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Does Alzheimer's Disease Protect against Cancers? A Nationwide Population-Based Study

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Key Words
Alzheimer's disease · Cancer · Epidemiology · Risk factors

Abstract
Background: Previous studies suggested a decreased risk of cancer among patients with Alzheimer's disease (AD). There is still a lack of data on the specific types of cancer, the risk factors, and the impact of cholinesterase inhibitors on developing cancer in AD. ***Methods:*** We performed a nationwide population-based study of 6,960 patients with AD between 1997 and 2006 using Taiwan's National Health Insurance database. Patterns of cancer incidence in AD patients were compared with those of the general population using standardized incidence ratios (SIRs). ***Results:*** Patients with AD had a reduced risk of developing overall cancer [SIR = 0.88, 95% confidence interval (CI) = 0.80–0.97]. Specifically, patients with AD were protected from lung cancers (SIR = 0.75, 95% CI = 0.57–0.98), especially men (SIR = 0.61, 95% CI = 0.40–0.88). In subgroup analyses, women, patients aged 60–79 years, and those diagnosed as having AD for more than 1 year were more likely to be protected from cancers. ***Conclusions:*** Our study demonstrates a decreased incidence of overall cancers in patients with AD, a finding lower than but consistent with Western countries. Patients with AD had a significantly decreased risk of lung cancer. Further investigation of genetic evidence linking AD to cancer is warranted.

Introduction

Alzheimer's disease (AD) increases with age and is characterized by the premature progressive loss of neuronal cells. Cancer, in contrast, is a disorder resulting from inappropriate cell proliferation and resistance to cell death [1]. A number of mechanisms might link cancer with AD and other neurodegenerative diseases [1, 2]. Both cancer and AD exhibit an increase in oxidative stress, which makes tumor or neuronal cells more vulnerable to cytotoxic amyloid Aβ and host defense peptides [3]. Acetylcholine and its receptors can stimulate the synthesis and release of growth, angiogenic and neurogenic factors in cancer cells [4]. Therefore, the degeneration of acetylcholine-secreting cells could play a protective role in cancer.

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Other potential mechanisms included cell cycle dysregulation and mutations in DNA repair enzymes [1].

In a seminal study, Burke et al. [5] conducted an epidemiologic necropsy study that found a higher prevalence of pancreatic cancer in AD patients; however, the findings are not supported by other autopsy series [2]. Recently, Roe et al. [6] used population-based data from the Cardiovascular Health Cognition study to confirm the negative correlation between cancer and AD, but not vascular dementia in Caucasian adults. However, data are still lacking on risk factors and specific types of cancer. Also, no data indicate whether extended exposure to acetylcholine could affect cancer incidence among patients treated with cholinesterase inhibitors compared to untreated patients. In addition, the opposite relationship between AD and cancer was found for non-Caucasians, although the number of non-Caucasian participants with a cancer history was small [6]. A large-scale study is needed to explore the ethnic factors of this association.

The comprehensive coverage of the Taiwanese national health insurance (NHI) offers an opportunity to investigate the association between AD and cancer. We conducted a nationwide population-based cohort study using data from the National Health Insurance Research Database (NHIRD) to investigate cancer incidence, specific types of cancer and the impact of cholinesterase inhibitors on developing cancer. The results could also facilitate comparison between prior findings in Caucasian and non-Caucasian populations.

Materials and Methods

Data Sources

The NHI program is a mandatory universal health insurance program offering comprehensive medical care for all the island's residents since 1995, with a coverage rate of up to 98.29% in 2006 [7, 8]. Medical coverage for outpatient, inpatient, emergency, dental and traditional Chinese medicine services, pharmacy and for procedures is all included. This study used the NHIRD publicly released by the Taiwan National Health Research Institute. In the Taiwan NHI system, severe diseases such as AD and cancer were defined as 'catastrophic illnesses' and insured affected individuals were able to apply for a catastrophic illness certificate. Patients with a catastrophic illness certification were exempted from copayments under the NHI program. The NHI database of catastrophic illness includes multiple NHI databases, such as NHI enrollment files, claims information, and the drug prescription registry, and provides comprehensive utilization and enrollment information. All information that would potentially expose a specific individual patient to be identified is encrypted. The confidentiality of the data abides by the data protection regulation of the Bureau of National Health Insurance and the National Health Research Institute.

