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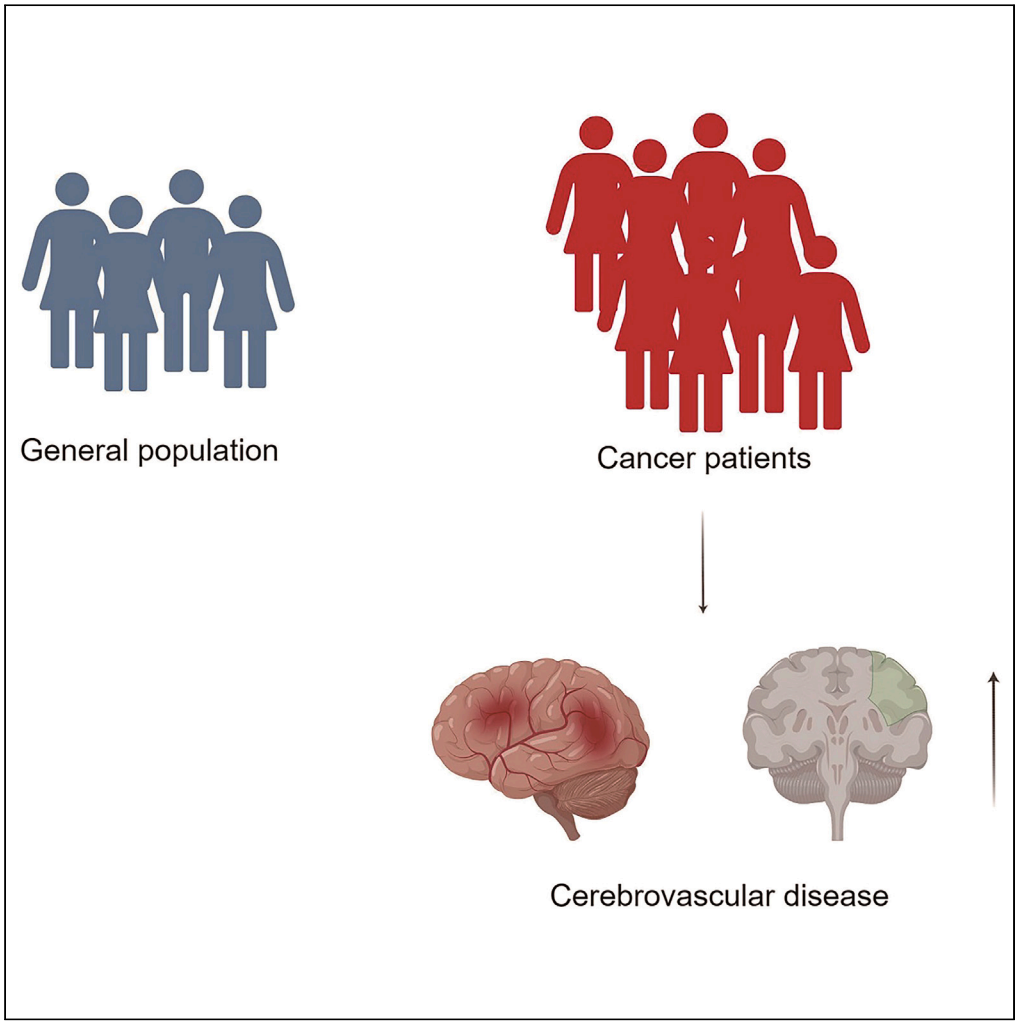

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Highlights

We found greater risk of cerebrovascular disease among certain cancer patients

The risk of cerebrovascular disease was highest within the first 2 months

The risk profile of cerebrovascular diseases among cancer patients may have changed

More proactive strategies for cerebrovascular disease prevention are required

Liu et al., iScience 26, 107165
July 21, 2023
https://doi.org/10.1016/j.isci.2023.107165

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Risk of cerebrovascular disease after cancer diagnosis in the United States

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SUMMARY

The risk of subsequent cerebrovascular disease among cancer patients of multiple cancers in the US is not well understood. A total of 3,843,261 cancer patients diagnosed from 1975 to 2018, were included from the surveillance, epidemiology, and end results (SEER) database. Standardized mortality ratios (SMRs) and absolute excess risks (AERs) were estimated. The overall cerebrovascular disease SMR was 1.04 (95% CI, 1.03–1.04), and the AER per 10,000 person-years at risk was 0.89. When compared with the US general population, greater cerebrovascular disease risk was correlated with certain cancer sites, American Indian/Alaska Native race, Asian or Pacific Islander race, unmarried marital status, distant metastasis, younger age, and an earlier time of cancer diagnosis. Clinically, more precision and proactive strategies for cerebrovascular disease prevention are required to subgroup of cancer patients with a greater risk of cerebrovascular disease, especially within the first two months.

INTRODUCTION

Cerebrovascular disease and cancer are both major global health problems and leading causes of death throughout the world.[1,2] In recent years, as advancements in cancer screening, diagnosis, and treatment strategies advancements have led to better prognosis, it is now critical to consider issues of cancer survivorship and the higher risk of cerebrovascular disease among patients with cancer. Currently, clinical guidelines from the National Comprehensive Cancer Network, the American Heart Association, and the American Cerebrovascular Disease Association offer few recommendations for the clinical prevention, identification, and management of cerebrovascular disease risk among cancer patients.[3,4]

Current evidence regarding the risk of cerebrovascular disease among cancer patients remains ambiguous.[5–7] A few prior small subsets of population-based studies supported that patients with head and neck, pancreatic, colorectal, lung, oral, or breast cancer are associated with the risk of cerebrovascular disease.[8–13] For instance, a population-based study from Sweden covering 20 years data reported the risk of cerebrovascular disease increased among several cancer types and decreased with time, and this risk is highest in the first six months after cancer diagnosis.[10] Another study also reported the increased risk of cerebrovascular disease in the first three months after cancer diagnosis, and that this risk attenuated over time, but limited to data of five types of cancer.[8] While another recent study reported cerebrovascular disease risk among cancer patients even increases with time, which is inconsistent with other studies.[7] One helpful strategy for better management of cerebrovascular disease among cancer patients is to find out which subsets of cancer patients are at higher risk, our knowledge regarding this is, however, ambiguous. We hypothesize that the risk of cerebrovascular disease is increased only in certain types of cancer and subsets of cancer patients, rather than in all cancer patients.

To fill this knowledge gap, we performed in-depth analyses of subsequent cerebrovascular disease risk among cancer patients with all primary sites and human organ systems and incorporated updated data ;from the US. Firstly, our study tried to answer whether and when the risk of cerebrovascular disease is increased among cancer patients. Secondly, we also identified the high-risk subsets of cancer patients.

