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Original article

Cardiovascular outcomes and mortality after incident ischaemic stroke in patients with a recent cancer history

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ABSTRACT

Background: Up to 10% of patients with ischaemic stroke have comorbid cancer and stroke in these patients is thought to have a poor short-term prognosis. There is little known about the long-term cardiovascular morbidity and mortality outcomes after incident ischaemic stroke in patients with recent cancer history.

Objective: To assess the risk of subsequent cardiovascular morbidity and mortality outcomes in patients with an incident ischaemic stroke and recent cancer history.

Methods: Patients aged ≥18 years with an incident ischaemic stroke between 1998 and 2017, with any diagnosis of cancer within 12 months before the stroke event, and no prior history of serious vascular event were identified from UK Clinical Practice Research Datalink (CPRD GOLD) linked to Hospital Episode Statistics (HES) data. To minimize selection bias, these patients were propensity-score matched with patients with incident ischaemic stroke and no history of cancer. Propensity-score matching was done using covariates such as demographic data, vascular risk factors, comorbid conditions, and prescribed medication. Multivariable models (Competing risks and Cox regression) were used to determine the risk of subsequent major adverse cardiovascular event (MACE) outcomes and all-cause mortality.

Results: Our cohort included 22,460 patients with a median age of 75 (IQR 64–83) years and a follow-up of 12.3 (IQR 7.2–16.7) years. Recent cancer was identified in 1,149 patients (5.1%) at the time of incident ischaemic stroke. The patients with recent cancer history had a lower risk of composite MACE (sub-distribution hazard ratio (SHR) 0.83 [95% CI: 0.75–0.92]) and recurrent stroke (SHR 0.85 95% CI:0.75–0.96]) and a higher risk of all-cause mortality (hazard ratio 1.67 [95% CI:1.47–1.91]). The risk of coronary heart disease, peripheral vascular disease, heart failure, and CVD-related death outcomes did not differ significantly between the groups.

Conclusions: After incident ischaemic stroke, patients with recent cancer history have a lower risk of composite MACE and recurrent stroke outcomes but a higher risk of all-cause mortality when compared with patients without a prior history of cancer.

1. Introduction

Evidence from previous studies suggests a relationship between ischaemic stroke and cancer such that 1 in 10 patients with ischaemic stroke has been shown to have comorbid cancer [1–3]. The most frequent types of cancer in patients with stroke are urogenital, breast and gastrointestinal [4]. Also, it has been shown that the incidence of stroke is highest in the short term in patients diagnosed with lung, colorectal and pancreatic cancers [5]. Cancer increases the risk of stroke through several mechanisms including hypercoagulability, nonbacterial endocarditis, direct tumor effects including compression of blood vessels by the primary tumor or metastases to the brain, and cancer-associated treatments such as chemotherapy, surgery and post-radiation vasculopathy [6]. Studies report that thrombolytic treatment for cancer-associated acute ischaemic stroke is generally a safe and effective treatment for patients who meet the criteria for reperfusion therapy and

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is not associated with an increased risk of intracerebral hemorrhage or mortality [7,8]. The guidance on optimal antithrombotic strategy for secondary stroke prevention in patients with cancer-related ischaemic strokes is less clear [1], with recent study findings showing no difference in rates of recurrent strokes and mortality between aspirin and rivaroxaban treatments in patients with embolic stroke and history of cancer [9].

While several small studies have assessed mortality risk associated with cancer-related strokes [10,11], there is little known about the independent long-term risk of cardiovascular morbidity and death after incident ischaemic stroke in patients with a recent history of cancer. Using a large population-based cohort in the United Kingdom, this study aimed to assess the risk of cardiovascular morbidity and mortality outcomes following incident ischaemic stroke in patients with a recent history of cancer, after controlling for potential confounding bias.

2. Methods

2.1. Data availability

The data supporting the findings of this study are available from Clinical Practice Research Datalink (www.cprd.com). Restrictions apply to the availability of these data used under license for the current study, hence it is not publicly available.

2.2. Data source

This prospective population-based cohort study used the UK Clinical Practice Research Datalink (CPRD) GOLD database of anonymised longitudinal primary care electronic health records [12], linked to secondary care hospitalization data (Hospital Episode Statistics [HES]) [13], national mortality data (Office for National Statistics [ONS]) [14], and social deprivation data (Index of Multiple Deprivation (IMD) 2015) [15]. Patients included in CPRD GOLD database, from a network of general practices across the UK, are representative of the UK general population in terms of sex, age, and ethnicity [12], thereby validating CPRD GOLD for epidemiological research. The study complied with the Declaration of Helsinki and was approved by the Independent Scientific Advisory Committee of the Medicines and Healthcare products Regulatory Agency (Protocol number 19_023R).

2.3. Study population

We identified a cohort of patients with incident non-fatal stroke in either primary care (CPRD GOLD) or secondary care (HES) between 1 January 1998 and 31 December 2017 [16]. Patients with a prior record of coronary heart disease (CHD), peripheral vascular disease (PVD), or heart failure before an incident stroke event were excluded. Patients were followed from the date of incident stroke diagnosis until they developed a major adverse cardiovascular event (MACE), died, ceased contributing data, or last data collection date (22-Aug-2019). Patients with a cancer diagnosis within 12 months before the incident stroke were considered to have a recent history of cancer. The study flow diagram is shown in Fig. 1.

