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Association between Incident Cancer and Subsequent Stroke

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Abstract

Objective—To examine the association between incident cancer and the subsequent risk of stroke.

Methods—Using the Surveillance Epidemiology and End Results-Medicare linked database, we identified patients with a new primary diagnosis of breast, colorectal, lung, pancreatic, or prostate cancer from 2001 through 2007. These patients were individually matched by age, sex, race, registry, and medical comorbidities to a group of Medicare enrollees without cancer, and each pair was followed through 2009. Validated diagnosis codes were used to identify a primary outcome of stroke. Cumulative incidence rates were calculated using competing risk survival statistics.

Results—Among 327,389 pairs of cancer patients and matched controls, the 3-month cumulative incidence of stroke was generally higher in patients with cancer. Cumulative incidence rates were 5.1% (95% confidence interval [CI], 4.9–5.2%) in patients with lung cancer compared to 1.2% (95% CI, 1.2–1.3%) in controls ($p < 0.001$), 3.4% (95% CI, 3.1–3.6%) in patients with pancreatic cancer compared to 1.3% (95% CI, 1.1–1.5%) in controls ($p < 0.001$), 3.3% (95% CI, 3.2–3.4%) in patients with colorectal cancer compared to 1.3% (95% CI, 1.2–1.4%) in controls ($p < 0.001$), 1.5% (95% CI, 1.4–1.6%) in patients with breast cancer compared to 1.1% (95% CI, 1.0–1.2%) in controls ($p < 0.001$), and 1.2% (95% CI, 1.1–1.3%) in patients with prostate cancer compared to 1.1% (95% CI, 1.0–1.2%) in controls ($p = 0.085$). Excess risks attenuated over time and were generally no longer present beyond 1 year.

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Potential Conflicts of Interest

None.

Interpretation—Incident cancer is associated with an increased short-term risk of stroke. This risk appears highest with lung, pancreatic, and colorectal cancers.

Introduction

Nearly 13 million Americans (4% of the population) have cancer and another 1.6 million receive a new cancer diagnosis each year.¹ Autopsy data indicate that 15% of these patients have pathological evidence of cerebrovascular disease upon death,² and several small, retrospective cohort studies have demonstrated that stroke is common in patients with cancer.^{3, 4} Pathophysiological considerations suggest that many of these strokes may arise from unique mechanisms related to cancer-mediated hypercoagulability or complications of oncological treatments.^{2, 3, 5, 6}

Few population-based data exist to support an independent association between cancer and stroke. Prior studies have found increased risk of stroke in patients with breast, lung, and head and neck cancer, patients undergoing radiotherapy for cervical cancer, and long-term survivors of Hodgkin lymphoma,^{7–11} but these findings in small subsets of cancer patients may not apply to the overall cancer population. Conversely, a recent study from Sweden reported that several cancer types were independently associated with stroke, but this study used only inpatient data from a demographically homogeneous population.¹²

To better assess the relationship between cancer and the risk of stroke, we used population-based Medicare claims data to assess the risk of stroke in patients with a new diagnosis of cancer compared to a matched cohort of patients without cancer. Our hypothesis was that a new diagnosis of cancer is associated with an increased risk of subsequent stroke, and that the risk is highest soon after cancer diagnosis. We also hypothesized that the risk would be highest in patients with pancreatic cancer because mucinous adenocarcinoma, which accounts for most pancreatic cancers, is the cancer histology most commonly associated with thromboembolism from cancer-mediated hypercoagulability.¹³

Methods

Design

We performed a retrospective matched cohort study using Surveillance, Epidemiology, and End Results (SEER) data linked with Medicare claims from 2001 through 2009. The SEER-Medicare dataset comprises national population-based cancer registries linked to Medicare enrollment and claims files, and provides detailed clinical information about a heterogeneous population of cancer patients. The SEER registries include approximately 28% of all patients diagnosed with cancer in the United States.¹ SEER also includes data from a 5% random sample of Medicare beneficiaries without cancer residing in SEER geographic regions, which enabled us to compare the risk of stroke in patients with cancer versus matched patients without cancer. Medicare data used for this study included the physician and supplier file, the outpatient standard analytic file, and the Medicare provider analysis and review file. The Memorial Sloan Kettering Cancer Center review board approved this study and waived the need for informed consent.

