Journal of Alzheimer's Disease 31 (2012) 177–182
DOI 10.3233/JAD-2012-120184
IOS Press

Tumor Diagnosis Preceding Alzheimer's Disease Onset: Is There a Link Between Cancer and Alzheimer's Disease?

Sabrina Realmuto, Antonio Cinturino, Valentina Arnao, Maria Antonietta Mazzola, Chiara Cupidi, Paolo Aridon, Paolo Ragonese, Giovanni Savettieri and Marco D'Amelio*
Dipartimento di Biomedicina Sperimentale e Neuroscienze Cliniche, Università di Palermo, Palermo, Italy

Handling Associate Editor: Chiara Cerami

Accepted 4 April 2012

Abstract. Studies reporting an inverse association between Alzheimer's disease (AD) and cancer are scant. Available data are mostly based on ancillary findings of mortality data or obtained from studies evaluating frequency of neoplasms in AD patients independently if they occurred before or after AD. Moreover, some studies estimated frequencies of neoplasms in demented individuals, who were not necessarily AD patients. We estimated frequency of tumors preceding the onset of AD in AD patients and compared it to that of age- and gender-matched AD-free individuals. Occurrence of tumors preceding AD onset was assessed through a semi-structured questionnaire. Tumors were categorized as benign, malignant, or of uncertain classification and as endocrine-related or not. Odds ratios (OR), used as measure of the association between the two diseases, were adjusted for tumor categories and known risk factors for AD and tumors. We included 126 AD patients and 252 matched controls. Tumor frequency before AD onset was 18.2% among cases and 24.2% among controls. There was a suggestive trend of an overall inverse association between the two diseases (adjusted OR 0.6; 95% CI 0.4–1.1; $p = 0.11$). Risk for neoplasms was significantly reduced only for women (adjusted OR, 0.5; 95% CI 0.3–0.9; $p = 0.03$) and for endocrine related tumors (adjusted OR, 0.5; 95% CI 0.2–1; $p = 0.04$). Our study confirms the inverse association reported in previous epidemiological studies. Though our findings might be explained by processes playing an opposite role in tumors development and neurodegeneration, they are also suggestive for a possible role of estrogen.

Keywords: Aging, Alzheimer's disease, case-control, estrogen, neurodegeneration, tumors

INTRODUCTION

With increasing longevity, frequency of diseases such as cancer and neurodegenerative disorders is constantly growing. Common molecular mechanisms underlying the development of neurodegenerative diseases and cancer have been suggested [1, 2]. Indeed, an inverse association between cancer and Parkinson's disease, the second most common neurodegenerative disorder, has been found by more than a study [3, 4]. As far as AD is concerned, an inverse association with cancer has been reported as ancillary findings of mortality studies or as a reduced frequency of neoplasms in AD patients independently whether cancer occurred before or after AD [5–8]. Epidemiological studies investigating the risk of AD in those people that experienced tumors before the onset of the dementia are limited [9–12] and their results are not conclusive, leaving unresolved the question regarding the link between tumors and AD. The aim of our study is to estimate

*Correspondence to: Marco D'Amelio, MD, Dipartimento di Biomedicina Sperimentale e Neuroscienze Cliniche, Università di Palermo, Via Gaetano La Loggia, 1, 90129 – Palermo, Italy. Tel.: +39 0916555160; Fax: +39 0916555152; E-mail: marco.damelio@unipa.it.

the association between tumors preceding AD onset and AD by mean of a case control-study design.

METHODS

Patients with probable AD were consecutively recruited from our department starting from January 2006 through July 2010. Only patients with probable AD were included. Diagnoses of AD were made according to DSM IV and NINCDS/ADRDA criteria [13, 14]. All patients underwent an extensive neurological examination and a complete neuropsychological battery. A detailed clinical history was collected. All patients also underwent brain computed tomography (59.5%) or magnetic resonance imaging (40.5%). Possible AD and vascular and other forms of dementia were excluded. AD patients were matched (1 : 2) by gender and age (±2 years) to individuals free of neurological diseases, randomly selected from the population of the municipality of residence of the case. Two neurologists, through an extensive analysis of medical history, neurological examination, and review of medical records, evaluated the absence of neurological disease in controls. Mini-Mental Status Examination (MMSE) was used as screening instrument for the presence of cognitive decline among controls. We excluded control subjects with MMSE $\leq$24.

