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Risk of Dementia in Gastric Cancer Survivors Who Underwent Gastrectomy: A Nationwide Study in Korea

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ABSTRACT

Purpose. This study was designed to compare the risk of dementia, including Alzheimer's disease (AD) and vascular dementia (VaD), between gastric cancer patients who underwent gastrectomy and the general population.

Methods. All patients (n = 63,998) aged $\geq$ 50 years who received a diagnosis of gastric cancer and underwent curative gastrectomy between 2007 and 2012 and a non-cancer control population (n = 203,276), matched by age and sex, were identified from the Korean National Health Insurance Services and traced until 2017. Hazard ratios and 95% confidence intervals for dementia were calculated with a Cox regression analysis.

Results. Gastric cancer patients who received a gastrectomy showed an increased risk of AD [adjusted hazard ration (aHR) 1.08, 95% confidence interval (CI) 1.03–1.14], and the risk was especially marked for those who received a total gastrectomy (aHR 1.39, 95% CI 1.25–1.54). Gastric cancer survivors showed a decreased risk for VaD (aHR 0.85; 95% CI 0.73–0.98) regardless of operation type. Those who received continual vitamin B_{12} supplementation after a total gastrectomy were less likely than controls to develop AD (aHR 0.71; 95% CI 0.54–0.92).

Conclusions. Compared with controls, gastric cancer patients who received a total gastrectomy had an increased incidence of AD and a decreased risk of VaD. Our results suggest that vitamin B_{12} deficiency might play a role in the development of AD and highlight the need for vitamin B_{12} supplementation after total gastrectomy.

Despite decreasing incidence, gastric cancer remains the fifth most common cancer and the third leading cause of cancer mortality worldwide.[1] However, as a result of advances in early detection and treatment, global gastric cancer mortality has decreased continuously.[2] Particularly in Korea, where nationwide gastric cancer screening has been provided, a substantial increase in the proportion of early gastric cancers, from 24.8% to 50%, has been found during the past two decades, and 5-year disease-free survival among patients treated for stage I gastric cancer has surpassed 90%.[3,4] As the number of gastric cancer survivors increases, late adverse outcomes of gastrectomy have become an important issue for this population.[5–7]

Dementia is the leading cause of disability among elderly people, and its prevalence is continuously increasing worldwide. Around half of gastric cancers are currently diagnosed in patients aged > 65 years.[8]

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Despite the increased use of endoscopic resection of the stomach for early lesions, surgical resection is still the main therapeutic modality for gastric cancer.[3] Approximately half of patients with stage I disease in South Korea undergo gastrectomy.[9] Gastric cancer survivors who underwent gastrectomy are at increased risk of vitamin B_{12} deficiency, which is linked to dementia risk.[10–12] On the other hand, patients who underwent gastrectomy show an improved cardiometabolic profile, which can decrease the risk of dementia, especially vascular dementia.[13] To date, however, no study has directly investigated the association between gastrectomy and dementia.

Therefore, in this study, we investigated the risk of dementia among gastric cancer survivors who underwent curative gastrectomy compared with the general population using nationwide Korean cohort data. We considered two types of gastrectomy [total gastrectomy (TG) vs. subtotal gastrectomy (STG)] and two subtypes of dementia [Alzheimer's disease (AD) vs. vascular dementia (VaD)]. Additionally, we examined whether supplementation with vitamin B_{12} reduces the risk of dementia among gastric cancer survivors after radical gastrectomy.

METHODS

Data Source

Our retrospective cohort is taken from the Korean National Health Insurance Services (NHIS) database. Korea has a social health insurance system that is mandatory for approximately 97% of the Korean population. People in the lowest income bracket are covered by Medicaid, which is funded by general taxes. NHIS is the single insurer and provides reimbursement to medical service providers. Therefore, the NHIS database contains beneficiary information, such as age, sex, place of residence, monthly insurance premium, and disability status, and medical claims information, such as disease codes, procedures, prescriptions, and costs incurred. The Korean NHIS database also contains pharmacy claims data that include the name of each medication, the date that each prescription was generated and filled, the formulation (i.e., oral pill or injectable drug), dosage, and the number of days prescribed. In Korea, the monthly insurance premium is determined by income level, not health risk, and therefore it can be used as a proxy for economic status.

