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Factors leading to the risk of stroke mortality: a cross-sectional study with lung cancer patient-based large sample

Lei Chen[a,*], Xinmin Zhao[b] and Sheng Wang[c,*]

To identify the risk factors for stroke mortality among lung cancer patients on the basis of the *Surveillance, Epidemiology, and End Results* (*SEER*) database. The clinical data of lung cancer patients diagnosed between 2004 and 2016 were collected in the *SEER* database. The stroke mortality of lung cancer patients was compared with the general population using standardized mortality ratios (SMRs). COX proportional hazard model was applied to analyze the risk factors for stroke mortality among lung cancer patients. Among 82 454 patients, 4821 (5.85%) died of stroke. The stroke mortality rate in lung cancer patients significantly increased compared with the general population [SMR: 1.73, 95% confidential interval (95% CI), 1.69–1.78]. Differences were pronounced between the patients with stroke death and those without regarding all the basic characteristics ($P<0.001$). Multivariate COX analysis showed that the risk factors for stroke mortality among lung cancer patients included increasing age, males, the black, grade II–III, distant metastasis and higher American Joint Committee on Cancer (AJCC) TNM stage, whereas adenocarcinoma was found to be a protective factor compared with squamous cell carcinoma. Increasing age, males, the black, grade II–III, distant metastasis and higher TNM stage are associated with an increased risk of stroke mortality among lung cancer patients, but adenocarcinoma with a lowered risk. *European Journal of Cancer Prevention* 31: 14–18 Copyright © 2021 The Author(s). Published by Wolters Kluwer Health, Inc.

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Department of [a]Respiratory Medicine, [b]Neurology, Ningbo First Hospital, Ningbo Hospital of Zhejiang University, Ningbo, Zhejiang and [c]Shenzhen Mental Health Center, Shenzhen Key Laboratory of Mental Health, Shenzhen Kangning Hospital, Shenzhen, China

Correspondence to Lei Chen, BSc, Department of Respiratory Medicine, Ningbo First Hospital, Ningbo Hospital of Zhejiang University, No. 59 Liuting Street, Haishu District, Ningbo 315010, Zhejiang, China
Tel: +86 13957832969; e-mail: chenldoc0824@outlook.com

*Lei Chen and Sheng Wang are co-corresponding authors.

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Introduction

Over the past decade, the development of lung cancer in epidemiology and its prevention have proceeded to some extent due to changes in cancer control, treatment options and understanding of the genetics. Despite these advances, lung cancer continues to be the leading cause of cancer death worldwide (Bade and Dela Cruz 2020). In 2018, 2.09 million new cases of lung cancer and 1.76 million deaths were estimated by GLOBOCAN, higher than that reported in
2012, 1.8 million new cases and 1.6 million deaths (Torre *et al.* 2015; Bray *et al.* 2018). Epidemiologic data show that various factors, such as tobacco use, radiation exposure, indoor and outdoor air pollution, hereditary susceptibility and unhealthy diet, contribute to increasing lung cancer incidence (Mao *et al.* 2016). Although treatment options, outcomes and disease understanding for lung cancer are improving, the survival remains low.

Cerebrovascular disease is thought to be the second most common central nervous system complication in cancer patients (Chen *et al.* 2011). Once stroke occurs in cancer patients, the patients' neurological outcomes will deteriorate significantly, and the prognosis tends to be poor (Zhang *et al.* 2006; Stefan *et al.* 2009). The study showed that cancer patients were prone to develop stroke, particularly within 1 year of cancer proliferation (Selvik *et al.* 2015). Cancer induces stroke possibly through several mechanisms, including nonbacterial thrombotic endocarditis, hypercoagulability, direct tumor compression of blood vessels and therapies (Dearborn *et al.* 2014). By evaluating the incidence of stroke in cancer patients, Cestari *et al.* (2004). found that lung cancer was the most common primary tumor, accounting for 30% of cases.. There is another study showing an association of lung cancer with a higher risk of subsequent stroke, especially within 6 months after cancer diagnosis (Chen *et al.* 2011).