2.4. Cohort demographics and baseline characteristics

Age was defined at the time of the incident stroke. Ethnicity was categorised into six groups: Asian, Black, Mixed, Other, White, and unknown [17]. To describe socioeconomic status, the English Index of Multiple Deprivation (IMD) 2015 [15] linked to the patient's residential postcode was used. IMD is a weighted mean across seven domains, hence

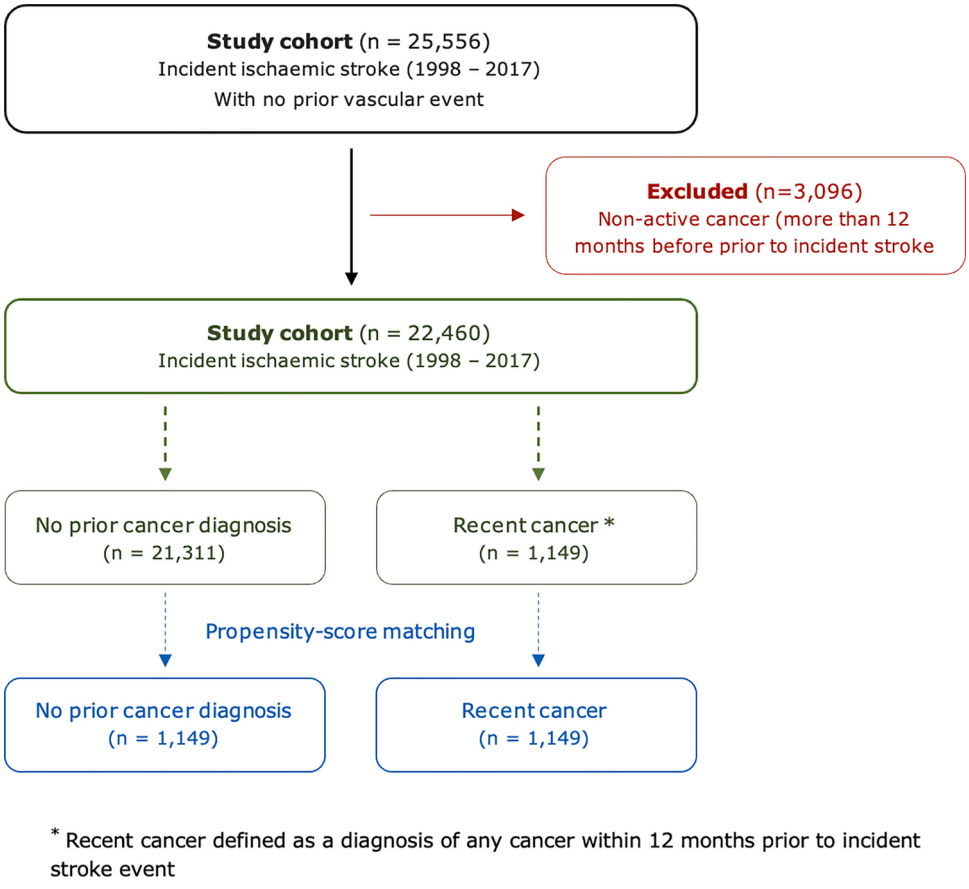

Fig. 1. Study flow diagram.

offering a single score to describe the concept of deprivation; categorised into quintiles (quintile 1 – least deprived group, to quintile 5 – most deprived group). Medication prescriptions (issue of a prescription) at baseline were defined as any prescription within the 12 months before the incident stroke. For cholesterol (low-density lipoprotein (LDL), high-density lipoprotein (HDL) and total), body mass index (BMI), and blood pressure measures (diastolic and systolic), the most recent values/measures within 24 months before the incident stroke were used. All other comorbidities were defined based on the latest record before the incident stroke.

2.5. Outcomes

First subsequent MACE after incident stroke was the primary outcome. MACE was defined as a composite of new onset coronary heart disease (CHD), recurrent stroke, PVD, heart failure, or cardiovascular-related mortality, identified from patients' records across the linked data sources (CPRD, HES or ONS registry). All-cause mortality was considered as a secondary outcome.

2.6. Statistical analysis

Continuous variables were summarised as mean (SD) or median (IQR); nominal variables were presented as counts and valid percentages. Normal distribution was graphically assessed by histograms and P-P plots. Kruskal-Wallis test for continuous data and chi-squared test for categorical data were used to compare baseline characteristics. Details on the proportion of missingness are provided in Supplemental Table I. To estimate missing values for BMI, systolic and diastolic blood pressures, HDL-cholesterol, LDL-cholesterol and total cholesterol levels, multiple imputation by chained equations was used to generate 10 imputed datasets using all the other available patient variables [18]. The imputed datasets were pooled into a single dataset using Rubin's rules [19].

A multivariable probit regression model was used to calculate propensity scores for the conditional probability of classification in 1149 patients with recent cancer history versus 21,311 patients with no prior cancer diagnosis. The propensity score (PS) matching model included age, sex, general practice, smoking status, socioeconomic status (IMD), blood pressure, BMI, HDL-C, LDL-C, clinical diagnosis of atrial fibrillation, alcohol problem, dementia, diabetes mellitus, dyslipidaemia, hypertension, severe mental illness, transient ischaemic attack, family history of cardiovascular disease, a prescription of antihypertensive, anticoagulant, antidepressant, antiplatelet, diuretic, NSAIDs, opioids and potency of prescribed statin. We matched 1149 patients with recent cancer history and those with no prior cancer diagnosis using a 1:1 greedy matching algorithm of nearest neighbor with a calliper of 0.01 and no replacement – Supplemental Figures I, II, and Supplemental Table II. Analyses were performed on the entire population of patients with ischaemic stroke event and the propensity-score matched cohort.

