in Taiwan. Geriatr Gerontol Int 14(1):231–232. doi:10.1111/ggi.12141
8. White RS, Lipton RB, Hall CB, Steinerman JR (2013) Non-melanoma skin cancer is associated with reduced Alzheimer disease risk. Neurology 80(21):1966–1972. doi:10.1212/WNL.0b013e3182941990
9. Ou SM, Lee YJ, Hu YW, Liu CJ, Chen TJ, Fuh JL, Wang SJ (2013) Does Alzheimer's disease protect against cancers? A nationwide population-based study. Neuroepidemiology 40(1):42–49. doi:10.1159/000341411
10. Musicco M, Adorni F, Di Santo S, Prinelli F, Pettenati C, Caltagirone C, Palmer K, Russo A (2013) Inverse occurrence of cancer and Alzheimer disease: a population-based incidence study. Neurology 81(4):322–328. doi:10.1212/WNL.0b013e31829c5ec1
11. Driver JA, Beiser A, Au R, Kreger BE, Splansky GL, Kurth T, Kiel DP, Lu KP, Seshadri S, Wolf PA (2012) Inverse association between cancer and Alzheimer's disease: results from the Framingham Heart Study. BMJ 344:e1442
12. Roe CM, Fitzpatrick AL, Xiong C, Sieh W, Kuller L, Miller JP, Williams MM, Kopan R, Behrens MI, Morris JC (2010) Cancer

linked to Alzheimer disease but not vascular dementia. Neurology 74(2):106–112. doi:10.1212/WNL.0b013e3181c91873
13. Roe CM, Behrens MI, Xiong C, Miller JP, Morris JC (2005) Alzheimer disease and cancer. Neurology 64(5):895–898. doi:10.1212/01.wnl.0000152889.94785.51
14. Yamada M, Sasaki H, Mimori Y, Kasagi F, Sudoh S, Ikeda J, Hosoda Y, Nakamura S, Kodama K (1999) Prevalence and risks of dementia in the Japanese population: RERF's adult health study Hiroshima subjects. Radiation Effects Research Foundation. J Am Geriatr Soc 47(2):189–195
15. Ganguli M (2012) A reduced risk of Alzheimer's disease in those who survive cancer. BMJ 344:e1662
16. DeSouky AL (1992) The relationship between cancer and Alzheimer's disease. J Am Geriatr Soc 40(10):1075
17. Driver JA, Yung R, Gaziano JM, Kurth T (2010) Chronic disease in men with newly diagnosed cancer: a nested case–control study. Am J Epidemiol 172(3):299–308. doi:10.1093/aje/kwq127
18. Attner B, Lithman T, Noreen D, Olsson H (2010) Low cancer rates among patients with dementia in a population-based register study in Sweden. Dement Geriatr Cogn Disord 30(1):39–42. doi:10.1159/000315509
19. Hototian SR, Lopes MA, Azevedo D, Tatsch M, Bazzarella MC, Bustamante SE, Litvoc J, Bottino CM (2008) Prevalence of cognitive and functional impairment in a community sample from Sao Paulo, Brazil. Dement Geriatr Cogn Disord 25(2):135–143. doi:10.1159/000112554
20. Realmuto S, Cinturino A, Arnao V, Mazzola MA, Cupidi C, Aridon P, Ragonese P, Savettieri G, D'Amelio M (2012) Tumor diagnosis preceding Alzheimer's disease onset: is there a link between cancer and Alzheimer's disease? J Alzheimers Dis 31(1):177–182. doi:10.3233/jad-2012-120184
21. Burke WJ, McLaughlin JR, Chung HD, Gillespie KN, Grossberg GT, Luque FA, Zimmerman J (1994) Occurrence of cancer in Alzheimer and elderly control patients: an epidemiologic necropsy study. Alzheimer Dis Assoc Disord 8(1):22–28
22. Desai MM, Bruce ML, Desai RA, Druss BG (2001) Validity of self-reported cancer history: a comparison of health interview data and cancer registry records. Am J Epidemiol 153(3):299–306
23. Hodgson KD, Hutchinson AD, Wilson CJ, Nettelbeck T (2013) A meta-analysis of the effects of chemotherapy on cognition in patients with cancer. Cancer Treat Rev 39(3):297–304. doi:10.1016/j.ctrv.2012.11.001
24. Surma-aho O, Niemela M, Vilkki J, Kouri M, Brander A, Salonen O, Paetau A, Kallio M, Pyykkonen J, Jaaskelainen J (2001) Adverse long-term effects of brain radiotherapy in adult low-grade glioma patients. Neurology 56(10):1285–1290
25. Caamano-Isorna F, Corral M, Montes-Martinez A, Takkouche B (2006) Education and dementia: a meta-analytic study. Neuroepidemiology 26(4):226–232. doi:10.1159/000093378
26. Roe CM, Xiong C, Miller JP, Morris JC (2007) Education and Alzheimer disease without dementia: support for the cognitive reserve hypothesis. Neurology 68(3):223–228. doi:10.1212/01.wnl.0000251303.50459.8a
27. Tanzi RE, Bertram L (2005) Twenty years of the Alzheimer's disease amyloid hypothesis: a genetic perspective. Cell 120(4):545–555. doi:10.1016/j.cell.2005.02.008
28. Driver JA, Lu KP (2010) Pin1: a new genetic link between Alzheimer's disease, cancer and aging. Curr Aging Sci 3(3):158–165
29. Pastorino L, Sun A, Lu PJ, Zhou XZ, Balastik M, Finn G, Wulf G, Lim J, Li SH, Li X, Xia W, Nicholson LK, Lu KP (2006) The prolyl isomerase Pin1 regulates amyloid precursor protein processing and amyloid-beta production. Nature 440(7083):528–534. doi:10.1038/nature04543
30. Liou YC, Sun A, Ryo A, Zhou XZ, Yu ZX, Huang HK, Uchida T, Bronson R, Bing G, Li X, Hunter T, Lu KP (2003) Role of the prolyl isomerase Pin1 in protecting against age-dependent neurodegeneration. Nature 424(6948):556–561. doi:10.1038/nature01832
31. van Heemst D, Mooijaart SP, Beekman M, Schreuder J, de Craen AJ, Brandt BW, Slagboom PE, Westendorp RG (2005) Variation in the human TP53 gene affects old age survival and cancer mortality. Exp Gerontol 40(1–2):11–15
32. Behrens MI, Lendon C, Roe CM (2009) A common biological mechanism in cancer and Alzheimer's disease? Curr Alzheimer Res 6(3):196–204
33. Holohan KN, Lahiri DK, Schneider BP, Foroud T, Saykin AJ (2012) Functional microRNAs in Alzheimer's disease and cancer: differential regulation of common mechanisms and pathways. Front Genet 3:323. doi:10.3389/fgene.2012.00323
34. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR (2010) A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Synth Method 1(2):97–111. doi:10.1002/jrsm.12
35. Rothstein HR, Sutton AJ, Borenstein M (2006) Publication bias in meta-analysis: prevention, assessment and adjustments. John Wiley & Sons