Cancer Population

Cancer cases consisted of all patients aged 66 years or older diagnosed with primary breast, colorectal, lung, pancreatic, or prostate cancer from January 1, 2001 to December 31, 2007. We *a priori* chose breast, colorectal, lung, and prostate cancers because these are the four most common malignant cancer types and thus are most representative of cancer in general (accounting for approximately 50% of all new malignant cancers).¹ We also included pancreatic cancer because it is the cancer type most commonly reported in association with thromboembolic events.^{13, 14} Data for each of the five cancer types were analyzed separately to account for variable risks across cancer types. Patients who were diagnosed with multiple primary cancers during the study period were assigned the cancer type diagnosed first.

We used site record definitions from the SEER Patient Entitlement and Diagnosis Summary File to identify patients with incident cancer.¹⁵ The specific site definitions used to define our specific cancer cohorts are based on the SiteR1 classification and are as follows: prostate (54: prostate), lung (37–41: nose, nasal cavity, and middle ear; larynx; lung and bronchus; pleura; trachea, mediastinum, and other respiratory organs), breast (46: breast), colorectal (15–23 and 25–27: cecum; appendix; ascending colon; hepatic flexure; transverse colon; splenic flexure; descending colon; large intestine not otherwise specified; rectosigmoid junction; rectum; anus, anal canal, and anorectum), and pancreas (33: pancreas).

We excluded patients with cancer if they lacked Part A or B Medicare coverage or belonged to a health maintenance organization in the year prior to their cancer diagnosis or during follow-up, their cancer diagnosis was made at death or by autopsy or death certificate only, their cancer diagnosis was made before 2001 or after 2007, their first cancer diagnosis during the study period was not their first-ever cancer, their age at the time of cancer diagnosis was less than 66 years (in order to allow time to fully ascertain comorbidities in the year prior to cancer diagnosis), their month of cancer diagnosis was missing, or we could not identify a control patient without cancer matched on our pre-defined factors.

In addition, to minimize ascertainment bias and restrict our evaluation to first-ever stroke, we excluded patients with a Medicare claim for stroke or cerebrovascular disease as defined by the Medicare comorbidity macro (an adaptation of the Charlson comorbidity index that comprises 15 comorbidity variables) in the year prior to cancer diagnosis.^{16–18} The specific comorbidity composites and their respective *International Classification of Diseases, 9th Revision, Clinical Modification (ICD9-CM)* codes are as follows: myocardial infarction (410.x, 412.x), congestive heart failure (428.x), peripheral vascular disease (443.9, 441.x, 785.4, V43.4, procedure 38.48), cerebrovascular disease (430.x–438.x), dementia (290.x), chronic pulmonary disease (490.x–505.x, 506.4), rheumatic disease (710.0, 710.1, 710.4, 714.0–714.2, 714.81, 725.x), peptic ulcer disease (531.x–534.x), mild liver disease (571.2, 571.4–571.6), diabetes without chronic complication (250.0–250.3, 250.7), diabetes with chronic complication (250.4–250.6), hemiplegia or paraplegia (344.1, 342.x), renal disease (582.x, 583.0–583.7, 585.x, 586.x, 588.x), moderate or severe liver disease (456.0–456.21, 572.2–572.8), and AIDS/HIV (042.x–044.x).^{19, 20}

Control Population

We compared the incidence of stroke in patients with cancer to the incidence in a matched cohort of fee-for-service Medicare enrollees without cancer identified from the 5% sample of Medicare beneficiaries residing in SEER areas. Each patient with cancer was individually matched to a cancer-free control patient by year of birth, sex, race (dichotomized into white or non-white), SEER registry (a proxy for geographic region categorized into Northeast, Midwest, South, and West regions), and Charlson comorbidity index in the year prior to study entry (dichotomized into 0 or 1). Since the Charlson comorbidity index doesn't include the important stroke risk factors hypertension and atrial fibrillation, we also matched each patient by *ICD9-CM* codes for hypertension (401–405, 437.2) or atrial fibrillation (427.31, 427.32) in the year prior to study entry. Similar to the cancer patients, we excluded patients without cancer if they lacked Medicare Part A or B coverage or were enrolled in a health maintenance organization in the year prior to study entry or during follow-up, or if they had a Medicare claim for stroke or cerebrovascular disease in the year prior to study entry.

