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Stroke mortality in cancer survivors: A population-based study in Japan

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ABSTRACT

Introduction: The association between cancer survivors and stroke deaths remains unclear. We aimed to evaluate the risk of fatal stroke in patients with cancer.
Materials and methods: This study was conducted using data from the Osaka Cancer Registry and vital statistics in Japan, collected from 1985 to 2013. We extracted patient data and investigated the causes of death. Standardized mortality ratios were calculated to compare the risk of stroke in patients with cancer to that in the general population. Poisson regression models were used to estimate the risk of stroke in patients with cancer and other cancer subgroups. Stroke types were used for risk stratification.
Results: We identified 688,473 eligible patients with cancer. The cohort contributed 2,668,126 person-years at risk. During the study period, 337,117 patients died; stroke was the cause of death in 5496 patients. Stroke types included cerebral infarction (3259), intracerebral hemorrhage (1539), subarachnoid hemorrhage (364), and other cerebrovascular diseases (334). The crude mortality rate from fatal stroke was 205.99 per 100,000 person-years. The standardized mortality ratio (95 % confidence interval) for fatal stroke was 1.75 (1.71–1.80). When stratified by stroke types, the ratios for cerebral infarction, intracerebral hemorrhage, and subarachnoid hemorrhage were 1.83 (1.76–1.89), 2.38 (2.26–2.50), and 2.28 (2.03–2.56), respectively. The risk of fatal stroke increased with time after cancer diagnosis. The multivariate Poisson regression model indicated that men were more likely to die of stroke than women.
Conclusions: Cancer survivors have a higher risk of fatal stroke than the general population across all stroke types.

1. Introduction

Cancer is a significant public health concern, with almost 10 million cancer deaths worldwide in 2020 [1,2]. In the European Union, 1,270,000 people were estimated to have died from cancer in 2020 [3]. In the United States, cancer is the third leading cause of death, accounting for approximately 600,000 deaths in 2020 [4]. In Japan, which has one of the most aged populations globally, cancer is the leading cause of death, with >380,000 cancer deaths (approximately 25 % of all deaths) in 2019 [5]. Although cancer deaths remain high, advances in cancer treatment have improved survival. The number of cancer survivors is expected to increase in the coming decades, and the management of comorbidities is becoming more significant.

Patients with cancer are at a high risk of developing stroke. Cancer type, stage, and histology are all associated with stroke risk [6–9]. Because of common risk factors, such as diabetes mellitus and smoking, cancer and stroke often go together. Numerous studies have shown a link between cancer and stroke development; however, the risk of stroke death in patients with cancer remains unclear. Recently, Zaorsky et al. investigated the causes of death in patients with cancer using the Surveillance, Epidemiology, and End Results (SEER) program and reported that patients with cancer had an increased risk of stroke mortality [10,11]. The risk of fatal stroke among patients with cancer was twice that of the general population and increased with longer follow-up. Chen et al. studied lung cancer and stroke death using SEER data and found that advanced age, male sex, and advanced cancer stage were associated with an increased risk of fatal stroke [12]. These findings emphasize the importance of stroke management in cancer survivors. However, the results remain controversial [13,14]. Furthermore, previous studies did not examine risk stratified by stroke types, such as

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cerebral infarction, intracerebral hemorrhage, and subarachnoid hemorrhage. Thus, the risk of death by stroke types in cancer survivors remains unknown.

This study aimed to evaluate the risk of fatal stroke after cancer diagnosis. We analyzed the risk of fatal stroke in patients with cancer compared to the general population and other patients with cancer stratified by stroke types.

2. Materials and methods

2.1. Data sources

This study was conducted as a part of the Neoplasms ANd other causes of DEath (NANDE) study, investigating the causes of death in patients with cancer. The NANDE database was created by linking the Osaka Cancer Registry (OCR) and vital statistics in Japan [15]. The OCR covered a population of 8.8 million and was monitored over 50 years, making it one of the largest population-based cancer registries in Japan. The OCR includes cancer-related information, such as sex, age at diagnosis, year of diagnosis, cancer type, stage at diagnosis, follow-up period, and death. All patients registered in the OCR were followed up for 10 years. The OCR only provides information on survival or death status, and vital statistics in Japan include the individual cause of death based on the death certificate completed by the doctor; hence, we collected the causes of death from vital statistics and merged them using sex, date of birth, date of death, and municipality of residence. Through this combination, information from 96.6 % of patients with cancer was collated. We deleted personal information after matching to create the database. Therefore, the NANDE database contains cancer-related patient information, including sex, age at diagnosis, year of diagnosis, cancer type, stage at diagnosis, survival time, and cause of death. However, the database does not contain information on cancer treatments, such as surgery, radiotherapy, and chemotherapy, or comorbidities, including hypertension, dyslipidemia, diabetes mellitus, and other stroke-related diseases.

Data from patients with cancer diagnosed between 1985 and 2013 were extracted from the NANDE database. A total of 1,007,199 patients with cancer during this period were identified. Of these, we excluded cases in which the following were uncertain: (1) date of death; (2) final date of survival confirmation; (3) date of first cancer diagnosis; (4) date of second cancer diagnosis; and (5) age at first cancer diagnosis. We also excluded cases with death certificate notification or death certification only, and patients with simultaneous or synchronous cancer. Simultaneous cancer refers to multiple tumors identified at the time of diagnosis, while synchronous tumors were defined as those diagnosed within two months of each other. The definition of synchronous tumors varies among studies from two to six months between diagnosis [16,17]. In total, 688,473 patients were included in the final analysis. The details are summarized in Fig. 1.