This study was approved by the Institutional Review Board of the Samsung Medical Center (IRB No SMC 2018-05-184). The requirement for informed consent was waived because the study was based on routinely collected administrative and medical claims data.

Study Population

A total of 101,811 subjects who underwent either STG or TG for gastric cancer (International Classification of Diseases, 10th revision; ICD-10, C16) from January 1, 2007, to December 31, 2012, were enrolled. Among the 77,913 gastric cancer patients aged $\geq$ 50 years, we excluded those with a history of other cancers (C00–C97 except C16, $N = 3159$), dementia (F00–03, G23.1, G 30, G31.0, G31.1, G31.82, G31.83, G31.88, or F10.7, $N = 687$), Parkinson's disease (G20, $N = 271$), or stroke (I63-64, $N = 1\ 733$) before their gastric cancer diagnosis. In addition, we excluded subjects who died within 2 years after gastrectomy ($N = 7279$), because most recurrence and early death from gastric cancer occur during this period.[14] We started follow-up with a 2-year time lag after gastrectomy, also excluding those who developed dementia within those 2 years ($n = 939$), because the effect of gastrectomy would not be immediate. In the end, we included 63,998 gastric cancer patients in this study.

For the control population, 233,739 noncancer subjects were selected as a 1:3 age- and sex-matched control group for the 77,913 gastric cancer patients. Matching was performed on an every-year basis such that incident gastric cancer cases were matched to control cases based on information at the year of cancer diagnosis (e.g., patients who were diagnosed in 2008 were matched to control subjects alive in 2008 whose baseline characteristics for matching were derived from 2007). The exclusion criteria applied to the control group were identical to those for the gastric cancer group. Matched comparison subjects ($N = 203,276$) were assigned an index date corresponding to the date of gastrectomy of their matched gastric cancer patient. The flow chart for the scheme of the study population is provided in Fig. 1.

Covariates

Income status was categorized by insurance premium quartiles, and Medicaid was merged into the lowest income group due to low numbers. Place of residence was categorized as metropolitan, city, and rural area. Hypertension (I10/I15 or antihypertensive medication), diabetes (E11–E14 or anti-diabetes medication), dyslipidemia (E78 or lipid-lowering medication), end-stage renal disease (V001, V003, and V005), and depression (F32–34) were defined using ICD-10 codes and prescriptions for a relevant medication.

Regarding the duration of supplementation with vitamin B_{12}, gastric cancer patients were divided into four groups as follows, because it is known that stored vitamin B_{12} is depleted 3 years after a gastrectomy:[15] those who did not receive supplementation, those who received

