Lung Cancer and Incidence of Stroke

A Population-Based Cohort Study

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Background and Purpose**—**Stroke is a known cerebrovascular complication in lung cancer patients; however, whether lung cancer patients are at elevated risk of developing stroke relative to the noncancer population remains unclear.

Methods**—**The present study used population-based claims data from the Taiwan National Health Insurance, which identified 52 089 patients with an initial diagnosis of lung cancer between 1999 and 2007, and 104 178 matched noncancer subjects from all insured subjects age 20 years and older. Subsequent occurrence of stroke was measured until 2008, and the association between lung cancer and the hazard of developing stroke was estimated using Cox proportional hazard models.

Results**—**The incidence of stroke was 1.5 times higher (25.9 versus 17.4 per 1000 person–years) in the lung cancer group compared with the comparison group. The multivariate-adjusted hazard ratio (HR) comparing lung cancer patients with the noncancer group was 1.47 (95% CI, 1.39–1.56) for stroke, 1.78 (95% CI, 1.54–2.05) for hemorrhagic stroke, and 1.43 (95% CI, 1.34–1.51) for ischemic stroke. The risk of stroke fell over time, decreasing after 1 year of follow-up for men and after 2 years of follow-up for women. Within the first year of follow-up, the risk of stroke peaked during the first 3 months for men and within 4 to 6 months for women.

Conclusions**—**Lung cancer is associated with increased risk of subsequent stroke within 1 year after diagnosis for men and 2 years after diagnosis for women. **(*Stroke*. 2011;42:00-00.)**

Key Words: epidemiology [8]; lung cancer ■ cerebrovascular disease

Cancer and stroke are among the 3 most common causes of death in developed countries, both of which lead to enormous health and economic burdens. In cancer patients, cerebrovascular disease is recognized as the second most common central nervous system complication.[1] Once cancer occurs in stroke patients, or vice versa, neurological outcomes significantly worsen and prognosis tends to be poor.[2,3] Median survival after concurrence of the 2 diseases is estimated to be less than 4.5 months.[4,5]

Type of cancer is one of the most important clues for determining stroke etiology in cancer patients.[6] In studies analyzing a neurological database from a cancer center, lung cancer was the most common cancer, occurring in 30% of patients with ischemic stroke[4] and in 14% of patients with intracranial hemorrhage.[5] However, these investigations were hospital-based chart reviews for selected stroke or cancer patients and did not determine the nature of the association between lung cancer and stroke. Thus, whether lung cancer is associated with elevated risk of subsequent stroke occurrence remains undetermined.

The occurrence of stroke subsequent to lung cancer has been discussed in a case report[7]; however, to the best of our knowledge, population-based data examining the temporal association between lung cancer and incidence of stroke are not available. A population-based cohort study was conducted using a nationwide representative database to examine this issue.

Materials and Methods

Data Sources

Data used in this study were obtained from the research database of Taiwan National Health Insurance (NHI), a mandatory program established in 1996 providing coverage to 99% of the entire 23.7 million people of Taiwan.[8,9] The NHI research database contains medical claims for all beneficiaries who access comprehensive medical care services in any 1 of the more than 90% of the hospitals and healthcare institutions that have a contract with the NHI. These claims data are subject to periodic review by the Bureau of NHI to ensure accuracy. Personal identification information was encrypted before the release of the research database to protect patient privacy.

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Study Subjects

Patients with lung cancer (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] code 162) were identified from the Registry for Catastrophic Illness Patients, a subdata set of the NHI research database. Registration for catastrophic illness requires a diagnosis made by a physician and pathological confirmation or other supporting medical information; these documents are formally reviewed by the Bureau of NHI. Patients age 20 years and older with an initial lung cancer diagnosis between 1999 and 2007 were selected. The date on which the lung cancer patient registered for the catastrophic illness was defined as the index date. Subjects who had been diagnosed with any cancer before the index date were excluded.

A noncancer comparison group was randomly selected from all NHI beneficiaries age 20 years and older and was matched with the lung cancer group at a 2:1 ratio based on age, sex, and month of lung cancer diagnosis. An index date for each comparison subject was defined using the middle date of the index month of a lung cancer patient. In both groups, subjects who suffered a stroke (ICD-9-CM codes 430–438, excluding traumatic strokes) and were diagnosed before the index date were excluded from the data analysis.

