ORIGINAL ARTICLE

Risk of Cancer Following an Ischemic Stroke in the Canadian Longitudinal Study on Aging

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ABSTRACT: ***Background:*** Stroke survivors may be at higher risk of incident cancer, although the magnitude and the period at risk remain unclear. We conducted a retrospective cohort study to compare the risk of cancer in stroke survivors to that of the general population. ***Methods:*** The Canadian Longitudinal Study on Aging is a large population-based cohort of individuals aged 45–85 years when recruited (2011–2015). We used data from the comprehensive subgroup (n = 30,097) to build a retrospective cohort with individual exact matching for age (1:4 ratio). We used Cox proportional hazards models to estimate hazard ratios of new cancer diagnosis with and without a prior stroke. ***Results:*** We respectively included 920 and 3,680 individuals in the stroke and non-stroke groups. We observed a higher incidence of cancer in the first year after stroke that declined afterward (p-value = 0.030). The hazard of new cancer diagnosis after stroke was significantly increased (hazard ratio: 2.36; 95% CI: 1.21, 4.61; p-value = 0.012) as compared to age-matched non-stroke participants after adjustments. The most frequent primary cancers in the first year after stroke were prostate (n = 8, 57.1%) and melanoma (n = 2, 14.3%). ***Conclusions:*** The hazard of new cancer diagnosis in the first year after an ischemic stroke is about 2.4 times higher as compared to age-matched individuals without stroke after adjustments. Surveillance bias may explain a portion of post-stroke cancer diagnoses although a selection bias of healthier participants likely led to an underestimation of post-stroke cancer risk. Prospective studies are needed to confirm the potentially pressing need to screen for post-stroke cancer.

RÉSUMÉ : Le risque de cancer à la suite d'un accident vasculaire cérébral ischémique dans l'Étude longitudinale canadienne sur le vieillissement. ***Contexte*** **:** Il est possible que le risque de nouveau cancer soit plus élevé à la suite d'un accident vasculaire cérébral (AVC), mais on n'en connaît pas très bien l'importance, et la période à risque est mal définie. Les auteurs ont donc réalisé une étude de cohorte, rétrospective, visant à comparer le risque de cancer chez les survivants d'un AVC à celui de la population générale. ***Méthode*** **:** L'Étude longitudinale canadienne sur le vieillissement est une imposante étude de cohorte, basée sur la population et composée d'hommes et de femmes âgés de 45-85 ans au moment de la sélection (2011-2015). L'équipe de recherche a d'abord utilisé des données provenant du sous-groupe globale (n = 30 097) afin de constituer une cohorte rétrospective de participants exactement appariés selon l'âge (rapport : 1/4). Elle s'est ensuite appuyée sur des modèles de risques proportionnels de Cox afin d'estimer les rapports de risque de nouveau cancer dans le contexte ou non d'un AVC. ***Résultats*** **:** Dans l'ensemble, 920 sujets et 3680 sujets ont été répartis respectivement dans les groupes d'AVC et d'absence d'AVC. Une augmentation de l'incidence du cancer a été observée au cours de la première année suivant l'AVC, mais celle-ci a diminué par la suite (valeur de $p = 0{,}030$). Le risque de diagnostic de nouveau cancer après un AVC était sensiblement plus élevé dans le groupe d'AVC (rapport des risques instantanés : 2,36; IC à 95 % : 1,21-4,61; valeur de $p = 0{,}012$) que dans le groupe d'absence d'AVC, apparié selon l'âge, et ce, après ajustement des données. Les types de cancer primitifs les plus fréquents au cours de l'année suivant l'AVC étaient celui de la prostate (n = 8; 57,1 %) et le mélanome (n = 2; 14,3 %). ***Conclusion*** **:** Le risque de nouveau cancer au cours de l'année suivant un AVC ischémique est environ 2,4 fois plus élevé qu'en l'absence d'AVC, et ce, après ajustement des données. Certes, un biais de surveillance peut expliquer en partie un certain nombre de cancers à la suite d'un AVC, mais le biais de sélection en faveur de participants en bonne santé a sans doute entraîné, lui, une sous-estimation du risque de cancer après un AVC. Il faudrait donc réaliser des études prospectives afin de confirmer le besoin potentiellement pressant de dépistage de nouveaux cancers à la suite d'un AVC.