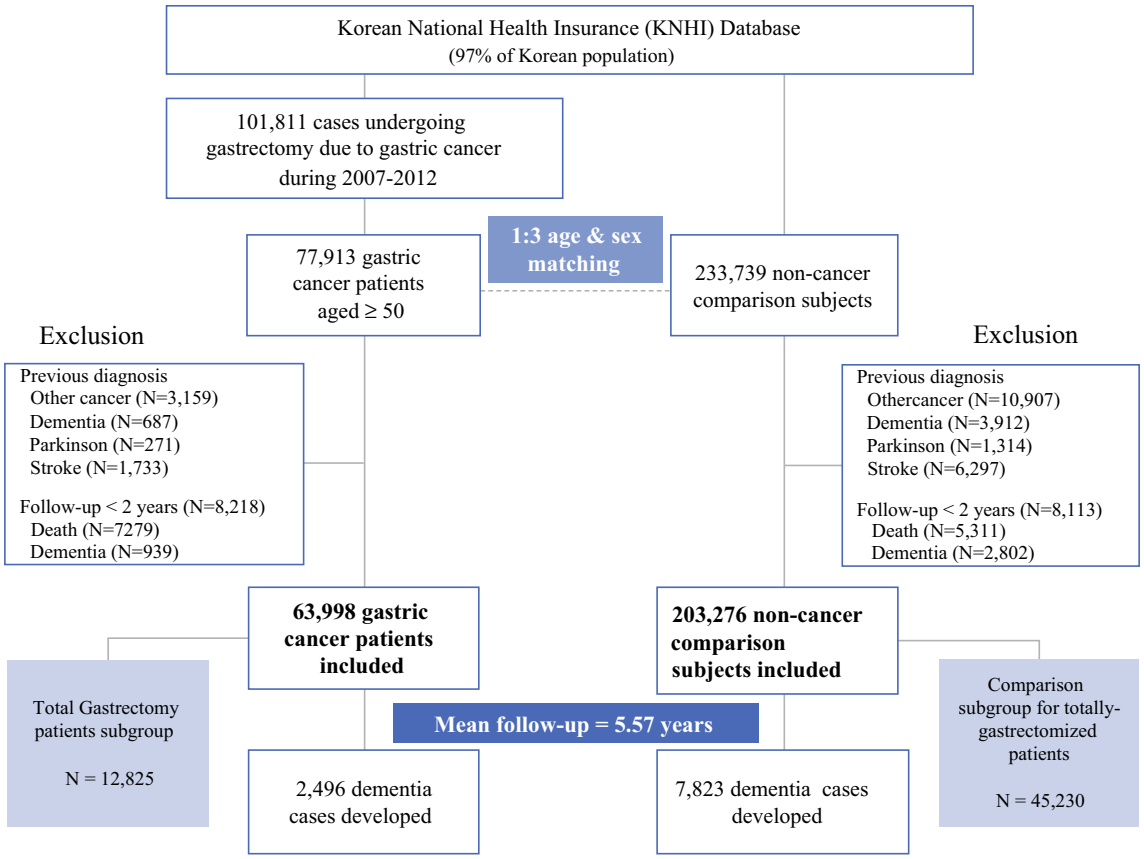

FIG. 1 Flow diagram of study participants

supplementation within 3 years of surgery but quit within the 3 years, those who started supplementation 3 or more years after surgery, and those who began supplementation within 3 years of surgery and continued to receive it thereafter.

Outcomes and Measures

Dementia was defined if antidementia drugs were prescribed at least two times and the codes for AD (ICD-10 F00 or G30), VaD (ICD-10 F01.0, F01.1, F01.2, F01.3, F01.8, or F01.9), or other dementia (ICD-10 F02, F03, G23.1, G31.0, G31.1, G31.82, G31.83, G31.88, or F10.7) were used on medical expense claims submitted to the NHIS up to the end of follow-up (31 December 2015). Antidementia drugs included the following: rivastigmine, galantamine, memantine, and donepezil hydrochloride. In South Korea, fulfillment of Korean National Health Insurance Reimbursement Criteria is required to claim expenses. To be paid for the prescription of an antidementia drug, physicians must document evidence of cognitive dysfunction according to the relatively strict criteria of (1) Mini-Mental State Examination $\leq$ 26 and (2) either a Clinical Dementia Rating $\geq$ 1 or a Global Deterioration Scale $\geq$ 3.[16]

Statistical Analysis

Basic characteristics of the study population are presented using descriptive statistics. A Cox regression analysis was performed to determine the risk of dementia according to gastrectomy status and was adjusted for age, sex, income, place of residence, hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, and depression. To investigate whether vitamin B_{12} supplementation affected the development of dementia among gastric cancer patients who underwent TG, the risk of dementia in TG patients was stratified by the duration of vitamin B_{12} supplementation. All statistical analyses were performed using SAS 9.3 (Cary, NC), and results with two-sided P values < 0.05 are considered significant.

Patient and Public Involvement

No patients were involved in the setting of the research question or the outcome measures, nor were they involved in developing the plans for design or implementation of the

study. No patients were asked for advice on data interpretation or writing up the results. There are no plans to disseminate the results of the research to the study participants or relevant patient community.