Outcome Measures

The follow-up duration began on the index date and lasted until the stroke diagnosis; withdrawal from NHI; death; or December 31, 2008; whichever came first. Stroke was identified using the hospital discharge diagnosis. The history of hypertension (ICD-9-CM codes 401–405), diabetes (ICD-9-CM code 250), coronary artery disease (ICD-9-CM codes 410–413, 414.0, 414.8, 414.9), atrial fibrillation (ICD-9-CM code 427.31), and chronic obstructive pulmonary disease (ICD-9 491.1, 491.2, and 496) were identified as diagnosed by hospital admissions before the index date to deal with the potential confounding effect of cardiovascular risk factors.

Statistical Analysis

Demographic and clinical characteristics of lung cancer patients and noncancer comparison controls were presented using the total number (proportion) for categorical variables and the mean (SD) for continuous variables. The level of urbanization was based on areas registered for the insurance developed by Liu et al from the National Health Research Institute.[10] In brief, all 316 cities and townships of Taiwan were classified into 7 ordered levels of urbanization computed by scores of population density (people/km^2), proportion of higher education, elderly and agricultural population, and the number of physicians per 100 000 people. Levels 5, 6, and 7 were combined into Level 4 because of the small number of subjects in these categories. Level 1 is the most urbanized, whereas Level 4 is the least.

Hazard ratios (HRs) and 95% CIs were calculated using Cox proportional hazard models, with the noncancer comparison group as the reference group, to assess the association between lung cancer and risk of developing a stroke. Potential confounding factors were listed based on established risk factors and an assessment was performed to find whether these variables were substantially associated with lung cancer and stroke in descriptive analyses. The effect of these variables on the lung cancer–stroke relationship was also evaluated by comparing crude and adjusted associations, and by selecting those yielding more than a 10% change in HRs for inclusion into the final models. The follow-up period was partitioned into 4 segments (year 0–1, 1–2, 2–3, and >3 years), and the Cox proportional hazard regression analyses were repeated to investigate whether the association between lung cancer and stroke risk differed over time. The first follow-up year was further stratified into 4 periods, namely, 0–3, 4–6, 7–9, and 10–12 months, to observe short-term risks. These stratified analyses were performed separately for men and women. Data analysis also evaluated the contribution of comorbidities to the risk of stroke.

For all models, the proportional hazard assumption was examined using a test of scaled Schoenfeld residuals. In models evaluating the stroke risk throughout the overall follow-up period, results of the test revealed a significant relationship between Schoenfeld residuals for lung cancer and follow-up time, suggesting that the assumption was violated. In analyses that stratified the follow-up duration, the assumption held for all predictors, including for lung cancer. All analyses were performed using SAS version 9.1 (SAS Institute Inc.) and STATA SE 11 (Stata Corp). All statistical tests were 2-sided.

Table 1. Demographic Characteristics and Comorbidities of Lung Cancer Patients and Subjects in the Comparison Group

	Patients With Lung Cancer		Comparison Group		
Characteristics	n	%	n	%	*P*
No. of patients	52 089		104 178		
Age, y (SD)*	67.2 (12.3)		67.1 (12.4)		0.035
Women	17 701	34.0	35 402	34.0	1.00
Occupation					<0.001
White collar*	20 723	39.8	43 368	41.6	
Blue collar†	23 974	46.0	43 822	42.1	
Others‡	7 392	14.2	16 988	16.3	
Urbanization§					<0.001
1	14 121	27.1	29 300	28.1	
2	14 164	27.2	28 265	27.1	
3	8487	16.3	17 181	16.5	
4	15 317	29.4	29 432	28.3	
Medical history					
Hypertension	12 762	24.5	12 716	12.2	<0.001
Diabetes mellitus	6632	12.7	7199	6.9	<0.001
Coronary heart disease	5100	9.8	7387	7.1	<0.001
Atrial fibrillation	1212	2.3	1391	1.3	<0.001
COPD	740	13.7	4127	4.0	<0.001

COPD indicates chronic obstructive pulmonary disease; SD, standard deviation.

*White collar: civil services, institution workers, enterprise, business and industrial administration personnel.

