

Original Article



Association between Alzheimer's Disease and Cancer Risk in South Korea: an 11-year Nationwide Population-Based Study

Ji Eun Lee ,¹ DongWook Kim ,² Jun Hong Lee ¹

¹Department of Neurology, National Health Insurance Service Ilsan Hospital, Goyang, Korea

²Institute of Health Insurance & Clinical Research, National Health Insurance Service Ilsan Hospital, Goyang, Korea



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Correspondence to

Jun Hong Lee, MD

Department of Neurology, National Health Insurance Service Ilsan Hospital, 100 Ilsan-ro, Ilsandong-gu, Goyang 10444, Korea.
E-mail: jhlee@nhimc.or.kr

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ORCID iDs

Ji Eun Lee

<https://orcid.org/0000-0002-6380-0465>

DongWook Kim

<https://orcid.org/0000-0002-4478-3794>

Jun Hong Lee

<https://orcid.org/0000-0002-5023-6009>

Conflict of Interest

The authors have no financial conflicts of interest.

Author Contributions

Conceptualization: Lee JE, Lee JH; Data curation: Lee JE; Formal analysis: Lee JE, Kim D; Investigation: Lee JE; Methodology: Lee JE, Lee JH; Supervision: Lee JE, Lee JH; Validation: Lee JE; Visualization: Lee JE; Writing - original draft: Lee JE; Writing - review & editing: Lee JE.

ABSTRACT

Background and Purpose: Previous studies have suggested a decreased cancer risk among patients with Alzheimer's disease (AD). There remains a lack of data on the specific types of cancer and risk factors for developing cancer in AD. We evaluated the association between AD and cancer risk, and we examined specific types of cancer.

Methods: A population-based longitudinal study was conducted using the National Health Insurance Service-Senior cohort for 2002–2013. A total of 4,408 AD patients were included in the study, as were 19,150 matched controls. Potential associations between the risk of cancer and AD were analyzed using Cox proportional hazard regressions.

Results: Cancer developed in 12.3% of the AD group patients and in 18.5% of control group subjects. AD was associated with a reduced risk of cancer (hazard ratio [HR], 0.70; 95% confidence intervals, 0.64–0.78). The risk of head and neck cancers was significantly reduced (HR, 0.49), as were risks for cancers of the digestive tract, including stomach cancer (HR, 0.42), colorectal cancer (HR, 0.61), liver and biliary tract cancers (HR, 0.68), and pancreatic cancer (HR, 0.55). Lung and prostate cancer risks were also significantly lower for the AD group (HR, 0.52 and HR, 0.72, respectively).

Conclusions: Our results showed an inverse association between AD and cancer. Further research involving a large number of patients in a hospital based-study is needed to address the biological associations between cancer development and dementia, including AD.

Keywords: Alzheimer's Disease; Epidemiology; Cancer

INTRODUCTION

As the number of elderly adults increases, the frequency of diseases, such as cancer and neurodegenerative disorders has also increased. Alzheimer's disease (AD) is the most common neurodegenerative disorder. The prevalence of AD is over 13% in populations >65 years old and 35%–50% in elderly populations >85 years old.¹⁻³ AD is characterized by the premature progressive loss of neuronal cells.⁴ In contrast, cancer is characterized by inappropriate cell proliferation and resistance to cell death.⁵ Several mechanisms are hypothesized to link cancer with AD. One of them is that both AD and cancer increase oxidative stress, which makes tumor or neuronal cells more vulnerable to cytotoxic amyloid

A β and host defense peptides.^{4,5} Acetylcholine and its receptors can stimulate the synthesis, growth, and angiogenesis of cancer cells. Therefore, the degeneration of acetylcholine-secreting cells seen in AD may ultimately protect against development of cancer cells.⁶ Several studies have reported conflicting results regarding the association between AD and cancer risk.^{4,7,12}

Recent studies have reported that AD was associated with a 36%–80% reduction in the risk of developing cancer, although the rate of reduction varied by study design. With the exception of 1 Taiwanese study, the studies investigated primarily white populations.^{7,10,13} This study analyzed a recently-developed National Health Insurance Service-Senior (NHIS-Senior) cohort database to evaluate the relationship between AD and cancer incidence over an 11-year follow-up period. We further examined the association between AD and the rates of risk reduction for site-specific cancers in patients with AD.