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https://doi.org/10.1016/j.isci.2023.107165

RESULTS

Overall findings and baseline characteristics

Overall, we identified 3,843,261 patients with first primary or primary only cancer (51.3% male and 48.7% female) aged 0 to 80+ years from 1975 to 2018. Among the study population, 63.4% of patients were older than 60 years old when diagnosed with cancer. In total, we identified 73,857 patients with cancer (35,777 male and 38,080 female) died with cerebrovascular disease, which represents 1.92% of all deaths. Characteristics of the study population are summarized in Table 1, which has a mean survival time of 7.77 years with a range of 0–43.91 years. Herein, we report the overall standardized mortality ratio (SMR) for the whole population was 1.04 (95% CI, 1.03–1.04) and the overall absolute excess risk (AER) per 10,000 person-years with risk was 0.89, only slightly greater than the US general population. We discovered significant differences in cerebrovascular disease risks in primary cancer sites, the time after cancer diagnosis, and characteristics of patients and disease, including race, age of diagnosis, tumor stage, marital status, and year of diagnosis, but not sex. (Table 1). For the whole population, SMR and AER of cerebrovascular disease decreased among cancer patients in recent years (2000–2018), no significant difference in cerebrovascular disease risk was found among cancer patients compared with the US general population. A higher risk of cerebrovascular disease was only found among the ten primary cancer sites.

Differences in risk of cerebrovascular disease by primary cancer sites and human organ systems

We found variations in SMRs and AERs for both primary cancer sites and human organ systems. SMRs and AERs for all human organ systems and primary cancer sites recorded in the surveillance, epidemiology, and end results (SEER) database are summarized in Table 2. Interestingly, among patients with cancer of the breast, prostate, melanoma of the skin, lymphocytic leukemia, chronic lymphocytic leukemia, thyroid, and other lymphocytic leukemia, there was even a lower risk of cerebrovascular disease. (Table S1). Cerebrovascular disease rates were higher in cancers of the brain and other nervous systems, oral cavity and pharynx, respiratory system, myeloma, digestive system, lymphoma, and urinary system than in the general population in the United States, but not in cancers of bones and joints, soft tissue including heart, eye and orbit, female genital system, leukemia (Table S2). Interestingly, a lower risk of cerebrovascular disease was found among patients with cancer of the breast, skin excluding basal and squamous, male genital system and endocrine system. Among all primary cancer sites, patients with cancer of brain experienced the greatest SMR and AER, experiencing a 4.96-fold higher risk than the general population, which correlated with 10.6 additional deaths per 10,000 person-years. The cerebrovascular disease risk was followed by nasopharynx, acute lymphocytic leukemia, oropharynx, cranial nerves other nervous system, floor of mouth, pancreas, liver and intrahepatic bile duct, tonsil, hypopharynx, etc. Among all human organ systems, the greatest SMR was found among patients with cancers of the brain and other nervous system, experiencing a 4.25-fold risk compared to the general population, which correlated with 10.47 additional deaths per 10,000 person-years. (Tables S1, and S2).

Risk of cerebrovascular disease over time after cancer diagnosis

We depicted the changing pattern of cerebrovascular disease risk by different primary cancer sites and human organ systems over time after cancer diagnosis (Figure 1, Table S3). For all cancers combined, the SMR was highest in the first two months after patients were diagnosed with cancer (SMR, 1.90; 95% CI, 1.80–2.01; AER, 18.89), and decreased over time to 1.06-fold risk at 10 years after diagnosis (Figure 1), and this phenomenon was observed in most of the organ systems. Notably, patients with cancers of brain and other nervous system had the highest SMR throughout the follow-up period, as well as clearly higher AER than cancers of other organ systems than the US general population, this risk decreased over time, but reached a new peak at 10 years after cancer diagnosis (Figure 1). The greatest cerebrovascular disease risk was found in patients with brain cancer in the first two months after diagnosis, experiencing a 7.8-fold risk compared to the general population, which correlated with 10.6 additional deaths per 10,000 person-years at risk, followed by cancers of the nose, nasal cavity and middle, miscellaneous, the small intestine, cervix uteri, the esophagus, the large intestine, the pancreas, the lung and bronchus, the descending colon, acute myeloid leukemia, etc. (Table S3).

Risk of cerebrovascular disease by age at diagnosis

We depicted the changing pattern of cerebrovascular disease risk for different primary cancer sites and human organ systems across different age groups. For all patients combined, the risk of cerebrovascular

Table 1. Cerebrovascular disease SMRs and AERs per 10,000 person-years at risk according to key patient characteristics for all cancer combined

Characteristics	Patients with cancer No. (%)	Total death No. (%)	Death of cerebrovascular disease No. (%)	% Cerebrovascular disease of total	Cerebrovascular disease per 10,000 Person-years	Person-years	SMR[b] (95%CI)	AERs per 10,000 Person-Years
Total	3843261	2450702	73857	1.92	25.14	29,379,410.68	1.04[a](1.03–1.04)	0.89
Sex								
Male	1971526 (51.3)	1319677 (53.8)	35777 (48.4)	1.81	26.22	13,643,239.43	1.03[a](1.02–1.05)	0.87
Female	1871735 (48.7)	1131025 (46.2)	38080 (51.6)	2.03	24.20	15,736,171.25	1.04[a](1.03–1.05)	0.9
Race								
White	3200474 (83.3)	2059691 (84.0)	63496 (86.0)	1.98	25.26	25,133,378.16	1.02[a](1.01–1.03)	0.49
Black	368900 (9.6)	240015 (9.8)	5923 (8.0)	1.61	25.56	2,317,517.96	1.05[a](1.03–1.08)	1.31
American Indian/ Alaska Native	21728 (0.6)	12516 (0.5)	239 (0.3)	1.10	16.48	145,056.61	1.44[a](1.26–1.64)	5.05
Asian or Pacific Islander	252159 (6.6)	138480 (5.7)	4199 (5.7)	1.67	23.54	1,783,457.94	1.31[a](1.27–1.35)	5.58
Age group								
≤19	50414 (1.3)	13343 (0.5)	61 (0.1)	0.12	0.86	707,400.99	5.46[a](4.17–7.01)	0.7
20–29	74168 (1.9)	19736 (0.8)	130 (0.2)	0.18	1.20	1,079,586.39	1.90[a](1.59–2.26)	0.57
30–39	172827 (4.5)	59320 (2.4)	411 (0.6)	0.24	1.84	2,235,080.05	1.25[a](1.13–1.38)	0.37
40–49	373390 (9.7)	156789 (6.4)	1682 (2.3)	0.45	4.07	4,132,063.78	1.11[a](1.06–1.17)	0.41
50–59	737406 (19.2)	383644 (15.7)	6419 (8.7)	0.87	9.69	6,624,691.57	1.05[a](1.02–1.07)	0.44
60–69	1041742 (27.1)	670350 (27.4)	17877 (24.2)	1.72	23.03	7,763,678.81	1.03[a](1.01–1.04)	0.67
70–79	906630 (23.6)	715159 (29.2)	27451 (37.2)	3.03	52.85	5,194,444.13	1.01(1–1.02)	0.49
≥80	486684 (12.7)	432361 (17.6)	19826 (26.8)	4.07	120.71	1,642,464.96	1.06[a](1.05–1.08)	7.23
Tumor stage								
In situ	45642 (1.2)	18326 (0.7)	782 (1.1)	1.71	22.79	343,089.82	0.88[a](0.82–0.94)	−3.13
Localized	998510 (26.0)	319085 (13.0)	12684 (17.2)	1.27	15.97	7,944,438.79	0.88[a](0.87–0.9)	−2.1
Regional	430882 (11.2)	211244 (8.6)	3974 (5.4)	0.92	15.01	2,647,732.85	1.02(0.99–1.05)	0.26
Distant	349152 (9.1)	281936 (11.5)	1768 (2.4)	0.51	20.04	882,061.71	1.33[a](1.27–1.39)	4.95
Unknown	2019075 (52.5)	1620111 (66.1)	54649 (74.0)	2.71	31.12	17,562,087.51	1.08[a](1.07–1.09)	2.21
Marital status								
Single (never married)	508334 (13.2)	270180 (11.0)	5580 (7.6)	1.10	13.91	4,010,268.37	1.18[a](1.14–1.21)	2.07
Married	2210450 (57.5)	1375307 (56.1)	40593 (55.0)	1.84	22.02	18,438,699.72	0.98[a](0.97–0.99)	−0.46
Separated	45685 (1.2)	35731 (1.5)	1049 (1.4)	2.30	37.31	281,133.81	1.03(0.97–1.09)	1.01

