Ref.: MS ID#: STROKE/2011/615534 (Revision 2)

Title: Lung cancer and incidence of stroke: A population-based cohort study

Cover title: Lung cancer and incidence of stroke

Pei-Chun Chen, PhD; Chih-Hsin Muo, MS; Yuan-Teh Lee, M.D., Ph.D.; Yang-Hao Yu, MD;

Fung-Chang Sung, PhD

From the Department of Public Health (PCC, FCS); Divisions of Cardiovascular Medicine and

General Medicine; Department of Internal Medicine (YTL), Divisions of Pulmonary and

Critical Care Medicine (YHY); and Management Office for Health Data (PCC, CHM, FCS),

China Medical University and Hospital, Taichung 404, Taiwan.

Correspondence and reprints:
Fung-Chang Sung, PhD, MPH
Professor and Deputy Superintendent
China Medical University and Hospital
91 Hsueh Shih Road
Taichung 404, Taiwan
Tel: 886-4-2206-2295
Fax: 886-4-2201-9901
E-mail: fcsung@mail.cmu.edu.tw; eliz0118@gmail.com

Word count: 240 in abstract; 4084 in manuscript.

Abstract

Background and purpose--Stroke is a known cerebrovascular complication in lung cancer patients; however, whether or not lung cancer patients are at an elevated risk of developing stroke relative to the non-cancer population remains unclear.

Methods--The present study used population-based claims data from Taiwan National Health Insurance, which identified 52,089 patients with an initial diagnosis of lung cancer between 1999–2007 and 104,178 matched non-cancer subjects from all insured subjects aged 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 vs. 17.4 per 1000 person-years) in the lung cancer group compared with the comparison group. The multivariable-adjusted hazard ratio comparing lung cancer patients with the non-cancer group was 1.47 (95% confidence interval [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 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 4–6 months for women.

Conclusions-- Lung cancer is associated with an increased risk of subsequent stroke within 1

year after diagnosis for men and 2 years after diagnosis for women.

Key words: epidemiology [8]; lung cancer; cerebrovascular disease/stroke [13].

Cancer and stroke are among the three 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] The median survival after concurrence of the two diseases is estimated to be no longer than 4.5 months.[4,5]

The type of cancer is one of the most important clues for determining stroke etiology in cancer patients.[6] In studies analyzing a neurologic database from a cancer center, lung cancer was the most common cancer, occurring in 30% of patients with ischemic stroke[4] and 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 or not lung cancer is associated with an 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 the 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

The 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 one of 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 National Health Insurance to ensure accuracy. Personal identification information was encrypted before the release of the research database to protect patient privacy.

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 sub-dataset 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 aged 20 years and older with an initial lung cancer diagnosis between 1999

and 2007 were selected. The date during 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 non-cancer comparison group was randomly selected from all NHI beneficiaries aged 20 years and older and 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 prior to 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 primary 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 non-cancer comparison controls were presented using the total number (proportion) for categorical variables and the mean (standard deviation) for continuous variables. The level of urbanization was based on the 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), proportions of higher education, elderly and agricultural population, and the number of physicians per 10^5 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% confidence intervals (CIs) were calculated using Cox proportional hazard models with the non-cancer comparison group as the reference group to assess the association between lung cancer and the risk of developing a stroke. Potential confounding factors were listed based on established risk factors and an assessment of whether or not these variables were substantially associated with lung cancer and stroke in descriptive analyses was made. The effect of these variables on the lung cancer-stroke relationship was also evaluated by comparing crude and adjusted associations, and selecting those yielding more than a 10% change in HRs for inclusion into the final models. The follow-up period was partitioned into four segments (year >0 to 1, >1 to 2, >2 to 3, and

>3 years), and the Cox proportional hazard regression analyses were repeated to investigate whether or not the association between lung cancer and stroke risk differed over time. The first follow-up year was further stratified into four periods, namely, 0 to 3, 4 to 6, 7 to 9, and 10 to 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, the 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 lung cancer. All analyses were performed using SAS version 9.1 (SAS Institute Inc., Cary, NC) and STATA SE 11 (Stata Corp, College Station, TX). All statistical tests were two-sided.