RESULTS

Characteristics of the Study Population

A total of 63,998 gastric cancer patients and 203,276 matched comparison subjects were included in the final analyses (Fig. 1). Their mean (± SD) age was 63.2 (± 8.1) years, and 30.6% of the study population was female. Regarding major comorbidities, 37.8% had hypertension, 14.7% had diabetes, 17.0% had dyslipidemia, 0.3% had chronic kidney disease, and 5.8% had depression at baseline. Among the gastric cancer patients, 80.1% received an STG, and 19.9% underwent a TG. Compared with the noncancer matched control group, a lower proportion of individuals in the gastric cancer group reported the lowest income and resided in urban areas; the gastric cancer group included a higher proportion of individuals with hypertension, diabetes mellitus, or depression than the noncancer control group. Subjects in the noncancer group were more likely to have dyslipidemia than those with cancer (Table 1).

Dementia Incidence in Gastric Cancer Patients Compared with the Matched Control Group

In the total study population, the mean follow-up period after the 2-year time lag was 3.57 years (3.41 years for the gastric cancer patient group and 3.63 years for the matched comparison group). The maximum follow-up after gastrectomy was 9 years. Compared with the matched controls, gastric cancer patients who received gastrectomy did not show an increased risk for all types of dementia [adjusted HR (aHR) 1.04; 95% confidence interval (CI), 0.99–1.09; Table 2]. In the analysis by surgery type, patients who underwent TG showed an increased risk of developing any type of dementia (aHR 1.30; 95% CI 1.20–1.42), whereas patients who underwent STG did not show a significant association (aHR 0.99, 95% CI 0.94–1.04; Table 2; Fig. 2).

When examined by the subtype of dementia, gastric cancer patients who underwent gastrectomy showed an increased risk of AD (aHR 1.08, 95% CI 1.0–1.14), and the risk was markedly increased for those who received a TG (aHR 1.39, 95% CI 1.25–1.54; Table 2; Fig. 2). Gastric cancer survivors showed a decreased risk of VaD (aHR 0.85; 95% CI 0.73–0.98) compared with the matched noncancer control group (Table 2).

Effect of Vitamin B_{12} Supplementation on the Risk of Dementia in Gastric Cancer Patients who Underwent Total Gastrectomy

Because patients who underwent TG had an increased risk for dementia, we further analyzed whether vitamin B_{12} supplementation reduced the risk for dementia in that population. Compared with the matched controls, the risk of developing dementia was significantly increased in those who did not receive vitamin B_{12} supplements (aHR 1.96; 95% CI 1.63–2.36) and those who quit supplementation within 3 years after surgery (aHR 2.66; 95% CI 2.05–3.43; Table 3). Patients who started vitamin B_{12} supplementation 3 years after surgery showed no significant risk reduction (aHR, 0.92, 95% CI 0.63–1.34), but those who continued to take vitamin B_{12} after surgery were less likely to develop dementia than the controls (aHR 0.71; 95% CI 0.54–0.92). When the dementia was stratified as AD or VaD, the analyses among patients with AD showed the same trends as those among patients with overall dementia. In contrast, vitamin B_{12} supplementation was not associated with a reduction in the risk of VaD among gastric cancer patients undergoing TG (Table 3).

DISCUSSION

To the best of our knowledge, this study is the first to investigate directly the relative risk of dementia incidence among gastric cancer survivors who underwent curative gastrectomy compared with a matched noncancer comparison group. We found that gastric cancer survivors who underwent TG had an up to 1.3-fold higher risk of dementia than the non-cancer controls, whereas those who underwent STG did not show an increased susceptibility. Stratified analyses implied that supplementation with vitamin B_{12} after surgery could play a key role in preventing the development of AD in the TG group. The strengths of our study are its large and representative sample, use of a noncancer control group extensively matched for sociodemographic characteristics and major comorbidities, and the low attrition rate.

We found that the TG group, but not the STG group, had an increased risk of developing AD compared with the non-cancer controls. Patients who undergo TG generally show vitamin B_{12} depletion, because the levels of gastric acid and intrinsic factors necessary for vitamin B_{12} absorption are greatly reduced by removal of the stomach.[17] One noticeable finding of our study was the lower incidence of AD in patients who received continual supplementation with vitamin B_{12} after TG. These observations suggest that vitamin B_{12} deficiency could play a major role in the development of AD in gastric cancer survivors. Signs of vitamin B_{12} deficiency have been