(*Continued on next page*)

Table 1. *Continued*

Characteristics	Patients with cancer No. (%)	Total death No. (%)	Death of cerebrovascular disease No. (%)	% Cerebrovascular disease of total	Cerebrovascular disease per 10,000 Person-years	Person-years	SMR[b] (95%CI)	AERs per 10,000 Person-Years
Divorced	297503 (7.7)	188976 (7.7)	3875 (5.2)	1.30	19.02	2,036,977.84	1.22[a](1.18–1.25)	3.37
Widowed	539055 (14.0)	462104 (18.9)	18566 (25.1)	3.44	66.87	2,776,431.56	1.12[a](1.1–1.13)	6.97
Unmarried or Domestic Partner	4077 (0.1)	925 (0.0)	4 (0.0)	0.10	3.82	10,475.78	0.62(0.17–1.58)	−2.38
Unknown	238157 (6.2)	117479 (4.8)	4190 (5.7)	1.76	22.95	1,825,423.61	1(0.97–1.03)	−0.09
Year of diagnosis								
1975–1979	345316 (9.0)	325232 (13.3)	12233 (16.6)	3.54	44.54	2,746,307.30	1.08[a](1.06–1.11)	2.87
1980–1989	635840 (16.5)	573222 (23.4)	20090 (27.2)	3.16	30.18	6,655,939.74	1.09[a](1.07–1.1)	2.73
1990–1999	884745 (23.0)	697121 (28.4)	23647 (32.0)	2.67	27.01	8,755,920.09	1.03[a](1.01–1.04)	0.73
2000–2009	1008074 (26.2)	565436 (23.1)	13976 (18.9)	1.39	17.21	8,118,563.28	0.96[a](0.95–0.98)	−0.64
2010–2018	969286 (25.2)	289691 (11.8)	3911 (5.3)	0.40	12.61	3,102,680.27	0.97(0.94–1)	−0.35

SMR, standardized mortality ratio; AER, absolute excess risk.

[a]Means that 95% confidence interval does not cross 1.0 and also the SMR is significant.

[b]Patients with single primary cancer only recorded in the SEER registry, and only for persons with those forms of cancer in whom 100,000 person-years or more of survival time were presented.

Table 2. Cerebrovascular disease SMRs and AERs per 10,000 person-years at risk according to single primary cancer sites and organ systems

Cancer sites[b]	Observed	Expected	SMR[c] (95%CI)	AER	Person years at risk	Mean age at exposure	Mean age at event
All Sites	73,857	71245	1.04[a](1.03–1.04)	0.89	29379411	63.34	82.5
Oral Cavity and Pharynx	2,151	1393	1.54[a](1.48–1.61)	10.65	712444	61.58	78.63
Lip	499	387	1.29[a](1.18–1.41)	9.46	118866	66.06	83.37
Tongue	367	252	1.46[a](1.31–1.62)	7.45	154746	61.29	77.47
Salivary Gland	246	187	1.31[a](1.16–1.49)	5.83	100929	59.89	82.3
Gum and Other Mouth	373	252	1.48[a](1.33–1.64)	11.82	102514	64.45	79.23
Digestive System	14,044	13046	1.08[a](1.06–1.09)	2.66	3746881	67.18	83.69
Stomach	859	651	1.32[a](1.23–1.41)	10.11	205689	67.45	81.39
Colon and Rectum	11,702	11393	1.03[a](1.01–1.05)	1.02	3035376	67.76	84.6
Colon excluding Rectum	8,887	8550	1.04[a](1.02–1.06)	1.6	2103866	68.79	85.11
Cecum	2,119	2068	1.02 (0.98–1.07)	1.2	428344	71.18	86.26
Ascending Colon	1,449	1403	1.03 (0.98–1.09)	1.51	307074	70.98	86.35
Transverse Colon	837	755	1.11[a](1.03–1.19)	4.64	175903	69.82	84.98
Descending Colon	606	549	1.10[a](1.02–1.2)	3.79	151155	66.86	83.27
Sigmoid Colon	2,884	2853	1.01 (0.97–1.05)	0.4	784201	66.94	84.24
Rectum and Rectosigmoid Junction	2,815	2842	0.99 (0.95–1.03)	−0.29	931510	65.38	83.01
Rectosigmoid Junction	958	978	0.98 (0.92–1.04)	−0.69	290227	66.28	83.89
Rectum	1,857	1864	1 (0.95–1.04)	−0.11	641282	64.99	82.56
Respiratory System	4,497	3071	1.46[a](1.42–1.51)	10.45	1364798	66.61	76.68
Larynx	896	635	1.41[a](1.32–1.51)	9.48	275476	63.69	76.49
Lung and Bronchus	3,456	2347	1.47[a](1.42–1.52)	10.75	1031234	67.04	76.62
Soft Tissue including Heart	339	315	1.08 (0.97–1.2)	1.07	228476	51.51	81.39
Skin excluding Basal and Squamous	2,634	2809	0.94[a](0.9–0.97)	−0.91	1915207	56.73	83.23
Melanoma of the Skin	2,318	2527	0.92[a](0.88–0.96)	−1.18	1768551	56.35	83.03
Other Non-Epithelial Skin	316	282	1.12[a](1–1.25)	2.34	146656	61.03	84.68
Breast	14,370	14980	0.96[a](0.94–0.98)	−0.94	6463636	61.24	84.42
Female Genital System	5,768	5635	1.02 (1–1.05)	0.51	2626808	60.36	82.56
Cervix Uteri	633	528	1.20[a](1.11–1.3)	1.95	540025	50.27	76.68
Corpus and Uterus, NOS	4,057	4057	1 (0.97–1.03)	0	1511315	63.05	83.71
Corpus Uteri	4,027	4039	1 (0.97–1.03)	−0.08	1500204	63.05	83.74
Ovary	654	675	0.97 (0.9–1.05)	−0.48	437018	60.42	80.45
Male Genital System	16,772	17855	0.94[a](0.93–0.95)	−1.86	5837230	67.27	83.08
Prostate	16,561	17655	0.94[a](0.92–0.95)	−2.05	5340203	68.83	83.19
Testis	93	106	0.88 (0.71–1.08)	−0.28	462893	34.8	64.79
Urinary System	6,449	6239	1.03[a](1.01–1.06)	0.98	2152230	66.59	82.48
Urinary Bladder	4,802	4715	1.02 (0.99–1.05)	0.63	1396998	69.34	83.48
Kidney and Renal Pelvis	1,508	1387	1.09[a](1.03–1.14)	1.68	718695	61.75	79.32
Brain and Other Nervous System	413	97	4.25[a](3.85–4.69)	10.47	301629	48.59	67.1
Endocrine System	701	799	0.88[a](0.81–0.94)	−0.88	1113285	47.12	78.15
Lymphoma	2,373	2273	1.04[a](1–1.09)	0.67	1501487	57.97	80.58
Hodgkin Lymphoma	187	145	1.29[a](1.11–1.49)	1.04	402268	38.59	70.71
Non-Hodgkin Lymphoma	2,186	2128	1.03 (0.98–1.07)	0.53	1099219	61.73	81.42