Measurements

Patients with cancer and their matched controls entered the study at the date of the cancer patient's cancer diagnosis. The primary outcome was a composite of ischemic or hemorrhagic stroke, defined as any *ICD-9-CM* diagnosis of ischemic stroke (433.x1, 434.x1, or 436) or hemorrhagic stroke (430 or 431) without concurrent codes for rehabilitation (V57) in the primary diagnosis position or trauma (800–804 or 850–854) in any diagnosis position.²¹ Patients with codes for both ischemic and hemorrhagic stroke were considered to have had hemorrhagic stroke alone. Our secondary outcomes were ischemic stroke alone and hemorrhagic stroke alone. Medicare claims data have been shown previously to have good sensitivity and excellent specificity and negative predictive value for identifying acute stroke diagnoses.²²

Statistical Analysis

We used descriptive statistics to characterize patient characteristics at study entry. Since death is a frequent competing risk in patients with cancer, we used competing risk survival statistics to calculate the cumulative incidence of stroke and the associated 95% confidence intervals (CI).²³ We specifically chose this technique over standard survival statistics (e.g., Kaplan-Meier method) because the occurrence of death (i.e., frequent competing event) may prevent stroke (i.e., outcome of interest) from being observed and standard survival statistics ignore competing risks, which can produce bias and invalid results. In contrast, the competing risk method estimates the hazard of stroke in the presence of death and unlike the Kaplan-Meier method doesn't censor patients at the time of their death, but instead considers them as failures in the event-free survival portion of its calculation.

We did not calculate hazard ratios for the entirety of patient follow-up because the risks associated with cancer varied over time and therefore the proportional hazards assumption was not satisfied. Instead, we calculated hazard ratios during discrete time periods when the proportional hazard assumption for the specific cancer types was generally met. We also formally compared the 3-month cumulative incidence of stroke between groups by

performing the non-parametric test of Robert Gray (i.e., log-rank test for competing risk survival statistics).²⁴ Follow-up was calculated from the case's date of cancer diagnosis until stroke, death, or end of study on December 31, 2009 (whichever occurred first). Strokes and deaths were considered events and patients without these events were censored. Statistical analyses were performed using SAS software (version 9.3, SAS Institute Inc., Cary, NC) and R software (version 2.13.1).

Results

Patient Characteristics

The final cohort comprised 327,389 pairs of cancer patients and controls matched 1:1 on age, sex, race, registry, history of hypertension or atrial fibrillation, and Charlson comorbidity index (Table 1). More than 95% of eligible cancer patients were successfully matched to a control. Most patients were white, older than 70 years of age, and had a history of hypertension or atrial fibrillation. There were slightly more women in the colorectal and pancreatic cancer cohorts, and an approximately equal number of women and men in the lung cancer cohort. The presence of any medical comorbidity (as defined by the Charlson Comorbidity Index) besides hypertension or atrial fibrillation depended on the cancer type, ranging from 29% in the prostate cancer cohort to 50% in the lung cancer cohort. Cancer stage at the time of cancer diagnosis also varied depending on cancer type, and was generally more advanced for colorectal, lung, and pancreatic cancers. Median survival for patients with cancer was 4.1 years (interquartile range [IQR] 0.9–not reached) for colorectal cancer, 0.6 years (IQR 0.2–1.7) for lung cancer, and 0.3 years (IQR 0.1–0.8) for pancreatic cancer; median survival had not been reached by the end of follow-up for patients with breast and prostate cancer, nor for matched control patients without cancer. Due to differences in survival, median follow-up time was shorter in the cancer cohorts as compared to matched controls: 4.3 versus 4.7 years for breast cancer, 2.9 versus 4.5 years for colorectal cancer, 0.6 versus 4.5 years for lung cancer, 0.3 versus 4.3 years for pancreatic cancer, and 4.5 versus 4.6 years for prostate cancer.