TABLE 1 Baseline characteristics of the study participants

Variables	Gastric cancer patients (n = 63,998)	Matched control subjects (n = 203,276)	P value
Age at diagnosis (mean ± SD)	63.3 ± 8.1	63.2 ± 8.1	0.035
Sex			0.313
Male	44,491 (69.5)	140,888 (69.3)	
Female	19,507 (30.5)	62,388 (30.7)	
Income			< 0.001
Highest quartile	17,578 (27.5)	56,227 (27.7)	
2nd quartile	15,304 (23.9)	46,844 (23.0)	
3rd quartile	13,681 (21.4)	42,642 (21.0)	
Lowest quartile and Medicaid	17,435 (27.2)	57,563 (28.3)	
Place of residence			< 0.001
Metropolitan	37,321 (58.3)	122,389 (60.2)	
City	18,035 (28.2)	55,439 (27.3)	
Rural	8642 (13.5)	25,448 (12.5)	
Comorbidity			< 0.001
Hypertension	25,910 (40.5)	75,238 (37.0)	< 0.001
Diabetes mellitus	11,258 (17.6)	28,139 (13.8)	< 0.001
Dyslipidemia	10,085 (15.8)	35,462 (17.5)	< 0.001
Chronic kidney disease	183 (0.3)	491 (0.2)	0.051
Depression	4481 (7.0)	11,029 (5.4)	< 0.001

SD standard deviation

TABLE 2 Incidence of dementia in gastric cancer patients and matched control subjects according to type of gastrectomy

Group	n	Person-years	Event	Rate (per 1000 p-y)	HR (95% CI)	aHR (95% CI)
All dementia						
All participants						
Comparison group	203,276	736,878.0	7823	6.84	1 (ref.)	1 (ref.)
Gastric cancer	63,998	218,000.8	2496	7.21	1.08 (1.04, 1.13)	1.04 (0.99, 1.09)
Subtotal gastrectomy	51,173	176,857.0	1984	7.11	1.06 (0.01, 1.11)	0.99 (0.94, 1.04)
Total gastrectomy	12,825	41,144.9	512	7.67	1.18 (1.08, 1.29)	1.30 (1.20, 1.42)
Alzheimer's disease						
All participants						
Comparison group	203,276	736,878.0	5801	5.07	1 (ref.)	1 (ref.)
Gastric cancer	63,998	218,001.8	1928	5.57	1.13 (1.07, 1.19)	1.08 (1.03, 1.14)
Subtotal gastrectomy	51,173	176,857.0	1529	5.48	1.10 (1.04, 1.17)	1.02 (0.97, 1.08)
Total gastrectomy	12,825	41,144.9	399	5.97	1.25 (1.13, 1.38)	1.39 (1.25, 1.54)
Vascular dementia						
All participants						
Comparison group	203,276	736,878.0	891	0.78	1 (ref.)	1(ref.)
Gastric cancer	63,998	218,001.8	231	0.67	0.88 (0.76, 1.02)	0.85 (0.73, 0.98)
Subtotal gastrectomy	51,173	176,857.0	195	0.70	0.91 (0.78, 1.07)	0.86 (0.74, 1.01)
Total gastrectomy	12,825	41,144.9	36	0.54	0.73 (0.52, 1.02)	0.77 (0.55, 1.07)

Incidence rate: per 1000 person-years

Multivariate model adjusted for age, sex, income, place of residence, hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, and depression

CI confidence interval; *HR* hazard ratio; *aHR* adjusted hazard ratio; *p-y* person-years