(*Continued on next page*)

Table 2. *Continued*

Cancer sites[b]	Observed	Expected	SMR[c] (95%CI)	AER	Person years at risk	Mean age at exposure	Mean age at event
NHL - Nodal	1,360	1366	1 (0.94–1.05)	−0.08	735096	61.69	80.75
NHL - Extranodal	826	762	1.08[a](1.01–1.16)	1.76	364123	61.81	82.53
Myeloma	567	447	1.27[a](1.16–1.38)	6.1	195853	67.44	78.03
Leukemia	1,243	1265	0.98 (0.93–1.04)	−0.33	677096	57.66	80.83
Lymphocytic Leukemia	955	1056	0.90[a](0.85–0.96)	−2.05	494817	57.38	82.71
Acute Lymphocytic Leukemia	30	11	2.66[a](1.79–3.79)	1.26	148871	20.31	60.61
Chronic Lymphocytic Leukemia	878	972	0.90[a](0.84–0.96)	−3.09	304989	69.13	83.5
Myeloid and Monocytic Leukemia	239	174	1.38[a](1.21–1.56)	4	163004	57.62	72.72
Miscellaneous	1,209	726	1.67[a](1.57–1.76)	16.64	290552	67.91	80.73

SMR, standardized mortality ratio; AER, absolute excess risk.

[a]Means that 95% confidence interval does not cross 1.0 and also the SMR is significant.

[b]Patients with single primary cancer only recorded in the SEER registry, and only for persons with those forms of cancer in whom 100,000 person-years or more of survival time were presented.

[c]Reference population: general US population based on the 2000 US standard population; patients with multiple primary tumors were excluded automatically; adjusted for age, sex, and race distributions of cancer patients.

disease decreased with the increase in age group, and the greatest SMR was found among patients aged less than 19 years, experiencing a 5.46-fold higher risk than the general population when compared with the US general population. (Figure 2A, Table S4). The association between the risk of cerebrovascular disease and age showed a similar pattern among cancers of different organ systems and anatomic sites (Figure 2A). Notably, AER increased with age in all cancer patients, and this feature was shared by most cancers of different organ systems (Figure 2B). As shown in Figure 2B, the greatest risk of cerebrovascular disease was found among cancer patients of brain and other nervous system throughout all the age groups. Patients with cancers of respiratory system, myeloma, urinary system, and lymphoma experienced the peak of AER at ages between 60 and 69 years old and even showed lower risk than the US general population among patients older than 80 years old.

Risk of cerebrovascular disease by year of diagnosis

We illustrated the changing pattern of cerebrovascular disease risk by primary cancer site and human organ system across different diagnosis years. For the population as a whole, patients diagnosed from 1980 to 1989 years experienced the greatest cerebrovascular disease risk with a 1.08-fold higher risk than the general population, which correlated with 2.73 additional deaths per 10,000 person-years with risk, and we observed the SMR and AER decreased in more recent years and even experienced lower risk of cerebrovascular disease than the general population (Table 1 and Figure 3). We found most cancers with different organ systems showed decreased SMR and AER in patients diagnosed since the 2000 years, and showed a lower risk of cerebrovascular disease than the general population. However, cancer patients of the brain and other nervous system, respiratory system, myeloma, and digestive system showed greater risk of cerebrovascular disease than the general population. Notably, among cancer patients diagnosed in more recent years (2010–2018), we found only patients from ten cancer sites were associated with a significant greater risk of cerebrovascular disease (Table S5), including acute lymphocytic leukemia, brain, followed by intrahepatic bile duct, acute myeloid leukemia, liver, pancreas, stomach, miscellaneous, myeloid and monocytic leukemia, lung and bronchus, myeloma, and kidney and renal pelvis. Furthermore, patients with skin, breast, prostate, and thyroid cancer had a significantly lower risk of cerebrovascular disease in recent years when compared to the general population in the United States (Table S5).

Risk of cerebrovascular disease by race and marital status

The predominant patients who died by cerebrovascular disease were white (63496, 86.0%). For all cancers combined, patients of American Indian/Alaska Native race experienced the highest SMR (1.44, 95% CI, 1.26–1.64), followed by Asian or Pacific Islander, black, and white (Table 1), among whom the cerebrovascular disease risk of white and black showed only a slightly higher risk of cerebrovascular disease than the general population. Patients with divorced marital status experienced the highest SMR (SMR, 1.22, 95% CI, 1.18–1.25),