Until now, the studies on the risk factors for stroke mortality in cancer patients are rare. This study was performed to identify the risk factors for stroke mortality among lung cancer patients based on the *Surveillance, Epidemiology, and End Results* (*SEER*) database, aiming at early prevention and treatment of patients at high risk of stroke to improve the prognosis.

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Methods

Data sources

Patients were collected from the *SEER* program, a network of population-based cancer registries in the United States. It provides information on cancer statistics, including incidence, survival and surgical treatment, aiming at decreasing the cancer burden among the US population (National Cancer Institute XXXX). The data accessed from the *SEER* database include patients' demographic characteristics, primary tumor site, stage at diagnosis, tumor morphology, first cancer treatment and follow-up for vital status. The *SEER* 18 registry system that covers approximately 27.8% of all American population consists of 18 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterey, Los Angeles, Alaska Native Registry, Rural Georgia, California excluding SF/SJM/LA, Kentucky, Louisiana, New Jersey and Georgia excluding ATL/RG). Information was recorded including age at diagnosis, sex, race, laterality, histology, year of diagnosis, grade, SEER stage, American Joint Committee on Cancer (AJCC) T, N, M, as well as tumor size.

The approval from the Institutional Review Board of Ningbo First Hospital was not required because the data obtained from the *SEER* database were freely available.

Study population and study parameters

All patients with lung cancer diagnosis were involved. The diagnosis of lung cancer was confirmed through the International Classification of Diseases-Oncology 3 (ICD-O-3) site codes C34.0-C34.9. Inclusion criteria: (1) lung cancer diagnosed between 2004 and 2016; (2) age ≥40 years and (3) primary site codes C34.0-C34.9. Exclusion criteria: (1) ICD-O-3 histological codes 9050–9055, 9140 and 9590–9992; (2) patients only diagnosed by autopsy or death certificates and (3) incomplete information. Cases aged <40 years were excluded due to the low incidence of lung cancer in this age group (available at *http://ghdx.healthdata.org/gbd-results-tool*).

The information below was acquired from the *SEER* database, including age at diagnosis (40–49, 50–59, 60–69, 70–79 and ≥80 years), sex, race (white, black and others), laterality (unilateral and bilateral), histological types (squamous cell, small cell, adenocarcinoma and other nonsmall cell lung cancer), year of diagnosis (2004–2006, 2007–2009, 2010–2012 and 2013–2015), *SEER* stage (local, regional and distant), AJCC T, N and M as well as tumor size (<5 and ≥5 cm).

According to death certificates, mortality codes in the *SEER* database were assigned. Generally, the diagnosis of stroke was made as central nervous system infarction due to ischemia on the basis of clinical evidence of permanent injury or neuroimaging and neuropathological evidence. In our study, however, patients were thought to die of stroke when the following death certificates existed, including cerebrovascular accident, ICD-9 code 434.11, or ICD-10 code I63.9. *SEER* data for stroke as the cause of death were collected as the primary endpoint.

Statistical analysis

Data were analyzed using R software (The R Foundation for Statistical Computing, Vienna, Austria). Enumeration data were compared by the χ^2 test or Fisher's exact test and manifested with *N* (%). The stroke mortality of lung cancer patients in the *SEER* database was compared with that of the US general population using standardized mortality ratios (SMRs). SMRs were defined as the ratio of total number of the observed death cases/total number of the expected death cases (The source of calculation was available at *https://seer.cancer.gov/stdpopulations/stdpop.singleages.html*.). COX proportional hazard model was used to analyze the risk factors for stroke mortality among lung cancer patients. $P < 0.05$ was considered statistically significant.

Results

Characteristics of study population

There were 147 256 lung cancer patients aged ≥40 years and diagnosed between 2004 and 2016. Their ICD-O-3 site codes were C34.0-C34.9. After ICD-O-3 histological codes 9050–9055, 9140 and 9590–9992 were excluded, 132 793 cases were left. Finally, 82 454 cases were included into the study when autopsy or death certificate cases and those with incomplete information, such as survival months, SEER stage, tumor size, AJCC T, N and M, were excluded. Among these patients included, 4821 cases (5.85%) died of stroke, whereas 77 633 did not. The characteristics of included patients were shown in Table 1.