Frequency of tumors, preceding onset of AD symptoms for patients, and before the index year for controls (equal to the date of onset of AD of the relative case), wase assessed through a semi-structured questionnaire. Questionnaires were administered to caregivers of AD patients, while controls were directly interviewed.

Information regarding localization and grading of neoplasms were confirmed by the review of medical records. Both cases and controls were asked if they had ever been diagnosed with any of following diagnoses: cancer, neoplasm, cyst, or nodule. Information regarding tumors (malignant/non malignant, localization, endocrine system relationship) and risk factors (smoking habit) was also collected. Endocrine-related tumors were considered those neoplasms affecting the endocrine system (i.e., endocrine pancreas, thyroid, parathyroid, pituitary gland) and those for which a hormonal influence has been demonstrated (breast cancer, corpus of the uterus, prostate). Subjects were classified as nonsmokers (less than an average of a pack of cigarettes per month during their adult life) and smokers (at least an average of a pack of cigarettes per month during their adult life). Education level, taken as a completed years of education, was stratified in four groups: 0 years, 1 to 8 years, 9 to 13 years, more than 13 years. Occupational status was classified in four different categories: housewives, manual working, intellectual workers, and all others.

A case-control matched pair design was used. Odds ratio (OR) was used as measure of the association between AD and tumors. ORs were calculated by conditional logistic regression analysis and adjusted (ORa) for smoking habit and education. In order to evaluate the effect of smoking, we also stratified cases and controls by smoking habit (smokers and nonsmokers) and OR were calculated in each strata by mean of Mantel Haenzel analysis. The study was approved by the ethic committees of the University.

RESULTS

We included 126 AD patients (36 males and 90 females) and 252 gender- and age-matched controls (72 males and 180 females). Demographics characteristics of AD patients are described in Table 1. Because of the rigid matching, age and gender distribution were similar in the control group. Mean MMSE controls raw score was 28 ± 2.04 (MMSE adjusted score 28.87 ± 1.62). Information on tumors and risk factors were collected indirectly by interview of proxies (49.2% spouse, 44.4% sons, and 6.4% siblings). Level of education and occupation of cases and controls is shown in Table 2. Mean years of education was significantly lower ($p < 0.001$) among cases (6.1 ± 4.6) compared to controls (7.8 ± 4.5). Neoplasm diagnoses preceding AD were reported in 23 AD patients (18.3%; 5 men and 18 women) and 61 controls (24.2%, 6 men and 55 women; see Table 3). Mean age at tumor diagnosis was 60.3 years for cases and 57.3 years for controls ($p = 0.3$). Mean time interval between tumor diagnosis and onset of AD or index year was 17.3 years for cases and 16.1 for controls ($p = 0.7$).

No statistically significant inverse association between AD and tumors was observed at multivariate

Table 1
Characteristics of AD patients

	All individuals	Males	Females
Age at AD onset (years)	71.1 ± 7.5	71.2 ± 8.3	71.1 ± 6.5
Age at interview (years)	76.9 ± 6.8	76.7 ± 8.3	77.1 ± 6.1
MMSE raw score	11.3 ± 7.4	14.1 ± 7.8	10.1 ± 7.3
MMSE adjusted score	12.9 ± 8.3	15.5 ± 8.0	11.8 ± 8.2
AD duration (years)	5.8 ± 2.8	5.5 ± 2.6	5.9 ± 2.8

AD, Alzheimer disease; MMSE, Mini-Mental State Examination; SD, standard deviation.