Results

Between 1999 and 2007, 52,089 lung cancer patients and 104,178 subjects in the non-cancer comparison group were identified. The mean age of the lung cancer group was 67 years (standard deviation, 12.3 years); 34% were women (Table 1). The comparison group had an age and sex distribution similar to 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 multivariable-adjusted models, the HR of the lung cancer group to the non-cancer 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.

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** vs. 5.8 per 1000 person-years) and women (27.2 vs. 4.0 per 1000 person-years) (Table 3). The adjusted HRs for both hemorrhagic and ischemic strokes associated with lung cancer fell over time compared with non-cancer 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 1 shows the 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 4–6 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 and 6 months for men and women, respectively.

Table 4 shows that almost all demographic characteristics associated with stroke were statistically significant. All the analyzed cerebrovascular risk factors, including hypertension, diabetes, coronary heart disease, and atrial fibrillation, increased the risk of stroke in lung cancer patients. However, with comorbidity, the stroke risk 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. The 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 multi-center 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 the stroke events in non-cancer patients are associated with the cryptogenic mechanism. This discrimination indicates the importance of determining the 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 non-cancer subjects, lung cancer patients have a greater risk of hemorrhagic stroke than 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% vs. 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 non-cancer 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 due to 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 observed, after the cancer diagnosed among patients, the 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 triggering off the earlier stroke events.

Limitations to the current study exist, primarily due to 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 female adults 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, warrant further 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 non-cancer group, its influence on the estimated HR would not be substantial.

Summary

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. Further studies need to be conducted to investigate the risk differences associated with stroke subtypes and risk duration.

Source of funding: The current study was supported in part by the National Sciences Council, Executive Yuan (Grant No. NSC 99-2621-M-039-001), China Medical University Hospital (Grant Nos. DMR-99-119 and 1MS1), Taiwan Department of Health Clinical Trial and Research Center of Excellence (No. DOH100-TD-B-111-004), and the Cancer Research Center of Excellence (No. DOH100-TD-C-111-005).

Conflicts of Interest: None.

References

1. Graus F, Rogers LR, Posner JB. Cerebrovascular complications in patients with cancer. Medicine (Baltimore). 1985; 64:16–35.

2. Oberndorfer S, Nussgruber V, Berger O, Lahrmann H, Grisold W. Stroke in cancer patients: a risk factor analysis. J Neurooncol. 2009; 94:221–226.

3. Zhang YY, Chan DKY, Cordato D, Sheng AZ. Stroke risk factor, pattern and outcome in patients with cancer. Acta Neurol Scand. 2006; 114:378–383.

4. Cestari DM, Weine DM, Panageas KS, Segal AZ, DeAngelis LM. Stroke in patients with cancer: incidence and aetiology. Neurology. 2004; 64:2025–2030.

5. Navi BB, Reichman JS, Berlin D, Reiner AS, Panageas KS, Segal AZ et al. Intracerebral and subarachnoid hemorrhage in patients with cancer. Neurology. 2010; 74:494–501.

6. Rogers LR. Cerebrovascular complications in cancer patients. Oncology (Williston Park). 1994; 8:23–30.

7. Lim BR, Henry DH. Stroke syndrome secondary to hypercoagulability of lung cancer. Commun Oncol. 2008; 5:595–596.

8. Lu JF, Hsiao WC. Does universal health insurance make health care unaffordable? Lessons from Taiwan. Health Aff. 2003; 22:77–88.

9. NHI profile (updated 2009.06.05). Available at http://www.nhi.gov.tw/webdata/AttachFiles/Attach_13787_1_NationalHealthInsuranc

einTaiwan2009.pdf. Accessed January 26, 2011.