The cumulative incidence of subsequent cardiovascular morbidity and mortality outcomes were estimated using a competing risk-sensitive estimator. The method proposed by Fine and Gray for competing risks analysis was used to estimate the sub-distribution hazards ratio (SHR) for the individual cardiovascular morbidity outcomes (with death from any cause as a competing risk), composite MACE, and CVD-related mortality outcomes (with non-CVD-related mortality as competing risk). Multivariable adjustment for pre-specified covariates based on relevant literature or biological plausibility [age at time of incident stroke, sex, socioeconomic status, smoking status, body mass index, blood pressure, cholesterol concentration (high-density lipoprotein, low-density lipoprotein, and total cholesterol), diagnosis of alcohol problem, atrial fibrillation, chronic kidney disease, diabetes mellitus, dyslipidaemia, hypertension, transient ischaemic attack, a prescription of antihypertensive, anticoagulant, antidiabetic, and potency of prescribed statin] were used for the entire cohort (non-PS-matched). Subgroup analyses evaluated short-term outcomes by assessing the incidence rates and sub-distribution hazard ratios for MACE and mortality outcomes between recent cancer and non-cancer patients at 1-year and 2-year follow-ups after an incidence of ischaemic stroke.

As a sensitivity analysis, multivariable Cox proportion hazards models using the same covariates used in the competing risks models were used to estimate the hazard ratio (HR) with a 95% confidence interval (95% CI) for subsequent cardiovascular morbidity and mortality outcomes between patients with no prior cancer diagnosis and those with a recent history of cancer. The proportional hazards assumption was assessed using Schoenfeld residuals. For composite MACE outcome, patients were censored at the time of the first outcome event. Cox regression models with shared frailty on matched sets were used for the PS-matched cohort, to account for the 'cluster effect' within matched pairs [20].

All statistical analyses were performed using Stata SE version 17 (StataCorp LP). An alpha level of 0.05 was used for all analyses and all tests were 2-tailed. No formal power calculations were performed as all available data from this large study with 22,460 patients and 16,379 MACE outcomes of interest were used.

3. Results

3.1. Characteristics of the study cohort

A total of 22,460 patients in CPRD had records of incident non-fatal ischaemic stroke in primary or secondary care between 1 January 1998 and 31 December 2017, with no pre-existing vascular event and no record of cancer up to 12 months before stroke incidence. Females made up 52.4% of these patients. The median patient age at the time of the incident stroke was 75 (IQR 64–83) years and the median follow-up after incident stroke for the entire study population was 12.3 (IQR 7.2–16.7) years. Recent cancer (defined as cancer diagnosed within the preceding 12 months) was identified in 1149 patients (5.1%) at the time of incident ischaemic stroke. Patient characteristics at the time of the incident stroke, are shown in Table 1.

Compared with patients with no record of cancer, a significantly higher proportion of those with a recent history of cancer were male, of older age at the time of stroke incidence, and had lower levels of deprivation. Patients with a history of recent cancer at the time of stroke diagnoses also had a significantly higher prevalence of atrial fibrillation, chronic kidney disease, hypertension, family history of cardiovascular disease, and significantly more of these patients were on anti-coagulant medication, anti-platelets, anti-arrhythmic drugs, diuretics, non-steroidal anti-inflammatory drugs (NSAIDs) and opioids, compared with patients with no record of cancer. There were no significant differences in current smoking status, alcohol misuse problems, the prevalence of diabetes, dyslipidaemia, dementia, severe mental illness, and previous history of transient ischaemic attacks (TIA) between patients with recent cancer compared with patients with no prior history of cancer at the time of stroke diagnosis. Similarly, the use of anti-diabetic medication, antidepressants, antihypertensives and statins did not differ between both groups of patients.

3.1.1. Propensity-score matched cohort

A total of 2298 patients were in the propensity-matched cohort, comprising 1149 patients who had a history of recent cancer at the time of ischaemic stroke diagnosis and 1149 patients with no record of cancer at stroke diagnosis. The baseline characteristics of these patients are described in Supplemental Table II. Baseline sociodemographic and clinical characteristics were relatively well balanced across both groups of individuals, and median follow-up (in years) for the individuals in the propensity-matched cohort (0.08 [0.02–0.59]) was similar to follow-up time for the entire study cohort (0.08 [0.02–0.73]).

Table 1
Characteristics of the entire study population at the time of incident stroke according to prior cancer status ($n = 22,460$).