We grouped age at diagnosis into six categories: ≤39, 40–49, 50–59, 60–69, 70–79, and ≥80 years. In Japan, recombinant tissue-plasminogen activator and mechanical thrombectomy were approved in 2005 and 2010, respectively. Therefore, we divided the year of diagnosis into four periods: 1985–1994, 1995–2004, 2005–2009, and 2010–2013. The stage at diagnosis was classified into six groups: (i) intraepithelial (abnormal cells are present but have not spread to nearby tissues); (ii) localized (cancer is limited to the organ where it originated, with no sign of spread); (iii) lymph node metastasis (cancer has spread to regional lymph nodes); (iv) infiltration to adjacent organs (cancer has spread to nearby tissues or organs); (v) distant metastasis (cancer has metastasized to distant parts of the body); and (vi) unknown (there is insufficient information to determine the stage). Histology was classified into five categories according to Berg's classification [18]: squamous or basal cell carcinomas, adenocarcinomas, other carcinomas, hematopoietic tumors, and other histology. Baseline characteristics are shown in Table 1. Detailed histological groupings are described in Supplementary Table S1.

Cancers were coded according to the International Classification of Diseases (ICD)–Oncology Third Edition. Details concerning the assignment of codes and the number of patients (those included, excluded, and

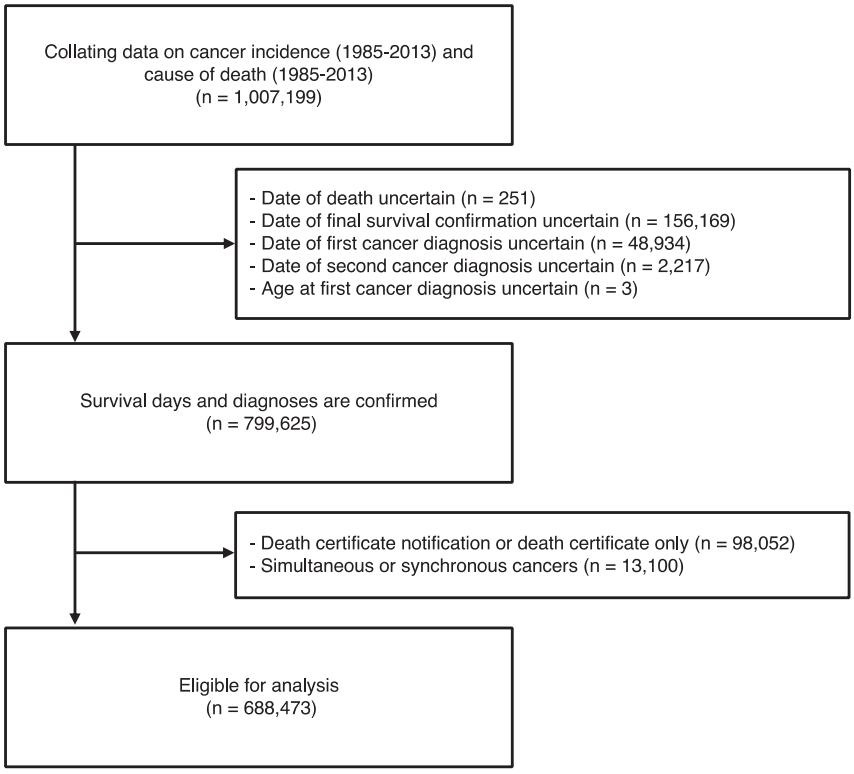

Fig. 1. Flow chart of eligible patients.

Table 1
Baseline characteristics.

	All		Female		Male	
	N	%	*N*	%	*N*	%
Patients	688,473	100.0 %	303,893	100.0 %	384,580	100.0 %
Age at diagnosis						
≤39	34,991	5.1 %	23,671	7.8 %	11,320	2.9 %
40–49	58,951	8.6 %	38,618	12.7 %	20,333	5.3 %
50–59	119,528	17.4 %	54,963	18.1 %	64,565	16.8 %
60–69	202,050	29.3 %	75,051	24.7 %	126,999	33.0 %
70–79	190,590	27.7 %	71,761	23.6 %	118,829	30.9 %
≥80	82,363	12.0 %	39,829	13.1 %	42,534	11.1 %
Period of diagnosis						
1985–1994	139,988	20.3 %	60,621	19.9 %	79,367	20.6 %
1995–2004	199,373	29.0 %	87,898	28.9 %	111,475	29.0 %
2005–2009	165,316	24.0 %	72,986	24.0 %	92,330	24.0 %
2010–2013	183,796	26.7 %	82,388	27.1 %	101,408	26.4 %
Stage at diagnosis						
Intraepithelial	36,331	5.3 %	21,637	7.1 %	14,694	3.8 %
Localized	277,236	40.3 %	123,411	40.6 %	153,825	40.0 %
Lymph node metastasis	87,716	12.7 %	43,990	14.5 %	43,726	11.4 %
Infiltration to adjacent organs	91,283	13.3 %	37,621	12.4 %	53,662	14.0 %
Distant metastasis	116,293	16.9 %	43,281	14.2 %	73,012	19.0 %
Unknown	64,105	9.3 %	27,340	9.0 %	36,765	9.6 %
N/A	15,509	2.3 %	6613	2.2 %	8896	2.3 %
Histology						
Adenocarcinoma	405,559	58.9 %	194,223	63.9 %	211,336	55.0 %
Squamous or basal carcinoma	105,537	15.3 %	38,855	12.8 %	66,682	17.3 %
Other carcinomas	77,049	11.2 %	24,972	8.2 %	52,077	13.5 %
Hematopoietic tumors	33,317	4.8 %	14,460	4.8 %	18,857	4.9 %
Other histology	67,011	9.7 %	31,383	10.3 %	35,628	9.3 %

N/A, not applicable.

lost to follow-up) are shown in Supplementary Table S2.