Table 2
Frequency distribution of education and occupation among cases and controls

	AD patients (%)	Controls (%)	*p*
Education (years)			
0	42 (33.3)	22 (8.8)	–
1–8	61 (48.4)	157 (62.3)	–
9–13	16 (12.7)	52 (20.6)	–
>13	7 (5.6)	21 (8.3)	<0.001
Occupation			
Housewives*	64/90 (71.1)	97/180 (53.9)	0.02
Manual workers	15/62 (21.2)	59/155 (38.1)	0.07
Intellectual workers	40/62 (64.5)	90/155 (58.1)	0.5
All others	7/62 (11.3)	6/155 (3.9)	0.08

Education: calculated *p* for trend; *percentages of housewives were calculated only for women; percentages of all other occupations (manual, intellectual, other workers) were calculated on remaining individuals after housewives were subtracted.

analysis (Table 3) (ORa 0.6; 95% confidence interval [CI] 0.4, 1.1; $p = 0.11$). The inverse association was statistically significant only for women (ORa 0.5; 95% CI 0.3, 0.9; $p = 0.03$). No significant differences were observed between cases and controls for tumor grading. When compared to controls, AD patients showed a significant decreased risk for endocrine-related neoplasms (ORa, 0.5; 95% CI 0.2, 1.0; $p = 0.04$), while no difference was observed for non endocrine-related neoplasms (ORa 1.3; 95% CI 0.6, 2.9; $p = 0.51$).

We analyzed the frequency distribution of endocrine- and non-endocrine-related tumors stratifying cases and controls according to gender (Table 4). In women, using tumor-free individuals as a reference group, only endocrine-related tumors were significantly less common among AD patients (14.4%) compared to controls (25%), while no difference was observed for endocrine- and non-endocrine-related tumors among men. Tumor frequencies by site are shown in Table 5.

Using the Mantel-Haenszel analysis, cases and controls were stratified by smoking habits (smokers versus non-smokers). The result suggested that the inverse association between AD and tumors is independent from smoking habits (Breslow-Day test for homogeneity $p = 0.7838$; chi-squared = 0.0753, DF = 1).

DISCUSSION

In the present study, we found an inverse association between AD and tumors diagnosed before the onset of dementia. This association is gender-specific and is limited to endocrine-related tumors.

Table 3
Association between AD and cancer preceding AD onset

Variable	AD (%)	Controls (%)	OR (95% CI)	*p*	ORa (95% CI)	*p*
Tumor frequency						
No	103 (81.7)	191 (75.8)	1.0		1.0	
Yes	23 (18.3)	61 (24.2)	0.7 (0.4–1.2)	0.19	0.6 (0.4–1.1)*	0.11
Tumors by gender						
Males	5 (13.9)	6 (8.3)	1.8 (0.5–6.3)	0.37	2.1 (0.5–8.5)*	0.29
Females	18 (20)	55 (30.6)	0.6 (0.3–1.0)	0.06	0.5 (0.3–0.9)*	0.03
Tumor Grading						
No neoplasm	103 (81.7)	191 (75.8)	1.0		1.0	
Non malignant	15 (11.9)	42 (16.7)	0.7 (0.4–1.3)	0.24	0.6 (0.3–1.2)**	0.16
Malignant	8 (6.3)	15 (5.9)	1.2 (0.5–2.5)	0.65	0.9 (0.4–2.1)**	0.90
Uncertain	0 (0)	4 (1.6)	—		—	
Tumor endocrine relationship						
No neoplasm	103 (81.7)	191 (75.8)	1.0		1.0	
Not endocrine related	8 (6.3)	15 (5.9)	1.4 (0.6–2.9)	0.42	1.3 (0.6–2.9)**	0.51
Endocrine related	15 (11.9)	46 (18.3)	0.6 (0.3–1.0)	0.09	0.5 (0.2–1)**	0.04

AD, Alzheimer disease; CI, confidence interval; *ORa, odds ratio adjusted for smoking habit and education; **ORa, odds ratio adjusted for age, gender, education, and smoking habit.