All Strokes

At 3 months, the cumulative incidence of stroke was higher in patients with cancer than in matched controls (Table 2; Fig 1A to 1E). Cumulative incidence rates were 5.1% (95% confidence interval [CI], 4.9–5.2%) in patients with lung cancer compared to 1.2% (95% CI, 1.2–1.3%) in controls (Gray test: $p<0.001$), 3.4% (95% CI, 3.1–3.6%) in patients with pancreatic cancer compared to 1.3% (95% CI, 1.1–1.5%) in controls ($p<0.001$), 3.3% (95% CI, 3.2–3.4%) in patients with colorectal cancer compared to 1.3% (95% CI, 1.2–1.4%) in controls ($p<0.001$), 1.5% (95% CI, 1.4–1.6%) in patients with breast cancer compared to 1.1% (95% CI, 1.0–1.2%) in controls ($p<0.001$), and 1.2% (95% CI, 1.1–1.3%) in patients with prostate cancer compared to 1.1% (95% CI, 1.0–1.2%) in controls ($p=0.085$). Excess risks attenuated over time and generally were no longer present beyond 1 year (Tables 2 and 3).

Stroke Subtypes

As in the general population,²⁵ most strokes were ischemic, accounting for 89 to 93% of all strokes depending on cancer type. The 3-month cumulative incidence of ischemic stroke closely mirrored that of all stroke (Table 4). The cumulative incidence of hemorrhagic stroke was also increased among patients with cancer as compared to matched controls, but in contrast to the pattern seen with ischemic stroke, the increased cumulative incidence of hemorrhagic stroke attenuated less over time (Table 5).

Discussion

In a large, heterogeneous, nationally representative group of elderly patients in a prospective cancer registry, we found an independent association between new primary diagnosis of cancer and subsequent stroke. As in the general stroke population, most strokes were ischemic, although the risk of hemorrhagic stroke was also increased and remained elevated for longer. The heightened risk of stroke was greatest in the first 3 months after cancer diagnosis and then slowly decreased over time, supporting the biological plausibility of an association between cancer and stroke given that cancer-mediated hypercoagulability and the effects of cancer therapy are generally greatest during this time period.^{13, 26} In addition, stroke risk appeared to correlate with the general aggressiveness of the underlying cancer type, as the risk was highest among patients with lung, pancreas, and colorectal cancers who more often presented with advanced stage disease, and lowest among patients with breast and prostate cancer who often had localized tumor. This finding further supports the biological plausibility of an association between cancer and stroke because cancer-mediated hypercoagulability and thrombotic risk is closely linked to cancer activity.²⁷

Prostate cancer, which is, generally-speaking, the least aggressive cancer type we studied, was only weakly associated with ischemic stroke risk within the first 3 months after cancer diagnosis, but was strongly associated with hemorrhagic stroke risk, even up to 3 years after diagnosis. This difference in risk by stroke subtype may reflect the pathophysiological differences between ischemic and hemorrhagic stroke, as well as the effects of the standard course and treatment of prostate cancer.

Prior studies have shown an increased risk of stroke in patients with breast cancer, cervical cancer treated with radiotherapy, head and neck cancer, lung cancer, and remote Hodgkin lymphoma.^{7–11} However, these studies were limited by relatively small sample sizes, single cancer types, homogeneous populations, and likely incomplete accounting for confounders. Conversely, a recent large study from Sweden reported that patients diagnosed with cancer of any type between 1987 and 2008 had a higher incidence of stroke as compared to patients without cancer after adjusting for age, sex, time period, region, socioeconomic status, and comorbidities.¹² Similar to our study, the risk was highest soon after cancer diagnosis and existed for both ischemic stroke and hemorrhagic stroke. Although the Swedish study included a more homogenous population, its similar results strengthen the validity and generalizability of our main finding that cancer is independently associated with subsequent stroke.