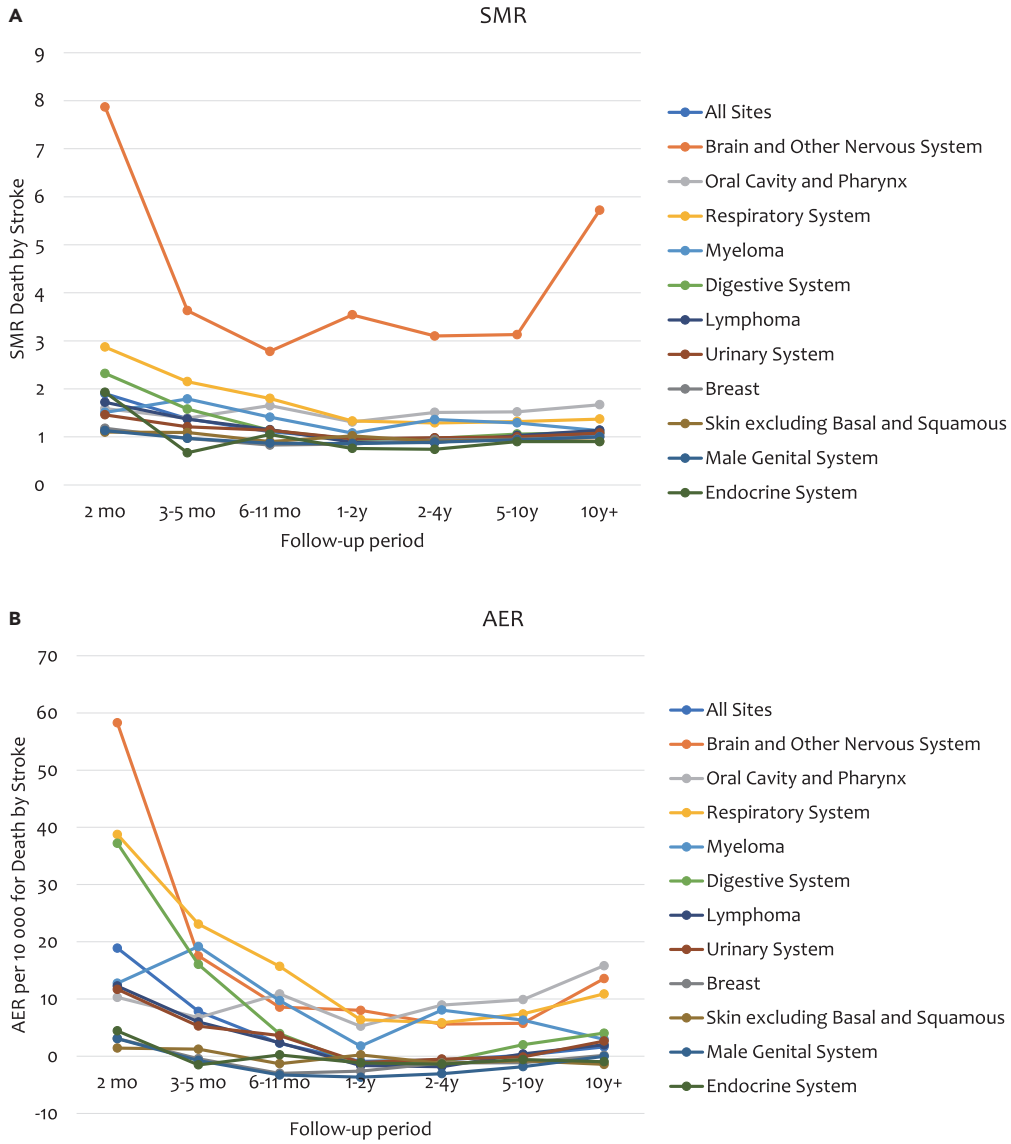
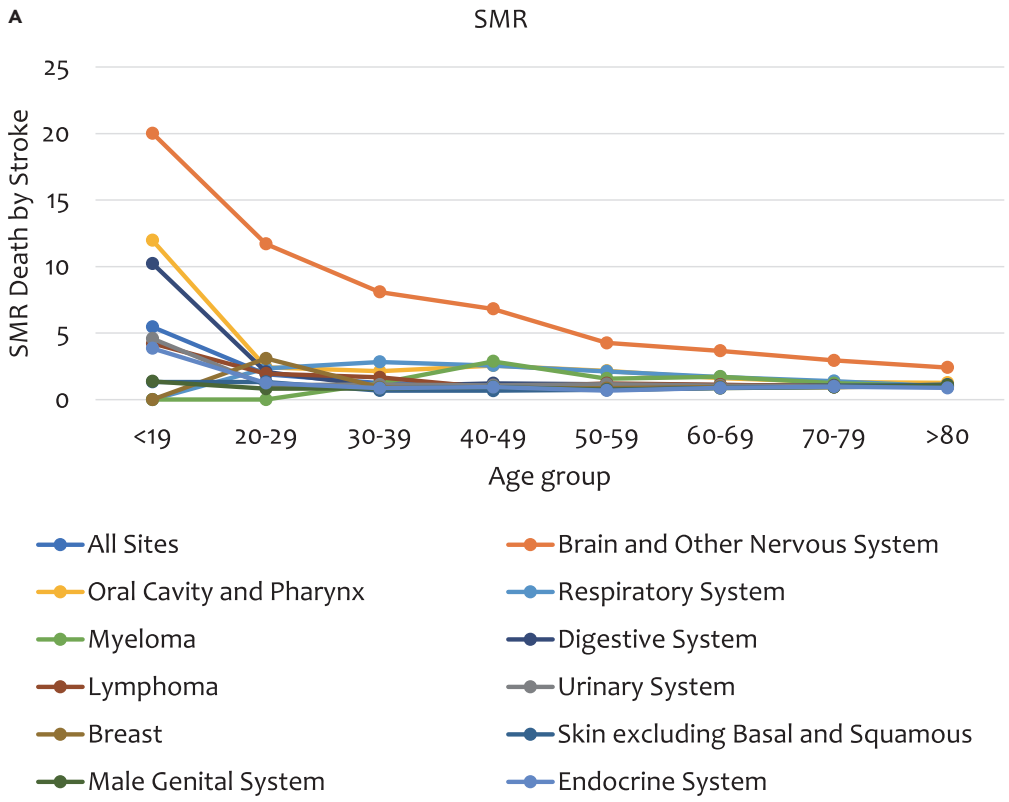
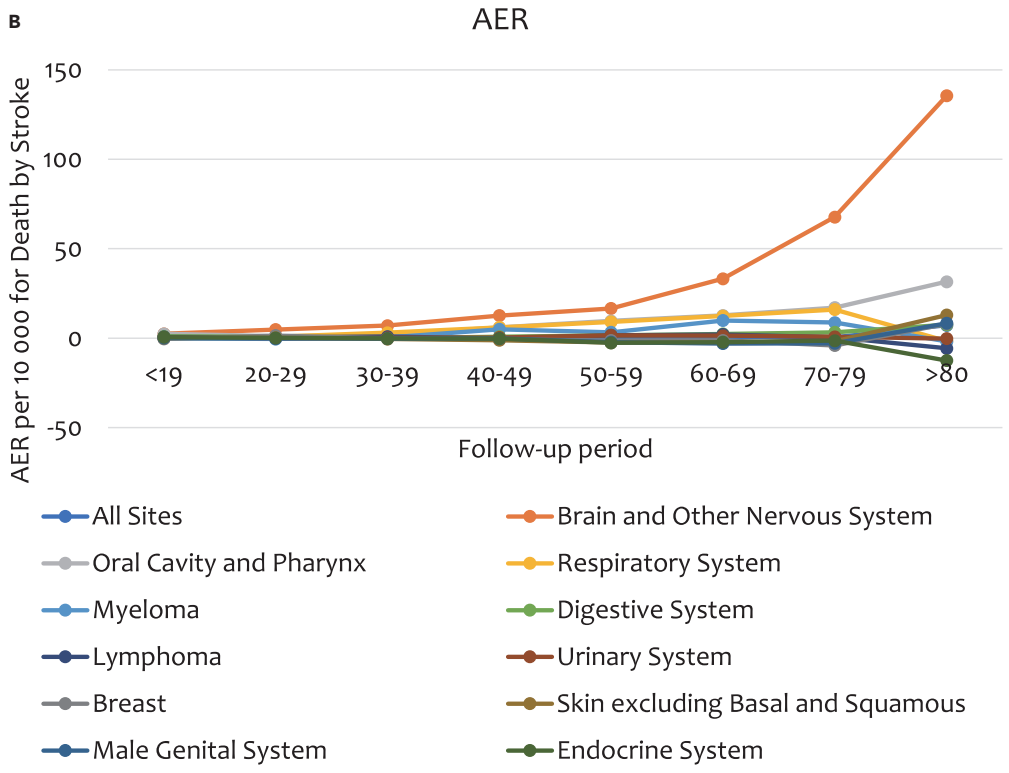


Figure 1. Standardized mortality ratios (SMRs) and absolute excess risks (AERs) per 10,000 person-years at the risk of cerebrovascular diseases according to human organ systems by follow-up period