Study Population

We conducted a retrospective cohort study from March 1, 1995 to December 31, 2009. Newly diagnosed patients with AD were retrieved from the registry of catastrophic illness from January 1, 1997 to December 31, 2006. AD diagnosis was further validated by the prescription of at least one of the antidementia drugs rivastigmine, memantine, galantamine or donepezil. To apply for any of these drugs, in-charge neurologists or psychiatrists are requested to provide information including at least one report of computed tomography, magnetic resonance imaging or Hachinski ischemic score, a thorough laboratory exam report (composed of complete blood cell count, venereal disease research laboratory test, blood urea nitrogen, creatinine, alanine aminotransferase, aspartate aminotransferase, thyroxine, and thyroid-stimulating hormone), a detailed medical summary, and a report of Mini Mental State Exam (MMSE) or Clinical Dementia Rating (CDR) to indicate patient's current cognitive function. The AD diagnosis and approval of these medications are reviewed and confirmed by a board-certified neurologist or psychiatrist. Only patients with MMSE scores of 10–26 or CDR scores of 1–2 are allowed to be reimbursed for antidementia medications. Therefore, our enrolled patients had mild-to-moderate severity AD. Patients who had antecedent malignancies or were lost to follow-up were excluded from the study. In the analysis of association between AD medications and cancer development, we calculated medications only within 1 year and cancer occurrence 1 year after AD diagnosis to account for a latency period. The use of medications was defined as more than 28 cumulative defined daily doses of treatment within the first year of AD diagnosis [9].

Statistical Analyses

The main dependent variable was incidence of cancer. AD patients were followed until the development of cancer, death, dropping out from the NHI program, or the end of the study period (2006). We examined the associations among the cohort members and specific types of cancer using the standardized incidence ratio (SIR), defined as observed cancer occurrences divided by expected. Expected number of cancers was calculated by multiplying the national incidence rate of cancers based on sex, calendar year and age in 5-year intervals by the corresponding stratum-specific person-time accrued in the cohort. The incidence of cancer in the general population was obtained from the Taiwan National Cancer Registry. SIR with 95% confidence intervals (CIs) was estimated under the assumption that the observed number of cancers followed a Poisson probability distribution. SIRs were determined for subgroups according to sex and age group. Because of potential detection bias and the possibility that newly diagnosed AD might be surveyed extensively, subgroup analysis stratified by duration of AD diagnosis was carried out. Demographic information such as age, sex, comorbidities and medications of patients with or without cancer were compared using a χ^2 test for categorical variables and t test for continuous variables. Multivariate analysis was undertaken using Cox proportional hazards regression using a forward selection, likelihood ratio model to identify independent predictors of cancer development among patients with AD. Risk factors with a p value < 0.1 were entered into multivariate analysis. Perl programming language (version 5.12.2) was used to extract and compute data. Microsoft SQL Server 2005 (Microsoft Corp., Redmond,

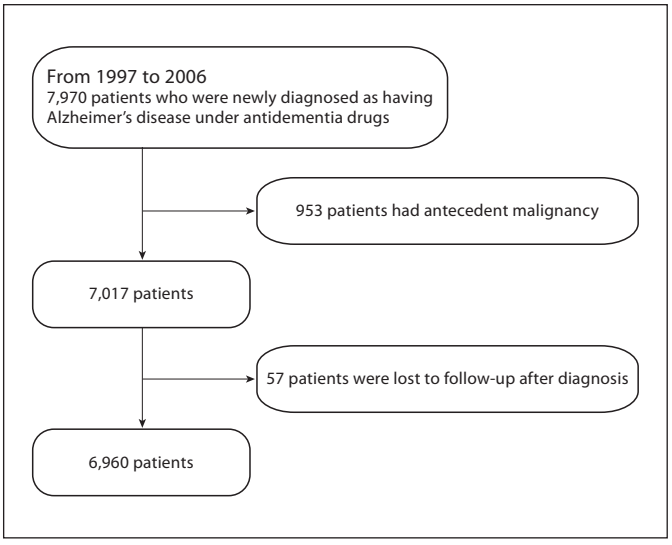

Fig. 1. Patient selection flowchart.