Cancer and its treatments routinely cause alterations in platelet, coagulation, and endothelial function, which in turn can cause thrombosis or hemorrhage.^{13, 26} These factors usually lead to venous thromboembolism, but arterial events may occur as well.^{28–30} Although cancer-mediated hypercoagulability has been described for centuries, its exact mechanisms remain poorly understood. Some potential prothrombotic mechanisms include increased production of tissue factor and cancer procoagulant, inflammatory cytokine release including vascular endothelial growth factor, and tumor-cell adhesion and activation of endothelium.^{13, 26} The specific mechanisms by which these alterations may lead to stroke are also poorly understood. One common theory, which is supported by autopsy and transcranial Doppler microemboli studies, is that the hypercoagulability of cancer leads to the formation of non-bacterial thrombotic endocarditis, a condition in which small, sterile, platelet-fibrin vegetations on normal cardiac valves embolize to the brain and cause ischemic stroke.^{2, 31, 32} An alternative possibility is that cancer predisposes to ischemic stroke through paradoxical embolism of deep vein thromboses, which are greatly increased with cancer. In addition, cancer and its treatments may also predispose to hemorrhagic forms of stroke through intratumoral hemorrhage, coagulopathy from bone marrow suppression or liver dysfunction, and disseminated intravascular coagulation.³³ Our study design did not allow evaluation of these mechanistic hypotheses; further investigations will be needed to elucidate the biological mechanisms that link cancer to stroke.

This study has several limitations. First, because we used SEER-Medicare data, we excluded patients under the age of 66, patients not enrolled in Medicare, and patients enrolled in a Medicare managed care plan. Second, our reliance on medical claims data may have led to misclassification of events, but Medicare *ICD-9-CM* codes have been shown previously to reliably identify stroke and other cardiovascular outcomes with high specificity.^{22, 34} Third, even though we attempted to account for confounding by performing a robust and detailed matching schema, our cases and controls may have differed in regards to unmeasured confounders, which could have led to a false association between stroke and cancer. However, this seems unlikely as stroke risk increased dramatically after cancer diagnosis and then decreased over time, which would be unexpected if our results were due to residual confounding. Similarly, it is unlikely that our findings are due to detection bias (i.e., cancer patients monitored more closely resulting in more detected strokes) because stroke risk was not uniform among cancer types and appeared to instead correlate with the general aggressiveness of the underlying cancer. Fourth, we did not have data on diagnostic evaluations (e.g., echocardiography) or stroke etiology, and thus could not determine the biological mechanisms that account for the association between cancer and stroke. Fifth, we were unable to identify or selectively analyze patients with Medicare Advantage plans; since these patients generally have increased healthcare benefits, their stroke risk after cancer diagnosis may be different.

We found an increased risk of stroke after a new cancer diagnosis, especially during the first 3 months after diagnosis and predominantly with more advanced malignancies. Our findings suggest that cancer may be an underappreciated yet common risk factor for stroke. Future studies will be needed to determine the precise mechanisms by which cancer may be

associated with stroke, the need to include a cancer diagnosis in cardiovascular risk prediction instruments, and the optimal strategies to prevent stroke in patients with cancer.

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Figure 1.

Cumulative incidence of stroke in cancer patients compared to matched controls.

Cumulative incidence is stratified by cancer type, (A) Breast, (B) Colorectal, (C) Lung, (D) Pancreatic, (E) Prostate. Competing risk survival statistics were used to calculate incidence.

Data are shown through the median period of follow-up for cancer patients for each cancer type up to a maximum of 3 years. 95% confidence intervals are noted by dashed lines.