Table 4
Frequencies of tumors according to endocrine relationship across genders

	Women			Men		
	AD patients (%)	Controls (%)	OR (95% CI; *p*)	AD patients (%)	Controls (%)	OR (95% CI; *p*)
No tumors	72 (80.0)	135 (75.0)	Ref.	31 (86.1)	66 (91.7)	Ref.
NEC	5 (5.6)	10 (5.0)	0.8 (0.2–2.5; $p = 0.66$)	3 (8.3)	5 (6.9)	1.5 (0.3–7.7; $p = 0.64$)
EC	13 (14.4)	45 (25.0)	0.4 (0.2–0.8; $p = 0.01$)	2 (5.6)	1 (1.4)	4.9 (0.4–67.2; $p = 0.23$)

NEC: non endocrine related tumors; EC: endocrine related tumors.

Table 5
Distribution of neoplasm by site

Cancer Site	Cases (%)	Controls (%)
Ovary	0 (0)	1 (0.4)
Uterus	8 (6.3)	28 (11.1)
Breast	4 (3.2)	12 (4.8)
Skin	1 (0.8)	3 (1.2)
Central nervous system	0 (0)	1 (0.4)
Prostate	1 (0.8)	0 (0)
Intestine	1 (0.8)	2 (0.8)
Others	8 (6.3)	14 (5.6)

The main limitations of the study are the use of prevalent cases and, in AD patients, the indirect collection of information on tumors diagnoses (supported by medical records) and risk factors (i.e., smoking habit). However, studies focusing on AD looking at validity and reliability of surrogate information for controls support the use of surrogate information for controls in etiologic case-control study of AD, without neither unacceptable loss of information nor unacceptable biases [15].

An inverse association between cancer and dementia has been already reported [9, 11, 12]. This association was considered due to the reduced medical attention demented people receive and consequently to an underestimation of cancer incidence [9, 11, 12].

This hypothesis is correct for those studies investigating the occurrence of tumors in AD patients [11], but not for those investigating frequency of tumors preceding the onset of dementia [11], where alternatively, the prevalence-incidence bias must be considered. Individuals with a not yet evident clinical picture of dementia also affected by tumors might in fact have a shorter survival than individuals affected only by tumors.

Indeed, other than methodological explanations, there are different ways to interpret the described inverse association. Both cancer and neurodegenerative disorders are characterized by a disarrangement of cell regulation mechanisms, with increased cell survival and proliferation in the former and with increased cell death in the latter process.

This hypothesis seems further supported by the results of a recent study that investigated the association between cancer and dementia, separating pure AD from vascular dementia (VaD) [11]. While prevalent cancer was inversely associated with a significant reduced risk of dementia characterized mainly by a neurodegenerative process (pure AD HR = 0.57; 95% CI 0.36–090), cancer history was not associated with time to diagnosis of dementia due to vascular pathology (i.e., not being neurodegenerative in origin) (any VaD HR = 1.01; 95% CI 0.69–1.48).

Our findings of an inverse association between tumors and AD in women, in particular, for endocrine-related neoplasms, suggest in fact an additional biologically plausible interpretation.

The association between breast and uterus cancers and levels of estrogen has been demonstrated [16, 17], with mechanisms ranging from the participation of genotoxic estrogen metabolites to estrogen-receptor-mediated genomic and non-genomic signaling, affecting cell proliferation and apoptosis in neoplastic tissues [16, 17]. The role of estrogens in the development of AD is strongly supported by data from cellular and molecular research. In general, actions of estrogens on the brain cover both genetic, molecular, and biochemical mechanisms [18, 19]. Estrogens, in particular, appear to reduce neuronal apoptosis [20], modulate growth and synaptic plasticity [21], operate mitochondrial activity [22], reduce the formation of amyloid-β [23], and induce tau protein synthesis [24].