10. Liu CY, Hung YT, Chuang YL, Chen YJ, Weng WS, Liu JS et al. Incorporating development stratification of Taiwan townships into sampling design of large scale health interview survey. J Health Manag. 2006; 14 :1 –22.
11. Kim SG, Hong JM, Kim HY, Lee J, Chung PW, Park KY et al. Ischemic stroke in cancer patients with and without conventional mechanisms: a multicenter study in Korea. Stroke. 2010; 41:798–801.
12. Seok JM, Kim SG, Kim JW, Chung CS, Kim GM, Lee KH et al. Coagulopathy and embolic signal in cancer patients with ischemic stroke. Ann Neurol. 2010; 68:213–219.
13. Grisold W, Oberndorfer S, Struhal W. Stroke and cancer: a review. Acta Neurol Scand. 2009; 119:1–16.
14. Rogers LR. Cerebrovascular complications in cancer patients. Neurol Clin. 2003; 21:167–192.
15. Navi BB, Segal AZ. Cancer and Stroke. In: Geyer JD, Gomez CR, eds. Stroke: A Practical Approach. 1st Ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008: 48–55.
16. Ogawa R, Tanaka K, Satoh H, Sekizawa K. Intra-tumor hemorrhage associated with brainstem metastasis from lung cancer. Intern Med. 2006; 45:487–488.
17. Mandybur TI. Intracranial hemorrhage caused by metastatic tumors. Neurology. 1977;27:650-655.

18. Wen CP, Levy DT, Cheng TY, Hsu CC, Tsai SP. Smoking behaviour in Taiwan, 2001. Tobacco Control. 2005; 14(Suppl I):i51–i55.

19. Olak J, Colson Y. Gender differences in lung cancer: Have we really come a long way, baby? J Thorac Cardiovasc Surg. 2004; 128:346–351.

20. Wisnivesky JP, Halm EA. Sex differences in lung cancer survival: do tumors behave differently in elderly women? J Clin Oncol. 2007; 25:1705–1712.

21. **Cancer Registry Annual Report, 2007 Taiwan. 2011. Available at http://www.bhp.doh.gov.tw/bhpnet/portal/StatisticsShow.aspx?No=200911300001. Assessed June 3, 2011.**

22. Phillips LH, Whisnant JP, Reagan TJ. Sudden death from stroke. Stroke. 1977; 8:392–395.

Table 1. Demographic characteristics and comorbidities of lung cancer patients and subjects in the comparison cohort

	Patients with lung cancer (N=52,089)		Comparison cohort (N=104,178)		
	n	(%)	n	(%)	*p* value
Age, years*	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	8,487	(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	6,632	(12.7)	7,199	(6.9)	<0.001
Coronary heart disease	5,100	(9.8)	7,387	(7.1)	<0.001
Atrial fibrillation	1,212	(2.3)	1,391	(1.3)	<0.001
COPD	7,140	(13.7)	4,127	(4.0)	<0.001

*Values are means and standard deviations.

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.

COPD, chronic obstructive pulmonary disease.

Table 2. Hazard ratios for stroke occurrence relative to lung cancer

	Comparison group (N=104,178)			Patients with lung cancer (N=52,089)			Hazard ratio (95% confidence interval)	
	Person-years at risk	No. of events	Incidence, per1,000 person-years	Person-years at risk	No. of events	Incidence, per 1,000 person-years	Unadjusted	Adjusted
All strokes	468,842	8,172	17.43	66,800	1,728	25.87	1.42 (1.35-1.50)	1.47 (1.39-1.56)
Hemorrhagic stroke		1,093	2.33		272	4.07	1.69 (1.47-1.94)	1.78 (1.54-2.05)
Ischemic stroke		7,079	15.10		1,456	21.80	1.38 (1.30-1.46)	1.43 (1.34-1.51)

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

Table 3. Hazard ratios for stroke occurrence relative to lung cancer by follow-up duration

	Comparison group			Patients with lung cancer			
	Person-years at risk	n	Incidence rate*	Person-years at risk	n	Incidence rate*	Adjusted hazard ratio (95% confidence interval)
Men							
Hemorrhagic stroke							
Follow-up duration							
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	8,450	31	3.7	1.35 (0.91-2.02)
Year 2-3	48,754	120	2.5	4,440	14	3.2	1.46 (0.83-2.57)
After year 3	130,609	359	2.8	7,252	13	1.8	0.66 (0.38-1.15)
Ischemic stroke							
Follow-up duration							
Year 0-1	67,095	1,086	16.2	20,089	609	30.3	1.81 (1.63-2.01)
Year 1-2	59,477	1,033	17.4	8,450	148	17.5	1.06 (0.89-1.26)
Year 2-3	48,754	815	16.7	4,440	62	14.0	0.86 (0.66-1.12)
After year 3	130,609	2,230	17.1	7,252	128	17.7	1.04 (0.87-1.25)
Women							
Hemorrhagic stroke							
Follow-up duration							
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	6,212	28	4.5	3.53 (2.16-5.77)
Year 2-3	25,766	38	1.5	3,377	7	2.1	1.61 (0.70-3.67)

After year 3	71,017	144	2.0	5,059	15	3.0	1.39 (0.81-2.41)
Ischemic stroke							
Follow-up duration							
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	6,212	100	16.1	1.55 (1.23-1.94)
Year 2-3	25,766	292	11.3	3,377	31	9.2	0.88 (0.61-1.29)
After year 3	71,017	862	12.1	5,059	54	10.7	0.91 (0.69-1.20)

*Per 1000 person-years.