Table 1

Baseline Characteristics of Matched Pairs of Cancer Patients and Control Patients, 2001–2007, Stratified by Cancer Type

Characteristic	Breast Cohort (N=69234)*	Colorectal Cohort (N=65829)	Lung Cohort (N=80984)	Pancreatic Cohort (N=16571)	Prostate Cohort (N=94771)
Age, mean (SD), y	76 (7)	78 (7)	76 (7)	78 (7)	75 (6)
Sex:					
Women	68662 (99)	36026 (55)	39387 (49)	9456 (57)	0 (0)
Men	572 (1)	29803 (45)	41597 (51)	7115 (43)	94771 (100)
Race:					
White	61118 (88)	56390 (86)	70116 (87)	13758 (83)	79337 (84)
Non-white	8116 (12)	9439 (14)	10868 (13)	2813 (17)	15434 (16)
Geographic region:					
Northeast	16842 (24)	17439 (26)	18113 (22)	4029 (24)	22158 (23)
Midwest	13044 (19)	12863 (20)	15189 (19)	3121 (19)	19011 (20)
South	12553 (18)	12507 (19)	18535 (23)	2973 (18)	16865 (18)
West	27095 (39)	23020 (35)	29147 (36)	6448 (39)	36737 (39)
Charlson Comorbidities:					
0	48713 (69)	40593 (62)	40870 (50)	8562 (52)	67286 (71)
1 or more	21421 (31)	25236 (38)	40114 (50)	8009 (48)	27485 (29)
Hypertension or Atrial Fibrillation	49788 (72)	47668 (72)	58003 (72)	12299 (74)	63466 (67)
Census Tract Poverty Level <10% [†]	43662 (63)	38637 (59)	45152 (56)	9746 (59)	57870 (61)
Cancer Stage [‡] :					
0 or T0	10566 (15)	4783 (7)	55 (0)	26 (0)	47 (0)
1 or T1	27622 (40)	13507 (21)	12483 (15)	605 (4)	41172 (43)
2 or T2	17792 (26)	16593 (25)	2554 (3)	1859 (11)	44038 (46)
3 or T3	4792 (7)	14063 (21)	20154 (25)	714 (4)	2144 (2)
4 or T4	3471 (5)	10504 (16)	31499 (39)	4413 (27)	4684 (5)
Unknown	4991 (7)	6379 (10)	14239 (18)	8954 (54)	2686 (3)

Abbreviations: SD, standard deviation

* Data are presented as Number (%) unless otherwise specified. Total numbers represent the total number of matched pairs. Due to rounding, some values may not add up to 100.

[†] Number and proportion of patients who live in areas where less than 10% of people are below the poverty line according to the 2000 census.

[‡] Refers to the American Joint Committee on Cancer (AJCC) staging schema, except for patients with prostate cancer, who were staged according to the T (clinical) staging classification. Cancers diagnosed from 2001 through 2003 were staged according to the AJCC third edition definitions, while cancers diagnosed from 2004 through 2007 were staged according to the sixth edition. There are a higher proportion of pancreas cancer patients with an unknown stage because AJCC staging prior to 2004 is not available in SEER for these patients.

Table 2

Cumulative Incidence of Stroke, Stratified by Cancer Type*

Cancer Type:	Time Since Diagnosis of Cancer [†]					
	3 Months	6 Months	1 Year	2 Years	3 Years	
Breast:						
Patients	1.5 (1.4–1.6)	2.3 (2.2–2.4)	3.9 (3.8–4.1)	6.3 (6.2–6.5)	8.4 (8.1–8.6)	
Controls	1.1 (1.0–1.2)	2.1 (2.0–2.2)	3.9 (3.7–4.0)	6.7 (6.5–6.9)	8.9 (8.7–9.1)	
Colorectal:						
Patients	3.3 (3.2–3.4)	4.7 (4.5–4.8)	6.2 (6.0–6.4)	8.4 (8.2–8.7)	10.1 (9.9–10.3)	
Controls	1.3 (1.2–1.4)	2.4 (2.3–2.6)	4.6 (4.4–4.7)	8.0 (7.8–8.2)	10.4 (10.2–10.7)	
Lung:						
Patients	5.1 (4.9–5.2)	6.6 (6.4–6.7)	8.1 (8.0–8.3)	--	--	
Controls	1.2 (1.2–1.3)	2.4 (2.3–2.5)	4.4 (4.2–4.5)	--	--	
Pancreas:						
Patients	3.4 (3.1–3.6)	4.3 (4.0–4.6)	--	--	--	
Controls	1.3 (1.1–1.5)	2.3 (2.1–2.6)	--	--	--	
Prostate:						
Patients	1.2 (1.1–1.3)	2.1 (2.0–2.2)	3.6 (3.5–3.8)	6.3 (6.2–6.5)	8.3 (8.1–8.5)	
Controls	1.1 (1.0–1.2)	2.1 (2.0–2.2)	3.8 (3.6–3.9)	6.5 (6.4–6.7)	8.7 (8.5–8.8)	