Stroke and its types, including cerebral infarction (ischemic stroke), intracerebral hemorrhage, subarachnoid hemorrhage, and other cerebrovascular diseases, were defined using ICD-9 and ICD-10 codes. In Japan, the causes of death were registered in the vital statistics record based on ICD-9 codes between 1979 and 1994, and ICD-10 codes since 1995. Details on the assignment of ICD-9 and ICD-10 codes are as follows: stroke, ICD-9 (430–438) and ICD-10 (I60–I69); cerebral infarction, ICD-9 (433–434, 437.7A, and 437.7B) and ICD-10 (I63 and I69.3); intracerebral hemorrhage, ICD-9 (431–432) and ICD-10 (I61 and I69.1); subarachnoid hemorrhage, ICD-10 (I60 and I69.0); and other cerebrovascular diseases, ICD-9 (435–436, 437.0–437.6, 437.8, 437.9, and 438) and ICD-10 (I62, I64–I67, I68, I69.2, I69.4, and I69.8). Until 1994, the Japanese government used ICD-9 codes and classified subarachnoid hemorrhage into the "other cerebrovascular diseases" category. Therefore, ICD-9 430 was assigned to other cerebrovascular diseases.

2.2. Statistical analysis

We analyzed the risk of stroke death after cancer diagnosis. Stroke death was defined as that in which the cause of death on the death certificate was a stroke. The observation period was from January 1985 to December 2013. Patients diagnosed with a second cancer during the observation period were censored at the time of diagnosis of the second cancer. The survival time was measured in days, with a minimum of 1 day and a maximum of 3652 days.

To compare the risk of fatal stroke in patients with cancer to that of the general population, we calculated standardized mortality ratios (SMRs), and their 95 % confidence intervals (CIs), as the ratio of the observed to the expected number of deaths. The expected number of deaths was computed using the annual Japanese sex- and age-specific death rates. These death rates were calculated by dividing the number of deaths by the national population within each 5-year age group and sex category for a calendar year. Both the national population and the number of deaths—including patients with and without cancer—were available from the Portal Site of Official Statistics of Japan, also known as the Japanese government statistics portal site. SMRs were calculated for stroke and its types. The SMR for subarachnoid hemorrhage was calculated only from 1995 to 2013, because the reference rate between 1985 and 1994 was unavailable in Japan.

To compare the risk of fatal stroke in patients with cancer and various cancer subgroups, we used Poisson regression models to estimate the relative risk (RR) and 95 % CIs. RRs were adjusted for sex, age at diagnosis, period of diagnosis, stage at diagnosis, and histology.

Statistical analysis was performed using Stata 17/MP (StataCorp, College Station, TX, USA) and R (https://cran.r-project.org/) software. The level of significance was set at $P < 0.05$. All tests were two-tailed.

3. Results

The cohort contributed a total of 2,668,126 person-years at risk, with a median follow-up period of 4.12 years after cancer diagnosis. By the end of December 2013, 337,117 patients had died. Of these, 5496 deaths were attributable to stroke, including cerebral infarction (3259), intracerebral hemorrhage (1539), subarachnoid hemorrhage (364), and other cerebrovascular diseases (334). The number of deaths in relation to cancer and stroke type is shown in Supplementary Table S3.

3.1. Risk of fatal stroke in patients with cancer compared to the general population

Among all patients with cancer, the crude mortality rate due to fatal stroke was 205.99 per 100,000 person-years, and the overall SMR for fatal stroke was 1.75 (95 % CI: 1.71–1.80). Table 2 shows the characteristics of all patients with cancer and those who died of stroke. Patients who were diagnosed with cancer at a younger age had a higher SMR for

Table 2
Standardized mortality ratios for fatal stroke in patients with cancer compared to the general population.

	Person-years	Stroke death		Stroke death rate[a]	SMR (95 % CI)[b]
		Observed	Expected		
All patients	2,668,126	5496	3135.07	205.99	1.75 (1.71–1.80)
Sex					
Female	1,327,194	2056	1120.68	154.91	1.84 (1.76–1.92)
Male	1,340,932	3440	2014.39	256.54	1.71 (1.65–1.77)
Age at diagnosis					
≤39	137,302	15	0.24	10.92	61.36 (36.99–101.78)
40–49	235,581	71	4.52	30.14	15.72 (12.46–19.84)
50–59	467,639	232	41.26	49.61	5.62 (4.94–6.39)
60–69	762,290	859	192.63	112.69	4.46 (4.17–4.77)
70–79	738,614	1892	657.02	256.16	2.88 (2.75–3.01)
≥80	326,700	2427	2239.39	742.88	1.08 (1.04–1.13)
Period of diagnosis					
1985–1994	620,728	1799	1101.54	289.82	1.63 (1.56–1.71)
1995–2004	1,026,769	2092	1214.74	203.75	1.72 (1.65–1.80)
2005–2009	675,886	1128	570.19	166.89	1.98 (1.87–2.10)
2010–2013	344,741	477	248.60	138.35	1.92 (1.75–2.10)
Stage at diagnosis					
Intraepithelial	176,976	208	90.20	117.53	2.31 (2.01–2.64)
Localized	1,447,590	2954	1619.46	204.06	1.82 (1.76–1.89)
Lymph node metastasis	388,820	722	425.91	185.69	1.70 (1.58–1.82)
Infiltration to adjacent organs	235,055	504	334.51	214.42	1.51 (1.38–1.64)
Distant metastasis	154,395	409	281.05	264.90	1.46 (1.32–1.60)
Unknown	219,581	628	338.63	286.00	1.86 (1.72–2.01)
N/A	45,710	71	45.31	155.33	1.57 (1.24–1.98)
Histology					
Adenocarcinoma	1,760,219	3355	1859.64	190.60	1.80 (1.74–1.87)
Squamous or basal carcinoma	410,921	962	596.88	234.11	1.61 (1.51–1.72)
Other carcinomas	207,771	476	307.18	229.10	1.55 (1.42–1.70)
Hematopoietic tumors	111,465	175	109.35	157.00	1.60 (1.38–1.86)
Other histology	177,751	528	262.03	297.05	2.02 (1.85–2.19)