METHODS

Database

In Korea, all national citizens are required to enroll in the Korean National Health Insurance Service (KNHIS). A total of 97% and 3% of the Korean population is covered by the Medical Assistance Program and the Medical Care for Patriots and Veterans Affairs Scheme, respectively. Thus, nearly all data in the health system are centralized in large databases.

In Korea, patients with KNHIS pay approximately 30% of their total medical expenses when using medical facilities, and medical providers are required to submit claims for the remaining 70% of medical expenses. Claims are accompanied by data regarding diagnostic codes, procedures, prescription drugs, patients' personal information, hospital information, direct medical costs for both inpatient and outpatient care, and dental services. No patient healthcare records are duplicated or omitted because all Korean residents receive a unique identification number at birth. This number is used by the Korean government for purposes related to the healthcare system. Furthermore, the KNHIS uses the Korean Classification of Diseases (KCD), which is similar to the International Classification of Diseases (ICD) to provide consistent diagnostic codes. Our study was approved by the Institutional Review Board of the NHIS Ilsan Hospital (NHIMC 2015-07-007). The requirement for written informed consent from participants was waived because the data were analyzed anonymously.

Study population

This study used NHIS-Senior data (NHIS-2017-2-551), which was released by the KNHIS in 2015. The database is comprised of 550,000 nationally-representative random subjects, amounting to approximately 10% of the 5.5 million individuals aged ≥ 60 years. These data were produced by the KNHIS using a systematic sampling method to generate an NHIS-Senior database from all 46,605,433 Korean residents in 2002. This database includes all medical claims filed from January 2002 to December 2013.

Diagnoses in the NHIS-Senior database are based on the KCD-6, which is essentially a revision of the ICD-10. Diagnoses obtained from medical insurance claims data may be inaccurate compared with diagnoses obtained from medical charts. Therefore, to increase the accuracy of diagnoses, the patients were regarded as having AD if they had at least 1

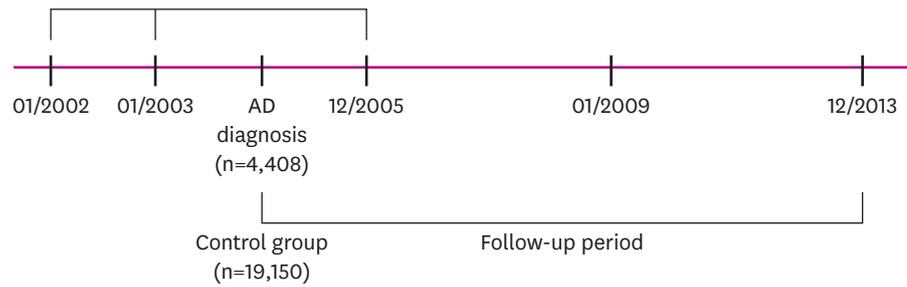


Fig. 1. Definition of study cohorts. Among NHIS-Senior 2002–2013 data, the patients diagnosed with AD in 2002 were excluded (wash-out period). The patients diagnosed with AD ($n=4,408$) in the 3 years period from January 2003 to December 2005 (index period) and the control group ($n=19,150$) extracted using propensity score matching, were enrolled. During an 11-year follow-up period, the risk of cancers between the 2 groups was analyzed. NHIS-Senior: National Health Insurance Service-Senior, AD: Alzheimer's disease.

medical claim with a diagnostic code of AD (KCD-6 codes G300, G301, G308, G309, F000, F001, F002, and F009), and they had received prescriptions for antedementia medications (donepezil, rivastigmine, memantine, or galantamine) one or more times after their first-time diagnosis between January 2003 and December 2005. Subjects with any record of AD before 2003, or those with a diagnostic code of vascular dementia (KCD-6 codes F010, F011, F012, F013, F018, and F019) were excluded. We also excluded subjects who had cancer before the diagnosis of AD. After exclusions, a total of 4,408 patients with newly-diagnosed AD were included in the study cohort (**Fig. 1**). Five control subjects ($n=19,150$) were selected from the NHIS-Senior to match each AD patient in terms of age, sex, residential area, and household income using 1:5 propensity score matching.

Each AD patient was tracked on the basis of medical insurance claims data after the diagnosis of AD until December 2013, to identify those patients who developed cancer (KCD-6 codes C00–C97 were used for the main diagnosis or sub-diagnosis).