However, though findings of observational studies [25] and randomized controlled trials of hormonal therapy [26, 27] are conflicting, a protective role for estrogens seems likely, with a time-dependent effect [28].

Therefore, considering the overall role of estrogens in AD and tumor development, it is plausible to hypothesize that as result of the missing protective action of estrogens toward AD, patients with dementia would be somehow protected from the development of tumors, especially those endocrine related.

Other explanations of the inverse association might be found in other pathophysiological mechanisms common to both diseases, one generating an AD phenotype characterized by cell death and a neoplastic phenotype characterized by uncontrolled cell proliferation [29]. These include Pin1 that acts on multiple proteins, some of which are oncogenes or tumor suppressor genes and others are involved in the degenerative process of AD [30], p53 [31–33] and the molecular pathway of Wnt (wingless-type murine-mammary tumor virus integration site) [34, 35]. Processes of DNA methylation, histone acetylation, and other epigenetic modifications might be involved as well in tumorigenesis and the mechanisms responsible for AD [36–39].

Another recently proposed biological link is based on the action of acetylcholine (ACh), which is considered a mitogenic factor [40]. The degeneration of cholinergic neurons is the basis of one of etiopathogenetic mechanisms proposed for AD and it is also the foundation of current treatment being used. An increase in receptor of ACh activity was found in

some tumors [41]. One could therefore hypothesize that the inverse association between cancer and AD may partially be explained by hypercholinergic and hypocholinergic tones, simultaneously affecting ACh receptors on the brain and cancer target tissue, hypotheses that according to some authors might suggest an evaluation of cancer incidence in AD patients treated with anticholinesterase drugs [42].

To our knowledge, our study is the first case-control study evaluating the association of tumors preceding AD onset and AD. In addition, it is the first looking at grading of tumors and their correlation with endocrine-system.

In conclusion, our study showed an inverse association between AD and cancer preceding AD. The inverse association, between tumors and AD, was more evident in women and for endocrine-related tumors. These findings might underline a possible role of estrogens in a more complex picture that involves other environmental and genetic factors that interplaying with each other might predispose an individual to develop AD or conversely cancer. One or more biological mechanisms, inversely operating in the two disorders, may link AD and cancer. One leading to increased cell growth or survival, and the other to higher risk of cell death, could explain these results. The identification of such a mechanism may provide insight into therapeutic strategies that could aid in preventing both disorders [43].

ACKNOWLEDGMENTS

This study was supported in part by a donation of the Cesare Serono Foundation. The Serono Foundation funded the research without having any role in the study design or the conduct of the research.

Authors' disclosures available online (http://www.j-alz.com/disclosures/view.php?id=1249).

REFERENCES

[1] Staropoli JF (2008) Tumorigenesis and neurodegeneration: Two sides of the same coin? *BioEssays* **30**, 719-727.

[2] Migliore L, Coppodè F (2002) Genetic and environmental factors in cancer and neurodegenerative diseases. *Mutat Res* **512**, 135-153.

[3] D'Amelio M, Ragonese P, Sconzo G, Aridon P, Savettieri G (2009) Parkinson's disease and cancer. Insights for pathogenesis from epidemiology. *Ann N Y Acad Sci* **1155**, 324-334.

[4] Bajaj A, Driver JA, Schernhammer ES (2010) Parkinson's disease and cancer risk: A systematic rewiew and meta-analysis. *Cancer Causes Control* **21**, 697-707.

[5] Tirumalasetti F, Han L, Birret DP (1991) The relationship between cancer and Alzheimer's disease. *J Am Geriatr Soc* **39**, 840.

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

[7] Ganguli M, Dodge HH, Shen C, Pandav RS, DeKosky ST (2005) Alzheimer's disease and mortality. A 15-years epidemiological study. *Arch Neurol* **62**, 779-784.