As shown in Table 1, the stroke mortality rate in lung cancer patients significantly increased compared with the US general population [SMR: 1.73; 95% confidential interval (95% CI), 1.69–1.78]. All subgroup analyses exhibited the stroke mortality rate in lung cancer patients was higher than that in the general population. The stroke mortality rates were different among different age groups. The SMR was up to 3.58 in patients aged 40–49 years (95% CI, 3.03–4.20). Between the patients who died of stroke and those without, the differences were pronounced in all basic characteristics ($P < 0.001$), including age, sex, laterality, race, histological types, year of diagnosis, SEER stage, AJCC T, N and M, as well as tumor size.

Analysis of the risk factors for stroke mortality among lung cancer patients

The influencing factors for stroke mortality among lung cancer patients were analyzed using the COX proportional hazard model, as shown in Table 2. The results showed that compared with those aged 40–49 years, the patients aged 50–59 years (hazard ratio, 1.809; 95% CI, 1.209–2.707), 60–69 years (hazard ratio, 3.534; 95% CI, 2.410–5.181), 70–79 years (hazard ratio, 9.96; 95% CI, 6.826–14.534) and ≥80 years (hazard ratio, 27.196; 95%

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Table 1 Characteristics of included patients and standardized mortality ratios of stroke, *n*(%)

Variables	Total cases	Stroke cases	Nonstroke cases	*P* value	SMRs	95% CI
Total	82454	4821	77633		1.73	1.69–1.78
Age, years				<0.001		
40–49	3641 (4.42)	150 (3.11)	3491 (4.50)		3.58	3.03–4.20
50–59	14619 (17.73)	723 (15.00)	13896 (17.90)		2.35	2.18–2.53
60–69	25695 (31.16)	1688 (35.01)	24007 (30.92)		1.84	1.76–1.93
70–79	25098 (30.44)	1659 (34.41)	23439 (30.19)		1.55	1.48–1.63
≥80	13401 (16.25)	601 (12.47)	12800 (16.49)		1.35	1.25–1.47
Sex				0.001		
Female	40170 (48.72)	2387 (49.51)	37783 (48.67)		1.93	1.85–2.01
Male	42284 (51.28)	2434 (50.49)	39850 (51.33)		1.58	1.52–1.64
Race				<0.001		
White	63722 (77.28)	3925 (81.42)	59797 (77.03)		1.74	1.68–1.79
Black	10501 (12.74)	538 (11.16)	9963 (12.83)		1.75	1.60–1.90
Others	8076 (9.79)	358 (7.43)	7718 (9.94)		1.74	1.57–1.93
Laterality				<0.001		
Unliteral	81503 (98.84)	4801 (99.59)	76702 (98.80)		1.74	1.69–1.79
Bilateral	951 (1.16)	20 (0.42)	931 (1.20)		1.12	1.73–18.83
Histology				<0.001		
Squamous cell carcinoma	18132 (21.99)	1271 (26.36)	16816 (21.66)		1.85	1.75–1.95
Small cell lung cancer	8999 (10.91)	215 (4.46)	8784 (11.31)		1.24	1.08–1.41
Adenocarcinoma	37994 (46.08)	2628 (54.51)	35366 (45.56)		1.81	1.74–1.88
Other NSCLCs	17329 (21.02)	707 (14.67)	16622 (21.41)		1.51	1.40–1.63
Year of diagnosis				<0.001		
2004–2006	14895 (18.07)	1137 (23.58)	13758 17.72)		1.62	1.53–1.72
2007–2009	20937 (25.39)	1553 (32.21)	19384 (24.97)		1.80	1.71–1.89
2010–2012	22509 (27.30)	1314 (27.26)	21195 (27.30)		1.78	1.69–1.88
2013–2015	24113 (29.24)	817 (16.95)	23296 (30.00)		1.71	1.60–1.83
SEER stage				<0.001		
Local	18108 (21.96)	2196 (45.55)	15912 (20.50)		1.95	1.87–2.03
Regional	23209 (28.14)	1863 (38.64)	21346 (27.50)		1.87	1.79–1.96
Distant	41137 (49.89)	762 (15.81)	40375 (52.01)		1.16	1.08–1.24
AJCC T				<0.001		
T1	21304 (25.84)	2020 (41.67)	19284 (24.84)		1.91	1.83–2.00
T2	29153(35.36)	1873 (38.85)	27280 (35.14)		1.74	1.67–1.83
T3	4833 (5.86)	208 (4.31)	4625 (5.96)		1.63	1.42–1.87
T4	27164 (32.94)	720 (14.93)	26444 (34.06)		1.39	1.29–1.50
AJCC N				<0.001		
N0	34562 (41.92)	3303 (68.51)	31259 (40.26)		1.92	1.86–1.99
N1	7784 (9.44)	459 (9.52)	7325 (9.44)		1.72	1.57–1.89
N2	28124 (34.11)	825 (17.11)	27299 (35.16)		1.38	1.29–1.48
N3	9926 (12.04)	192 (3.98)	9734 (12.54)		1.21	1.05–1.40
NX	2058 (2.50)	42 (0.87)	2016 (2.59)		1.06	0.76–1.43
AJCC M				<0.001		
M0	47982 (58.19)	4242 (87.99)	43740 (56.34)		1.87	1.81–1.92
M1	33413 (40.52)	542 (11.24)	32871 (42.34)		1.13	1.04–1.23
MX	1059 (1.28)	37 (0.77)	1022 (1.32)		1.22	0.86–1.68
Tumor size, cm				<0.001		
<5	57822 (70.13)	3964 (82.22)	53858 (69.37)		1.77	1.71–1.82
≥5	27314 (33.13)	998 (120.70)	26316 (30.63)		1.64	1.54–1.74