Regression models were adjusted for a patient's age (<70, 70–74, 75–79, 80–84, ≥ 85 years), sex, comorbidities, and household income (<20%, 20%–40%, 40%–60%, 60%–80%, >80% of the median). Comorbidities included diabetes mellitus (DM) (KCD-6 codes E10–E14), hypertension (KCD-6 codes I10–I15), chronic obstructive pulmonary disease (COPD) (KCD-6 code J44), chronic kidney disease (CKD) (KCD-6 code N18), dyslipidemia (KCD-6 code E78), and stroke (KCD-6 codes I60–I64), diagnosed on the basis of the KCD. These diagnostic codes were used for the main diagnosis or sub-diagnosis at the enrollment of this study cohort. Also, detailed histories of smoking status, alcohol consumption, and physical activity (including amount and frequency) were obtained via questionnaire. We conducted statistical analyses using the simplified status classification of smoking (current, former, or never), alcohol (≥ 3 times/week, ≤ 2 times/week, or non-drinker) and physical activity (≥ 5 times/week, 3–4 times/week, 1–2 times/week, or never).

Statistical analysis

All statistical analyses were performed using the SAS System, version 9.4 (SAS Institute Inc., Cary, NC, USA). Descriptive statistics of the study population are presented, and χ^2 tests were performed to examine the differences between AD and control groups. The Cox proportional hazards model was used to calculate the hazard ratio (HR) and 95% confidence intervals (CIs) for the risk of cancer in AD patients versus the risk of cancer in the control group, as well as to calculate HRs for individual cancer sites. Multivariate Cox proportional hazard regression was performed to determine the adjusted HR of prospective cancer development

after adjusting for confounding comorbidities, age, and sex. The Kaplan-Meier method was used to estimate the risk for developing cancer over the 11-year follow-up period, and the log-rank test was used to examine differences in cancer development between the AD and control groups. A $p < 0.05$ was considered statistically significant.

RESULTS

Characteristics of the study population

Among the 558,147 subjects included in the cohort, 4,408 patients were newly-diagnosed with AD from January 1, 2003 to December 31, 2005. During the 11-year study period, a total of 540 (12.3%) AD patients developed cancer. During the same follow-up period, 3,536 (18.5%) of the 19,013 control subjects developed cancer. The incidence of cancer was significantly lower for the AD group than for the control group. **Table 1** presents baseline characteristics of the study population for the control and AD group. Patients with AD were predominantly female ($n=2,933$; 66.5%), and 1,904 AD patients (43.2%) were in the

Table 1. Baseline demographic characteristics and comorbidities of patients with AD and control groups

Variables	AD group (n=4,408)	Control group (n=19,150)	p value
Sex			0.0035
Male	1,475 (33.5)	6,855 (35.8)	
Female	2,933 (66.5)	12,295 (64.2)	
Age (yr)			0.0140
<70	1,189 (27.0)	5,645 (29.5)	
70–74	996 (22.6)	4,232 (22.1)	
75–79	1,035 (23.5)	4,232 (22.1)	
80–84	769 (17.5)	3,195 (16.7)	
≥85	419 (9.5)	1,846 (9.6)	
Household income relative to the medication			<0.0001
<20%	616 (14.0)	3,648 (19.1)	
20%–40%	458 (10.4)	2,462 (12.9)	
40%–60%	525 (11.9)	2,652 (13.9)	
60%–80%	905 (20.5)	3,941 (20.6)	
>80%	1,904 (43.2)	6,447 (33.7)	
Comorbidity			
DM	1,974 (44.8)	5,714 (29.8)	<0.0001
Hypertension	3,185 (72.3)	10,546 (50.1)	<0.0001
Stroke	1,868 (42.4)	2,291 (12.0)	<0.0001
CKD	136 (3.1)	258 (1.4)	<0.0001
COPD	648 (14.7)	2,557 (13.4)	0.0186
Dyslipidemia	1,680 (38.1)	4,314 (22.5)	<0.0001
Smoking			0.1011
Never	347 (78.3)	1,813 (77.3)	
Ever or current	96 (21.7)	532 (22.7)	
Alcohol consumption			0.0264
Non-drinkers	360 (79.5)	1,742 (73.0)	
≤2 (wk)	60 (13.2)	389 (16.3)	
≥3 (wk)	33 (7.3)	256 (10.7)	
Physical activity			0.5353
Never	320 (72.6)	1,698 (71.6)	
1–2 (wk)	59 (13.4)	278 (11.7)	
3–4 (wk)	16 (3.6)	122 (5.2)	
≥5 (wk)	46 (10.4)	273 (11.5)	

Values are presented as number (%).