* Cumulative incidence is reported as Percent (95% confidence interval).

[†] Data are shown through the median period of follow-up for cancer patients for each cancer type up to a maximum of 3 years.

Table 3

Relative Hazards of Stroke during Discrete Time Periods, Stratified by Cancer Type and Stroke Type*

	Time Periods After Cancer Diagnosis [†]					
	0–1 Months	1–3 Months	3–6 Months	6–9 Months	9–12 Months	
<i>All Stroke</i>						
Breast	1.71 (1.48–1.99)	1.17 (1.03–1.32)	0.86 (0.77–0.96)	0.92 (0.82–1.04)	0.93 (0.83–1.04)	
Colorectal	4.16 (3.66–4.72)	1.80 (1.62–2.00)	1.37 (1.25–1.51)	0.92 (0.83–1.03)	0.85 (0.75–0.95)	
Lung	7.43 (6.65–8.29)	2.66 (2.42–2.91)	1.95 (1.79–2.12)	1.63 (1.47–1.80)	1.69 (1.51–1.88)	
Pancreas	4.25 (3.32–5.45)	2.14 (1.73–2.65)	1.62 (1.31–2.01)	--	--	
Prostate	1.25 (1.09–1.43)	0.97 (0.88–1.08)	0.96 (0.88–1.05)	0.90 (0.81–0.99)	0.93 (0.84–1.03)	
<i>Ischemic Stroke</i>						
Breast	1.72 (1.47–2.00)	1.11 (0.98–1.26)	0.85 (0.76–0.96)	0.91 (0.81–1.03)	0.92 (0.81–1.04)	
Colorectal	4.33 (3.80–4.94)	1.79 (1.61–2.00)	1.35 (1.22–1.49)	0.88 (0.79–0.99)	0.81 (0.72–0.91)	
Lung	7.12 (6.35–7.99)	2.54 (2.31–2.79)	1.85 (1.69–2.02)	1.51 (1.35–1.68)	1.55 (1.39–1.74)	
Pancreas	4.15 (3.22–5.36)	2.12 (1.70–2.64)	1.55 (1.25–1.93)	--	--	
Prostate	1.22 (1.06–1.40)	0.97 (0.87–1.08)	0.94 (0.86–1.04)	0.88 (0.80–0.98)	0.90 (0.81–1.00)	
<i>Hemorrhagic Stroke</i>						
Breast	1.67 (0.96–2.93)	2.23 (1.37–3.65)	0.97 (0.65–1.46)	1.07 (0.71–1.60)	1.03 (0.68–1.56)	
Colorectal	2.17 (1.35–3.48)	1.88 (1.24–2.84)	1.67 (1.15–2.42)	1.58 (1.05–2.37)	1.55 (0.98–2.47)	
Lung	11.06 (7.40–16.52)	4.75 (3.19–7.08)	3.43 (2.47–4.76)	3.30 (2.34–4.66)	3.54 (2.46–5.10)	
Pancreas	6.00 (2.08–17.30)	2.44 (0.99–6.05)	3.59 (1.35–9.55)	--	--	
Prostate	1.78 (1.03–3.07)	1.04 (0.71–1.54)	1.27 (0.88–1.83)	1.06 (0.74–1.52)	1.46 (1.00–2.14)	

* Relative hazards are reported as Number (95% confidence interval).

[†] Data are shown through the median period of follow-up for each cancer type up to a maximum of 1 year.