AJCC, American Joint Committee on Cancer; CI, confidential interval; NSCLC, nonsmall cell lung cancer; SEER, surveillance, epidemiology, and end results; SMRs, standardized mortality ratios.

CI, 18.579–39.811) had a significantly increased risk of stroke mortality; the risk of stroke mortality in males was higher than that in females (hazard ratio, 1.177; 95% CI, 1.082–1.282); the black people had an increased risk of stroke mortality than the white people (hazard ratio, 1.37; 95% CI, 1.198–1.567); the risk of stroke mortality in patients with adenocarcinoma was lower than those with squamous cell carcinoma (hazard ratio, 0.843; 95% CI, 0.754–0.942); patients with grade II (hazard ratio, 1.237; 95% CI, 1.046–1.461) and III (hazard ratio, 1.494; 95% CI, 1.260–1.772) had a higher risk of stroke mortality by comparison to grade I; the risk of stroke mortality in patient with distant metastasis was greater than those with local metastasis (hazard ratio, 1.422; 95% CI, 1.13–1.789). Additionally, compared with T1, N0 and M0 patients, those with T2-T4, N2-NX and D M1-MX, had a higher risk of stroke mortality; see Table 2.

Discussion

In this population-based cohort study, 82454 out of 147256 lung cancer patients were eligible, among whom 4821 cases died of stroke. It can be observed that the risk of stroke mortality in lung cancer patients significantly increased compared with the general population. Multivariate analysis exhibited that increasing age, males, the black, grade II–III, distant metastasis and higher TNM stage were associated with a greater risk of stroke mortality among lung cancer patients, but adenocarcinoma was related to a reduced risk of stroke mortality.