Table 1. Demographic characteristics of patients with AD

	Total	Male	Female
Number of patients	6,960	2,762	4,198
Person-years at risk	31,116.3	11,510.8	19,605.5
Median follow-up, years (interquartile range)	4.25 (2.81–5.92)	4.01 (2.47–5.73)	4.43 (3.04–6.09)
Age at diagnosis, years			
40–59	334	127	207
60–79	4,578	1,769	2,809
≥80	2,048	866	1,182

Wash., USA) was used for data linkage, processing, and sampling. All statistical analyses were performed using IBM SPSS statistical software (version 19.0 for Windows; IBM Corp., New York, N.Y., USA). A p value <0.05 was considered to be statistically significant.

Results

Characteristics of the Study Population

During the 10-year study period, 7,970 patients with AD treated with antidementia drugs were identified in the catastrophic illness database and NHIRD. Figure 1 shows a flowchart for patient selection. After excluding patients who had antecedent malignancies (n = 953) or those lost to follow-up after diagnosis (n = 57), we enrolled 6,960 patients for analysis. We observed a total of 31,116.3 person-years in this cohort. Study subjects were predominantly female (60.3%) and the median age was 76 years (interquartile range = 70–80 years). The median follow-up period was 4.25 years (interquartile range = 2.81–5.92 years). The demographic characteristics of this cohort are shown in table 1.

Risk for Cancers Stratified by Age, Sex and Disease Duration

A total of 405 cancers occurred within the observation interval. Overall cancer was less frequent in those with AD than in the general population, with an SIR of 0.88 (95% CI = 0.80–0.97; p = 0.009). When the relationship between AD and overall cancer was stratified by sex, only women with AD had a decreased risk (SIR = 0.81, 95% CI = 0.70–0.93; p = 0.003), whereas men with AD did not (SIR = 0.95, 95% CI = 0.83–1.08). In a subanalysis according to age, the reduced risk was more pronounced for patients aged 60–79 years (SIR = 0.80, 95% CI = 0.69–0.92; p = 0.001). Of note, women aged 60–79 years were significantly protected from cancer (SIR = 0.76, 95% CI = 0.61–0.93; p = 0.006). In another subgroup analysis based on disease duration, the cancer risk of patients with an AD duration of more than 1 year was lower than for the general population (SIR = 0.85 95% CI = 0.76–0.95; p = 0.004). The results of these statistical analyses are summarized in table 2.

Specific Types of Cancer

The most common cancer site in this cohort was the colon and rectum (n = 80), followed by the lung and mediastinum (n = 58) and liver and biliary tract (n = 56). In women with AD, the decreased risk of cancer was most evident in the head and neck (SIR = 0.39), skin (SIR = 0.53), hematologic malignancies (SIR = 0.70), liver and biliary tract (SIR = 0.70), colon and rectum (SIR = 0.75), central nervous system (SIR = 0.80), genitourinary system (SIR = 0.81), and stomach (SIR = 0.91). The greatest decrease in risk in men with AD was for the pancreas (SIR = 0.40), kidney (SIR = 0.54) and esophagus (SIR = 0.78). However, none of these associations reached statistical significance. An exception was the lung and mediastinum, for which patients with AD had a significantly decreased risk (SIR = 0.75, 95% CI = 0.57–0.98; p = 0.03). The reduction in cancer of the lung and mediastinum occurred primarily among men (SIR = 0.61, 95% CI = 0.40–0.88; p = 0.007), and was not significant among women. SIRs for specific types of cancer are presented in detail in table 3.