CI, confidence interval; N/A, not applicable; SMR, standardized mortality ratio.
[a] Per 100,000 person-years.
[b] SMRs may not equal the number of observed deaths divided by expected deaths because expected deaths are only listed to two decimal places.

fatal stroke, and SMRs gradually decreased as patients were diagnosed at an older age. SMRs gradually increased as patients were diagnosed later in the diagnostic period and were similar for those diagnosed in the periods 2005–2009 and 2010–2013. The SMR by stage at diagnosis was highest for intraepithelial cancer and lowest for distant metastases. The SMR was higher in all histologies than in the general population.

3.2. Risk of cerebral infarction, intracerebral hemorrhage, and subarachnoid hemorrhage in patients with cancer

Table 3 shows the SMRs stratified by stroke types. The number of observed and expected deaths in relation to stroke type is shown in Supplementary Table S4. The crude mortality rates due to cerebral infarction, intracerebral hemorrhage, and subarachnoid hemorrhage were 122.15, 57.68, and 14.07 per 100,000 person-years, respectively. The SMRs for cerebral infarction, intracerebral hemorrhage, and subarachnoid hemorrhage were 1.83 (95 % CI: 1.76–1.89), 2.38 (95 % CI: 2.26–2.50), and 2.28 (95 % CI: 2.03–2.56), respectively. Females had higher SMRs for cerebral infarction, intracerebral hemorrhage, and subarachnoid hemorrhage than males. Regarding age at diagnosis, SMRs for cerebral infarction and subarachnoid hemorrhage were highest in patients with a younger age at diagnosis. In contrast, the SMR for intracerebral hemorrhage was highest in patients aged 40–49 years at diagnosis. Patients diagnosed with cancer between 2010 and 2013 had higher SMRs for all stroke types than those who had been diagnosed earlier in the diagnostic period. Regarding stage at diagnosis, patients with intraepithelial cancers had higher SMRs than those at other stages. The histological types differed in terms of the SMRs for cerebral infarction, intracerebral hemorrhage, and subarachnoid hemorrhage. Since adenocarcinomas are reportedly associated with developing cerebral infarction, we hypothesized that patients with adenocarcinomas had a higher risk of death from cerebral infarction than those with other histological types. However, our analysis showed that the SMR for cerebral infarction was highest in those with other histological types, rather than in those with adenocarcinomas.

3.3. SMR for fatal stroke among patients with cancer stratified by cancer site

Fig. 2 shows the SMRs for fatal stroke stratified by cancer site. The details are listed in Supplementary Table S5. The SMR was highest in brain tumors, followed by skin, ovarian, pancreatic, and uterine cancer. The SMR was lowest in bone tumors, followed by lung, prostate, laryngeal, and bladder cancer.

3.4. Risk of fatal stroke according to time after cancer diagnosis

Fig. 3 shows the trend in SMR after cancer diagnosis. The details are shown in Supplementary Tables S6–S9. The SMR for fatal stroke was 1.64 (95 % CI: 1.53–1.83) within the first three months; it tended to decrease by two years after cancer diagnosis and increased thereafter. The trend in SMR for cerebral infarction was similar to that for stroke. The SMR for intracerebral hemorrhage increased until the fifth year, decreased once in the sixth year, and increased thereafter. The SMR for subarachnoid hemorrhage was the lowest within the first three months and highest in the ninth year after cancer diagnosis.

3.5. Fatal stroke risk by cancer patient subgroups

Table 4 shows the RRs of fatal stroke in patients with cancer stratified by subgroup. Males were 1.4 times more likely to die from stroke than females. RRs gradually increased as the patients were diagnosed at an older age and also decreased later in the diagnostic period. Among the known cancer stages, patients with distant metastases had the highest

Table 3
Standardized mortality ratios for fatal stroke stratified by stroke types in patients with cancer compared to the general population.