Characteristics	Entire cohort22,460 (100%)	No prior cancer21,311 (94.9%)	Recent cancer history1149 (5.1%)	*p*-value
Follow-up, median (IQR)	12.3 (7.2 – 16.7)	12.4 (7.3 – 16.8)	11.2 (6.3 – 15.7)	0.0001
Females	11,779 (52.4)	11,251 (52.8)	528 (46.0)	<0.001
Age (years), median (IQR)	75 (64 – 83)	75 (64 – 83)	77 (69 – 84)	0.0001
Ethnicity				<0.001
Asian	346 (1.5)	340 (1.6)	6 (0.5)	
Black	193 (0.9)	189 (0.9)	4 (0.4)	
Mixed	45 (0.2)	43 (0.2)	2 (0.2)	
Other	175 (0.8)	162 (0.8)	13 (1.1)	
White	20,306 (90.4)	19,231 (90.2)	1075 (93.6)	
Unknown	1395 (6.2)	1346 (6.3)	49 (4.3)	
Socioeconomic status				<0.001
1 (Least deprived)	4672 (20.8)	4388 (20.6)	284 (24.7)	
2	4854 (21.6)	4591 (21.5)	263 (22.9)	
3	4820 (21.5)	4581 (21.5)	239 (20.8)	
4	4268 (19.0)	4055 (19.0)	213 (18.5)	
5 (Most deprived)	3815 (17.0)	3665 (17.2)	150 (13.1)	
Unknown	31 (0.1)	31 (0.2)	0	
Current smokers	4551 (20.3)	4332 (20.3)	219 (19.1)	0.298
DBP (mmHg)	80 (74 – 84)	80 (75 – 84)	79 (70 – 82)	0.0001
SBP (mmHg)	140 (130 – 148)	140 (131 – 148)	139 (130 – 146)	0.0001
HDL cholesterol (mmol/L)	1.46 (1.30 – 1.62)	1.46 (1.30–1.61)	1.42 (1.22–1.63)	0.0004
LDL cholesterol (mmol/L)	2.98 (2.70–3.28)	2.98 (2.70–3.28)	2.92 (2.58–3.23)	0.0001
Total cholesterol (mmol/L)	5.10 (4.75–5.46)	5.10 (4.77–5.46)	5.00 (4.51–5.40)	0.0001
Comorbid conditions				
Alcohol problem	702 (3.1)	662 (3.1)	40 (3.5)	0.477
Atrial fibrillation	2349 (10.5)	2202 (10.3)	147 (12.8)	0.008
Chronic kidney disease	2679 (11.9)	2493 (11.7)	186 (16.2)	<0.001
Dementia	798 (3.6)	757 (3.6)	41 (3.6)	0.977
Diabetes mellitus	2908 (13.0)	2756 (12.9)	152 (13.2)	0.771
Dyslipidaemia	1995 (8.9)	1884 (8.8)	111 (9.7)	0.341
Family history of CVD	3946 (17.6)	3716 (17.4)	230 (20.0)	0.025
Hypertension	10,610 (47.2)	10,016 (47.0)	594 (51.7)	0.002
Severe mental illness	281 (1.3)	269 (1.3)	12 (1.0)	0.517
Transient ischaemic attack	1447 (6.4)	1364 (6.4)	83 (7.2)	0.268
Prescribed medications				
Anti-arrhythmic	1033 (4.6)	965 (4.5)	68 (5.9)	0.028
Anti-coagulant	1209 (5.4)	1091 (5.1)	118 (10.3)	<0.001
Anti-diabetic	2355 (10.5)	2246 (10.5)	109 (9.5)	0.257
Anti-depressant	4661 (20.8)	4397 (20.6)	264 (23.0)	0.056
Anti-hypertensive	11,166 (49.7)	10,563 (49.6)	603 (52.5)	0.054
Anti-platelet	6283 (28.0)	5930 (27.8)	353 (30.7)	0.033
Diuretics	7752 (34.5)	7302 (34.3)	450 (39.2)	0.001
NSAIDS	5635 (25.1)	5299 (24.9)	336 (29.2)	0.001
Opioids	8576 (38.2)	7957 (37.3)	619 (53.9)	<0.001
Statin				0.070
Low intensity	655 (2.9)	620 (2.9)	35 (3.1)	
Moderate intensity	3543 (15.8)	3332 (15.6)	211 (18.4)	
High intensity	860 (3.8)	812 (3.8)	48 (4.2)	

DBP: diastolic blood pressure; HDL: high density lipoprotein; LDL: IQR: interquartile range; low density lipoprotein; n: frequency/numbers; NSAIDS: non-steroidal anti-inflammatory drug; SBP: systolic blood pressure; %: percent.

3.2. Major adverse cardiovascular morbidity and mortality outcomes

As shown in Table 2, there were a total of 1563 (68.0%) composite MACE outcomes among individuals in the propensity-matched cohort over the period of follow-up. Higher unadjusted incidence rates of composite MACE (per 100 person-years) were observed in those with recent cancer history (65.11 [95% CI 60.55–70.01]) compared with those with no prior history of cancer (51.16 [95% CI 47.80–54.75]). Patients with a recent history of cancer were less likely to have a composite MACE outcome after incident ischaemic stroke when compared with propensity-matched patients with no history of cancer (sub-distribution hazard ratio (SHR) 0.83 [95% CI 0.75–0.91]). Similarly, the risk of recurrent stroke was significantly lower in those with recent cancer history compared with those with no history of cancer (SHR 0.85 [0.75–0.96]).

The sub-distribution hazards ratio, however, showed no statistical difference in subsequent risk for CHD (SHR 0.82 [95% CI 0.50–1.32]), PVD (SHR 0.86 [95% CI 0.23–3.14]), heart failure (SHR 0.79 [95% CI 0.44–1.43]), and CVD-related mortality (SHR 0.97 [95% CI 0.80–1.18]) after incident ischaemic stroke when patients with recent cancer history were compared with their propensity-matched cohort of patients without a prior history of cancer. The cumulative incidence function plots are presented in Fig. 2.

The unadjusted incidence rate for all-cause mortality (per 100 person-years) was considerably higher in patients who had a recent history of cancer at the time of ischaemic stroke than those with no history of cancer (incidence rate 21.26 [19.50–23.17] vs 10.23 [9.07–11.08]), and patients with a recent history of cancer had a 67% higher risk of all-cause mortality than matched propensity-matched non-cancer patients (hazard ratio (HR) 1.67 [95% CI 1.47–1.91]).

Using data from the entire cohort, the findings were similar to those obtained from the propensity-matched cohort analyses. The risk of subsequent composite MACE (SHR 0.80 [95% CI 0.74–0.86]) and recurrent stroke (SHR 0.82 [95% CI 0.75–0.90]) was significantly lower; no observed significant differences in the risk of subsequent risk of CHD (SHR 0.83 [95% CI 0.57–1.21]), PVD (SHR 0.49 [95% CI 0.18–1.31]), heart failure (SHR 0.79 [95% CI 0.49–1.27]), and CVD-related mortality (HR 0.97 [95% CI 0.84–1.13]); and a significantly higher risk of all-cause mortality (HR 1.72 [95% CI 1.57–1.88]) after incident stroke in patients with a recent cancer history when compared with patients with no prior history of cancer – see Table 2.