Keywords: Clsa, Epidemiology, Stroke, Cancer

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Introduction

Cancer promotes thromboembolism through inflammation and hypercoagulability, and an ischemic stroke may be the first sign of an occult malignancy.[1] Early recognition of cancer in stroke survivors represents an opportunity to tailor antithrombotic therapy and offer cancer treatments to improve secondary prevention.[1] The benefits of routine cancer screening, however, are uncertain, partly because estimates of cancer incidence after stroke are conflicting. Additional research with adjustments for potential confounders is needed to reach valid estimates of post-stroke cancer risk. We conducted a retrospective cohort study to compare the risk of cancer in people who experienced

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an ischemic stroke to that of the general population, using data from the Canadian Longitudinal Study on Aging (CLSA).

Methods

We used the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement to report our work.[2]

Data Source

The CLSA is a large, national population-based cohort study on adult aging. It consists of 51,338 Canadian women and men aged 45–85 years at the time of enrolment, intended to be followed every three years for up to 20 years or death in one of two complementary cohorts (tracking and comprehensive).[3] The comprehensive cohort includes 30,097 participants randomly drawn (mostly using random digit dialing of landline telephones) from people living within 25–50 km of 11 designated data collection sites located in seven Canadian provinces. Participants were asked to report information relevant to health and aging, such as sociodemographics and prior diagnoses. Exclusion criteria at enrolment included people living in institutions and long-term care facilities, as well as those with physical or cognitive impairments limiting their ability to participate with the study. Recruitment and baseline data collection were completed between 2011 and 2015, while the first follow-up period began in 2015 and ended in 2018. Further details on the study methods are available.[4]

Data Extraction and Retrospective Cohort

We limited our analyses to data from the comprehensive cohort, as a formal definition of stroke was read to participants during data collection ('when blood flow to a part of the brain stops') which allowed for a distinction to be made between ischemic and hemorrhagic stroke, while the tracking cohort did not. In addition to stroke, participants were asked to report a prior diagnosis of 'ministroke' or transient ischemic attack (TIA). We used the first two questions of the CLSA's cerebrovascular event algorithm derived from the validated Questionnaire for Verifying Stroke-Free Status (QVSFS) to ascertain stroke and TIA status in our study.[5] We extracted data from the first follow-up on current age, sex at birth, past alcohol use, self-reported medical diagnoses (including cancer and stroke) and age at the time of diagnosis. Smoking and ethnicity were extracted from the baseline data.

We defined index age in the exposed group as the age of either TIA or stroke and defined that of nonexposed as the age of matching. When both TIA and stroke were reported by a participant (n = 128), we only considered the first event. We defined incident cancer as any self-reported diagnosis of a first cancer occurring after the index age, excluding non-melanomatous skin cancers (n = 896) given their benign course.[6] Time from stroke to cancer diagnosis was a priori defined as the difference in the self-reported age at the time of cancer and stroke diagnoses, to adequately manipulate interval-censored data.[7] We excluded participants whose age at the time of TIA (n = 84), stroke (n = 21) or cancer (n = 74) was missing. We also excluded individuals reporting cancer before (n = 303) or at the same age (n = 36) as that of index stoke to exclude pre-stroke cancer, and those without at least one year of follow-up after the index event (n = 145).

We built our cohort of exposed and unexposed participants using individual exact matching for age. We randomly sampled each participant from the base without replacement, in chronological order by age at the time of the index event.[8] For each participant with stroke at a given index age, four unexposed participants without a prior cancer or stroke were drawn from the base cohort.

Statistical Analyses

We compared baseline characteristics with Student's t-test for continuous variables and chi-squared test for categorial variables. We calculated the cumulative incidence of cancer per 1,000 individuals along with 95% confidence intervals (CIs) using the Wilson interval for binomial proportions. We compared the first three years of post-stroke cancer incidence with a theoretical homogeneous distribution using the chi-squared goodness of fit test. We used Cox proportional hazards models to estimate the hazard ratios of new cancer diagnosis with and without a prior stroke. We built three parallel models, each with an alternative dependent variable for time of follow-up (any time, four years, and one year after stroke) as we hypothesized that the risk of cancer would be time-dependent.[9] We identified potential confounders with causal graphs and built a family of three models per dependent variable adjusted for i) demographics alone (sex, ethnicity), ii) demographics plus lifestyle habits (smoking status, alcohol consumption), and iii) demographics and lifestyle habits plus comorbidities (hypertension, diabetes mellitus). We selected the final model for each dependent variable with the Akaike information criterion. We dichotomized the ethnicity variable in our model (white or other) to respect requirements on minimum outcome events per predictor variable.[10] We included index age in our models to adequately account for matching and verified the proportional hazards assumption with graphs and tests based on the Schoenfeld residuals.[11,12] We performed sensitivity analyses after excluding people who reported a cognitive decline and those reporting a TIA to reduce misclassification of self-reported diagnoses.[13] We analyzed our data with R Studio (v.1.2) and defined statistical significance as a p-value <0.05.[14]