AD: Alzheimer's disease, CKD: chronic kidney disease, COPD: chronic obstructive pulmonary disease, DM: diabetes mellitus.

highest income group. Patients in the AD group were significantly more likely than those in the control group to have DM ($p<0.001$), stroke ($p<0.001$), hypertension ($p<0.001$), CKD ($p<0.001$), COPD ($p=0.0186$), and dyslipidemia ($p<0.001$). There were no significant differences in smoking history or physical activity, but the number of subjects with no history of drinking alcohol was significantly higher in the AD group than in the control group.

Incidence of cancer

A total of 540 (12.3%) of the 4,408 patients with AD developed cancer within the follow-up period. After adjusting for age, sex, household income, and comorbidities (including hypertension, DM, stroke, COPD, CKD, and dyslipidemia), the risk of developing cancer was significantly lower for the AD group than for the control group (HR, 0.70; 95% CI, 0.64–0.78), based on multivariate Cox regression analysis of all variables. **Fig. 2** presents Kaplan-Meier survival curves and the results of log-rank tests to examine differences in cancer incidence between the 2 groups.

When the relationship between AD and overall cancer was stratified by sex, both males with AD (HR, 0.67; 95% CI, 0.58–0.77) and females with AD (HR, 0.74; 95% CI, 0.65–0.84) exhibited reduced risk. When the associations were evaluated for different age groups, AD was associated with an increased risk of cancer among those aged 70–74 years (HR, 1.11; 95% CI, 1.02–1.20) and those aged 75–79 years (HR, 1.13; 95% CI, 1.04–1.23), compared to those <70 years. However, risk was reduced for AD patients aged 80–84 years (HR, 0.88; 95% CI, 0.80–0.97) and those aged ≥ 85 years (HR, 0.53; 95% CI, 0.45–0.61) when compared with those <70 years. Of note, males with AD aged 70–74 years (HR, 1.22; 95% CI, 1.08–1.36) and those aged 75–79 years (HR, 1.24; 95% CI, 1.10–1.39) had significantly increased risks of cancer when compared with those <70 years of age, but males with AD aged ≥ 80 years (HR, 0.63; 95% CI, 0.50–0.78) were significantly protected from cancer. Females with AD who belonged to the 2 oldest age groups of 80–84 years (HR, 0.85; 95% CI, 0.74–0.98) and ≥ 85 years (HR, 0.44; 95% CI, 0.36–0.55) were significantly protected from cancer when compared to those <70 years of age.

There was no association between AD and incidence of cancer in terms of household income group. Comorbidities, such as DM (HR, 1.29; 95% CI, 1.20–1.38), COPD (HR, 1.44; 95% CI, 1.33–1.56), and dyslipidemia (HR, 1.20; 95% CI, 1.11–1.29) were significantly associated

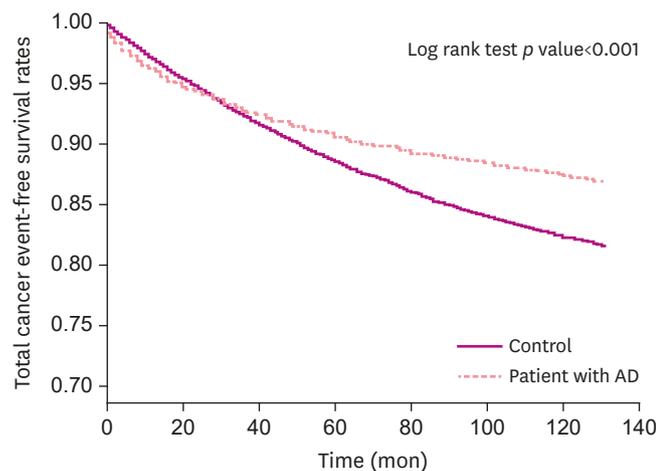


Fig. 2. Kaplan-Meier survival analysis for patients with and without AD who developed cancer. AD: Alzheimer's disease.