	Cerebral infarction		Intracerebral hemorrhage		Subarachnoid hemorrhage	
	Rate[b]	SMR (95 % CI)	Rate[b]	SMR (95 % CI)	Rate[b]	SMR (95 % CI)
All patients	122.15	1.83 (1.76–1.89)	57.68	2.38 (2.26–2.50)	14.07	2.28 (2.03–2.56)
Sex						
Female	88.61	1.85 (1.75–1.96)	37.45	2.46 (2.25–2.68)	16.55	2.65 (2.27–3.08)
Male	155.34	1.81 (1.73–1.89)	77.71	2.34 (2.20–2.49)	11.65	1.92 (1.61–2.29)
Age at diagnosis						
≤39	2.18	175.68 (56.66–544.70)	5.10	14.79 (7.05–31.01)	4.11	72.63 (27.26–193.52)
40–49	8.91	67.32 (43.89–103.25)	13.58	18.10 (12.80–25.60)	3.20	6.14 (2.55–14.74)
50–59	16.68	16.23 (13.00–20.27)	20.10	4.87 (3.98–5.96)	10.45	5.40 (3.86–7.56)
60–69	50.24	7.29 (6.60–8.06)	44.60	4.27 (3.84–4.75)	10.87	3.21 (2.51–4.10)
70–79	151.09	3.53 (3.33–3.74)	72.70	2.83 (2.60–3.08)	15.51	2.39 (1.95–2.92)
≥80	507.50	1.17 (1.12–1.23)	161.92	1.48 (1.36–1.62)	31.78	1.46 (1.18–1.80)
Period of diagnosis						
1985–1994[a]	163.68	1.46 (1.37–1.55)	81.19	2.09 (1.92–2.28)	–	–
1995–2004	124.08	1.72 (1.63–1.82)	56.00	2.14 (1.98–2.33)	15.88	1.90 (1.63–2.22)
2005–2009	101.35	2.49 (2.31–2.68)	47.79	2.96 (2.65–3.30)	12.43	2.62 (2.12–3.25)
2010–2013	82.38	3.95 (3.51–4.44)	39.74	4.72 (3.99–5.58)	11.89	4.96 (3.65–6.73)
Stage at diagnosis						
Intraepithelial	63.85	2.42 (2.01–2.91)	37.86	4.33 (3.41–5.50)	9.73	4.64 (2.80–7.70)
Localized	119.30	1.86 (1.77–1.95)	57.54	2.56 (2.40–2.74)	15.07	2.88 (2.47–3.35)
Lymph node metastasis	107.25	1.71 (1.55–1.88)	54.01	2.26 (1.97–2.59)	12.39	1.89 (1.35–2.65)
Infiltration to adjacent organs	130.61	1.67 (1.49–1.87)	55.73	1.86 (1.56–2.20)	14.54	1.74 (1.20–2.53)
Distant metastasis	167.75	1.66 (1.47–1.88)	73.19	1.77 (1.47–2.13)	11.88	0.98 (0.59–1.63)
Unknown	179.43	1.95 (1.77–2.15)	75.14	2.38 (2.04–2.77)	15.39	1.88 (1.28–2.76)
N/A	91.88	1.74 (1.29–2.36)	43.75	2.06 (1.33–3.19)	13.93	1.97 (0.82–4.74)
Histology						
Adenocarcinoma	114.82	1.91 (1.83–2.00)	51.07	2.39 (2.24–2.55)	13.44	2.51 (2.17–2.90)
Squamous or basal carcinoma	144.55	1.71 (1.58–1.86)	60.84	2.06 (1.82–2.33)	14.36	2.14 (1.59–2.88)
Other carcinomas	86.63	1.10 (0.95–1.27)	110.22	3.06 (2.69–3.49)	21.05	2.01 (1.44–2.80)
Hematopoietic tumors	98.69	1.86 (1.55–2.25)	33.19	1.60 (1.16–2.21)	14.70	2.40 (1.39–4.13)
Other histology	199.16	2.22 (2.00–2.47)	69.76	2.41 (2.02–2.88)	10.49	1.32 (0.77–2.28)

CI, confidence interval; N/A, not applicable; SMR, standardized mortality ratio.
[a] Mortality rates for subarachnoid hemorrhage from 1985 to 1994 were not available in Japan; therefore, we calculated the standardized mortality ratio for subarachnoid hemorrhage from 1995 to 2013.
[b] Per 100,000 person-years.

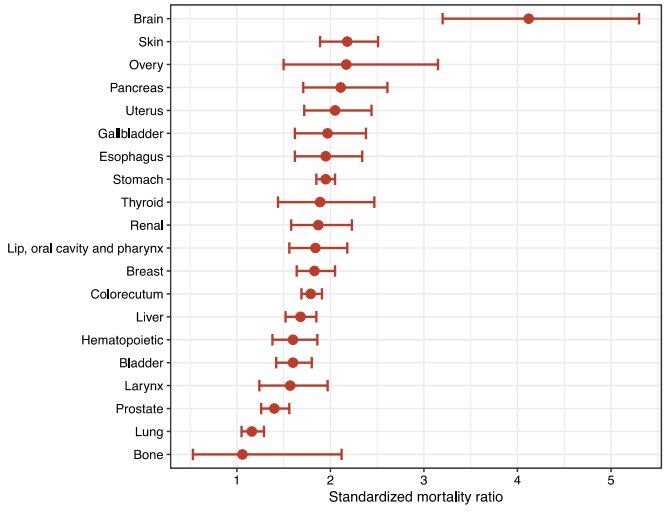

Fig. 2. Standardized mortality ratio for fatal stroke stratified by cancer site. The ordinate shows that the cancer site and the abscissa indicate the standardized mortality ratio (SMR) for fatal stroke. The error bar shows the 95 % confidence interval. The plots are in order of increasing SMR. Patients with cancer, except for those with bone tumors, had a higher SMR for fatal stroke than the general population. Brain tumors had the highest SMR of all cancer sites, while prostate cancer, with one of the highest survival rates, had a relatively low SMR for fatal stroke. Conversely, pancreatic cancer, with a low survival rate, had a high SMR for fatal stroke.

RR. Table 5 shows the RRs for stroke types. Males were more likely to die from cerebral infarction and intracerebral hemorrhage than females, whereas females were more likely to die from subarachnoid hemorrhage than from cerebral infarction and intracerebral hemorrhage. The RRs were higher for patients who were older at diagnosis and lower for those more recently diagnosed across all stroke types. When analyzed according to stage at diagnosis, the RR was highest for distant metastasis in cerebral infarction and intracerebral hemorrhage and for infiltration to adjacent organs in subarachnoid hemorrhage among the known stages. The RRs varied according to histological and stroke types. The results in relation to cerebral infarction showed that squamous or basal carcinoma and other histologies had higher RRs than adenocarcinoma.