†Blue collar: farmers, fishermen, vendors, and industrial laborers.

‡Others: retired, unemployed, and low-income populations.

§Urbanization: level 1 is the most urbanized; level 4 is the least urbanized.

Results

Between 1999 and 2007, 52 089 lung cancer patients and 104 178 subjects in the noncancer comparison group were identified. The mean age of the lung cancer group was 67 years (SD, 12.3 years); 34% of the patients were women (Table 1). The comparison group had an age and sex distribution similar to that of the lung cancer group. The majority of the patients with lung cancer were blue-collar workers and tended to have hypertension, diabetes, coronary artery disease, atrial fibrillation, and/or chronic obstructive pulmonary disease compared with the comparison group.

During a median follow-up duration of 0.7 years for the lung cancer group and 4.1 years for the comparison group, the incidence of stroke was 25.9 per 1000 person–years and 17.4 per 1000 person–years, respectively (Table 2). Patients with lung cancer had a higher incidence of both ischemic and hemorrhagic strokes. In multivariate-adjusted models, the HR of the lung cancer group to the noncancer group was 1.47 (95% CI, 1.39–1.56) for stroke, 1.78 (95% CI, 1.54–2.05) for

Table 2. Hazard Ratios for Stroke Occurrence in Lung Cancer Patients Relative to Comparison Group

	Comparison Group (n=104 178)			Patients With Lung Cancer (n=52 089)			HR (95% CI)	
Strokes	Person-Years at Risk	No. of Events	Incidence per 1000 Person-Years	Person-Years at Risk	No. of Events	Incidence per 1000 Person-Years	Unadjusted	Adjusted
All strokes	468 842	8172	17.43	66 800	1728	25.87	1.42 (1.35–1.50)	1.47 (1.39–1.56)
Hemorrhagic stroke		1093	2.33		272	4.07	1.69 (1.47–1.94)	1.78 (1.54–2.05)
Ischemic stroke		7079	15.10		1456	21.80	1.38 (1.30–1.46)	1.43 (1.34–1.51)

HR indicates hazard ratio; CI, confidence interval.

Models were adjusted for age, level of urbanization, and history of hypertension, diabetes, coronary heart disease, atrial fibrillation, and chronic obstructive pulmonary disease.

hemorrhagic stroke, and 1.43 (95% CI, 1.34–1.51) for ischemic stroke.

During the first year after lung cancer diagnosis, the incidence of ischemic stroke was much higher than that of hemorrhagic stroke in both men (30.3 versus 5.8 per 1000 person–years) and women (27.2 versus 4.0 per 1000 person–years; Table 3). Adjusted HRs for both hemorrhagic and ischemic strokes associated with lung cancer fell over time compared with noncancer subjects. The differences were even greater for hemorrhagic stroke in year 1 for both men and women, as well as in year 2 for women.

Figure shows stratified analyses of the association between lung cancer and the risk of developing stroke within the first year of follow-up at 3-month intervals. Overall, the highest risk of stroke occurred during the first 3 months for men and during 4 to 6 months for women. The HR appreciably increased for ischemic in each of the 4 periods in both sexes, with a greater increase during the first 2 periods (the first 6 months). The elevated risk of occurrence of hemorrhagic stroke decreased after 9 months for men and after 6 months for women.

Table 4 shows that almost all demographic characteristics associated with stroke were statistically significant. All the

Table 3. Hazard Ratios for Stroke Occurrence in Lung Cancer Patients Relative to Comparison Group by Follow-Up Duration