Table 4

Cumulative Incidence of Ischemic Stroke, Stratified by Cancer Type*

Cancer Type:	Time Since Diagnosis of Cancer [†]					
	3 Months	6 Months	1 Year	2 Years	3 Years	
Breast:						
Patients	1.3 (1.3–1.4)	2.1 (2.0–2.2)	3.6 (3.5–3.7)	5.8 (5.6–6.0)	7.6 (7.4–7.8)	
Controls	1.0 (0.9–1.1)	2.0 (1.9–2.1)	3.6 (3.5–3.7)	6.3 (6.1–6.4)	8.3 (8.1–8.5)	
Colorectal:						
Patients	3.1 (3.0–3.3)	4.4 (4.2–4.5)	5.8 (5.6–6.0)	7.8 (7.6–8.0)	9.3 (9.1–9.5)	
Controls	1.2 (1.1–1.3)	2.3 (2.2–2.4)	4.3 (4.2–4.5)	7.5 (7.3–7.7)	9.8 (9.6–10.1)	
Lung:						
Patients	4.6 (4.4–4.7)	5.9 (5.8–6.1)	7.3 (7.1–7.5)	--	--	
Controls	1.2 (1.1–1.2)	2.3 (2.2–2.4)	4.1 (4.0–4.2)	--	--	
Pancreas:						
Patients	3.1 (2.9–3.4)	4.0 (3.7–4.3)	--	--	--	
Controls	1.2 (1.1–1.5)	2.2 (2.0–2.5)	--	--	--	
Prostate:						
Patients	1.1 (1.0–1.2)	1.9 (1.9–2.0)	3.3 (3.2–3.5)	5.8 (5.6–5.9)	7.6 (7.4–7.7)	
Controls	1.0 (1.0–1.1)	1.9 (1.9–2.0)	3.5 (3.4–3.6)	6.1 (5.9–6.3)	8.1 (7.9–8.3)	

* Cumulative incidence is reported as Percent (95% confidence interval).

[†] Data are shown through the median period of follow-up for cancer patients for each cancer type up to a maximum of 3 years.

Table 5

Cumulative Incidence of Hemorrhagic Stroke, Stratified by Cancer Type*

Cancer Type:	Time Since Diagnosis of Cancer [†]					
	3 Months	6 Months	1 Year	2 Years	3 Years	
Breast:						
Patients	0.12 (0.10–0.15)	0.19 (0.16–0.22)	0.32 (0.28–0.37)	0.53 (0.48–0.59)	0.72 (0.65–0.78)	
Controls	0.06 (0.04–0.08)	0.12 (0.10–0.16)	0.26 (0.22–0.30)	0.40 (0.38–0.50)	0.56 (0.50–0.60)	
Colorectal:						
Patients	0.17 (0.14–0.21)	0.28 (0.24–0.32)	0.43 (0.38–0.48)	0.65 (0.59–0.71)	0.82 (0.75–0.88)	
Controls	0.09 (0.07–0.10)	0.16 (0.13–0.19)	0.27 (0.23–0.31)	0.48 (0.43–0.54)	0.60 (0.54–0.66)	
Lung:						
Patients	0.51 (0.46–0.56)	0.66 (0.60–0.71)	0.86 (0.80–0.92)	--	--	
Controls	0.07 (0.05–0.09)	0.13 (0.11–0.16)	0.25 (0.22–0.29)	--	--	
Pancreas:						
Patients	0.23 (0.16–0.30)	0.30 (0.20–0.40)	--	--	--	
Controls	0.07 (0.03–0.10)	0.10 (0.05–0.20)	--	--	--	
Prostate:						
Patients	0.09 (0.07–0.10)	0.16 (0.14–0.19)	0.30 (0.26–0.33)	0.53 (0.48–0.60)	0.73 (0.68–0.79)	
Controls	0.07 (0.06–0.09)	0.12 (0.11–0.15)	0.24 (0.21–0.27)	0.42 (0.38–0.46)	0.57 (0.52–0.62)	

* Cumulative incidence is reported as Percent (95% confidence interval).

[†] Data are shown through the median period of follow-up for cancer patients for each cancer type up to a maximum of 3 years.