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Risk of Ischemic Stroke in Patients With Gastric Cancer

A Nationwide Population-Based Cohort Study

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Abstract: Improvements in therapeutic modalities have prolonged the survival of gastric cancer patients. Comorbidities such as thromboembolic events that emerge as a result of disease complexities and/or treatments received have not been considered. The objectives of this study are to examine the relationship between gastric cancer and ischemic stroke, and to determine predictive risk factors.

A nationwide population-based cohort study was conducted using data from the Taiwan National Health Insurance database. A total of 45,060 gastric cancer patients and non-cancer counterparts without antecedent stroke were recruited. Hazard ratios (HRs) and the cumulative incidence of ischemic stroke were calculated, and risk factors for ischemic stroke were assessed.

Gastric cancer patients were associated with higher risk of ischemic stroke (HR 1.11, 95% confidence interval [CI] 1.03–1.19, $P = 0.007$), especially in participants younger than 65 years (HR 1.61, 95% CI 1.39–1.86, $P < 0.001$) and in female participants (HR 1.30, 95% CI 1.14–1.49; $P < 0.001$) when compared with the matched cohort. Independent risk factors of ischemic stroke in gastric cancer patients included age, hypertension, atrial fibrillation, dyslipidemia, and having received major surgery for gastric cancer.

Our findings suggest the importance of stroke surveillance and prevention strategies in high-risk patients. Having received major surgery for gastric cancer is a significant risk factor in these patients.

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Abbreviations: ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, NHI = National Health Insurance, PAOD = peripheral arterial occlusion disease, RCIP = Registry for Catastrophic Illness Patients.

INTRODUCTION

Cancer will continuously increase the burden on society when the world's population is increasing and aging. Malignancies of the gastrointestinal tract are among the common forms of cancer diagnosed. Each year, approximately a million new gastric cancers are estimated to occur worldwide.[1] Although improvements in surgical techniques, chemotherapy, and radiotherapy have brought cancer survivors a longer life expectancy, few studies have focused on understanding their emerging comorbidities. Factors that determine quality of life in these patients, therefore, demand our further consideration.

A variety of cancers have been shown to be associated with coagulation disorders.[2,3] A large autopsy study demonstrated that up to 14.6% of patients with cancer had cerebrovascular complications.[4] Strokes of embolic origin are the common most type and the role of underlying malignancy should not be ruled out.[5] In addition, a study on ovarian cancer patients revealed that receiving chemotherapy increases the risk for subsequent ischemic stroke.[6] Thus, it is vital that we promote increased surveillance for ischemic stroke in cancer survivors at risk.

Regarding patients with gastric cancer, few reports have mentioned the occurrence of ischemic stroke.[7] The association between ischemic stroke and this cancer, however, has so far not been examined in large-scale studies. Some uncertainties about whether patients with gastric cancer exhibit a higher risk for subsequent ischemic stroke, compared with the general population, thus remain. A population-based cohort study using Taiwan's National Health Insurance (NHI) database was conducted to examine this issue.

METHODS

Data Sources

Data used in this study were obtained from the NHI database. Implemented in 1995, NHI is a national healthcare program covering >99.5% of the population in Taiwan.[8] Computerized medical claims, inpatient and ambulatory care records, participant's demographic information, data from the Registry for Catastrophic Illness Patients (RCIP), and other

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healthcare data were included in our analysis. Diagnosis of cancer is supported by histopathological data, as required by the RCIP, and accuracy of diagnoses in the NHI database has been validated for several diseases, including ischemic stroke.[9] Diseases are coded in accordance with the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic codes, 2001 edition. The ethics committee of Taipei Veterans General Hospital has approved all research protocols included in this study and has exempted the necessity of written consent from study participants because all information retrieved from the database is encrypted computerized data (2014-05-001BE).

Study Subjects

A gastric cancer cohort and a matched cohort were enrolled in this study. The former, identified from the RCIP, consisted of gastric cancer patients with the ICD-9-CM code of 151.X. Patients with new cancer diagnoses made between January 1, 2003 and December 31, 2011 were included. Participants younger than 20 years, as well as those who had cerebrovascular disease in the past or who were lost to follow-up, were excluded from our study. Individuals without cancer were selected by means of multistage stratified random sampling from the NHI database to form a one-to-one matched cohort with the gastric cancer cohort on the basis of age, sex, time of enrollment, and comorbidities related to ischemic stroke.

Outcome Measures

Ischemic strokes (ICD-9-CM code 436, 433.X, 434.X, and 437.1X) accompanied by computed tomographic or magnetic resonance images were identified using medical claims data from NHI. Participants in both cohorts were followed until occurrence of ischemic stroke, death, end of the follow-up period (December 31, 2011), or withdrawal from NHI.