	Comparison Group			Patients With Lung Cancer			
Follow-Up Duration	Person-Years at Risk	n	Incidence per 1000 Person-Years	Person-Years at Risk	n	Incidence per 1000 Person-Years	Adjusted HR (95% CI)
Men							
Hemorrhagic stroke							
Year 0–1	67 095	175	2.6	20 089	116	5.8	2.29 (1.79–2.92)
Year 1–2	59 477	153	2.6	8450	31	3.7	1.35 (0.91–2.02)
Year 2–3	48 754	120	2.5	4440	14	3.2	1.46 (0.83–2.57)
After year 3	130 609	359	2.8	7252	13	1.8	0.66 (0.38–1.15)
Ischemic stroke							
Year 0–1	67 095	1086	16.2	20 089	609	30.3	1.81 (1.63–2.01)
Year 1–2	59 477	1033	17.4	8450	148	17.5	1.06 (0.89–1.26)
Year 2–3	48 754	815	16.7	4440	62	14.0	0.86 (0.66–1.12)
After year 3	130 609	2230	17.1	7252	128	17.7	1.04 (0.87–1.25)
Women							
Hemorrhagic stroke							
Year 0–1	34 840	57	1.6	11 921	48	4.0	2.52 (1.69–3.75)
Year 1–2	31 284	47	1.5	6212	28	4.5	3.53 (2.16–5.77)
Year 2–3	25 766	38	1.5	3377	7	2.1	1.61 (0.70–3.67)
After year 3	71 017	144	2.0	5059	15	3.0	1.39 (0.81–2.41)
Ischemic stroke							
Year 0–1	34 840	400	11.5	11 921	324	27.2	2.35 (2.02–2.74)
Year 1–2	31 284	361	11.5	6212	100	16.1	1.55 (1.23–1.94)
Year 2–3	25 766	292	11.3	3377	31	9.2	0.88 (0.61–1.29)
After year 3	71 017	862	12.1	5059	54	10.7	0.91 (0.69–1.20)

HR indicates hazard ratio; CI, confidence interval.

Models were adjusted for age, level of urbanization, and history of hypertension, diabetes, coronary heart disease, atrial fibrillation, and chronic obstructive pulmonary disease.

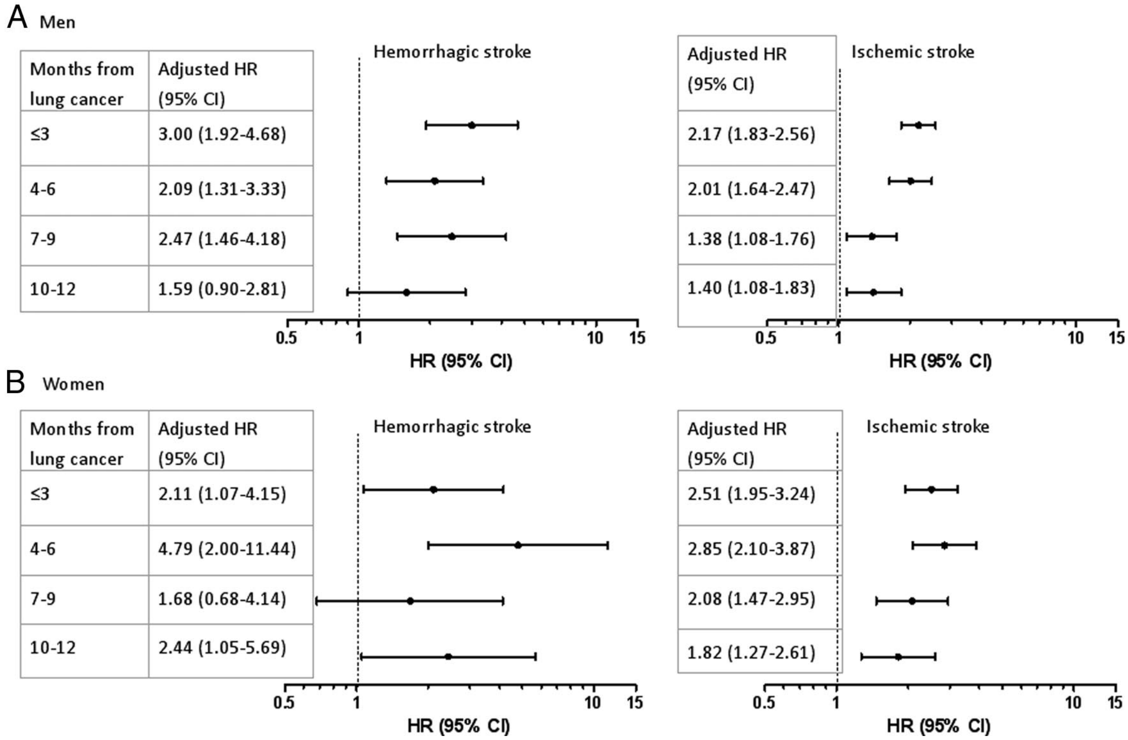

Figure. Adjusted HR (95% CI) of stroke measured for lung cancer patients comparing with noncancer subjects in the first-year follow-up by sex and 3-month intervals controlling for age, urbanization, hypertension, diabetes, coronary heart disease, atrial fibrillation, and chronic obstructive pulmonary disease. **A**, men; **B**, women. HR indicates hazard ratio; CI, confidence interval.