3.3. Outcomes at 1- and 2-year follow-up periods

Further analyses restricted to outcomes in the one- and two-year periods after incident ischaemic stroke (Table 3) showed that the incidence rates of MACE and mortality outcomes in both patients with a recent history of cancer and patients with no prior cancer history were considerably higher in the first year after incident ischaemic stroke when compared with incidence over the 2 years.

Similar to findings from the analyses using the entire study and propensity score-matched cohorts, there was a lower risk of composite MACE (SHR at 1 year 0.87 [95% CI 0.80–0.95]; SHR at 2 years 0.85 [95% CI 0.79–0.93]) and recurrent stroke (SHR at 1 year 0.84 [95% CI 0.76–0.94]; SHR at 2 years 0.83 [95% CI 0.76–0.92]); no significant differences in the risk of CHD (SHR at 1 year 0.99 [95% CI 0.60–1.64]; SHR at 2 years 1.00 [95% CI 0.64–1.55]), PVD (SHR at 1 year 1.13 [95% CI 0.40–3.18]; SHR at 2 years 0.74 [95% CI 0.27–2.03]), heart failure (SHR at 1 year 0.41 [95% CI 0.15–1.09]; SHR at 2 years 0.67 [95% CI 0.35–1.31]) and CVD-related mortality (SHR at 1 year 1.05 [95% CI 0.89–1.23]; SHR at 2 years 1.02 [95% CI 0.87–1.19]); and higher risk of all-cause mortality (HR at 1 year 1.86 [95% CI 1.68–2.07]; HR at 2 years 1.85 [95% CI 1.68–2.05]) in ischaemic stroke patients with recent history of cancer when compared with patients with no prior history of cancer.

Table 2
Subsequent cardiovascular morbidity and mortality outcomes according to prior cancer status for the entire and propensity-score-matched cohorts.

Outcomes	Entire study cohort (n = 22,460)				Propensity-score matched cohort (n = 2298)			
	Entire cohort22,460 (100%)	No prior cancer21,311 (94.9%)	Recent cancer1149 (5.1%)	p-value	Cohort$n$ = 2298 (100%)	No prior cancer$n$ = 1149	Recent cancer$n$ = 1149	p-value
Major adverse cardiovascular event (composite)								
Number (percent)	16,379 (72.9)	15,649 (73.4)	730 (63.5)	<0.001	1563 (68.0)	833 (72.5)	730 (63.5)	<0.001
Follow-up time	0.08 (0.02 – 0.73)	0.08 (0.02 – 0.75)	0.06 (0.02 – 0.48)	0.0001	0.08 (0.02 – 0.59)	0.09 (0.02 – 0.67)	0.06 (0.02 – 0.48)	0.0093
Incident rate [a]	49.14 (48.40 –49.90)	48.59 (47.83 – 49.35)	65.11 (60.55 – 70.01)	–	56.85 (54.10 – 59.74)	51.16 (47.80 0 54.75)	65.11 (60.55 – 70.01)	–
SHR (95% CI)	–	Reference	0.80 (0.74 – 0.86)	<0.001	–	Reference	0.83 (0.75 – 0.92)	<0.001
Coronary heart disease								
Number (percent)	757 (3.4)	729 (3.4)	28 (2.4)	0.072	66 (2.9)	38 (3.3)	28 (2.4)	0.212
Follow-up time	1.36 (0.25 – 3.93)	1.42 (0.26 – 4.00)	0.67 (0.04 – 1.95)	0.0131	1.15 (0.11 – 2.75)	2.17 (0.51 – 3.01)	0.67 (0.04 – 1.95)	0.0112