Statistical Analysis

All statistical analyses were performed using SAS 9.2 software (SAS Institute Inc., Cary, NC) or STATA statistical software, version 12.1 (StataCorp., College Station, TX). Baseline characteristics of the gastric cancer cohort and the matched cohort were presented as total number (n) and proportion (%). Categorical variables and continuous variables between the 2 groups were compared using Pearson chi-squared test and the Mann-Whitney *U* test, respectively. Study subjects were further divided into subgroups of different ages and sex to assess their effects. The association between gastric cancer and ischemic stroke was tested using Cox proportional hazards models and presented as hazard ratios (HRs) and 95% confidence intervals (CIs) that were adjusted for age, sex, and comorbidities. Cumulative incidences of ischemic stroke between the gastric cancer cohort and the matched cohort were calculated using the Kaplan–Meier method and were tested using a log-rank test. Mortality events that happened prior to the occurrence of ischemic stroke were important competing risks. Therefore, risk factors for ischemic stroke such as diabetes mellitus and hypertension, and therapeutic modalities such as surgery, chemotherapy, and radiotherapy, were adjusted for competing mortality and were assessed in Fine and Gray proportional hazards model for their effect on the association between gastric cancer and ischemic stroke. Therapeutic modalities were assessed as time-dependent covariates to avoid immortal time bias. Sensitivity analyses were performed to avoid misclassification bias caused by perioperative strokes and gastric cancer with brain metastases. Factors with *P* values <0.1 in the univariate model were further analyzed in the multivariate model. A *P* value of <0.05 was considered to be statistically significant.

RESULTS

Clinical Characteristics of the Study Population

A total of 30,786 patients with gastric cancer were identified. Patients aged 20 years and younger (n = 16), those diagnosed with cerebrovascular disease (n = 8229), and those lost to follow-up (n = 11) were excluded. As a result, 22,530 gastric cancer patients were included in our study (Figure 1). The demographic characteristics of our study subjects and matched cohort are displayed in Table 1. Participants in both groups were similar in distribution of age (median, 65 years), sex (62.2% were men), and cerebrovascular-related comorbidities, such as diabetes mellitus (27.8%), hypertension (49.3%), chronic kidney disease, (14.8%) and dyslipidemia (30.3%). There were no differences between the distribution of comorbidities between the study subjects and matched cohort in our study. In the gastric cancer cohort, 15,075 patients received surgery, 12,067 patients received chemotherapy, and 3476 patients received radiotherapy.

Incidence of Ischemic Stroke and Risk Factors

After an observation period of 9 years, the incidence of ischemic stroke was found to be higher in the gastric cancer cohort, at 22.6 per 1000 person-years compared with 21.4 per 1000 person-years in the matched cohort. After adjustment for age, sex, and the comorbidities listed in Table 1, the HR for subsequent ischemic stroke after gastric cancer was 1.11 (95% CI 1.03–1.19, $P = 0.007$). The risk was more prominent in participants younger than 65 years (13.4 vs 8.2 per 1000 person-years), with an adjusted HR of 1.61 (95% CI 1.39–1.86, $P < 0.001$). Although the risk was significant in women (adjusted HR 1.30, 95% CI 1.14–1.49, $P < 0.001$), it was not in men (adjusted HR 1.03, 95% CI 0.94–1.12, $P = 0.590$) (Table 2). A higher cumulative incidence of ischemic stroke was also found in the gastric cancer cohort following cancer diagnosis, but it was not statistically significant (log-rank $P = 0.221$) (Figure 2).

The multivariate Cox proportion hazards model revealed that factors independently determining the risk of subsequent ischemic stroke in gastric cancer patients included age (per year) (HR 1.02, 95% CI 1.02–1.03, $P < 0.001$), comorbidities such as hypertension (HR 1.52, 95% CI 1.32–1.76, $P < 0.001$), atrial fibrillation (HR 1.32, 95% CI 1.00–1.73, $P = 0.048$), dyslipidemia (HR 1.25, 95% CI 1.10–1.43, $P = 0.001$), and having received cancer treatment such as major surgery for gastric cancer (HR 1.56, 95% CI 1.36–1.79, $P < 0.001$). Although female participants possessed higher risk after they were diagnosed with gastric cancer compared with non-cancer women in the matched group, being female did not predict a future ischemic stroke in the gastric cancer cohort (HR 1.04, 95% CI 0.92–1.17, $P = 0.566$). Additionally, gastric cancer patients who received chemotherapy (HR 1.06, 95% CI 0.93–1.21, $P = 0.368$) and radiotherapy (HR 0.90, 95% CI 0.73–1.10, $P = 0.306$) did not show an increased risk for subsequent ischemic stroke (Table 3).