analyzed cerebrovascular incidence factors, including hypertension, diabetes, coronary heart disease, and atrial fibrillation, increased the risk of stroke in lung cancer patients. However, with comorbidity, stroke incidence was not greater for the lung cancer group than for the comparison group.

Discussion

In this population-based cohort study, we found an appreciably increased risk of developing stroke among patients with lung cancer relative to subjects without cancer, and the risk was stronger for hemorrhagic stroke than for ischemic stroke. Excess risk decreased over time, declining beyond 1 year after the diagnosis of lung cancer for men and 2 years after the diagnosis for women.

Previous studies have suggested that the mechanism of stroke may differ between patients with and without cancer, and vary by the type, extent, and stage of the tumors.[5,11,12] A recent Korean multicenter study showed that 60% of stroke events among cancer patients are associated with conventional mechanisms, such as atherosclerotic and cardioembolic causes. The remaining 40% are of the cryptogenic mechanism, likely including cancer-related causes.[11] Only 18% of stroke events in noncancer patients are associated with the cryptogenic mechanism. This discrimination indicates the importance of determining stroke mechanisms for stroke prevention in patients with cancer.[11] The present study also demonstrated a similar relationship.

Tumor-related causes, such as embolism, cerebral metastasis, coagulation disorders, cerebral infections, and therapeutic side-effects, underlie the association between cancer and stroke.[12–14] All of these have been detected in patients with lung cancer.[7,13,14] We observed that the incidence of stroke was higher in the lung cancer group than in the comparison group among patients without conventional stroke risk factors, but not in those with conventional risk factors. This result may support the findings of the Korean study, which suggested that stroke patients with conventional mechanisms may not have cancer-related mechanisms.[11]

The findings in the current study reveal that, relative to noncancer subjects, lung cancer patients have a greater risk of hemorrhagic stroke than of ischemic stroke. An Austrian study involving 1274 stroke patients showed a similar pattern: the proportion of hemorrhagic stroke was almost twice as high in lung cancer patients than in those without cancer (27% versus 14%).[2] They also found that those with lung cancer had the highest incidence of hemorrhagic stroke among all types of cancer.[2] This result is consistent with the current finding, indicating a higher tendency to hemorrhage in lung cancer patients compared with noncancer subjects.

Navi et al have found that tumor-related hemorrhage and coagulopathy are the common etiologic factors of hemorrhagic stroke in cancer patients.[15] Another recent study also reported that, among cancer patients with intracranial hemorrhage, intratumoral hemorrhage and coagulopathy account for 61% and 46% of hemorrhages, respectively.[5] Tumor-related hemorrhaging is most commonly observed in intratumoral hemorrhages associated with brain metastasis in patients with solid cancer.[14,16] Lung tumor is a common cancer with a high tendency to progress to brain metastasis.[13,14,17] The pathophysiological mechanisms of these cerebrovascular complications are likely multifactorial. Tumor cell necrosis, vascular invasion, invasion of the bridging vein, and rupture

Table 4. Risk Factors of Stroke in Lung Cancer Patients and in Subjects in the Comparison Group