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

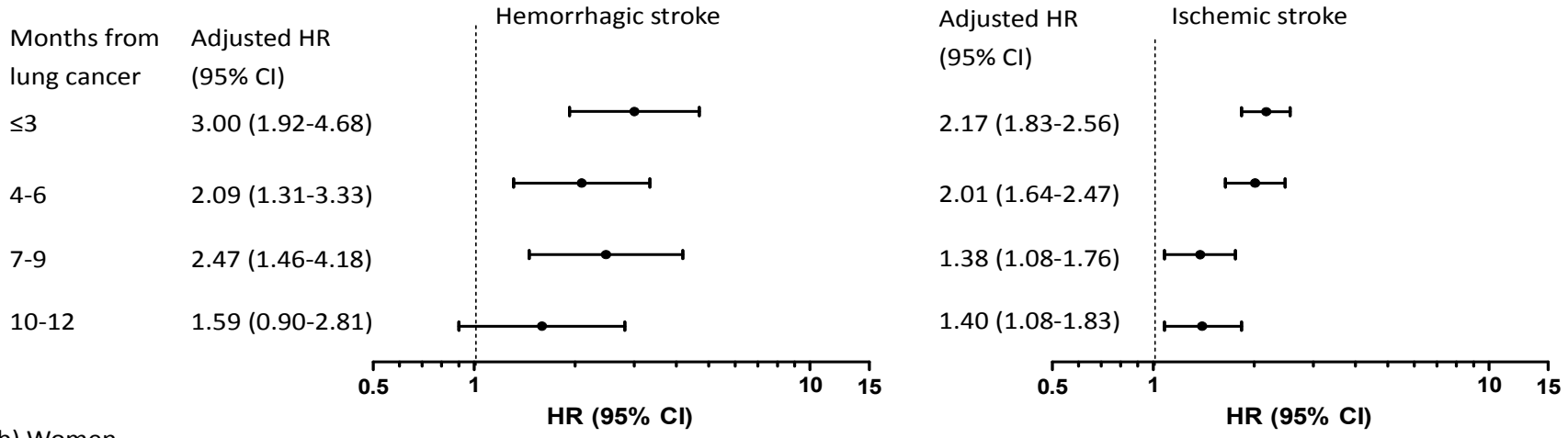
Table 4. Risk factors of stroke in lung cancer patients and in subjects in the comparison group

	Comparison group			Lung cancer patients		
	No. of events	Incidence, per1,000 person-years	Unadjusted hazard ratio (95% CI)	No. of events	Incidence, per1,000 person-years	Unadjusted hazard ratio (95% CI)
Age, per year			1.06 (1.06-1.06)			1.03 (1.03-1.04)
Sex						
Women	2,201	13.5	1.00	607	22.8	1.00
Men	5,971	19.5	1.45 (1.38-1.52)	1,121	27.9	1.17 (1.06-1.29)
Occupation						
White collar	2,676	13.6	1.00	670	22.8	1.00
Blue collar	3,640	18.5	1.36 (1.29-1.43)	810	28.5	1.21 (1.09-1.34)
Others	1,856	24.9	1.84 (1.73-1.95)	248	27.5	1.19 (1.03-1.38)
Urbanization						
1	1,911	14.4	1.00	425	21.5	1.00
2	2,038	16.0	0.68 (0.64-0.72)	471	24.6	0.73 (0.64-0.83)
3	1,410	18.3	0.75 (0.71-0.79)	301	28.7	0.83 (0.73-0.94)
4	2,813	21.4	0.86 (0.81-0.91)	531	30.6	0.95 (0.82-1.09)
Medical history						
Hypertension						
No	6,464	15.2	1.00	1,159	22.7	1.00
Yes	1,708	38.8	2.58 (2.44-2.72)	569	36.2	1.58 (1.43-1.75)
Diabetes						
No	7,091	16.0	1.00	1,453	24.5	1.00
Yes	1,081	43.9	2.77 (2.60-2.95)	275	36.4	1.45 (1.27-1.65)
Coronary heart Disease						
No	7,166	16.2	1.00	1,522	24.9	1.00
Yes	1,006	38.9	2.42 (2.27-2.59)	206	36.6	1.43 (1.24-1.66)
Atrial fibrillation						
No	7,938	17.1	1.00	1,666	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	7,920	16.8	1.00	1,671	25.4	1.00
Yes	252	38.0	2.27 (2.08-2.49)	57	30.4	1.11 (0.96-1.29)