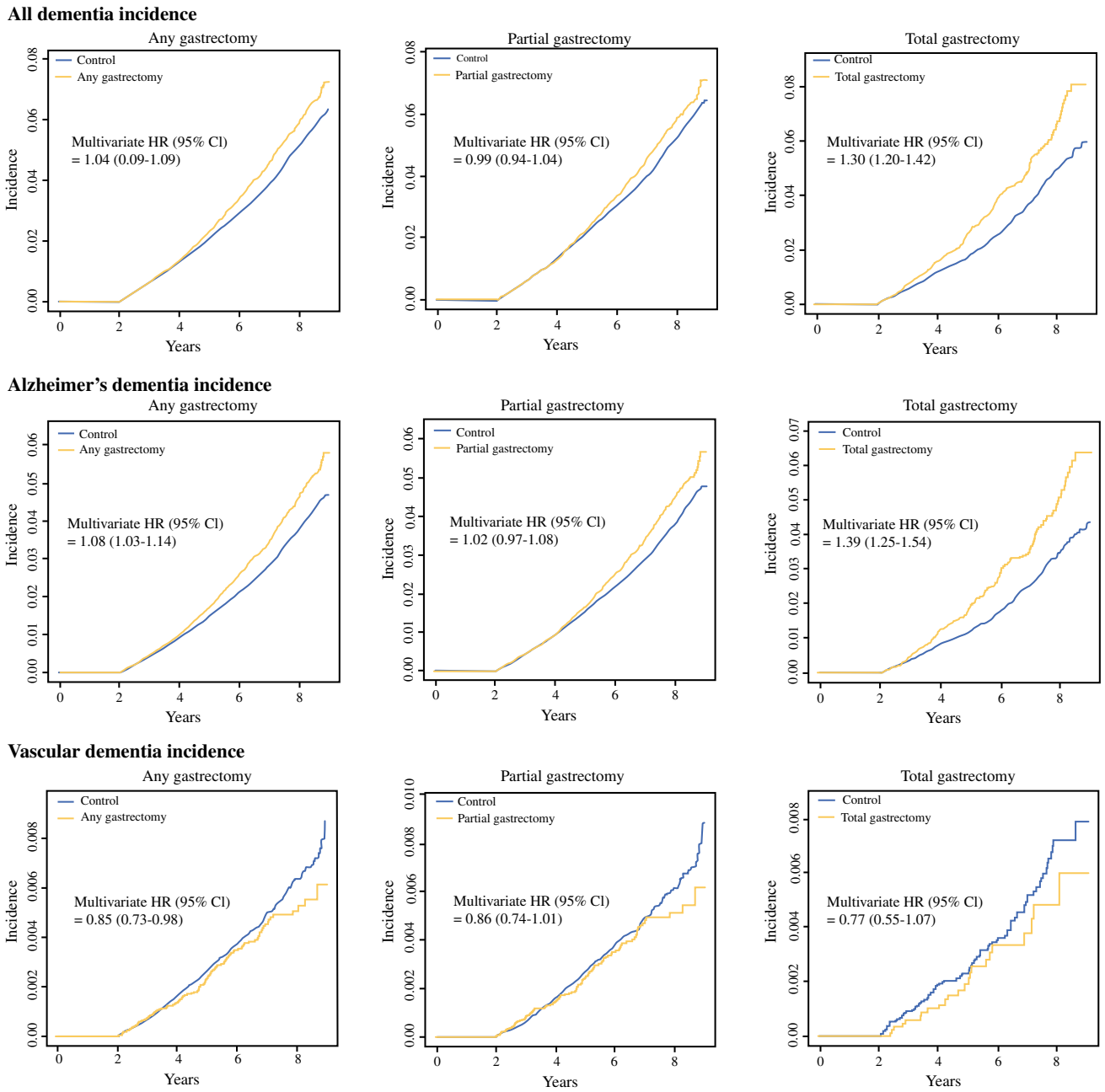

FIG. 2 Incidence of dementia in gastric cancer patients and matched control subjects according to the type of gastrectomy

associated with various neurologic sequelae, including dementia, paresthesia, loss of cutaneous sensation, and weakness.[18] Potential mechanisms linking vitamin B_{12} deficiency and dementia include an increased level of plasma homocysteine, which is thought to have neurotoxic effects.[19] Furthermore, many epidemiologic studies have shown that hyperhomocysteinemia is an AD risk factor.[20] Because homocysteine is converted to methionine using vitamin B_{12}, vitamin B_{12} depletion could increase the plasma homocysteine level.[21] Indeed, many studies have shown that vitamin B_{12} deficiency is commonly found in AD patients, with the incidence of low vitamin B_{12} levels among dementia patients as high as 47%.[22–24]

Other mechanisms might account for the increased dementia risk in gastric cancer survivors who receive TG. For example, anemia is common in gastric cancer survivors and might be associated with dementia incidence, although we could not investigate the possibility of such an association due to a lack of clinical data in the NHIS database.[12,25] In addition, TG alters the physiology of digestion and damages the delicate mechanisms at the