	Comparison Group			Lung Cancer Patients		
Risk Factor	No. of Events	Incidence per 1000 Person-Years	Unadjusted HR (95% CI)	No. of Events	Incidence per 1000 Person-Years	Unadjusted HR (95% CI)
Age, y			1.06 (1.06–1.06)			1.03 (1.03–1.04)
Sex						
Women	2201	13.5	1.00	607	22.8	1.00
Men	5971	19.5	1.45 (1.38–1.52)	1121	27.9	1.17 (1.06–1.29)
Occupation						
White collar	2676	13.6	1.00	670	22.8	1.00
Blue collar	3640	18.5	1.36 (1.29–1.43)	810	28.5	1.21 (1.09–1.34)
Others	1856	24.9	1.84 (1.73–1.95)	248	27.5	1.19 (1.03–1.38)
Urbanization*						
1	1911	14.4	1.00	425	21.5	1.00
2	2038	16.0	0.68 (0.64–0.72)	471	24.6	0.73 (0.64–0.83)
3	1410	18.3	0.75 (0.71–0.79)	301	28.7	0.83 (0.73–0.94)
4	2813	21.4	0.86 (0.81–0.91)	531	30.6	0.95 (0.82–1.09)
Medical history						
Hypertension						
No	6464	15.2	1.00	1159	22.7	1.00
Yes	1708	38.8	2.58 (2.44–2.72)	569	36.2	1.58 (1.43–1.75)
Diabetes						
No	7091	16.0	1.00	1453	24.5	1.00
Yes	1081	43.9	2.77 (2.60–2.95)	275	36.4	1.45 (1.27–1.65)
Coronary heart disease						
No	7166	16.2	1.00	1522	24.9	1.00
Yes	1006	38.9	2.42 (2.27–2.59)	206	36.6	1.43 (1.24–1.66)
Atrial fibrillation						
No	7938	17.1	1.00	1666	25.4	1.00
Yes	234	57.5	3.39 (2.97–3.86)	62	55.3	2.07 (1.60–2.66)
COPD						
No	7920	16.8	1.00	1671	25.4	1.00
Yes	252	38.0	2.27 (2.08–2.49)	57	30.4	1.11 (0.96–1.29)

HR indicates hazard ratio; COPD, chronic obstructive pulmonary disease; CI, confidence interval.
*Urbanization: level 1 is the most urbanized; level 4 is the least urbanized.

caused by vessel compression are possible mechanisms implicated in lung cancer patients.[5,15] In addition, neoplastic aneurysm also potentially underlies the intracranial hemorrhage in lung cancer patients.[15]

This is the first study that has observed, after cancer diagnosed among the patients, increased stroke risk is the greatest within the first 6 months, which diminished beyond 1 year for men and 2 years for women. The high stroke risk in the earlier period after lung cancer diagnosed is likely associated with the high fatality of the disease diagnosed in late stage. The risk of brain metastasis may have already occurred, triggered by earlier stroke events.

Limitations to the current study exist, primarily because of the use of an administrative database. The most important limitation is the lack of information on behavioral factors and lifestyle variables in the claims data. Smoking is an important risk factor associated with lung cancer and stroke. We were unable to adjust for the confounding effect of smoking, and this could lead to overestimation of the lung cancer–stroke association. However, sex-stratified analysis shows an appreciably increased risk of stroke associated with lung cancer in women, whereas the smoking rate of women has constantly been only 4.3% in Taiwan.[18] In addition, the stroke risk markedly decreased over time after lung cancer diagnosis. These observations suggest that the confounding effect of smoking cannot fully explain the lung-cancer-related risk of stroke. Second, in lung cancer patients, lung adenocarcinoma occurs more frequently in women than in men, and men are more likely to have squamous cell carcinoma.[19–21] However, information on the histology of lung tumors, laboratory values, and neuroimaging data were unavailable in the claims data. We were unable to determine the histology-specific risk of stroke and the etiology of stroke associated with these factors. Differences in lung cancer histology and other biological factors between men and women play a role in sex differences in stroke risk over time, and warrant additional investigation. Third, to reduce the likelihood of misclassification of a stroke subtype, inpatient claims were used to identify stroke patients. Thus, we were unable to include subjects with stroke who died outside the hospital. Excluding these patients can lead to underestimation of the incidence of stroke. However, sudden death caused by stroke was estimated to be only 5.2% in stroke patients.[22] Even if sudden death from stroke occurs differently between lung cancer patients and the noncancer group, its influence on the estimated HR would not be substantial.

Conclusions

The current study suggests that patients with lung cancer are at an increased risk of subsequent stroke. This risk is at the highest within 6 months after the diagnosis of cancer. Awareness of the stroke risk and prevention of stroke incidents during this period is critical. Additional studies need to be conducted to investigate the risk differences associated with stroke subtypes and risk duration.

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Disclosures

None.

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