At present, the death of most cancer patients results from noncancer causes (Zaorsky *et al.* 2017). Our results suggested that the stroke mortality rate of lung cancer patients was significantly higher than that in the general population, which might be attributed to the fact that

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Table 2 Analysis of the risk factors for stroke mortality among lung cancer patients

	Cox proportional hazard model	
Variables	Hazard ratio	95% CI
Age, years		
40–49	–	–
50–59	1.809	1.209–2.707
60–69	3.534	2.41–5.181
70–79	9.96	6.826–14.534
≥80	27.196	18.579–39.811
Sex		
Female	–	–
Male	1.177	1.082–1.282
Race		
White	–	–
Black	1.37	1.198–1.567
Others	0.701	0.586–0.839
Laterality		
Unliteral	–	–
Bilateral	0.711	0.366–1.378
Histology		
Squamous cell carcinoma	–	–
Small cell lung cancer	1.226	0.995–1.512
Adenocarcinoma	0.843	0.754–0.942
Other NSCLCs	1.241	1.089–1.414
Year of diagnosis		
2004–2006	–	–
2007–2009	0.629	0.564–0.703
2010–2012	0.323	0.286–0.365
2013–2015	0.133	0.116–0.154
Grade		
I	–	–
II	1.237	1.046–1.461
III	1.494	1.26–1.772
IV	1.167	0.848–1.606
Unknown	1.958	1.653–2.319
SEER stage		
Local	–	–
Regional	0.944	0.82–1.085
Distant	1.422	1.13–1.789
AJCC T		
T1	–	–
T2	1.131	1.008–1.268
T3	1.356	1.064–1.729
T4	1.469	1.263–1.708
AJCC N		
N0	–	–
N1	1.148	0.966–1.364
N2	1.508	1.321–1.722
N3	1.675	1.352–2.076
NX	1.663	1.225–2.258
AJCC M		
M0	–	–
M1	1.67	1.376–2.028
MX	1.466	1.026–2.097
Tumor size, cm		
<5	–	–
≥5	1.036	0.92–1.165

AJCC, American Joint Committee on Cancer; CI, confidential interval; NSCLC, nonsmall cell lung cancer; SEER, surveillance, epidemiology, and end results.

cancer increased the risk of stroke (Wei *et al.* 2019). There are different mechanisms of stroke between cancer and noncancer patients. A multicenter study in Korea indicated that conventional mechanisms, such as atherosclerotic and cardioembolic causes, may be related to 60% of stroke events in cancer patients; cryptogenic mechanisms, such as cancer-related causes, were associated with the remaining 40%, but only with 18% of stroke events in noncancer patients (Kim *et al.* 2010; Chen *et al.* 2011). In most studies, the association of stroke with cancer is highlighted by tumor-related causes, including coagulation disorders, embolism, brain infection and metastasis, as well as treatment-induced adverse reactions (Seok *et al.* 2010; Bang *et al.* 2011; Dardiotis *et al.* 2019). All these have been clearly embodied in lung cancer patients (Selvik *et al.* 2015; Xie *et al.* 2016; Yoon *et al.* 2019).

In this study, it was found that the increased age was a significant risk factor for stroke mortality, supported by a previous study that the prevalence of any kinds of vascular diseases increased distinctly with advanced age (Savji *et al.* 2013). Compared with women, men showed a greater risk of stroke mortality. A nationwide population-based survey reported that the age-specific mortality rate of stroke in males aged ≥60 years was markedly higher than that in females (Wang *et al.* 2017). Females are seemingly protected from cerebrovascular diseases even after menopause, probably through hormone-independent and hormone-dependent mechanisms (Herson and Hurn 2010). Studies have affirmed that estrogens are not only conductive to improving the vasculature by ameliorating endothelial dysfunction, reinforcing vasodilatation and promoting blood flow after vascular occlusion, but also have neuroprotective effects in several brain cell types, such as microglia, neurons, oligodendrocytes and astrocytes, thus accelerating the recovery from brain injury (Liu *et al.* 2009; Katsiki *et al.* 2011). Our results also indicated that lung adenocarcinoma was a protective factor for stroke mortality relative to squamous cell lung carcinoma. Previous studies have suggested that among lung cancer patients, adenocarcinoma was more common in women than men, and squamous cell carcinoma often occurs in men (Wisnivesky and Halm 2007; Sereno *et al.* 2012; Welcker 2015). Additionally, in our study, the black participants showed an increased risk of stroke mortality than the white participants, supported by the results of the study made by Marron *et al.* (2018). This racial difference in mortality may be explained by pervasive and longstanding socioeconomic and health disadvantages in the black people (Pathak 2018).