Estimates of SMRs (A) and AERs (B) are presented in Table S1 in the Supplement. X axe denotes the time after cancer diagnosis. Y axe denotes SMR (A) and AER (B) of cerebrovascular diseases by different latency periods. Color code denotes different cancer sites/organ systems.

followed by widowed, single (never married), and patients with married status were associated with a lower risk of cerebrovascular disease than the general population (Table 1). Cerebrovascular disease risk of different primary cancer sites and human organ systems by race and marital showed a varied pattern (Figures S1 and S2). Cancer patients who were American Indian/Alaska Native, and Asian or Pacific Islander showed a significant higher risk of cerebrovascular disease in most—human organ systems and primary sites compared with the US general population, particularly when diagnosed with cancers of the brain and other nervous system. Only cancers of the brain and other nervous systems, the oral cavity and pharynx, and the respiratory system were associated with a significantly higher risk of cerebrovascular disease in patients of white and black race (Table S6). For marital status, patients of all marital status were associated with a higher risk of cerebrovascular disease when diagnosed with cancers of the brain and other nervous system, oral cavity and pharynx, respiratory system and myeloma, while no significant difference or lower risk was found among cancers of the breast, male genital system, and endocrine system (Figure S2, Table S7).


A
SMR
SMR Death by Stroke
25
20
15
10
5
0
<19
20-29
30-39
40-49
50-59
60-69
70-79
>80
Age group
All Sites
Brain and Other Nervous System
Oral Cavity and Pharynx
Respiratory System
Myeloma
Digestive System
Lymphoma
Urinary System
Breast
Skin excluding Basal and Squamous
Male Genital System
Endocrine System


B
AER
AER per 10 000 for Death by Stroke
150
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>80
Follow-up period
All Sites
Brain and Other Nervous System
Oral Cavity and Pharynx
Respiratory System
Myeloma
Digestive System
Lymphoma
Urinary System
Breast
Skin excluding Basal and Squamous
Male Genital System
Endocrine System

Figure 2. Cerebrovascular disease standardized mortality ratios (SMRs) and absolute excess risks (AERs) per 10,000 person-years at risk according to human organ systems by age group

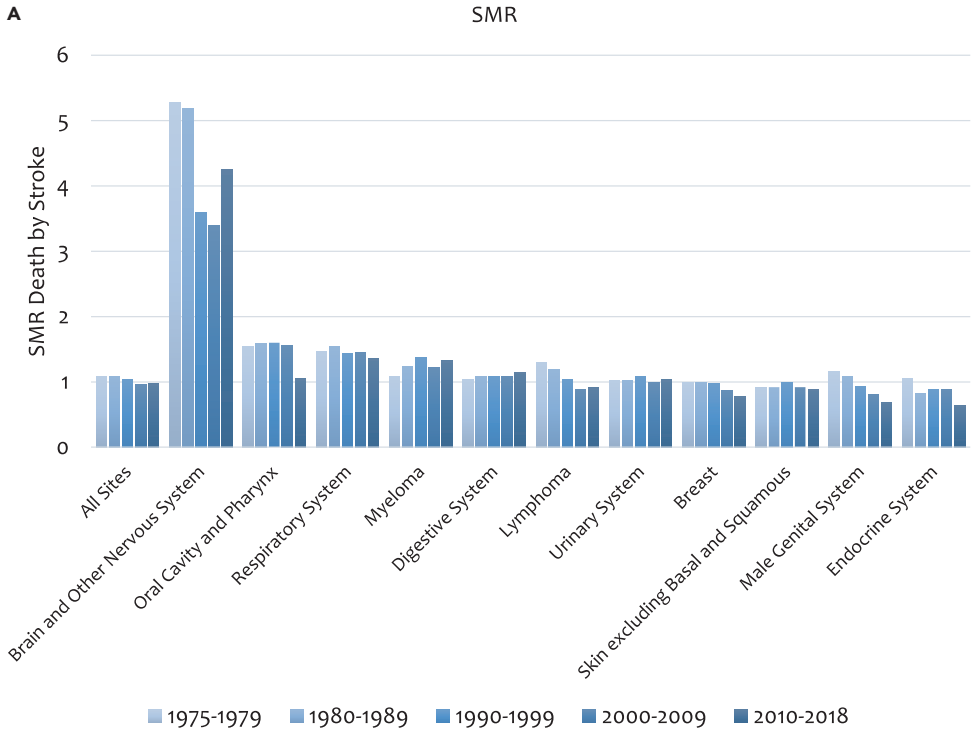
(Reference population is the general US population, SMR indicates standardized mortality ratio). X axe denotes different age group. Y axe denotes SMR (A) and AER (B) of cerebrovascular diseases by different age group. Color code denotes different cancer sites/organ systems.

DISCUSSION

In the current population-based study of 3,843,261 patients, our data revealed that cancer patients over the last 40 years of the US had only a slightly higher risk of cerebrovascular disease than the general population, accounting for 1.92% of all deaths. Notably, this risk has decreased in recent years, no significant difference of cerebrovascular disease risk was observed for the whole cancer population in the past 20 years. Since cancer is a highly heterogeneous disease and treatment of cancer is advancing, we believe the risk of cerebrovascular disease varies with different cancer sites and the year of diagnosis. In the recent ten years, we found only certain cancer patients were associated with a higher risk of cerebrovascular disease than the US general population. We discovered that the peak of cerebrovascular disease occurred within the first two months of cancer diagnosis and then declined over time, implying that more proactive cerebrovascular disease prevention strategies are needed when diagnosed with cancer types that are at high risk of cerebrovascular disease. Our findings will assist oncologists and neurologists make precision prevention strategies for high-risk subsets of cancer survivors.

We suggest that the observed associations between cancer diagnosis and cerebrovascular disease may be partially explained by cigarette smoking. Cigarette smoking is a well-known risk factor for many types of cancer,[14] as well as for cerebrovascular disease,[15,16] which includes stroke and other conditions that affect blood vessels in the brain. Smoking damages blood vessels, which can lead to inflammation and the buildup of plaque, increasing the risk of blood clots and narrowing of the blood vessels. This can lead to stroke, and may also contribute to the development of certain types of cancer. Furthermore, cancer may be linked to dysfunction of the immune system, either as a result of the cancer itself or due to treatments, such as chemotherapy or immunotherapy, thereby increasing the risk of cerebrovascular disease. Additionally, some genetic factors may predispose individuals to both cancer and cerebrovascular disease. Understanding the genetic links between these diseases may help to explain their associations. As suggested by our reviewer, we acknowledge that an explanation for the short time interval between the diagnosis of cancer and the diagnosis of a cerebrovascular disorder could be as a result of investigations for the primary cancer. The SEER definitions of a diagnosis do not exclude this as a reason for diagnosis. Another possibility is that the stress associated with a cancer diagnosis and the subsequent treatments may increase the risk of cerebrovascular disease in the short term. Stress has been shown to have a negative impact on cardiovascular health,[17,18] and cancer patients may experience elevated levels of stress during the initial period following diagnosis. Another potential explanation is that the peak in cerebrovascular disease may be related to changes in lifestyle and behavior following a cancer diagnosis. For example, some cancer patients may experience weight gain or loss, reduced physical activity, and changes in dietary habits, all of which can contribute to an increased risk of cerebrovascular disease.[19–21]