Table 2. SIRs according to age at diagnosis, gender and duration of AD

Characteristics	Total			Male			Female		
	observed	expected	SIR (95% CI)	observed	expected	SIR (95% CI)	observed		SIR (95% CI)
All cancers	405	460.90	0.88 (0.80–0.97)	215	226.58	0.95 (0.83–1.08)	190	234.31	0.81 (0.70–0.93)
Age at diagnosis, years									
40–59	6	5.57	1.08 (0.40–2.34)	3	2.08	1.44 (0.30–4.22)	3	113.50	0.86 (0.18–2.51)
60–79	189	237.26	0.80 (0.69–0.92)	97	115.80	0.84 (0.68–1.02)	92	121.46	0.76 (0.61–0.93)
≥80	210	218.07	0.96 (0.84–1.10)	115	108.71	1.06 (0.87–1.27)	95	109.36	0.87 (0.70–1.06)
Duration of AD									
0–1	93	95.08	0.98 (0.79–1.20)	47	48.78	0.96 (0.71–1.28)	46	46.31	0.99 (0.73–1.32)
≥1	312	365.81	0.85 (0.76–0.95)	168	177.81	0.94 (0.81–1.10)	144	188.01	0.77 (0.65–0.90)

Table 3. SIRs for specific cancer types among patients with AD

Site of cancers	Total			Male			Female		
	observed	expected	SIR (95% CI)	observed	expected	SIR (95% CI)	observed	expected	SIR (95% CI)
All cancers	405	460.90	0.88 (0.80–0.97)	215	226.58	0.95 (0.83–1.08)	190	234.31	0.81 (0.70–0.93)
Head and neck	10	17.12	0.58 (0.28–1.07)	8	11.96	0.67 (0.29–1.32)	2	5.16	0.39 (0.05–1.40)
Digestive	188	203.51	0.92 (0.80–1.07)	102	97.77	1.04 (0.85–1.27)	86	105.75	0.81 (0.65–1.00)
Esophagus	6	6.62	0.91 (0.33–1.97)	4	5.10	0.78 (0.21–2.01)	2	1.51	1.32 (0.16–4.78)
Stomach	34	34.46	0.99 (0.68–1.38)	20	19.10	1.05 (0.64–1.62)	14	15.35	0.91 (0.50–1.53)
Colon and rectum	80	83.03	0.96 (0.76–1.20)	45	36.50	1.23 (0.90–1.65)	35	46.54	0.75 (0.52–1.05)
Liver and biliary tract	56	67.53	0.83 (0.63–1.08)	31	32.02	0.97 (0.66–1.37)	25	35.51	0.70 (0.46–1.04)
Pancreas	12	11.88	1.01 (0.52–1.76)	2	5.05	0.40 (0.05–1.43)	10	6.83	1.46 (0.70–2.69)
Lung and mediastinum	58	76.90	0.75 (0.57–0.98)	27	44.39	0.61 (0.40–0.88)	31	32.51	0.95 (0.65–1.35)
Bone and soft tissue	4	2.22	1.80 (0.49–4.62)	2	1.16	1.73 (0.21–6.25)	2	1.06	1.89 (0.23–6.82)
Skin	16	24.33	0.66 (0.38–1.07)	8	9.14	0.87 (0.38–1.72)	8	15.18	0.53 (0.23–1.04)
Breast	15	17.06	0.88 (0.49–1.45)	0	0.25	0.00 (0.00–14.71)	15	16.81	0.89 (0.50–1.47)
Genitourinary system	77	81.15	0.95 (0.75–1.19)	48	45.16	1.06 (0.78–1.41)	29	35.99	0.81 (0.54–1.16)
Cervix	10	13.50	0.74 (0.36–1.36)	–	–	–	10	13.50	0.74 (0.36–1.36)
Uterus	2	2.60	0.77 (0.09–2.78)	–	–	–	2	2.60	0.77 (0.09–2.78)
Ovary	6	3.36	1.78 (0.65–3.88)	–	–	–	6	3.36	1.78 (0.65–3.88)
Prostate	35	28.62	1.22 (0.85–1.70)	35	28.62	1.22 (0.85–1.70)	–	–	–
Bladder	15	18.25	0.82 (0.46–1.36)	10	10.98	0.91 (0.44–1.68)	5	7.28	0.69 (0.22–1.60)
Kidney	9	14.81	0.61 (0.28–1.15)	3	5.57	0.54 (0.11–1.58)	6	9.25	0.65 (0.24–1.41)
Central nervous system	2	2.30	0.87 (0.11–3.14)	1	1.05	0.95 (0.02–5.29)	1	1.25	0.80 (0.02–4.46)
Thyroid	0	3.50	0.00 (0.00–1.06)	0	0.79	0.00 (0.00–4.68)	0	2.71	0.00 (0.00–1.36)
Hematologic malignancies	19	19.40	0.98 (0.59–1.53)	12	9.45	1.27 (0.66–2.22)	7	9.95	0.70 (0.28–1.45)
All others	16	13.41	1.19 (0.68–1.94)	7	5.46	1.28 (0.52–2.64)	9	7.95	1.13 (0.52–2.15)