Incident rate [a]	1.01 (0.94 – 1.08)	1.00 (0.93 – 1.08)	1.27 (0.88 – 1.85)	–	1.15 (0.91 – 1.47)	1.08 (0.78 – 1.48)	1.27 (0.88 – 1.85)	–
SHR (95% CI)	–	Reference	0.83 (0.57 – 1.21)	0.333	–	Reference	0.82 (0.50 – 1.32)	0.409
Recurrent stroke								
Number (percent)	11,396 (50.7)	10,909 (51.2)	487 (42.4)	<0.001	1044 (45.4)	557 (48.5)	487 (42.4)	0.003
Follow-up time	0.07 (0.02 – 0.41)	0.07 (0.02 – 0.41)	0.06 (0.02 – 0.35)	0.1079	0.07 (0.02 – 0.35)	0.08 (0.02 – 0.36)	0.06 (0.02 – 0.35)	0.1349
Incident rate [a]	32.83 (32.24 – 33.44)	32.55 (31.94 – 33.16)	40.89 (37.42 – 44.69)	–	36.24 (34.11 – 38.51)	32.96 (30.33 – 35.82)	40.89 (37.42 – 44.69)	–
SHR (95% CI)	–	Reference	0.82 (0.75 – 0.90)	<0.001	–	Reference	0.85 (0.75 – 0.96)	0.007
Peripheral vascular disease								
Number (percent)	168 (0.8)	164 (0.8)	4 (0.4)	0.106	9 (0.4)	5 (0.4)	4 (0.4)	0.738
Follow-up time	1.78 (0.58 – 3.78)	1.83 (0.59 – 3.82)	0.15 (0.01 – 0.56)	0.0129	0.85 (0.05 – 1.03)	1.03 (1.00 – 2.93)	0.15 (0.01 – 0.56)	0.0500
Incident rate [a]	0.22 (0.19 – 0.26)	0.22 (0.19 – 0.26)	0.18 (0.07 – 0.47)		0.15 (0.08 – 0.29)	0.14 (0.06 – 0.33)	0.18 (0.07 – 0.47)	–
SHR (95% CI)	–	Reference	0.49 (0.18 – 1.31)	0.153	–	Reference	0.86 (0.23 – 3.14)	0.816
Heart failure								
Number (percent)	438 (2.0)	420 (2.0)	18 (1.6)	0.334	44 (1.9)	26 (2.3)	18 (1.6)	0.223
Follow-up time	1.49 (0.37 – 4.11)	1.45 (0.37 – 4.08)	2.15 (1.30 – 4.58)	0.2095	1.93 (0.31 – 4.32)	1.72 (0.28 – 4.05)	2.15 (1.30 – 4.58)	0.5039
Incident rate [a]	0.57 (0.52 – 0.63)	0.57 (0.52 – 0.62)	0.80 (0.50 – 1.26)	–	0.75 (0.56 – 1.01)	0.72 (0.49 – 1.06)	0.80 (0.50 – 1.26)	–
SHR (95% CI)	–	Reference	0.79 (0.49 – 1.27)	0.327	–	Reference	0.79 (0.44 – 1.43)	0.439
Cardiovascular-related mortality								
Number (percent)	3620 (16.1)	3427 (16.1)	193 (16.8)	0.520	400 (17.4)	207 (18.0)	193 (16.8)	0.441
Follow-up time	0.08 (0.02 – 0.80)	0.09 (0.2 – 0.86)	0.05 (0.02 – 0.26)	0.0008	0.05 (0.02 – 0.33)	0.06 (0.02 – 0.39)	0.05 (0.02 – 0.26)	0.3140
Incident rate [a]	4.61 (4.47 – 4.77)	4.51 (4.36 – 4.66)	8.34 (7.24 – 9.61)	–	6.69 (6.06 – 7.38)	5.64 (4.92 – 6.46)	8.34 (7.25 – 9.61)	–
SHR (95% CI)	–	Reference	0.97 (0.84 – 1.13)	0.726	–	Reference	0.97 (0.80 – 1.18)	0.787
All-cause mortality								
Number (percent)	6694 (29.8)	6178 (29.0)	516 (44.9)	<0.001	900 (39.2)	384 (33.4)	516 (44.9)	<0.001
Follow-up time	0.25 (0.04 – 2.67)	0.27 (0.04 – 2.83)	0.15 (0.04 – 0.85)	0.0001	0.17 (0.04 – 1.46)	0.21 (0.04 – 2.62)	0.15 (0.04 – 0.85)	0.0114
Incident rate [a]	8.23 (8.03 – 8.42)	7.8 (7.63 – 8.02)	21.26 (19.50 – 23.17)	–	14.38 (13.47 – 15.35)	10.23 (9.07 – 11.08)	21.26 (19.50 −23.17)	–
Hazard ratio (95% CI)	–	Reference	1.72 (1.57 – 1.88)	<0.001	–	Reference	1.67 (1.47 – 1.91)	<0.001