Most of prior studies only investigated limited types of cancer sites, and with small subsets of the population included, which might not reflect the real risk among cancer survivors of different cancer sites.[5,8,9,13,22] More recently, large cohort studies from Sweden using data up to 2008 found that reported several types of cancer were associated with increased higher risk, with the, and this risk peaking peaked in at the first six months.[10] Our results are partly consistent with these results, and moving forward, we identified the SMR was being greatest in the first two months since patients were diagnosed with cancer of certain types in the US, but not at all cancer sites. As for the risk of cerebrovascular disease among cancer patients in the US, one study reported a short-term increase in the increased cerebrovascular disease risk of several cancer types, and a decrease decreased over time,[8] which is partly consistent with our data, the difference might be due to the changing pattern of cerebrovascular disease risk in recent years. In contrast, another study reported results that were clearly contradictory to ours and prior studies, including increased cerebrovascular disease risk across all cancer sites, and this risk even increased over time after cancer diagnosis and age.[7] We suppose these results might be misleading and should be considered cautiously. Our team found these opposite results might be due to unexpected errors in of calculating events and including populations, as it might be ignored that a patient might be diagnosed with multiple primary cancers. Interestingly, we found a few cancer sites even showed reduced risk of cerebrovascular diseases, including cancer site of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All Sites
Brain and Other Nervous System
Oral Cavity and Pharynx
Respiratory System
Myeloma
Digestive System
Lymphoma
Urinary System
Breast
Skin excluding Basal and Squamous
Male Genital System
Endocrine System
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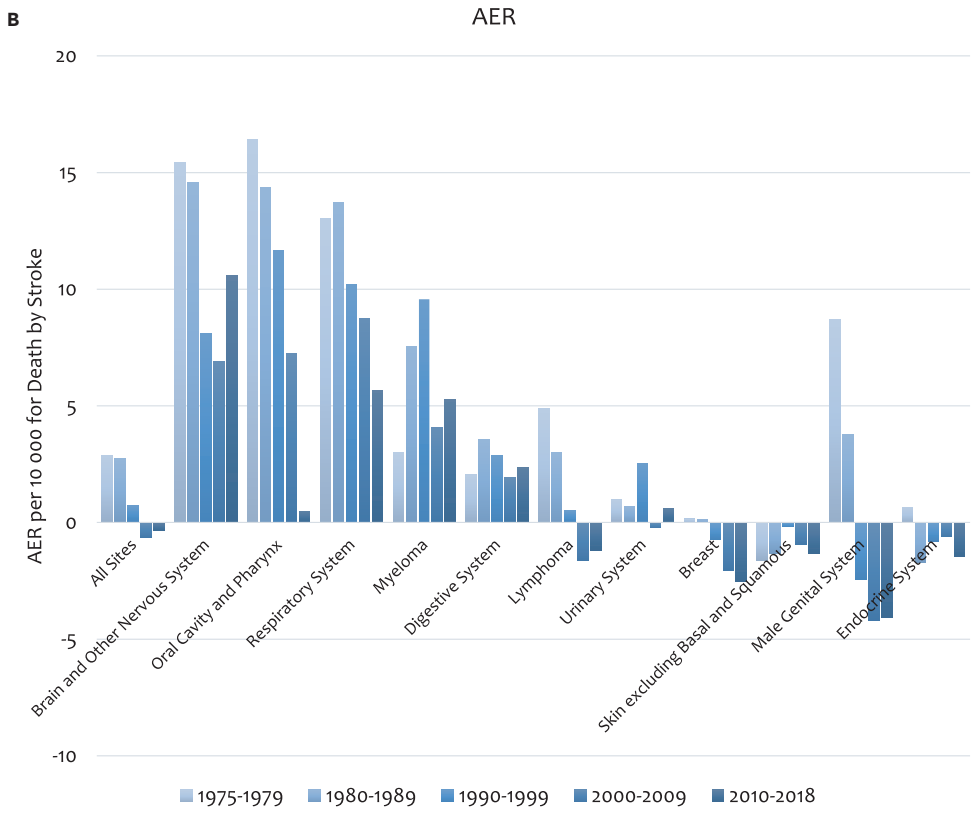
2010-2018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AER per 10 000 for Death by Stroke
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Male Genital System
Endocrine System
1975-1979
1980-1989
1990-1999
2000-2009
2010-2018

Figure 3. Cerebrovascular disease standardized mortality ratios (SMRs) and absolute excess risks (AERs) per 10,000 person-years at risk according to human organ systems by year of diagnosis

(Reference population is the general US population, SMR indicates standardized mortality ratio). X axe denotes different cancer sites/organ systems. Y axe denotes SMR death by cerebrovascular disease.

prostate, testis, thyroid, chronic lymphocytic leukemia, and lymphocytic leukemia. One possible explanation for the reduced risk of cerebrovascular diseases in some cancer sites may be related to diagnostic bias. It is possible that people who are diagnosed with cancer may receive more frequent medical attention, including more frequent screening for cerebrovascular diseases.[23] This could lead to earlier detection and treatment of cerebrovascular diseases, which could reduce the risk of stroke or other cerebrovascular events. Certain cancer treatments, such as chemotherapy and radiation therapy,[24] may also have a protective effect on the cardiovascular system.[25] For example, some chemotherapy drugs have been shown to reduce inflammation in blood vessels, which can help prevent the development of cerebrovascular diseases. Some types of cancer may produce substances that have a protective effect on the cardiovascular system, which could also reduce the risk of cerebrovascular diseases.

Despite the retrospective nature of this study, it has several strengths. Firstly, to answer the issues mentioned in this study, a large cohort population-based study might be the best method. Secondly, we used the largest cohort available to depict the profile of cerebrovascular disease risk among cancers stratified by characteristics of patients and disease. Thirdly, we are the first to describe the changing pattern of cerebrovascular disease risk after cancer diagnosis throughout the past 40 years, and we found important clues for making more precise strategies for cerebrovascular disease among cancer patients. Fourthly, this study considered an important issue usually ignored in prior studies: a patient might be diagnosed with multiple primary cancers.

Limitations of the study

However, the findings of this study should be considered in the context of potential limitations. The SEER database collects information on cancer cases from various registries throughout the United States, and while it provides a rich source of information on cancer diagnoses, treatments, and outcomes, it does have some limitations. One of the main limitations is that the database does not capture detailed information on the types of treatments used for cancer such as whether brain cancers were treated with radiotherapy or not, a patient's medical history, including concomitant morbidities, concomitant medications, and other risk factors such as obesity, smoking, drinking, and family history. This limits the ability to account for potential confounding factors that could be associated with both cerebrovascular disease and cancers. Furthermore, we acknowledge that including *in situ* cancer in our analysis has limitations. *In situ* cancer is not equivalent to invasive cancer and may have different clinical and biological characteristics, which may introduce confounding factors in our analyses. Moreover, *in situ* cancer is often detected through screening, which may result in different case selection and detection biases.

Conclusions

Overall, we found that cancer patients in the US experiences only slightly greater risk than the general US population in the past 40 years, but not in the recent 20 years. The risk of cerebrovascular disease varied greatly by cancer sites, patients and disease characteristics; more precision and proactive strategies for cerebrovascular disease prevention should be considered for subsets of cancer patients with a higher risk of developing the disease, especially during the first two months after cancer diagnosis.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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  - Ethics approval and consent to participate
- METHOD DETAILS

- QUANTIFICATION AND STATISTICAL ANALYSIS
- ADDITIONAL RESOURCES

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2023.107165.