Sensitivity analysis excluding patients diagnosed with ischemic strokes within 7 days following major surgery for gastric cancer was performed to avoid misclassification bias caused by perioperative strokes, and the results were not materially changed (Supplemental Tables 1–3, http://

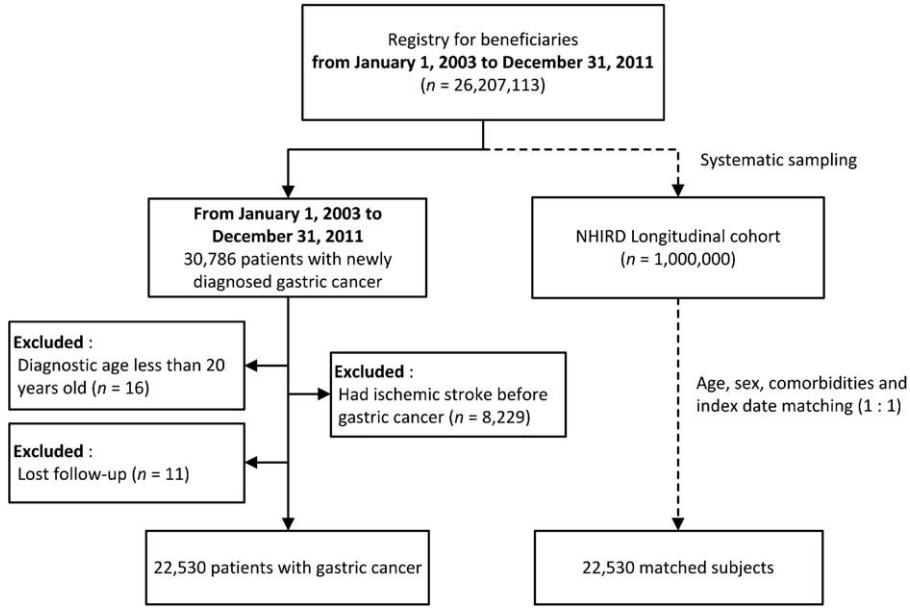

FIGURE 1. Selection flowchart.

links.lww.com/MD/A384 and Figure 1, http://links.lww.com/MD/A384). Analysis accounting for brain metastases-related ischemic strokes was also performed. Nevertheless, no patient who was diagnosed with brain metastases within 30 days following an ischemic stroke diagnosis was identified.

TABLE 1. Baseline Patient Characteristics of Patients With and Without Gastric Cancer

	Patients With Gastric Cancer (n = 22,530)		Matched Cohort (n = 22,530)		
Demographic Data	**n**	**%**	**n**	**%**	***P***
Age, y (interquartile range)	65 (53–76)		65 (53–76)		
≥65	11,716	52.0	11,716	52.0	1.000
<65	10,814	48.0	10,814	48.0	
Sex					
Male	14,010	62.2	14,010	62.2	1.000
Female	8520	37.8	8520	37.8	
Comorbidities					
Diabetes mellitus	6253	27.8	6256	27.8	0.975
Hypertension	11,103	49.3	11,115	49.3	0.910
Coronary artery disease	680	3.0	666	3.0	0.698
Atrial fibrillation	647	2.9	639	2.8	0.821
Chronic kidney disease	3329	14.8	3325	14.8	0.958
Dyslipidemia	6827	30.3	6832	30.3	0.959
PAOD	167	0.7	144	0.6	0.191
Treatment					
Major surgery	15,075	66.9			
Chemotherapy	12,067	53.6			
Radiotherapy	3476	15.4			

PAOD = peripheral arterial occlusion disease.

DISCUSSION

This is the first population-based study to determine the risk of newly onset ischemic stroke after gastric cancer diagnosis. Patients with gastric cancer exhibited elevated risks of subsequent ischemic stroke, especially those aged younger than 65 years and those who were women, compared with their non-cancer counterparts. Significant risk factors for ischemic stroke included age, hypertension, atrial fibrillation, dyslipidemia, and having received major surgery for gastric cancer.