Predictors of Cancer Risk

Cox proportional hazards analysis showed an increased risk of developing cancer in AD with one of the following characteristics: age, male sex, chronic obstructive pulmonary disease and cirrhosis (table 4). Multivariate Cox proportional hazards analysis indicated significance for the following variables: cirrhosis [hazard ratio (HR) = 3.13, 95% CI = 2.07–4.73; $p < 0.001$), male sex (HR = 1.86, 95% CI = 1.53–2.26; $p < 0.001$) and age (HR = 1.04, 95% CI = 1.02–1.05; $p < 0.001$). Of note, diabetes mellitus, autoimmune disorders or antidementia drugs were not independent cancer risk factors in patients with AD.

Discussion

This nationwide population-based study demonstrated that 6,960 patients with AD had a significantly lower risk of developing cancer, with an SIR of 0.88 compared

Table 4. Risk factors for patients with AD developing cancer

Variables	Univariate analysis		Multivariate analysis[a]	
	HR (95% CI)	p	HR (95% CI)	p
Age	1.04 (1.02–1.05)	<0.001	1.04 (1.02–1.05)	<0.001
Male sex	2.02 (1.62–2.53)	<0.001	1.96 (1.56–2.44)	<0.001
Comorbidities				
Diabetes mellitus	0.99 (0.78–1.27)	0.994		
COPD	1.39 (1.10–1.75)	0.006		
Chronic kidney disease	1.18 (0.86–1.61)	0.304		
Autoimmune diseases	1.37 (0.94–2.00)	0.099		
Cirrhosis	3.38 (2.10–5.45)	<0.001	3.23 (2.00–5.20)	<0.001
Prescriptions[b]				
Rivastigmine	0.98 (0.60–1.59)	0.924		
Memantine	0.05 (0.00–7.61×10^{19})	0.904		
Galantamine	2.21 (0.82–5.93)	0.116		
Donepezil	0.64 (0.41–1.01)	0.054		

COPD = Chronic obstructive pulmonary disease.

[a] All factors with $p < 0.1$ in univariate analyses were included in the Cox multivariate analysis.

[b] The use of medications was defined as more than 28 cumulative defined daily doses of treatment within the first year of AD diagnosis. Only patients with follow-up and cancer occurrence ≥1 year were calculated.

to the general population. Results from our study with a total follow-up of 31,116.3 person-years are consistent with those reported in the USA (HR = 0.31) [6], but with a much less protective effect. Specifically, AD cohorts were less likely to develop lung cancers. Furthermore, women, patients aged 60–79 years, and those diagnosed with AD for more than 1 year were even more likely to be protected from cancers than the general population.