TABLE 3 Incidence of dementia in patients undergoing total gastrectomy compared with matched control subjects according to vitamin B_{12} supplementation

Vitamin B_{12} supplement	*N*	Follow-up (person-years)	Overall dementia			Alzheimer's disease			Vascular dementia		
			Event (*n*)	Rate[a]	aHR (95% CI)	Event (*n*)	Rate[a]	aHR (95% CI)	Event (*n*)	Rate[a]	aHR (95% CI)
No supplements											
Control	10,707	38,322.7	421	7.05	1 (ref.)	309	5.17	1 (ref.)	49	0.82	1 (ref.)
TG	4094	10,426.6	226	12.14	1.79						
(1.52,2.10)	180	9.67	1.96		(1.63, 2.36)	14	0.75	0.90 (0.49, 1.64)			
Started supplementation but quit within 3 years											
Control	6019	19,456.3	198	6.29	1 (ref.)	142	4.51	1 (ref.)	23	0.73	1 (ref.)
TG	2320	5116.5	134	13.73	2.43						
(1.94,3.03)	106	10.86	2.66		(2.05, 3.43)	7	0.72	1.09 (0.46, 2.57)			
Started supplementation more than 3 years after surgery											
Control	4776	20,634.9	135	4.47	1 (ref.)	95	3.15	1 (ref.)	20	0.66	1 (ref.)
TG	1771	7836.0	49	4.31	0.84						
(0.60,1.16)	38	3.34	0.92		(0.63, 1.34)	6	0.53	0.70 (0.28, 1.76)			
Continual supplementation*											
Control	12,402	46,796.6	321	4.48	1 (ref.)	241	3.37	1 (ref.)	43	0.60	1 (ref.)
TG	4640	17,764.8	103	3.81	0.72						
(0.58,0.91)	75	2.77	0.71		(0.54, 0.92)	9	0.33	0.50 (0.24, 1.03)			

CI confidence interval; *Ref* reference; *aHR* adjusted hazard ratio; *TG* total gastrectomy; *N* number

Multivariate model adjusted for age, sex, income, place of residence, hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, and depression

*Started within 3 years of surgery and continually administered thereafter

[a]Per 1000 person-years

gastroesophageal junction and pylorus, which can lead to a voluntary reduction in calorie intake and subsequent weight loss in gastric cancer survivors who received a TG. Moreover, bypass of the gastrointestinal tract causes malabsorption of various nutrients, including calcium, carotene, and fat, as well as vitamin B_{12}.[26] Weight loss has been considered a possible risk factor for dementia because it is associated with a deficiency in micronutrients such as vitamins and essential fatty acids, with consequent oxidative tissue damage.[27]

One interesting finding was the lower incidence of AD in patients in the TG group who received continual supplementation with vitamin B_{12}. This is consistent with previous trial findings that vitamin B treatment in patients with hyperhomocysteinemia decreased the serum homocysteine level by 30.2% and slowed the rate of brain atrophy by 29.6% compared with the placebo group.[28] Patients who received TG show a significant deficiency of vitamin B_{12}, and reversion of this risk factor would be expected to decrease the risk of AD.[29] It also is highly likely that those who had vitamin B_{12} supplementation were also monitored for anemia and received iron supplementation if needed. Therefore, our study suggests that the risk of dementia can be successfully managed in this group with adequate supplementation of vitamin B_{12}, iron, and other micronutrients. The observed reduced risk for AD in subjects who underwent gastrectomy and received vitamin B_{12} replacement brings attention to the possible contributory role of vitamin B_{12} deficiency in the development of dementia.

In contrast, patients who underwent STG did not show an increased risk of AD, perhaps because only a minority of patients who receive STG experience vitamin B_{12} depletion (10–43%),[29] and anemia also is less frequent and less severe among STG patients.[30,31] However, it is probable that the minority of STG patients who experience

anemia and vitamin B_{12} deficiency are at risk for AD. Because we could not confirm that probability in this study due to a lack of clinical data, further studies are warranted.