It has been shown that cancers are associated with increased risk of coagulation disorders such as venous thrombosis[2] and strokes.[6,10–15] Studies have revealed a relative risk of between 4 and 7 times for developing venous thrombosis in cancer patients.[16] Given the variability between cancers, not every one of them displays similar characteristics. Those with high risk of developing venous thrombosis include pancreatic cancer, brain tumors, lung cancer, and gastric cancers, whereas the risk imposed by testicular cancer and thyroid cancer is comparable with that of the general population.[2] In addition to venous thromboembolism, increased incidence of arterial thromboembolism was also found in hospitalized cancer patients.[3] Previous studies have shown that head-and-neck cancer,[11,13] lung cancer,[10] cervical cancer,[15] breast cancer,[14] Hodgkin lymphoma,[12] and ovarian cancer[6] are associated with higher risks of between 1.44 and 2.20 for subsequent stroke.

Although the mechanism for cancer thromboembolism is still uncertain, it is believed that pathophysiology is associated with tumor proliferation-associated hypercoagulability. Experimental models have suggested that cancer cells contribute to the activation of coagulation cascade by inducing the production of tissue factor, thrombin, and fibrinogen, which enhances carcinogenesis via promoting tumor growth, angiogenesis, and metastasis.[17–19] This process might have contributed to the increased thromboembolism complications in our cancer patients, especially younger individuals who exhibited no established conventional stroke risk. It has been reported that approximately 40% of strokes in cancer patients are attributed to cryptogenic, nonconventional risk factors, compared with

TABLE 2. Incidence of Ischemic Stroke Occurrence in Patients With and Without Gastric Cancer

	Patients With Gastric Cancer		Matched Cohort					
	Ischemic Stroke No.	Per 1000 person –year	Ischemic Stroke No.	Per 1000 person-year	Crude HR (95% CI)	*P*	Adjusted HR* (95% CI)	*P*
Total	1106	22.6	1893	21.4	1.05 (0.97–1.13)	0.215	1.11 (1.03–1.19)	0.007
Age, y								
≥ 65	749	33.9	1515	35.5	0.95 (0.87–1.04)	0.262	0.94 (0.86–1.03)	0.170
<65	357	13.4	378	8.2	1.62 (1.40–1.88)	<0.001	1.61 (1.39–1.86)	<0.001
Sex								
Male	716	24.3	1329	24.6	0.98 (0.90–1.08)	0.686	1.03 (0.94–1.12)	0.590
Female	390	20.1	564	16.4	1.21 (1.07–1.38)	0.004	1.30 (1.14–1.49)	<0.001

CI = indicates confidence interval, HR = hazard ratio.
* Adjusted for age, sex, and comorbidities listed in Table 1.

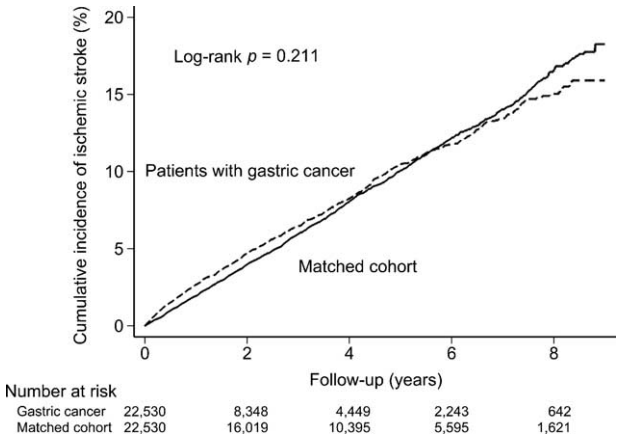

FIGURE 2. Cumulative incidence of ischemic stroke in patients with gastric cancer and matched cohort.

18% in non-cancer counterparts. Furthermore, brain imaging studies have revealed that cancer patients with stroke often exhibit multiple arterial territorial involvements, suggesting an embolic origin, compared with the single infarct seen in those with conventional stroke risks.[20] These findings indicate that stroke patterns and etiology are distinct between cancer patients and others, and that the effect of the underlying malignancy must be taken into consideration.

Our study reveals that gastric cancer patients have a higher risk of ischemic stroke following their cancer diagnosis. When compared with the matched cohort, the stroke risk imposed by gastric cancer is more profound in patients of younger age, with an adjusted HR of 1.61. This finding is compatible with a previous study on ovarian cancer, in which younger patients displayed a higher risk for subsequent ischemic stroke.[6] Cancer played a relatively less important role as soon as patients got older, when age and other risk factors became increasingly important.