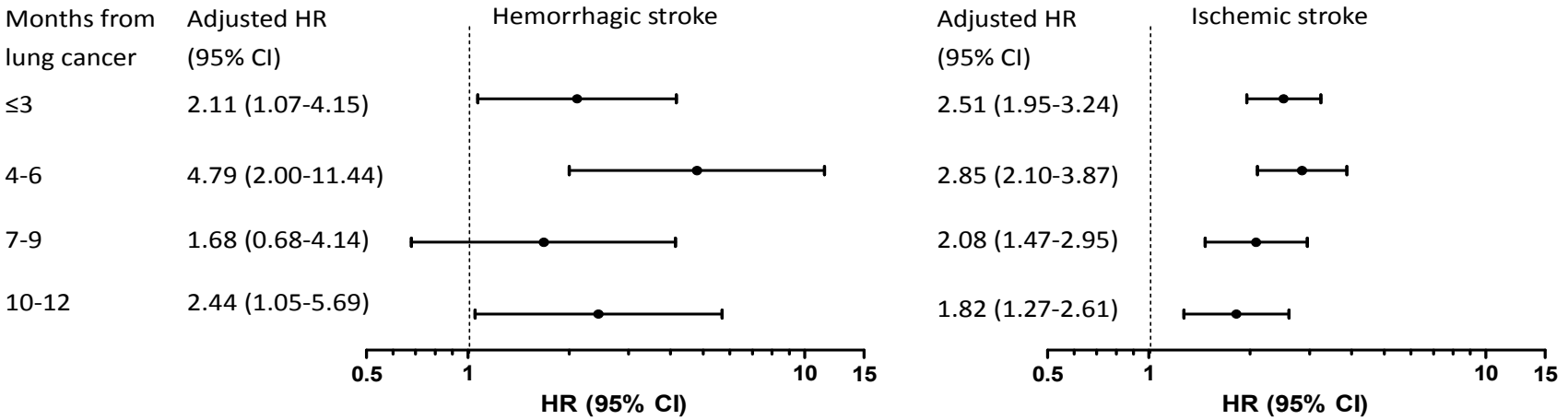
CI, confidence interval; COPD, chronic obstructive pulmonary disease

Figure 1. Adjusted HR (95% CI) of stroke measured for lung cancer patients comparing with non-cancer 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


Months from lung cancer
Adjusted HR (95% CI)
Hemorrhagic stroke
≤3
3.00 (1.92-4.68)
4-6
2.09 (1.31-3.33)
7-9
2.47 (1.46-4.18)
10-12
1.59 (0.90-2.81)
0.5
1
10
15
HR (95% CI)
Adjusted HR (95% CI)
Ischemic stroke
2.17 (1.83-2.56)
2.01 (1.64-2.47)
1.38 (1.08-1.76)
1.40 (1.08-1.83)
0.5
1
10
15
HR (95% CI)

(b) Women


Months from lung cancer
Adjusted HR (95% CI)
Hemorrhagic stroke
≤3
2.11 (1.07-4.15)
4-6
4.79 (2.00-11.44)
7-9
1.68 (0.68-4.14)
10-12
2.44 (1.05-5.69)
0.5
1
10
15
HR (95% CI)
Adjusted HR (95% CI)
Ischemic stroke
2.51 (1.95-3.24)
2.85 (2.10-3.87)
2.08 (1.47-2.95)
1.82 (1.27-2.61)
0.5
1
10
15
HR (95% CI)