4. Discussion

The current study used data across 29 years to analyze the risk of fatal stroke in patients with cancer stratified by stroke types. We found that cancer survivors have a significantly higher risk of death from cerebral infarction, intracerebral hemorrhage, and subarachnoid hemorrhage. This study is unique in that it focuses on the risk of fatal stroke according to stroke types, which was previously unavailable.

Limited data are available on stroke deaths after cancer diagnosis. The most extensive study to date is that of Zaorsky et al. [10]. They analyzed >7.5 million patients with cancer using SEER data and compared the risk of fatal stroke to that in the general population in the United States. The risk was approximately twice as high in patients with cancer compared to the general population. We observed a similar association in this study—patients with cancer had a risk of stroke death 1.7 times higher than that of the general population. The results were also similar in the subgroup analyses of sex, age at diagnosis, year of diagnosis, and stage at diagnosis. However, our results differed from

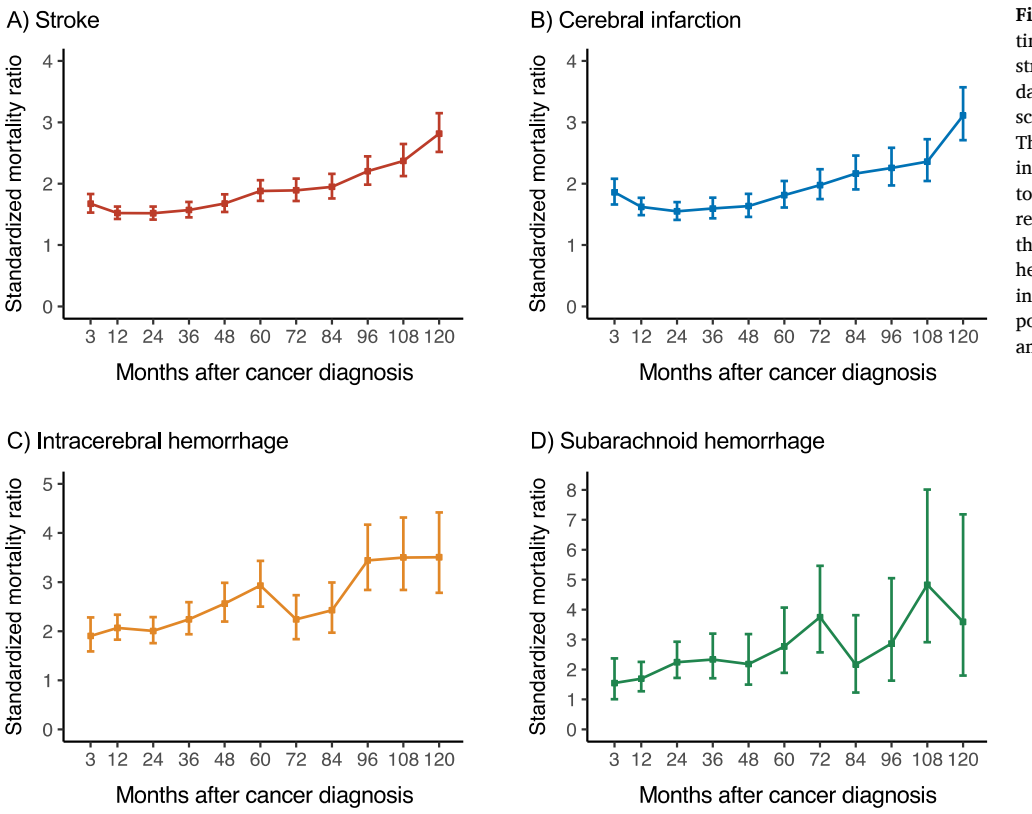

Fig. 3. Standardized mortality ratio and time after cancer diagnosis stratified by stroke types. The ordinate shows the standardized mortality ratio (SMR) and the abscissa indicates time after cancer diagnosis. The error bar shows the 95 % confidence interval. (A) The SMR for fatal stroke tended to increase with time. (B) The SMR for cerebral infarction showed a similar trend to that of stroke. (C–D) In the analysis of hemorrhagic stroke, the SMRs were higher in patients with cancer than in the general population throughout the follow-up period, and the values varied with time.

Table 4
Relative risk of fatal stroke in patients with cancer.

	RR	95 % CI	*P*-value
Sex			
Female	1.00	–	
Male	1.46	1.38–1.54	<0.001
Age at diagnosis			
≤39	1.00	–	
40–49	3.24	1.86–5.67	<0.001
50–59	5.08	3.01–8.57	<0.001
60–69	11.89	7.13–19.85	<0.001
70–79	28.34	17.02–47.20	<0.001
≥80	85.78	51.54–142.76	<0.001
Period of diagnosis			
1985–1994	1.00	–	
1995–2004	0.57	0.54–0.61	<0.001
2005–2009	0.41	0.38–0.44	<0.001
2010–2013	0.33	0.30–0.36	<0.001
Stage at diagnosis			
Intraepithelial	1.00	–	
Localized	1.17	1.01–1.35	0.03
Lymph node metastasis	1.26	1.07–1.47	0.004
Infiltration to adjacent organs	1.31	1.11–1.54	0.001
Distant metastasis	1.67	1.41–1.98	<0.001
Unknown	1.52	1.29–1.78	<0.001
N/A	1.78	1.28–2.48	0.001
Histology			
Adenocarcinoma	1.00	–	
Squamous or basal carcinoma	1.13	1.05–1.22	0.001
Other carcinomas	1.23	1.11–1.36	<0.001
Hematopoietic tumors	0.91	0.75–1.10	0.33
Other histology	1.57	1.43–1.73	<0.001

CI, confidence interval; N/A, not applicable; RR, relative risk.

those of previous studies. For instance, this study indicated that the SMR of liver cancer was 1.6, while a previous report has shown an SMR of 9 or higher. Additionally, the SMR by stage at diagnosis was highest in distant metastases and lowest in localized cancers in previous research but the opposite in our study, in which the SMR was lowest in distant metastases and highest in intraepithelial cancer. Although the SMRs cannot be compared due to the different populations, these findings are noteworthy in the context of prognosis and stroke risk management in patients with cancer. It is uncertain what influenced the results, but regional differences may have affected the findings.