Table 2. Adjusted HRs for cancer among patients with AD

Variables	AD group	Control group	Male with AD	Female with AD
	Adjusted HR (95% CI) [†]			
Age (yr)				
<70	1.00	1.00	1.00	1.00
70–74	1.11 (1.02–1.20)*	1.23 (1.12–1.34)*	1.22 (1.08–1.36)*	0.99 (0.88–1.12)
75–79	1.13 (1.04–1.23)*	1.44 (1.32–1.58)*	1.24 (1.10–1.39)*	1.02 (0.90–1.15)
80–84	0.88 (0.80–0.97)*	1.43 (1.29–1.59)*	0.90 (0.79–1.04)	0.85 (0.74–0.98)*
≥85	0.53 (0.45–0.61)*	1.10 (0.93–1.30)	0.63 (0.50–0.78)*	0.44 (0.36–0.55)*
Household income relative to the medication				
<20%	1.00	1.00	1.00	1.00
20%–40%	0.95 (0.84–1.06)	0.92 (0.81–1.04)	0.98 (0.83–1.15)	0.91 (0.77–1.08)
40%–60%	1.02 (0.92–1.14)	0.99 (0.88–1.11)	1.09 (0.93–1.27)	0.96 (0.82–1.12)
60%–80%	1.06 (0.96–1.18)	1.04 (0.94–1.16)	1.06 (0.92–1.22)	1.07 (0.93–1.23)
>80%	1.03 (0.94–1.12)	0.97 (0.88–1.07)	1.03 (0.90–1.17)	1.02 (0.90–1.16)
Comorbidity				
DM	1.29 (1.20–1.38)*	1.35 (1.26–1.46)*	1.32 (1.20–1.45)*	1.26 (1.14–1.39)*
Hypertension	1.03 (0.97–1.11)	1.01 (0.94–1.09)	0.98 (0.89–1.08)	1.09 (0.99–1.21)
Stroke	0.83 (0.76–0.91)*	0.98 (0.88–1.09)	0.80 (0.70–0.91)*	0.87 (0.76–0.99)*
CKD	0.90 (0.71–1.14)	1.38 (1.06–1.80)*	0.90 (0.67–1.21)	0.91 (0.62–1.35)
COPD	1.44 (1.33–1.56)*	1.55 (1.42–1.68)*	1.42 (1.28–1.58)*	1.45 (1.28–1.64)*
Dyslipidemia	1.20 (1.11–1.29)*	1.11 (1.03–1.21)*	1.30 (1.17–1.45)*	1.11 (1.00–1.23)

HR: hazard ratio, AD: Alzheimer's disease, CI: confidence interval, DM: diabetes mellitus, COPD: chronic obstructive pulmonary disease, CKD: chronic kidney disease. * $p < 0.05$; [†]Adjustments were made for age, sex, hypertension, diabetes, stroke, COPD, CKD, dyslipidemia, and household income.

with the development of cancer, but stroke (HR, 0.83; 95% CI, 0.76–0.91) was significantly associated with decreased risk of cancer. Neither hypertension nor CKD was significantly associated with the development of cancer.

Among males with AD, DM (HR, 1.32; 95% CI, 1.20–1.45), COPD (HR, 1.42; 95% CI, 1.28–1.58), and dyslipidemia (HR, 1.30; 95% CI, 1.17–1.45) were significantly associated with the development of cancer, but stroke (HR, 0.80; 95% CI, 0.70–0.91) was significantly associated with decreased risk of cancer. Among females with AD, DM (HR, 1.26; 95% CI, 1.14–1.39), and COPD (HR, 1.45; 95% CI, 1.28–1.64) were significantly associated with the development of cancer, but stroke (HR, 0.87; 95% CI, 0.76–0.99) was significantly associated with a decreased risk of cancer (**Table 2**).

Specific types of cancer

Among the 540 cancers that developed in AD patients, the most common cancer site in this cohort was the liver and biliary tract ($n=79$), followed by the colon and rectum ($n=76$), and the lung ($n=75$). Among males with AD who developed cancer ($n=256$), the most common cancer site was the prostate ($n=50$), followed by the lung ($n=49$), and the liver and biliary tract ($n=36$). Among female AD patients who developed cancer ($n=284$), the most common cancer site was the colon and rectum ($n=44$), followed by the liver and biliary tract ($n=43$), and the stomach ($n=40$).

Among all cancer patients with AD, the most significant decreases in cancer risk were for stomach cancer (HR, 0.42; 95% CI, 0.30–0.60), hematologic malignancies (HR, 0.46; 95% CI, 0.23–0.91), head and neck cancers (HR, 0.49; 95% CI, 0.31–0.80), lung cancer (HR, 0.52; 95% CI, 0.40–0.68), pancreatic cancer (HR, 0.55; 95% CI, 0.33–0.92), colorectal cancer (HR, 0.61; 95% CI, 0.44–0.84), liver and biliary tract cancers (HR, 0.68; 95% CI, 0.51–0.90), and prostate cancer (HR, 0.72; 95% CI, 0.52–0.99).