Results

We identified 920 individuals in the stroke group and 3,680 individuals in the age-matched non-stroke group. The stroke group had a significantly higher proportion of common risk factors for stroke (male sex, smoking, hypertension, diabetes mellitus), as well as more frequent comorbidities (myocardial infarction, chronic obstructive pulmonary disease, chronic kidney disease; Table 1). The index event in the stroke group was either TIA (n = 614; 66.7%), stroke (n = 252; 27.4%), or both (n = 54; 5.9%). The median follow-up after the index stroke event was 10 years in the stroke group (interquartile range [IQR]: 4, 17) and 11 years in the non-stroke group (IQR: 5, 19).

A total of 105 individuals with stroke (11.4%; 95% CI: 9.5, 13.6) and 418 age-matched non-stroke participants (11.4%; 95% CI: 10.4, 12.4) received a new diagnosis of cancer during follow-up, with a median time to diagnosis of 8 (IQR: 4, 17) and 10 years (IQR: 5, 18), respectively. In the first year of follow-up, 14 individuals in the stroke group (1.5%; 95% CI: 0.9, 2.5) and 26 individuals in the non-stroke group (0.7%; 95% CI: 0.5, 1.0) reported a new cancer. As compared to a theoretical

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Table 1: Baseline characteristics of participants with and without stroke

Characteristics	Stroke (n = 920)	No stroke (n = 3,680)	p-value
Age, mean (SD)	58.8 (14.0)	58.8 (14.0)	1
Male sex	508 (55.3)	1,833 (49.8)	**0.003**
Ethnicity			0.246
White	869 (94.8)	3,510 (95.7)	
African descent	7 (0.8)	17 (0.5)	
Asian	12 (1.3)	71 (1.9)	
Latin American	3 (0.3)	10 (0.3)	
Other	26 (2.8)	59 (1.6)	
Ever smoked ≥1 month	486 (53.0)	1,754 (47.9)	**0.007**
Ever consumed alcohol	896 (97.4)	3,574 (97.1)	0.739
Hypertension	290 (32.5)	875 (24.3)	**<0.001**
Diabetes mellitus	137 (15.1)	332 (9.1)	**<0.001**
Myocardial infarction	51 (5.5)	130 (3.5)	**0.007**
Chronic obstructive pulmonary disease	53 (5.8)	127 (3.5)	**0.002**
Chronic kidney disease	29 (3.2)	63 (1.7)	**0.008**

Numbers refer to n (%) unless otherwise specified. Bold characters indicate a p-value <0.05.
Abbreviation: SD = standard deviation.

homogeneous distribution of cancer diagnoses after stroke, the observed distribution of cancer in the first three years after stroke was uneven (p-value = 0.030), with a higher incidence of cancer in the first year that declined thereafter (Figure 1). The most frequent primary cancers diagnosed in the first year of follow-up were prostate (n = 8; 57.1% in the stroke group versus n = 8; 30.8% in the non-stroke group) and melanoma (n = 2; 14.3% versus n = 3; 11.5%). Less frequent sites were bladder (n = 1; 7.1% versus n = 1; 3.8%), non-Hodgkin lymphoma (n = 1; 7.1% versus n = 2; 7.7%), kidney (n = 1; 7.1% versus none) and other (n = 1; 7.1% versus n = 2; 7.7%).

The hazard of cancer in the first year after stroke was significantly higher as compared to people without stroke after adjusting for sex, ethnicity, alcohol use, smoking, hypertension, and diabetes mellitus, with a hazard ratio of 2.36 (95% CI: 1.21, 4.61; p-value = 0.012). The hazard of cancer was not significantly increased beyond the first year (Table 2). Analyses after excluding people with cognitive impairment (71 with stroke and 310 without stroke) yielded similar results (Table 3). The association was no longer significant in the first year after excluding TIAs (n = 614) and age-matched nonstroke participants (n = 2,456), although the hazard ratio point estimates were similar. Visual inspection and nonsignificant Schoenfeld residual-based tests supported the assumption of proportional hazards in all models.