The present study shows that gastric cancer survivors who received a gastrectomy had a reduced risk of VaD. VaD shares risk factors with cerebrovascular heart disease, such as diabetes mellitus, hypertension, dyslipidemia, and coronary heart disease.[32] Our result is thus in line with a previous study that reported decreased incidence of cardiovascular disease and beneficial postsurgical changes in anthropometric and metabolic profiles in gastric cancer patients who received gastrectomy.[33–35] After gastrectomy, visceral fat decreases, which might increase insulin sensitivity and improve glycemic control and the metabolic profile.[34,35] An increase in adiponectin, which has antiatherogenic properties, and plasminogen activator inhibitor type 1, an inhibitor of plasma fibrinolytic activity, also was observed among patients who underwent gastrectomy.[33] This might contribute to the regression of atherosclerosis or prevention of thrombosis, which would ultimately reduce the risk of VaD events.

The clinical importance of our study lies in the fact that vitamin B_{12} deficiency is preventable and easily corrected by regular follow-up. Vitamin B_{12} deficiency is an inevitable and rather early metabolic sequalae of TG. Elderly patients with low preoperative vitamin B_{12} levels are more likely than others to experience vitamin B_{12} deficiency after distal gastrectomy.[11] Thus, regular postoperative monitoring of vitamin B_{12} levels is necessary for early detection and treatment of post-gastrectomy vitamin B_{12} deficiency.

The results of our study can be extrapolated to patients who undergo bariatric surgery for weight loss. Because the surgical procedure and metabolic changes of gastrectomy for gastric cancer patients are similar to those of bariatric surgery, there has been concern that bariatric surgery might induce nutritional deficiencies, including vitamin B_{12} deficiency. A low serum vitamin B_{12} level has been observed in as many as 70% of patients who undergo gastric bypass surgery, and vitamin B_{12} deficiency has been observed in more than 30%.[36] Vitamin B_{12} deficiency most commonly occurs in patients who undergo biliopancreatic diversion and Roux-en-Y gastric bypass.[37]

Our study has several limitations. First, because we used administrative data, we did not have detailed clinical information about longitudinal serum levels of vitamin B_{12}, folate, homocysteine, hemoglobin, or other micronutrients. Therefore, we were limited in our investigation of the role played by each nutrient in the development of dementia. Second, we lacked data on the types of post-gastrectomy reconstruction methods[34] which could have different effects on the absorption of nutrients, including vitamin B_{12} and iron. Third, because our study was based on secondary data and was not a prospective cohort study specifically designed to study dementia, we did not have all the information relevant to a dementia study. For example, we did not have genetic information (e.g., *APOE4* carriers) or data on baseline cognitive function, educational, and literacy levels. Furthermore, the incidence of dementia was not determined through regular follow-up of cognitive function using formal cognitive testing. The follow-up period was relatively short; a longer follow-up might be helpful to determine long-term risk.

CONCLUSIONS

We found increased AD incidence among gastric cancer patients who received TG and decreased VaD risk among gastric cancer patients who received gastrectomy. Our results suggest that vitamin B_{12} deficiency plays a role in the development of AD, and they highlight the need for continual vitamin B_{12} supplementation after TG. Prospective cohort studies are required to evaluate the role of gastrectomy and accompanying deficiencies in micronutrients, including vitamin B_{12}, in the development of overall dementia, AD, VaD, and general cognitive impairment.

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AUTHORS CONTRIBUTION SDW and PYG designed the study. HKD and PS analyzed the data. CYJ, JW, and JS drafted the manuscript. LDH and PYG revised the article. All the authors read and revised the manuscript and approved its final version. SDW and PYG are responsible for the overall content as guarantors and accept full responsibility for the work and conduct of the study; they had access to all the data and controlled the decision to publish. The corresponding authors attest that all listed authors meet the authorship criteria and that no others meeting the criteria have been omitted, that they had full access to all the data in the study, and that they had final responsibility for the decision to submit for publication.

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RESEARCH INVOLVING HUMAN PARTICIPANTS The research committee of Helsinki University Hospital approved our study plan. Obtaining consent was not needed in our register-based study, because we did not contact any study patients or their caregivers.

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