SHR – sub-distribution hazard ratio using Fine and Gray competing risk model.
Follow-up time: Time from incident stroke event to mortality outcome reported as median with interquartile range. CI, confidence interval; HR, hazard ratio.
[a] Incident rate per 100 person-years.

Model adjusted for age at the time of incident stroke, sex, socioeconomic status, smoking status, body mass index, blood pressure, cholesterols (high-density lipoprotein, low-density lipoprotein, and total), diagnosis of an alcohol problem, atrial fibrillation, cancer, chronic kidney disease, diabetes mellitus, dyslipidaemia, hypertension, transient ischaemic attack, a prescription of antihypertensive, anticoagulant, antidiabetic, and potency of prescribed statin.

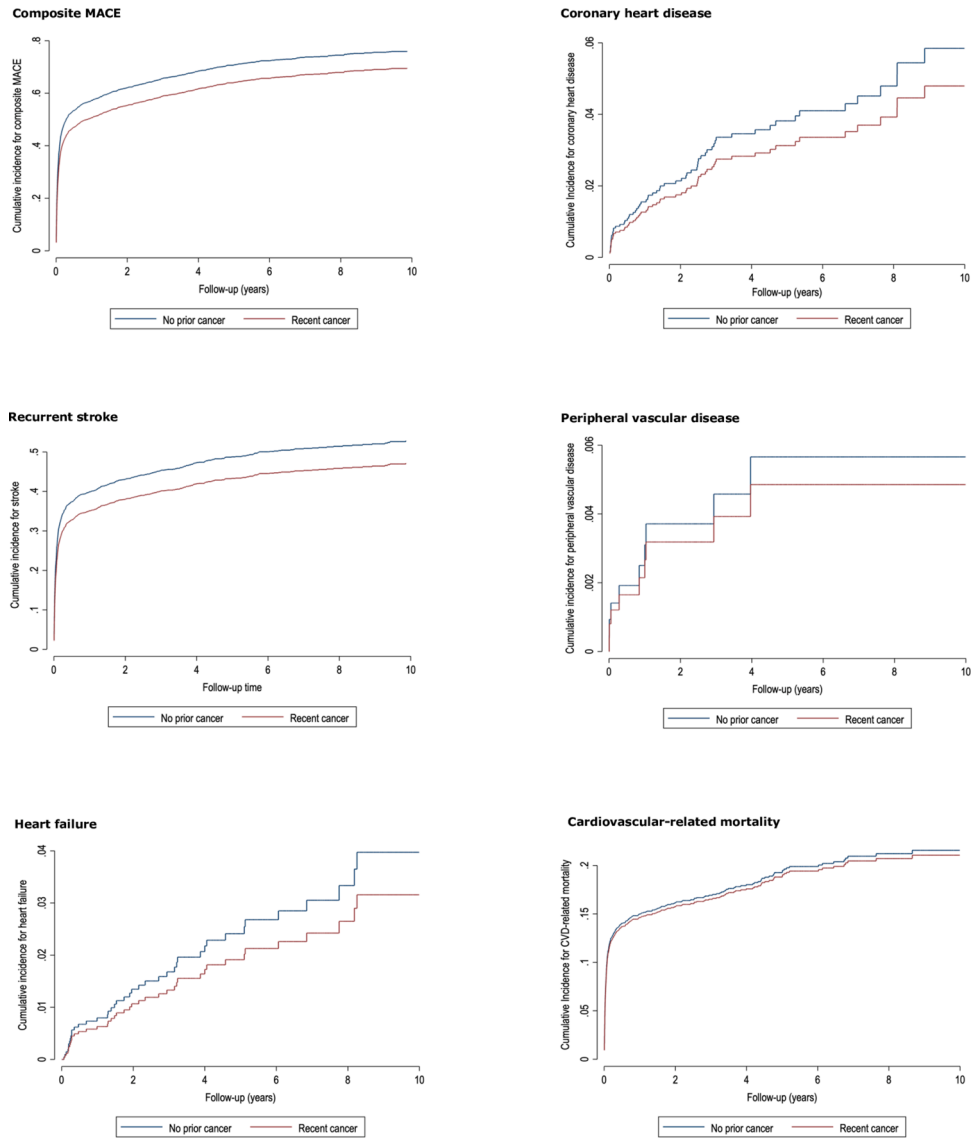

Fig. 2. Cumulative incidence function plot for subsequent morbidity and mortality outcomes for the propensity-score matched cohort ($n = 2298$).

3.3.1. Cox proportional hazards analyses

In a sensitivity analysis using Cox proportional hazard regression models (not accounting for competing risks/outcomes) for both the entire study population and propensity-score matched cohort, there were no significant differences observed in the risk of subsequent composite MACE outcome, individual cardiovascular morbidity outcomes (CHD, stroke, PVD, heart failure), and CVD-related mortality after incident ischaemic stroke within the two groups - see Supplemental Table III.

4. Discussion

In this large population-based cohort study of patients with incident ischaemic stroke, patients with a recent cancer history had a lower risk of composite major adverse cardiovascular events (MACE) and recurrent stroke, using a competing risks regression model. There was no significant difference between the groups for subsequent CHD, PVD, heart failure, and CVD-related outcomes in patients with a recent history of cancer compared with patients with no history of cancer. These findings were consistent over short-term and longer-term periods of follow-up after an incident ischaemic stroke. However, when Cox proportional hazard regression models were used, the risk of subsequent MACE and all the constituent MACE outcomes did not significantly differ between the groups. The risk of all-cause mortality was significantly higher in patients with a history of recent cancer when compared with those with no history of cancer.

There are conflicting reports from previous studies assessing the risk of recurrent stroke in patients with acute ischaemic stroke and a history of cancer. While studies of patients in hospital or emergency department settings demonstrate a high risk of recurrent stroke in the short-term post-stroke period in those with active cancer [11,21,22], an exploratory study of participants with ischaemic stroke in the NAVIGATE ESUS randomised trial found that history of cancer was not independently associated with risk of recurrent ischaemic stroke [23]. Using Cox proportional hazard regression models, our study found no significant difference in the long-term and short-term risk of recurrent stroke and other cardiovascular outcomes in patients with recent cancer history compared with those with no history of cancer and supports the findings from the NAVIGATE ESUS trial. However, in using a competing risks analyses approach, the risk of subsequent composite MACE and recurrent stroke is significantly lower because patients with a recent history of cancer are more likely to die earlier. Our study highlights the importance of accounting for competing events (i.e., events that hinder or change the possibility of observing the outcomes of interest). Until

Table 3
Subsequent cardiovascular morbidity and mortality outcomes according to prior cancer status for the entire cohort at 1- and 2-year follow-ups.