TABLE 3. Risk Factors for Ischemic Stroke Development in Patients With Gastric Cancer

	Univariate Analysis		Multivariate Analysis*	
Predictive Variables	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Age, y	1.03 (1.03–1.03)	<0.001	1.02 (1.02–1.03)	<0.001
Sex (female)	1.11 (0.98–1.26)	0.094	1.04 (0.92–1.17)	0.566
Comorbidities				
Diabetes mellitus	1.61 (1.42–1.81)	<0.001	1.13 (0.99–1.30)	0.065
Hypertension	2.20 (1.94–2.50)	<0.001	1.52 (1.32–1.76)	<0.001
Coronary artery disease	1.58 (1.19–2.09)	0.002	1.08 (0.81–1.44)	0.602
Atrial fibrillation	1.95 (1.49–2.54)	<0.001	1.32 (1.00–1.73)	0.048
Chronic kidney disease	1.45 (1.25–1.69)	<0.001	1.08 (0.92–1.26)	0.329
Dyslipidemia	1.65 (1.46–1.86)	<0.001	1.25 (1.10–1.43)	0.001
PAOD	1.33 (0.72–2.48)	0.362		
Treatment†				
Major surgery	1.40 (1.22–1.60)	<0.001	1.56 (1.36–1.79)	<0.001
Chemotherapy	0.89 (0.79–1.01)	0.061	1.06 (0.93–1.21)	0.368
Radiotherapy	0.81 (0.66–0.99)	0.040	0.90 (0.73–1.10)	0.306

CI = indicates confidence interval, HR = hazard ratio, PAOD = peripheral arterial occlusion disease.
* All factors with $P < 0.1$ in univariate analyses were included in the Cox multivariate analysis.
† Treatment was analyzed as a time-dependent covariate in the Cox regression model.

Stroke in cancer patients with conventional risk factors has been shown to be attributed to etiologies that are similar to those in non-cancer individuals.[20] Hypertension and diabetes mellitus are among the predictors for subsequent ischemic stroke that remain significant over an extended period of time into old age[21] and have been shown to be risk factors in various cancer patients.[6,10,11] Other factors such as transient ischemic attacks, atrial fibrillation, stress, smoking, and a history of chest pain included risk of stroke for a relatively shorter period.[21] These results suggest that conventional risk factors remain important in the pathogenesis for ischemic stroke in cancer patients. Our multivariate Cox proportional hazards analysis revealed a similar result, with additional significant risk factors including age and having received major surgery for gastric cancer.

Intraoperative and postoperative clinically significant hypotension and marked bleeding might provide a plausible explanation for the development of ischemic stroke[22] in our study, but the influence of tumors must not be overlooked. Sensitivity analysis excluding gastric cancer patients with perioperative stroke slightly attenuated the strength of association between gastric cancer and subsequent ischemic stroke, but the relationship was not materially changed. Coagulopathy induced by malignancy contributes to a higher rate of postoperative complication,[23] and it increases in-hospital mortality 2 to 5 times.[3] These findings suggest that a number of cancer patients are vulnerable to specific vascular events, including ischemic stroke, that may eventually lead to a lethal outcome. More research is required to clarify the interactions of surgery in the relationship of gastric cancer and ischemic stroke and whether receiving prophylactic antiplatelet therapy is essential in these high-risk patients.

Limitations of the present study include a lack of information such as lifestyle variables (eg, tobacco and alcohol use), behavioral factors (eg, exercise and dietary habits), and biochemistry profiles, such as serum D-dimer level. The interactions between these potential confounding factors and gastric cancer and their contributions to the risk of ischemic stroke were not taken into consideration. Second, gastric cancer staging data were not available in the NHI database, so its association with ischemic stroke could not be recognized. Third, information on how participants in the gastric cancer cohort and matched cohort managed their comorbidities were not analyzed. However, it has been reported that differences in quality of comorbid condition care between cancer survivors and non-cancer controls vary, and only colorectal cancer survivors have been found less likely to receive appropriate care.[24] Hence, we believe this factor had limited effect on our main result. Finally, information on cause of death was not available, resulting in exclusion of patients who had fatal ischemic strokes outside the hospital. Consequently, the association between gastric cancer and ischemic stroke could be underestimated. Despite these limitations, our data were retrieved systematically from a nationwide, population-based database that includes all patients with gastric cancer and ischemic stroke in Taiwan, with minimal selection bias in the study period. The large sample size of the present study contributes to substantial statistical power on the association between gastric cancer and ischemic stroke, even existence of subtle differences between the cohorts.

CONCLUSIONS

This nationwide population-based study demonstrates that gastric cancer patients are at an increased risk of subsequent ischemic stroke, especially patients younger than 65 years and those that are female, when compared with the matching group. Factors that predict subsequent risk of ischemic stroke include having received major surgery for gastric cancer, in addition to conventional risk factors. Further research is warranted to establish stroke prevention strategies in high-risk patients.

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