In a sub-analysis by sex, cancer risks were significantly reduced among male AD patients for hematologic malignancies (HR, 0.24; 95% CI, 0.07–0.81), stomach cancer (HR, 0.26; 95%

Table 3. Adjusted HRs for specific cancer sites among patients with AD

Site of cancers	Total			Male with AD		Female with AD	
	AD group, No. (%)	Control group, No. (%)	Adjusted HR (95% CI) [†]	No. (%)	Adjusted HR (95% CI) [†]	No. (%)	Adjusted HR (95% CI) [†]
All cancers	540 (100)	3,393 (100)	0.67 (0.59–0.75)*	256 (100)	0.66 (0.56–0.77)*	284 (100)	0.66 (0.56–0.79)*
Head and neck	46 (8.5)	307 (9.0)	0.49 (0.31–0.80)*	16 (6.3)	0.41 (0.20–0.82)*	30 (10.6)	0.58 (0.230–1.12)
Brain	10 (1.9)	27 (0.8)	0.89 (0.37–2.12)	1 (0.4)	0.69 (0.06–8.1)	9 (3.2)	0.95 (0.38–2.40)
Digestive							
Esophagus	11 (2.0)	44 (1.3)	1.19 (0.55–2.59)	8 (3.1)	1.01 (0.43–2.39)	3 (1.1)	3.14 (0.45–21.90)
Stomach	64 (11.9)	528 (15.6)	0.42 (0.30–0.60)*	24 (9.4)	0.26 (0.15–0.46)*	40 (14.1)	0.60 (0.39–0.94)*
Colon and rectum	76 (14.1)	477 (14.1)	0.61 (0.44–0.84)*	32 (12.5)	0.81 (0.50–1.31)	44 (15.5)	0.48 (0.31–0.76)*
Liver and biliary tract	79 (14.6)	395 (11.6)	0.68 (0.51–0.90)*	36 (14.1)	0.64 (0.42–0.97)*	43 (15.1)	0.72 (0.49–1.06)
Pancreas	20 (3.7)	130 (3.8)	0.55 (0.33–0.92)*	9 (3.5)	0.60 (0.28–1.28)	11 (3.9)	0.50 (0.25–0.98)*
Lung	75 (13.9)	75 (13.9)	0.52 (0.40–0.68)*	49 (19.1)	0.53 (0.37–0.74)*	26 (9.2)	0.51 (0.32–0.80)*
Skin	16 (3.0)	16 (3.0)	0.88 (0.39–1.99)	7 (2.7)	0.56 (0.11–2.74)	9 (3.2)	1.08 (0.41–2.81)
Breast	8 (1.5)	8 (1.5)	0.15 (0.02–1.15)	-	-	8 (2.8)	0.15 (0.02–1.19)
Genitourinary system							
Cervix	2 (0.4)	12 (0.4)	0.31 (0.04–2.57)	-	-	2 (0.7)	0.31 (0.04–2.57)
Uterus	7 (1.3)	53 (1.6)	0.61 (0.24–1.56)	-	-	7 (2.5)	0.61 (0.24–1.56)
Ovary	5 (0.9)	32 (0.9)	0.61 (0.23–1.64)	-	-	5 (1.8)	0.51 (0.11–2.44)
Prostate	50 (9.3)	96 (2.8)	0.72 (0.52–0.99)*	50 (19.5)	0.88 (0.57–1.35)	-	-
Bladder	9 (1.7)	8 (0.2)	0.36 (0.13–1.05)	4 (1.6)	0.25 (0.06–1.08)	5 (1.8)	0.63 (0.14–2.95)
Kidney	5 (0.9)	15 (0.4)	0.60 (0.23–1.58)	3 (1.2)	0.52 (0.14–1.90)	2 (0.7)	0.77 (0.09–6.81)
Renal pelvic	1 (0.2)	38 (1.1)	0.33 (0.04–2.88)	-	-	1 (0.4)	0.66 (0.06–7.43)
Ureter	1 (0.2)	280 (8.3)	0.57 (0.07–4.40)	1 (0.4)	0.76 (0.10–6.02)	-	-
Hematologic malignancies	10 (1.9)	91 (2.7)	0.46 (0.23–0.91)*	4 (1.6)	0.24 (0.07–0.81)*	6 (2.1)	0.17 (0.04–0.73)*
Thyroid	13 (2.4)	66 (1.9)	0.90 (0.48–1.68)	2 (0.8)	0.75 (0.05–10.60)	11 (3.9)	0.72 (0.25–2.07)
Central nervous system	3 (0.6)	7 (0.2)	0.95 (0.21–4.27)	-	-	3 (1.1)	1.48 (0.30–7.35)
Other	29 (5.4)	47 (1.4)	0.22 (0.05–0.92)*	10 (3.9)	0.43 (0.05–3.61)	19 (6.7)	0.18 (0.02–1.39)