[8] Wilkins K, Pearson GF, Gentleman JF, Forbes WF (2000) Death due to dementia: An analysis of Multiple-cause of death Data. *Chronic Dis Can* **20**, 26-35.

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

[10] Heflin LH, Meyerowitz BE, Hall P, Lichtenstein P, Johansonn B, Pedersen NL, Gatz M (2005) Cancer as a risk factor for long-term cognitive deficits and dementia. *J Natl Cancer Inst* **97**, 854-856.

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

[12] Attner B, Lithman T, Noreen D, Olsonn H (2010) Low cancer rates among patients with dementia in a population-based register study in Sweden. *Dement Geriat Cogn Disord* **30**, 39-41.

[13] Diagnostic and Statistical Manual of Mental Disorders (4th ed.), The American Psychiatric Association, Washington, 1994.

[14] McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984) Clinical diagnosis of Alzheimer's disease: Report of the NINCDS/ADRDA Work Group under the auspices of the Department of health and Human Services Task Force on Alzheimer's Disease. *Neurology* **34**, 939-944.

[15] Villanueva V, Garcia AM (2006) Validity and reliability of surrogate information for controls in a case-control study on Alzheimer's disease. *J Alzheimers Dis* **10**, 409-516.

[16] Flake GP, Andersen J, Dixon D (2003) Etiology and pathogenesis of uterine leiomyomas: A review. *Environ Health Perspect* **111**, 1037-1054.

[17] Yager JD, Davidson NE (2006) Estrogen carcinogenesis in breast cancer. *N Engl J Med* **354**, 270-282.

[18] Genazzani AR, Pluchino N, Luisi S, Luisi M (2010) Estrogen, cognition and female ageing. *Hum Reprod Update* **13**, 175-187.

[19] Wharton W, Gleason CE, Lorenze KR, Markgraf TS, Ries ML, Carlsson CM, Asthana S (2009) Potential role of estrogen in the pathobiology and prevention of Alzheimer's disease. *Am J Transl Res* **1**, 131-147.

[20] Nilsen J, Mor G, Naftolin F (2000) Estrogen-regulated developmental neuronal apoptosis is determined by estrogen receptor subtype and the Fas/Fas ligand system. *J Neurobiol* **43**, 64-78.

[21] Woolley C, McEwen BS (1993) Roles of estradiol and progesterone in regulation of hippocampal dendritic spine density during the estrous cycle in the rat. *J Comp Neurol* **336**, 293-306.

[22] Nilsen J, Brinton RD (2003) Mechanism of estrogen mediated neuroprotection: Regulation of mithocondrial calcium and Bcl-2 expression. *Proc Natl Acad Sci U S A* **100**, 2842-2848.

[23] Greenfield JP, Leung LW, Cai D, Kaasik K, Gross RS, Rodriguez-Boulan E, Greengard P, Xu H (2002) Estrogen lowers Alzheimer beta-amyloid generation by stimulating trans-Golgi network vescicle biogenesis. *J Biol Chem* **5**, 12128-12136.

[24] Brinton RD, Chen S, Montoya M, Hsieh D, Minaya J (2000) The estrogen replacement therapy of the Women's Health Initiative promotes the cellular mechanisms of memory and neuronal survival in neurons vulnerable to Alzheimer's disease. *Maturitas* **34**, 35-52.

[25] Yaffe K, Sawaya G, Lieberburg I, Grady D (1998) Estrogen therapy in postmenopausal women: Effects on cognitive function and dementia. *JAMA* **279**, 688-695.

[26] Shumaker SA, Legault C, Kuller L, Rapp SR, Thal L, Lane DS, Fillit H, Stefanick ML, Hendrix SL, Lewis CE, Masaki K, Coker LH, Women's Health Initiative Memory Study (2004) Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: Women's Health Initiative Memory Study. *JAMA* **291**, 2947-2958.