The findings of our study are valid and useful because the design includes a large sample size, strict diagnostic criteria, unbiased subject selection, and SIRs adjusted for age, sex and calendar year. Because patients with NHI-defined catastrophic illness including AD and cancers can be exempted from related medical expenses, the government has implemented a strict verification program. For cancer, pathologic proof is necessary and laboratory and imaging studies are peer reviewed. For AD, after exclusion of other causes of dementia, supported medical records, examination reports and image studies with comprehensive review by neurology or psychology specialists are required. These features make the diagnosis of AD and malignancy in our study reliable. Detailed claim data in NHIRD also allowed us to explore the potential confounding effects, if any, of comorbidities and antidementia drugs on the association between AD and cancers.

Previous epidemiological studies attempted to investigate the link between cancer and neurodegenerative disorders [1]. An inverse correlation was found between cancer and some neurodegenerative disorders, such as Parkinson's disease (PD) [10–12] and Huntington's disease [13]. A recent study conducted by Fois et al. [14] showed no significant association between cancer and either multiple sclerosis or motor neuron disease. Few data are available linking cancer with AD. Roe et al. [6] reported that a diagnosis of 'pure' AD (i.e. without coexisting vascular dementia) was associated with a 70% reduced risk of cancer and a history of cancer was associated with a 40% reduced risk of pure AD. Our findings of a decrease in overall cancer in AD patients are consistent with this prior study, but to a lesser extent, with an SIR of 0.88. This could account in part for race-based disparities, because the participants in Roe et al. [6] were mostly Caucasians. Reasons for this racial difference vary by cancer type, but could include differences in genetic, climatic and geographic features, sociocultural factors and lifestyle [15–17].

Our data showed a higher SIR of 0.98 in the first year after AD diagnosis, compared to that of 0.85 thereafter. Surveillance or detection bias may contribute in part to the observed difference. Increasing screening procedures after an initial diagnosis of AD might facilitate early cancer detection. This could partly explain the higher SIR without statistical significance in the first year.

In a subanalysis, women with AD (total follow-up of 19,605.5 person-years) were protected against cancer,

with an SIR of 0.81. Men with AD, on the other hand, did not show significant protection, with an SIR of 0.95 during a shorter follow-up period (total follow-up 11,510.8 person-years). This could be due, in part, to a relatively smaller sample size of men required to attain significance. Another possible explanation is that estrogen has antioxidant, antiapoptotic, neurotrophic and antiamyloidogenic properties [18–20], and laboratory studies have demonstrated that low concentrations of estrogen might cause apoptotic tumor cell death [21]. In a case-cohort study conducted by Manly et al. [22], postmenopausal women with AD had lower estradiol levels than normal subjects. However, the effect of early or late postmenopausal estrogen therapy to preserve cognitive function or prevent dementia is still controversial [23]. Whether a lower estrogen level promotes early tumor cell death and protects women with AD against cancers has not been determined and requires further investigation.

In another subanalysis, the reduced risk of developing cancer was more pronounced for patients aged 60–79 years, but not for those aged 80 years and over. Individuals of more advanced age might refuse aggressive or invasive procedures for cancer diagnosis. Malignancies are therefore possibly underdiagnosed, resulting in no significant difference between observed and expected cancers.

Previous studies found that PD protects against most types of cancers, such as lung, colorectal, bladder and prostate cancer, but not melanoma [12]. Huntington's disease protects against cancers of all major tissues and organs except the buccal cavity and the pharynx [13]. The specific types of cancer that AD might protect against are still controversial [2, 5]; however, our study found that patients with AD had a significantly decreased risk of lung cancer. In this subtype of cancer, we further identified a decreased risk of lung cancer in men with AD (but not in women). Nicotine, a major component of tobacco smoke, could affect the dopamine concentrations in the brain and thus reduce the risk of PD [24]. However, the relationship between smoking and AD is still conflicted. Some recent studies have even suggested that smoking is associated with increased incidence of AD [25]. According to a 2004 cross-sectional survey, Taiwanese men smoked more cigarettes per day than Taiwanese women (18 vs. 11), with the smoking rate ratio being 9.5 (45.7 vs. 4.8%) [26]. This sex difference in smoking behavior might be reduced in patients with AD, who have cognitive and function decline and tend to smoke less over their lives. Men with AD might smoke much less than men in the normal population, thus reducing the rate of developing lung cancer. Moreover, polymorphisms of the detoxifying enzyme P450 D6 (CYP2D6) were reported to possibly contribute to a small decrease in the susceptibility to lung cancer in PD, because these polymorphisms decrease the activation of procarcinogens in smoking [27]. Further studies are required to investigate whether CYP2D6 gene polymorphisms are also associated with the reduction in lung cancer in AD patients [28].