HR: hazard ratio, AD: Alzheimer's disease, CI: confidence interval, COPD: chronic obstructive pulmonary disease, CKD: chronic kidney disease.

**p*<0.05; [†]Adjustments were made for age, sex, hypertension, diabetes, stroke, COPD, CKD, dyslipidemia, and household income.

CI, 0.15–0.46), head and neck cancers (HR, 0.41; 95% CI, 0.20–0.82), lung cancer (HR, 0.53; 95% CI, 0.37–0.74), and liver and biliary tract cancers (HR, 0.64; 95% CI, 0.42–0.97). Among females with AD, the risks were most significantly reduced for hematologic malignancies (HR, 0.17; 95% CI, 0.04–0.73), cancers of the colon and rectum (HR, 0.48; 95% CI, 0.31–0.76), pancreatic cancer (HR, 0.50; 95% CI, 0.25–0.98), lung cancer (HR, 0.51; 95% CI, 0.32–0.80), and stomach cancer (HR, 0.60; 95% CI, 0.39–0.94) (Table 3).

DISCUSSION

This nationwide population-based study of elderly subjects aged ≥60 years of age demonstrated a 33% reduction in total cancer risk among AD patients compared to control subjects without AD over an 11-year follow-up period. The risk was significantly reduced for head and neck cancers, digestive cancers (stomach, colon and rectum, liver and biliary tract, and pancreas), lung cancer, and prostate cancer.

Our findings of reduced cancer risk among patients with AD correspond to those found in previous population-based studies, even though there were different diagnostic criteria, study designs, and follow-up durations. Other studies have found that the risk of cancer in dementia groups was reduced by 36%–80%,^{7,10,14,17} although these studies involved mostly white-populations. A recent study of a Taiwanese population showed a 23% reduction in total cancer risk among patients with dementia during a 7-year follow-up period.¹³ Our study group was limited to patients with AD, but our findings and the previous Taiwanese study

show that the risk of cancer was reduced among patients with dementia, regardless of race or other factors.

We reported that the risk for site-specific cancers was significantly reduced for head and neck cancer (HR, 0.49); digestive cancers, including stomach (HR, 0.42), colon and rectum (HR, 0.61), liver and biliary tract (HR, 0.68), and pancreas (HR, 0.55); lung cancer (HR, 0.52); and prostate cancer (HR, 0.72). Among them, head and neck cancer and stomach cancer showed a significant risk reduction for development in male AD patients, while the risk of pancreatic cancer was significantly reduced in female AD patients. Only a few studies have demonstrated risks for site-specific cancers.^{9,13,15} In the cancer register of the southern Sweden study, significant risk reductions were observed for colon cancer (HR, 0.60), lung cancer (HR, 0.53), melanoma (HR, 0.44), and prostate cancer (HR, 0.49).¹⁵ Cancer risk was significantly reduced in the cohort study in northern Italy for lung cancer (HR, 0.60) and colorectal cancer (HR, 0.43).⁹ In addition, the recent Taiwanese study of the nationwide population showed significant risk reductions for colon cancer (HR, 0.54) and prostate cancer (HR, 0.44).¹³ In all of these studies, including our present study, the risks of colon, lung, and prostate cancers were significantly reduced in dementia patients. These results present possibilities of an inverse association between the incidence of these site-specific cancers and AD. Therefore, further investigation into the relationship between AD and the mechanisms of cancer is needed.