There were findings in our study showing that higher TNM stage and distant metastasis were associated with a higher risk of stroke mortality in lung cancer patients, which might be ascribed to malignant degrees of the tumor and use of chemotherapy and radiation therapy. The higher the malignant degree, the poorer the patient's prognosis. Although chemotherapy only appears in the setting of advanced malignancies, it is usually considered as the cause of cerebral venous or arterial thrombosis. It can result in stroke through endothelial toxicity, coagulation and hemostasis disorders, and can also induce the stroke manifestation (Saynak *et al.* 2008, Zembower 2014). Previous studies reported that vasculopathy occurred in both intracranial and extracranial vessels

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after radiation, and the subsequent occlusion or stenosis was more extensive in the radiation portal (Rogers 2003, Dardiotis *et al.* 2019).

This was the first population-based, large-scale study to determine the risk factors for stroke mortality among lung cancer patients. The death-related information was credible because the follow-up data from the SEER database were relatively complete. Moreover, compared with single-center studies, our results might be more generalizable. However, some limitations remained to be concerned. First, the SEER database had lack of information on behavioral factors, such as smoking and commodities, that may increase the risk of stroke, such as hypertension and diabetes mellitus. Second, information on stroke subtypes, biomarkers (e.g. D-dimer levels and prothrombin time) and treatment methods was absent. Notably, there are no nationally representative databases to data involving the above-mentioned covariates. Despite these limitations, our findings were valuable in better understating the risk of stroke mortality among lung cancer patients.

Conclusions

Our study suggests that lung cancer patients are at a high risk of stroke mortality; increasing age, males, the black, grade II–III, distant metastasis and higher TNM stage are associated with an increased risk of stroke mortality among lung cancer patients, but adenocarcinoma is related to a reduced risk.

Acknowledgements

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Conflicts of interest

There are no conflicts of interest.

References

Bade BC, Dela Cruz CS (2020). Lung cancer 2020: epidemiology, etiology, and prevention. *Clin Chest Med* **41**:1–24.

Bang OY, Seok JM, Kim SG, Hong JM, Kim HY, Lee J, *et al.* (2011). Ischemic stroke and cancer: stroke severely impacts cancer patients, while cancer increases the number of strokes. *J Clin Neurol* **7**:53–59.

Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* **68**:394–424.

Cestari DM, Weine DM, Panageas KS, Segal AZ, DeAngelis LM (2004). Stroke in patients with cancer: incidence and etiology. *Neurology* **62**:2025–2030.

Chen PC, Muo CH, Lee YT, Yu YH, Sung FC (2011). Lung cancer and incidence of stroke: a population-based cohort study. *Stroke* **42**:3034–3039.

Dardiotis E, Aloizou AM, Markoula S, Siokas V, Tsarouhas K, Tzanakakis G, *et al.* (2019). Cancer-associated stroke: pathophysiology, detection and management (review). *Int J Oncol* **54**:779–796.

Dearborn JL, Urrutia VC, Zeiler SR (2014). Stroke and cancer- a complicated relationship. *J Neurol Transl Neurosci* **2**:1039.

Herson PS, Hurn PD (2010). Gender and the injured brain. *Prog Brain Res* **186**:177–187.

Katsiki N, Ntaios G, Vemmos, K. (2011). Stroke, obesity and gender: a review of the literature. *Maturitas* **69**:239–243.

Kim SG, Hong JM, Kim HY, Lee J, Chung PW, Park KY, *et al.* (2010). Ischemic stroke in cancer patients with and without conventional mechanisms: a multicenter study in Korea. *Stroke* **41**:798–801.