Several mechanisms have been suggested to explain the relationship between cancer and stroke. For example, cancer and stroke share common risk factors, such as diabetes mellitus and smoking; hence, patients with cancer and diabetes mellitus or those who smoke are also at a high risk of developing stroke [19,20]. Moreover, coagulation abnormalities from malignancies can lead to cerebrovascular complications of both ischemic and hemorrhagic stroke [21,22]. Tumors can directly compress surrounding tissues and vessels, resulting in thrombus formation and ischemic stroke [23]. Treatment-related factors, such as surgery or chemo- and/or radiation therapy, increase the risk of stroke [23–26]. Additionally, cancer patients have a high incidence of atrial fibrillation (AF) [27,28]. This is problematic because AF contributes to the increased risk of cardioembolism and hemorrhagic stroke due to the use of anticoagulants in AF treatment. AF is an independent risk factor for stroke in patients with cancer [7], and causes more severe symptoms than other stroke types [29,30]. These factors seem to be associated with stroke mortality in patients with cancer.

The SMRs and RRs analyzed by stroke types are informative because they provide previously unavailable information. It is noteworthy that patients with cancer have an increased risk of death due to intracerebral hemorrhage. Although there have been studies of an increased risk of cerebral infarction in patients with cancer [6,9,31–36], few reports are available on the risk of intracerebral hemorrhage [22]. In addition to the standard risk factors for cancer and stroke, coagulation abnormalities and secondary hemorrhage from primary and metastatic brain tumors in patients with malignancies are associated with an increased risk of fatal intracerebral hemorrhage. Thus, cancer is associated with worse outcomes in patients with intracerebral hemorrhage [37]. Furthermore, it is

Table 5
Relative risk of fatal stroke stratified by stroke types in patients with cancer.

	Cerebral infarction			Intracerebral hemorrhage			Subarachnoid hemorrhage		
	RR	95 % CI	*P*-value	RR	95 % CI	*P*-value	RR	95 % CI	*P*-value
Sex									
Female	1.00	–		1.00	–		1.00	–	
Male	1.55	1.44–1.67	<0.001	1.79	1.61–2.00	<0.001	0.62	0.49–0.78	<0.001
Age at diagnosis									
≤39	1.00	–		1.00	–		1.00	–	
40–49	5.07	1.51–17.00	0.009	3.01	1.33–6.85	0.009	0.78	0.21–2.91	0.71
50–59	8.97	2.83–28.44	<0.001	4.07	1.88–8.80	<0.001	2.60	0.91–7.40	0.07
60–69	27.79	8.91–86.67	<0.001	8.90	4.19–18.91	<0.001	2.91	1.04–8.09	0.04
70–79	87.18	28.03–271.10	<0.001	15.18	7.16–32.16	<0.001	4.23	1.53–11.67	0.005
≥80	301.65	97.06–937.47	<0.001	36.79	17.37–77.91	<0.001	8.45	3.06–23.32	<0.001
Period of diagnosis									
1985–1994[a]	1.00	–		1.00	–		–	–	
1995–2004	0.61	0.56–0.66	<0.001	0.58	0.51–0.65	<0.001	1.00	–	
2005–2009	0.43	0.39–0.47	<0.001	0.44	0.38–0.51	<0.001	0.74	0.57–0.97	0.03
2010–2013	0.33	0.29–0.38	<0.001	0.35	0.29–0.43		0.71	0.50–1.01	0.06
Stage at diagnosis									
Intraepithelial	1.00	–		1.00	–		1.00	–	
Localized	1.26	1.04–1.52	0.02	1.02	0.79–1.31	0.90	1.31	0.77–2.25	0.32
Lymph node metastasis	1.35	1.10–1.67	0.005	1.16	0.88–1.53	0.30	1.16	0.62–2.14	0.65
Infiltration to adjacent organs	1.46	1.17–1.81	0.001	1.06	0.79–1.42	0.71	1.34	0.71–2.53	0.36
Distant metastasis	1.93	1.54–2.42	<0.001	1.43	1.05–1.95	0.02	1.16	0.56–2.41	0.70
Unknown	1.70	1.37–2.10	<0.001	1.28	0.95–1.71	0.10	1.40	0.73–2.70	0.31
N/A	1.82	1.19–2.78	0.006	2.53	1.28–4.99	0.007	1.38	0.40–4.77	0.61
Histology									
Adenocarcinoma	1.00	–		1.00	–		1.00	–	
Squamous or basal carcinoma	1.15	1.05–1.26	0.003	1.09	0.95–1.26	0.23	1.15	0.82–1.61	0.43
Other carcinomas	0.78	0.67–0.91	0.002	2.12	1.83–2.46	<0.001	1.65	1.15–2.38	0.007
Hematopoietic tumors	0.98	0.77–1.25	0.86	0.56	0.35–0.89	0.02	1.26	0.61–2.61	0.53
Other histology	1.71	1.52–1.93	<0.001	1.44	1.18–1.75	<0.001	0.83	0.46–1.47	0.52

CI, confidence interval; N/A, not applicable; RR, relative risk.
[a] Mortality rates for subarachnoid hemorrhage from 1985 to 1994 were not available in Japan; therefore, we calculated the relative risk for subarachnoid hemorrhage from 1995 to 2013.

noteworthy that the SMRs were highest for all stroke types diagnosed between 2010 and 2013. Advances in cancer treatment have increased the number of cancer survivors, which is likely linked to a high risk of stroke-related death, because cancer and stroke share common risk factors. Subsequent risk management of stroke is essential for patients with cancers that can be detected and treated early.