The risk of cancer for the total population, and for males, was significantly higher for those aged 70–79 years than for those <70 years of age, but the risk of cancer was significantly lower for AD patients ≥80 years of age than for those <70 years of age. For females, cancer incidence was significantly lower for AD patients aged ≥80 years than for those aged <70 years. According to the 2016 National Health Screening Statistical Yearbook published by NHIS in 2017, the health check-up rates for males and females remained at over 70% until they reached their 70s.¹⁸ However, among those aged ≥80 years, check-up rates for males decreased to 52.7% and those for females decreased to 40.2%.¹⁸ Therefore, the decreased rate of health screening after the age of 80 may account for the significant decrease in cancer cases identified. Also, other studies have reported that many comorbidities, such as DM, CKD, COPD, and dyslipidemia increased cancer incidence.^{19–21} In this study, DM, COPD, and dyslipidemia were identified as risk factors for developing cancer in AD. However, this study showed that stroke was significantly associated with a decreased risk of cancer. The disability caused by stroke and the use of antiplatelet agents might have resulted in lower cancer health check-up rates compared to the control group.

Previous studies have suggested some mechanisms by which the risk of cancer is reduced in patients with previous dementia, including AD.^{8,10,22} Some researchers have suggested that AD patients do not undergo health screening as frequently as do control subjects due to the short life expectancy, and that their cancer-related symptoms may be ignored because of cognitive problems and behavioral symptoms associated with patients with AD,^{10,22} resulting in an apparent inverse-relationship between cancer risk and AD. However, 1 study showed that the risk of cancer was not lower for patients with vascular dementia than for control subjects.⁸ Conflicting results for different types of dementia raise the possibility that mechanisms besides life expectancy and cognitive difficulties may reduce the risk of cancer in AD.

Other researchers have theorized that genes or biological pathways may induce an inverse-association between dementia and cancer. Cancer is characterized by uncontrolled cellular

proliferation, whereas neurodegenerative changes in AD can be characterized by the premature progressive loss of neuronal cells.^{10,23,24} In particular, this study showed that patients with AD had a significantly lower risk for development of some types of cancers, such as colorectal, lung and prostate, than did control subjects.²⁵ Some studies, including a transcriptomic meta-analysis, suggested that the enzyme Pin was downregulated in AD, but upregulated in lung, colorectal and prostate cancers.²⁶ Tumor suppressor p53 promotes apoptosis and AD and protected against these cancers,²⁷ and the Wnt cell survival pathway was downregulated in AD,²⁸ but upregulated in these cancers. Therefore, upregulation of some downregulated genes and pathways could induce a bidirectional pathway which includes both neurodegeneration and cancer development. Feasibility of this mechanism is supported by the fact that patients with Parkinson's disease, one of the most neurodegenerative diseases, have reduced risks for developing cancer.²⁹⁻³¹

The major strength of this study is that it was a large, national, population-based study, and that it was the first study on the development of cancer in AD patients in South Korea using strict operational criteria. However, the current study had some limitations. First, this study was a retrospective observational design based on claims data, and the diagnoses for AD were identified using KCD-6 codes in the claims database, which may have been inaccurate compared with the diagnoses obtained from a medical chart, neuroimaging tests, or neuropsychological tests. Additionally, to improve the diagnostic accuracy of AD, we classified patients into the AD group when they had been prescribed antedementia medications. In South Korea, clinicians are required to document the clinical diagnosis of dementia from the medical record, as well as scores from such rating scales as the Mini-Mental State Examination,³² Clinical Dementia Rating,³³ or Global Deterioration Scale³⁴ in order to prescribe the medications named in the inclusion criteria of our study. Due to these strict operational criteria, AD patients not administered these drugs could not be included in this study. Second, the database used lacked clinical information related to dementia, so it was impossible to accurately distinguish AD from other types of dementia. Third, the incidence of cancers was low, and this study did not have sufficient power to evaluate the association between cancer and AD. Fourth, patients with AD tend to have less frequent contact with the healthcare system, including cancer examinations, which may have caused surveillance bias. Furthermore, we chose medical claim-based control subjects who were more likely to have comorbidities than control subjects from the general population who neither received a national health check-up nor medical care in hospitals, which may have induced selection bias. Among the potential confounders for cancer development, genetic factors and detailed clinical data, such as smoking intensity or alcohol amount could not be integrated into the analyses.

In conclusion, patients with AD exhibited a significantly lower risk for cancers than did control subjects without AD, based on an 11-year follow-up period, after adjusting for age, sex, hypertension, diabetes, stroke, COPD, CKD, dyslipidemia, and household income. Further research is needed to address the biological associations between cancer development and dementia, including AD.

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