[27] Grady D, Yaffe K, Kristof M, Lin F, Richards C, Barrett-Connor E (2002) Effect of postmenopausal hormone therapy on cognitive function: The Heart and Estrogen/progestin Replacement Study. *Am J Med* **113**, 543-548.

[28] Rocca WA, Grossardt BR, Shuster LT (2010) Oophorectomy, menopause, estrogen, and cognitive aging: The timing hypothesis. *Neurodegener Dis* **7**, 163-166.

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

[30] Takahashi K, Uchida C, Shin RW, Shimazaki K, Uchida T (2008) Prolyl isomerase, Pin1: New findings of post-translational modifications and physiological substrates in cancer, asthma and Alzheimer's disease. *Cell Mol Life Sci* **65**, 359-375.

[31] Ohyagi Y, Asahara H, Chui DH, Tsuruta Y, Sakae N, Miyoshi K, Yamada T, Kikuchi H, Taniwaki T, Murai H, Ikezoe K, Furuya H, Kawarabayashi T, Shoji M, Checler F, Iwaki T, Makifuchi T, Takeda K, Kira J, Tabira T (2005) Intracellular Abeta42 activates p53 promoter: A pathway to neurodegeneration in Alzheimer's disease. *FASEB J* **19**, 255-257.

[32] Cenini G, Sultana R, Memo M, Butterfield DA (2008) Elevated levels of pro-apoptotic p53 and its oxidative modification by the lipid peroxidation product, HNE, in brain from subjects with amnestic mild cognitive impairment and Alzheimer's disease. *J Cell Mol Med* **12**, 987-994.

[33] Hooper C, Meimaridou E, Tavassoli M, Melino G, Lovestone S, Killick R (2007) p53 is upregulated in Alzheimer's disease and induces tau phosphorylation in HEK293a cells. *Neurosci Lett* **418**, 34-37.

[34] Coombs GS, Covey TM, Virshup DM (2008) Wnt signaling in development, disease and translational medicine. *Curr Drug Targets* **9**, 513-531.

[35] Caricasole A, Bakker A, Copani A, Nicoletti F, Gaviraghi G, Terstappen GC (2005) Two sides of the same coin: Wnt signaling in neurodegeneration and neuro-oncology. *Biosci Rep* **25**, 309-327.

[36] Tremolizzo L, Rodriguez-Menendez V, Brighina L, Ferrarese C (2006) Is the inverse association between Alzheimer's disease and cancer the result of a different propensity to methylate DNA? *Med Hypotheses* **66**, 1251-1252.

[37] Esteller M (2008) Epigenetic in cancer. *N Engl J Med* **358**, 1148-1159.

[38] Mehler MF (2008) Epigenetics and the nervous system. *Ann Neurol* **64**, 602-617.

[39] Mastroeni D, McKee A, Grover A, Rogers J, Coleman PD (2009) Epigenetic differences in cortical neurons from a pair of monozygotic twins discordant for Alzheimer's disease. *PLoS One* **4**, e6617.

[40] Shuller HM (2009) Is cancer triggered by altered signalling of nicotinic acetylcholine receptors? *Nat Rec Cancer* **9**, 195-205.

[41] Paleari L, Catassi A, Ciarlo M, Cavalieri Z, Bruzzo C, Servent D, Cesario A, Chessa L, Cilli M, Piccardi F, Granone P, Russo P (2008) Role of alpha7-nicotinic acetylcholine receptor in human non-small cell lung cancer proliferation. *Cell Prolif* **41**, 936-959.

[42] Tavares AR, De Melo AC, Sternberg C (2010) Cancer linked to Alzheimer disease but not vascular disease. *Neurology* **75**, 1215.

[43] Tabarés-Seisdedos R, Dumont N, Baudot A, Valderas JM, Climent J, Valencia A, Crespo-Facorro B, Vieta E, Gómez-Beneyto M, Martínez S, Rubenstein JL (2011) No paradox, no progress: Inverse cancer comorbidity in people with other complex diseases. *Lancet Oncol* **12**, 604-608.