Liu M, Dziennis S, Hurn PD, Alkayed NJ (2009). Mechanisms of gender-linked ischemic brain injury. *Restor Neurol Neurosci* **27**:163–179.

Mao Y, Yang D, He J, Krasna MJ (2016). Epidemiology of lung cancer. *Surg Oncol Clin N Am* **25**:439–445.

Marron MM, Ives DG, Boudreau RM, Harris TB, Newman AB (2018). Racial differences in cause-specific mortality between community-dwelling older black and white adults. *J Am Geriatr Soc* **66**:1980–1986.

National Cancer Institute. SEER is an authoritative source for cancer statistics in the United States. https://seer.cancer.gov/. [Accessed 10 May 2020].

Pathak EB (2018). Mortality among black men in the USA. *J Racial Ethn Health Disparities* **5**:50–61.

Rogers LR (2003). Cerebrovascular complications in cancer patients. *Neurol Clin* **21**:167–192.

Savji N, Rockman CB, Skolnick AH, Guo Y, Adelman MA, Riles T, Berger JS (2013). Association between advanced age and vascular disease in different arterial territories: a population database of over 3.6 million subjects. *J Am Coll Cardiol* **61**:1736–1743.

Saynak M, Cosar-Alas R, Yurut-Caloglu V, Caloglu M, Kocak Z, Uzal, C. (2008). Chemotherapy and cerebrovascular disease. *J BUON* **13**:31–36.

Selvik HA, Thomassen L, Bjerkreim AT, Næss, H. (2015). Cancer-associated stroke: the Bergen NORSTROKE study. *Cerebrovasc Dis Extra* **5**:107–113.

Seok JM, Kim SG, Kim JW, Chung CS, Kim GM, Lee KH, Bang OY (2010). Coagulopathy and embolic signal in cancer patients with ischemic stroke. *Ann Neurol* **68**:213–219.

Sereno M, Esteban IR, Zambrana F, Merino M, Gómez-Raposo C, López-Gómez M, Sáenz EC (2012). Squamous-cell carcinoma of the lungs: is it really so different? *Crit Rev Oncol Hematol* **84**:327–339.

Stefan O, Vera N, Otto B, Heinz L, Wolfgang, G. (2009). Stroke in cancer patients: a risk factor analysis. *J Neurooncol* **94**:221–226.

Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal, A. (2015). Global cancer statistics, 2012. *CA Cancer J Clin* **65**:87–108.

Wang W, Jiang B, Sun H, Ru X, Sun D, Wang L, *et al.*; NESS-China Investigators. (2017). Prevalence, incidence, and mortality of stroke in China: results from a nationwide population-based survey of 480 687 adults. *Circulation* **135**:759–771.

Wei YC, Chen KF, Wu CL, Lee TW, Liu CH, Shyu YC, Lin CP (2019). Stroke rate increases around the time of cancer diagnosis. *Front Neurol* **10**:579.

Welcker, K. (2015). [Gender differences in lung cancer]. *Zentralbl Chir* **140**:260–265.

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

Xie X, Chen L, Zeng J, Qin C, Cheng D, Wei X, Liang, Z. (2016). Clinical features and biological markers of lung cancer-associated stroke. *J Int Med Res* **44**:1483–1491.

Yoon DW, Shin DW, Cho JH, Yang JH, Jeong SM, Han K, Park SH (2019). Increased risk of coronary heart disease and stroke in lung cancer survivors: a Korean nationwide study of 20,458 patients. *Lung Cancer* **136**:115–121.

Zaorsky NG, Churilla TM, Egleston BL, Fisher SG, Ridge JA, Horwitz EM, Meyer JE (2017). Causes of death among cancer patients. *Ann Oncol* **28**:400–407.

Zembower TR (2014). Epidemiology of infections in cancer patients. *Cancer Treat Res* **161**:43–89.

Zhang YY, Chan DK, Cordato D, Shen Q, Sheng AZ (2006). Stroke risk factor, pattern and outcome in patients with cancer. *Acta Neurol Scand* **114**:378–383.

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