Outcomes	1-year follow-up			2-year follow-up		
	Entire cohort22,460 (100%)	**No prior cancer**21,311 (94.9%)	**Recent cancer**1149 (5.1%)	**Cohort**22,460 (100%)	**No prior cancer**21,311 (94.9%)	**Recent cancer**1149 (5.1%)
Major adverse cardiovascular event (composite)						
Number (percent)	12,704	12,113	591	13,815	13,178	637
Incident rate [a]	131.13 (128.87 – 133.43)	130.67 (128.37 – 133.02)	141.32 (130.38 – 153.19)	86.89 (85.45 – 88.35)	86.38 (84.91 – 87.86)	98.98 (91.59 – 106.98))
SHR (95% CI)	–	Reference	0.87 (0.80 – 0.95)	–	Reference	0.85 (0.79 – 0.93)
Coronary heart disease						
Number (percent)	330	314	16	435	414	21
Incident rate [a]	2.02 (1.81 – 2.25)	2.00 (1.79 – 2.24)	2.44 (1.49 – 3.98)	1.50 (1.37 – 1.65)	1.49 (1.35 – 1.64)	1.94 (1.27 – 2.98)
SHR (95% CI)	–	Reference	0.99 (0.60 – 1.64)	–	Reference	1.00 (0.64 – 1.55)
Recurrent stroke						
Number (percent)	9366	8962	404	10,051	9619	432
Incident rate [a]	96.49 (94.56 – 98.47)	96.54 (94.56 – 98.56)	95.42 (86.55 – 105.19)	62.75 (61.54 – 63.99)	62.64 (61.40 – 63.90)	65.45 (59.56 – 71.92)
SHR (95% CI)	–	Reference	0.84 (0.76 – 0.94)	–	Reference	0.83 (0.76 – 0.92)
Peripheral vascular disease						
Number (percent)	58	54	4	92	88	4
Incident rate [a]	0.35 (0.27 – 0.46)	0.34 (0.26 – 0.45)	0.60 (0.23 – 1.60)	0.31 (0.26 – 0.39)	0.31 (0.25 – 0.39)	0.37 (0.14 – 0.97)
SHR (95% CI)	–	Reference	1.13 (0.40 – 3.18)	–	Reference	0.74 (0.27 – 2.03)
Heart failure						
Number (percent)	178	174	4	252	243	9
Incident rate [a]	1.08 (0.94 – 1.25)	1.10 (0.95 – 1.28)	0.60 (0.23 – 1.60)	0.86 (0.76 – 0.98)	0.87 – 0.76 – 0.98)	0.82 (0.43 – 1.58)
SHR (95% CI)	–	Reference	0.41 (0.15 – 1.09)	–	Reference	0.67 (0.35 – 1.31)
Cardiovascular-related mortality						
Number (percent)	2772	2609	163	2985	2814	171
Incident rate [a]	16.58 (15.97 – 17.21)	16.26 (15.65 – 16.89)	24.22 (20.78 – 28.24)	10.01 (9.66 – 10.38)	9.81 (9.44 – 10.17)	15.36 (13.22 – 17.84)
SHR (95% CI)	–	Reference	1.05 (0.89 – 1.23)	–	Reference	1.02 (0.87 – 1.19)
All-cause mortality						
Number (percent)	4178	3783	395	4735	4297	438
Incident rate [a]	24.56 (23.82 – 25.31)	23.18 (22.45 – 23.93)	57.03 (51.68 – 62.95)	15.51 (15.08 – 15.96)	14.63 (14.20 – 15.08)	37.88 (34.50 – 41.60)
Hazard ratio (95% CI)	–	Reference	1.86 (1.68 – 2.07)	–	Reference	1.85 (1.68 – 2.05)

SHR – sub-distribution hazard ratio using Fine and Gray competing risk model.
[a] Incident rate per 100 person-years.
Model adjusted for age at the time of incident stroke, sex, socioeconomic status, smoking status, body mass index, blood pressure, cholesterols (high-density lipoprotein, low-density lipoprotein, and total), diagnosis of an alcohol problem, atrial fibrillation, cancer, chronic kidney disease, diabetes mellitus, dyslipidaemia, hypertension, transient ischaemic attack, a prescription of antihypertensive, anticoagulant, antidiabetic, and potency of prescribed statin.

now, no large population-based studies had explored the risk of short- and long-term MACE and mortality outcomes following an acute ischaemic stroke in patients with recent cancer history.

The higher all-cause mortality observed among ischaemic stroke patients with recent cancer history compared with non-cancer patients may be explained by the additional burden of cancer in these patients, however, evidence from studies suggests that hypercoagulability in patients with active cancer, may also be a major driver for mortality [21, 24]. Findings from this study demonstrate higher all-cause mortality in ischaemic stroke patients with recent cancer history compared with those with no cancer. This highlights the need for optimal management of these patients to reduce the risk of mortality.

Strengths and limitations

To our knowledge, this is the first study to investigate the risk of MACE and all-cause mortality outcomes in a primary care population of patients with incident ischaemic stroke and recent cancer history. Strengths of the study include the large sample size and use of extensively validated linked routine electronic health records which enabled robust ascertainment of cardiovascular disease and mortality outcomes and enhanced generalisability of the study findings to the general population of individuals with ischaemic stroke and recent cancer history. Propensity-score matching of the study population using demographic characteristics, clinical risk factors, comorbidities, and prescribed medication use, minimised the risk of confounding in this large heterogeneous population.

We acknowledge certain limitations. These include a lack of recorded data on factors which are known to be associated with mortality after stroke, such as stroke severity and vascular territories [11]. Certain cancer histology types have been shown in previous studies to be associated with the risk of recurrent thromboembolism including recurrent ischaemic stroke [21] as well as mortality after stroke [25], but records of histology or cancer type were not included in the study and so any effect associated with cancer types may have been underestimated. In particular, the staging of cancer or the presence of metastases was not known for patients in the study, and this may underestimate any variation in subsequent cardiovascular disease and mortality risk within these clinically heterogeneous groups of patients. There is also the possibility of undiagnosed or occult cancers among non-cancer patients. Also, we cannot rule out the possibility of diagnostic bias in patients with advanced cancer who are in palliative care. Anticoagulant treatments have been shown in previous studies, to be associated with a higher rate of bleeding complications in individuals with cancer than in those without cancer [26]. Bleeding outcomes could not be assessed in our study population due to a lack of bleeding data. Lastly, there is a possibility of survivor bias in our study population whereby subjects with recent cancer and high cardiovascular risk may not have survived long enough to be included in the study. Despite these limitations, the findings from our study provide pragmatic estimates of cardiovascular morbidity and mortality risk after incident ischaemic stroke in patients with a history of broadly defined cancer in primary care.

In conclusion, all-cause mortality was higher in stroke patients with recent cancer compared with patients with no prior history of cancer.

Further research to elucidate the factors which increase mortality risk in ischaemic stroke patients with a recent cancer history are needed.

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Further reading

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