Notably, when assessed within the first year of cancer diagnosis, the risk of fatal stroke was highest in the first three months. One possible factor contributing to the results is cancer treatment, which is often initiated immediately after cancer diagnosis. Surgery has been reported to be a risk factor for stroke in brain tumors [23]. Reports also indicate that particular types of chemotherapy, such as cisplatin therapy, cause vascular toxicity—a risk factor for stroke [25,26]. Moreover, radiation to the head and neck can cause atherosclerosis, which is another risk factor for stroke [31]. Based on these insights, cancer treatment may be associated with an increase in the SMR for fatal stroke after cancer diagnosis.

When examining the SMR for fatal stroke by cancer site, brain tumors showed the highest risk of fatal stroke. This is most likely due to the direct compression of tissues by tumors and/or the surgical procedures for brain tumors [23,24]. Other notable findings show that cancers with a higher survival rate do not always have a higher SMR for fatal stroke. For instance, prostate cancer has a high survival rate, but low SMR; conversely, pancreatic cancer and gallbladder cancer have a low survival rate, but high SMR. These results indicate that other risk factors for stroke, such as cancer treatment and patient lifestyle, may be involved.

Adenocarcinoma with mucin production has been implicated in the development of cerebral infarction [38,39], possibly because it is frequently associated with clotting disorders via the production and secretion of mucin [19]. Based on these previous reports, we sought to determine whether adenocarcinoma was associated with fatal cerebral infarction. Our findings indicated that the RR for fatal cerebral infarction was higher in squamous or basal carcinoma and other histologies than in adenocarcinoma. It would appear that our results accord with previous findings that squamous cell carcinoma is generally associated with smoking; thus, increasing the risk of death [40,41]. It remains unclear why patients with other histologies had a higher risk of fatal stroke than those with adenocarcinoma; however, it may be because other histologies include histological types associated with brain tumors.

In the patients included in this study, a diagnosis of cancer is deemed to be reliable because physicians register the diagnosis following a full and thorough patient examination at a medical institution. However, there may be inaccuracies in stroke deaths reported on death certificates [42]. It is possible that actual deaths from stroke have been overlooked, or that sudden deaths of unknown cause have been incorrectly classified as stroke deaths. Because cancer survivors tend to be followed very carefully, it is likely that strokes are overlooked less frequently in cancer survivors than in the general population, which may lead to the appearance of an exaggerated increase in the incidence of stroke among cancer survivors. In terms of stroke diagnoses, as death certificates alone have been shown to be less accurate than hospital data [43], which is also a concern in previous studies examining the causes of death among patients with cancer using death certificates [10–14]. It is essential to understand these issues in studies investigating causes of death in cancer survivors based on death certificates.

This study has several limitations. First, we were unable to analyze risks by adjusting for confounding variables, such as vascular risk factors. Second, advances in cancer treatment influence prognosis; however, information regarding treatment was unavailable. Third, we excluded cases from the study with incomplete information concerning survival days or diagnosis dates, death certificate notification or death certificate only, as well as cases of simultaneous or synchronous cancers. Approximately 3.4 % of patients were lost to follow-up. When comparing cancer types between patients that were included, excluded, and lost to follow-up, the proportions were similar for many cancer

types. However, colorectal, breast, uterus, and prostate cancers were more common in the analyzed cases. In contrast, liver, gallbladder, pancreatic, and lung cancers were more common in the patients we excluded and those lost to follow-up. This may have resulted in selection bias. Fourth, patients who had a stroke prior to their cancer diagnosis were not excluded. We followed patients with stroke after their cancer diagnosis but could not strictly distinguish between first and recurrent stroke events. Fifth, the follow-up period of 10 years after cancer diagnosis may not have been sufficiently long enough to investigate stroke deaths. Finally, it should be noted that the results of this study are limited to the Japanese population. However, the risk of fatal stroke was similar to that found in previous studies that used SEER data [9,10]. Furthermore, data for people of Asian ethnicities are limited, and previous study results involving people of Asian ethnicity [12] have differed from results based on people of European ethnicity [13]. Therefore, we consider that the results of this study are likely to be highly informative.

In conclusion, cancer survivors are at increased risk of developing cerebrovascular diseases because of sharing risk factors such as obesity and smoking, which can lead to fatal outcomes. Careful follow-up for cancer survivors in clinical practice is required, given our findings concerning their greater risk of fatal stroke.

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Ethics approval and consent to participate

Informed consent was waived owing to the retrospective nature of the study. The Institutional Review Board of Osaka University, Suita, Japan, approved the study protocol (approval number: 17315-3).

CRediT authorship contribution statement

Y.G., T. Sasaki., H.M., T. Sobue., and I.M. contributed to the conception and design of the study. Y.G., L.Z., T.M., Y.O., T. Sobue., and I.S. contributed to the acquisition and analysis of data. Y.G., L.Z., T. Sasaki., T.M., T. Sobue., and I.M. contributed to the drafting of a significant portion of the manuscript or figures. All authors approved the final manuscript.

Declaration of competing interest

None.

Data availability

Data are available on reasonable request to the corresponding author.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2023.01.005.

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