ACKNOWLEDGMENTS

The authors thank the National Cancer Institute, Information Management Services, and SEER program registries for the creation and maintenance of the database. This work was supported by the China National Key R&D (or Research and Development) Program (No. 2020AAA0105000 and 2020AAA0105004), the Natural Science Foundation of China (No. 82173328), the Natural Science Foundation of China (No. 81872160), the Natural Science Foundation of China (No. 82072940), the Natural Science Foundation of China (No. 82103047), the Natural Science Foundation of China (No. 82102887), the CAMS Innovation Fund for Medical Sciences (CIFMS) (No. 2021-I2M-C&T-A-012), the CAMS Innovation Fund for Medical Sciences (CIFMS) (No. 2021-I2M-C&T-B-044), the CAMS Innovation Fund for Medical Sciences (CIFMS) (No. 2022-I2M-C&T-B-087), the Non-profit Central Research Institute Fund of Chinese Academy of Medical Sciences (No. 2022-JKCS-04), the Beijing Association for Science and Technology's "Golden-Bridge Seed Funding Program" (No. ZZ22027), the Beijing Hope Run Special Fund of Cancer Foundation of China (No. LC2020L01), the Beijing Hope Run Special Fund of Cancer Foundation of China (No. LC2019L07), the Beijing Hope Run Special Fund of Cancer Foundation of China (No. LC2022A19), the Chinese Young Breast Experts Research project (No. CYBER-2021-005), the XianSheng Clinical Research Special Fund of China International Medical Foundation (No. Z-2014-06-2103), the Beijing Xisike Clinical Oncology Research Foundation (No. Y-Young2021-0017), and the Beijing Xisike Clinical Oncology Research Foundation (No. Y-NESTLE2022QN-0018). The graphical abstract was draw by Figdraw (https://www.figdraw.com/).

AUTHOR CONTRIBUTIONS

Conception and design: Q.L., J.W.

Collection and assembly of data: Q.L. and X.W.

Data analysis and interpretation: Q.L., W.Z., Qi.Li., and L.C.

Manuscript writing: Q.,L., W.Z., Qi.Li., and L.C.

Final approval of manuscript: Q.L., W.Z., Qi.Li, L.C., X.W., Z.W., Y.W., and J.W.

DECLARATION OF INTERESTS

The authors declare no competing interests.

INCLUSION AND DIVERSITY

We support inclusive, diverse, and equitable conduct of research.

Received: December 13, 2022
Revised: February 22, 2023
Accepted: June 13, 2023
Published: June 18, 2023

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
The Surveillance, Epidemiology, and End Results (SEER)	SEER program	https://seer.cancer.gov/
Software and algorithms		
SEER*Stat 8.3.9	NCI SEER program	https://seer.cancer.gov/seerstat/
R version 4.0.3	R Foundation for Statistical Computing	https://www.r-project.org/foundation/

RESOURCE AVAILABILITY

Lead contact

Further information and requests should be directed to and will be fulfilled by the lead contact, Professor Jing Wang (wangjing@cicams.ac.cn).

Materials availability

This study did not generate new unique reagents.

Data and code availability

This paper analyzes existing, publicly available data from the SEER program. Deposited data and software used are listed in the key resources table. All original code is available in supplemental information. Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

We examined the risk of cerebrovascular disease among cancer patients in the United States through more than 40 years of data. All data were accessed from SEER Research Plus Data14, covering approximately 9.4% of the U.S. population (based on the 2010 census), among which, incidence data comes from the original nine registries, and associated mortality data are maintained by the National Center for Health Statistics. Comparisons with the general US population were made using the 2000 US standard population as well as the standard millions for the US population, which are widely accepted and statistically sound15. This study was approved by the institutional review board at the National Cancer Center of China, and written informed consent was waived. We identified 3,843,261 patients with first primary or primary only cancer (51.3% male and 48.7% female) aged 0 to 80+ years from1975 to 2018. Among the study population, 63.4% of patients were order than 60 years old when diagnosed with cancer.

Ethics approval and consent to participate

The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

METHOD DETAILS

Our inclusion criteria are as follows: 1) Only patients with primary cancer only or their first primary cancer were included in this study, since cerebrovascular disease in patients with multiple primary cancers would confuse the real association between primary cancer sites and cerebrovascular disease. 2) Malignant or *in situ* cases 3) patients from all cancer sites. Finally, we identified 3,843,261 cancer patients, 73,857 of whom died from cerebrovascular disease. Patients were identified as having died of cerebrovascular disease only if the "COD to site record" class in the SEER program was coded as "cerebrovascular disease". Information for cerebrovascular diseases derived from the SEER database was coded using the International Classification of Diseases (ICD) system. Specifically, cerebrovascular diseases in the SEER database were derived from the following versions of the ICD system: ICD-8 (1968-1978), ICD-9 (1979-1998), and ICD-10 (1999+). The ICD codes used to identify cases of cerebrovascular disease in our study population were 430-438

(ICD-8 and ICD-9) and I60-I69 (ICD-10). For analyses of all cancers combined, all patients diagnosed with malignant cancer were incorporated. Patients were classified according to cancer sites and human organ systems according to the "Site Recode ICD-O-3/WHO 2008" class, which includes cancer of all human cancer sites. Patients' data, including cancer sites, sex, age, race, marital status, time of diagnosis, tumour stage, cause of death, vital status, and survival time, were obtained. Patient race was classified into four major categories, including American Indian/Alaskan Native, Asian or Pacific Islander, white and black according to the "Race Recode (W, B, AI, API)" class. Patient marital status was classified as divorced, married, separated, unmarried or domestic partner, single (never married), widowed, and unknown. The ages were divided into eight groups based on 10-year intervals. Each 10-year interval divided the year of diagnosis into five periods.

QUANTIFICATION AND STATISTICAL ANALYSIS

To examine the differences in the risk of cerebrovascular disease among cancer patients and the US general population collected by the National Center for Health Statistics in that category, absolute excess risk (AER) and Standardized mortality ratio (SMR) were calculated using standardized method implemented in SEER*Stat software.[26] The SMR was defined as the actual count of deaths caused by cerebrovascular disease/ the number of events expected to be experienced. The AER was defined as ((Observed count - Expected count) x 10,000) / Person years at risk. These measures compared the rates and the absolute excess cerebrovascular disease rate with the general population and reflect the proportional increase in the cerebrovascular disease rate, respectively. We present only for persons with those forms of cancer in whom 100,000 person-years or more of survival time in the data obtained from the SEER registries. The rate of cerebrovascular disease - was adjusted to the age, sex, and race of the cancer patients in the SEER database. All statistical analyses were two-sided and carried out through the Surveillance Research Program, National Cancer Institute SEER*Stat software (seer.cancer.gov/seerstat) version 8.3.9 and R Statistical Software version 4.0.3 (R Foundation for Statistical Computing). $P < .05$ was set as the statistical significance cutoff value.

ADDITIONAL RESOURCES

This study has not generated or contributed to a new website.