Our data identified only 16 patients with skin cancers and the risk of developing skin cancer in AD did not reach significance, with an SIR of 0.66. This is in contrast to patients with PD, for whom the risk of melanoma is increased. Some studies suggested that levodopa therapy could be a risk factor for melanoma in patients with PD, which serves as a substrate for the enzyme tyrosine hydroxylase and ultimately converts levodopa to melanin. The tumor cells, or melanocytes, are rich in tyrosine hydroxylase. Levodopa also enhances the secretion of melanocyte-stimulating hormone [10, 29–31]. For AD, levodopa therapy was not the mainstream treatment. Moreover, in Asian populations, melanoma is a relatively rare occurrence compared to fair-skinned populations [32]. The differences in skin cancer incidence might be attributable to race, genetic background, temperate climate and ultraviolet light exposure [33].

In previous studies, many coexisting illnesses and comorbidities were reported to increase cancer incidence, such as diabetes mellitus [34–36], chronic kidney disease [37], chronic obstructive pulmonary disease [38] and various autoimmune diseases [8, 39, 40]. In our study, none of these were identified as independent risk factors for cancer with the exception of cirrhosis. This indicates that AD could, to some extent, reduce the effect of these comorbidities on cancer development, although further investigation is warranted. In a country such as Taiwan, with high endemic hepatitis B and C virus, hepatitis viruses might have a greater impact on the development of cancer in cirrhosis patients [41, 42].

Our study has limitations. First, we excluded patients who had antecedent malignancy, because this exclusion enabled us to clarify the relationship between AD and cancer incidence. In the US study among Caucasians, a cancer history was associated with a lower rate of AD diagnoses [6]. We do not know whether prior findings could also be applied to non-white populations. Second, as an innate limitation to the NHIRD, several potential confounders, including smoking status, obesity, alcohol use, environmental exposure and family history of malignancy, were not available for analysis. Therefore, analysis of a possible relationship between smoking-related

and non-smoking-related cancer is not possible. Third, we enrolled only patients with mild-to-moderate AD (MMSE scores of 10–26 or CDR scores of 1–2). Patients with severe AD or who are bedridden were excluded. Further studies to evaluate the relationships between severe AD and cancer risk are important. Finally, we did not include patients with in situ malignancies or benign tumors. The risk of subsequent progression into cancer could not be evaluated.

Conclusions

We confirmed the inverse relationship between Taiwanese AD and overall cancer, a finding that was lower, but consistent with that reported in Western countries. Regarding specific types of cancer, male patients with AD have a lower risk of developing lung cancers. Further large genetic and epidemiological studies investigating cancer incidence in patients with AD (and vice versa) will be required to find genetic factors linking the two diseases.

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Disclosure Statement

Dr. S.J. Wang has served on scientific advisory boards for Pfizer Inc., Allergan, Inc., and Eli-Lilly and Company, Taiwan; serves as Editor of the *Journal of the Chinese Medical Association*, Associate Editor of *Cephalalgia,* Associate Editor of *BMC Neurology,* Associate Editor (headache) for *MedLink Neurology,* and Co-Editor of *Acta Neurologica Taiwanica;* has received speaker honoraria from GlaxoSmithKline, Pfizer Inc., Eli Lilly and Company, Boehringer Ingelheim, Allergan, Inc., and Wyeth, and receives research support from the National Yang-Ming University, National Science Council, Taipei Veterans General Hospital, and Taiwan Headache Society.

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