Discussion

In this retrospective age-matched analysis of the CLSA cohort, the hazard of newly diagnosed cancer in the first year following an ischemic stroke is about 2.4 times higher as compared to people without stroke after adjusting for socio-demographics and shared risk factors. This one-year period at risk after stroke supports a phenomenon of reverse causation, whereby some cancers were truly occult at the time of stroke and acted as component cause. Neoplasms may evolve from several months to a few years before they reach a clinically overt phase, and the interval of greater risk of cancer diagnosis after stroke fits a plausible preclinical phase.[15]

We identified two published population-based studies that stratified the comparison of cancer risk by year after stroke.[9,16] Both found a higher risk of cancer in the first year after stroke that declined afterward. These studies, however, used external comparators (from Danish registries) and did not control for important confounders. One study only assessed colorectal cancer[9] and the other used data collected before the common use of contemporary diagnostic techniques (1977–1984).[16] We used, in contrast, an internal comparator which allowed us to control for common risk factors (i.e. sources of confounding bias) and included all cancer types. A more recent cohort study of young people followed up to nine years after a first-ever stroke reported a higher risk of cancer diagnosis overall, although the authors did not explore the risk by time after stroke.[17]

Prostate is the most frequent primary cancer site in both groups of our study in the first year of follow-up. Despite its lower thrombotic potential than other sites such as the pancreas, prostate cancer remains a common cause of cancer-associated thromboses because of its high prevalence in the general population.[18] In a large retrospective cohort study using the Surveillance, Epidemiology, and End Results program database, the risk of ischemic stroke was significantly increased by about 60% in the first month following a diagnosis of prostate cancer.[19] In a recent review, genitourinary cancers (including prostate) were the second most commonly reported after stroke (18.3% overall), and the most frequent post-stroke cancer in three studies.[20] Up to 50% of strokes associated with prostate cancer do not have a determined etiology, a finding that suggests less common causes of stroke may be involved in these patients.[21] Nonbacterial thrombotic endocarditis, a common but underdiagnosed cause of cancer-associated cryptogenic stroke, also occurs in prostate cancer.[22]

The strengths of our study include a large, population-based cohort and control for common risk factors in the association of stroke and cancer. Our study, however, has limitations. First, a selection bias likely led to an underestimation of the true association between stroke and cancer. Participants in the CLSA comprehensive cohort needed to be relatively mobile and independent at recruitment, reflected by our high proportion of TIAs (66.7%) as compared to hospital-based cohorts (about 15%).[23] People with stroke and occult cancer more often die or have a recurrent stroke as compared to those without cancer, which in combination with independence requirements at inclusion in our study likely led to a depletion of cancer-associated strokes.[22,24] People with a TIA preceding an ischemic stroke, on the other hand, do not appear to have a different risk of incident cancer diagnosis as compared to those with an ischemic stroke only.[9,25] The exclusion of cancers diagnosed at the same age as stroke and better self-rated general health in the CLSA cohort are additional factors that may explain the lower cancer incidence in the first year after stroke (1.5%) as compared to other prospective studies

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Table 2: Cumulative incidence and hazard ratios of cancer diagnosis after stroke

Index event	Cancer, n (%)	Hazard ratio, simple model*(95% CI)	p-value	Hazard ratio, adjusted model†(95% CI)	p-value
One year after the index event					
Stroke	14 (1.5)	2.17 (1.13, 4.15)	**0.020**	2.36 (1.21, 4.61)	**0.012**
No stroke	26 (0.7)	Reference		Reference	
Four years after the index event					
Stroke	34 (3.7)	1.38 (0.93, 2.03)	0.108	1.41 (0.95, 2.09)	0.089
No stroke	101 (2.7)	Reference		Reference	
Any time after the index event					
Stroke	105 (11.4)	1.17 (0.94, 1.45)	0.150	1.20 (0.97, 1.49)	0.096
No stroke	418 (11.4)	Reference		Reference	

*Matched for age. †Matched for age and adjusted for sex, ethnicity, alcohol use, smoking, hypertension, and diabetes mellitus. Bold characters indicate a p-value <0.05. Abbreviation: CI, confidence interval.

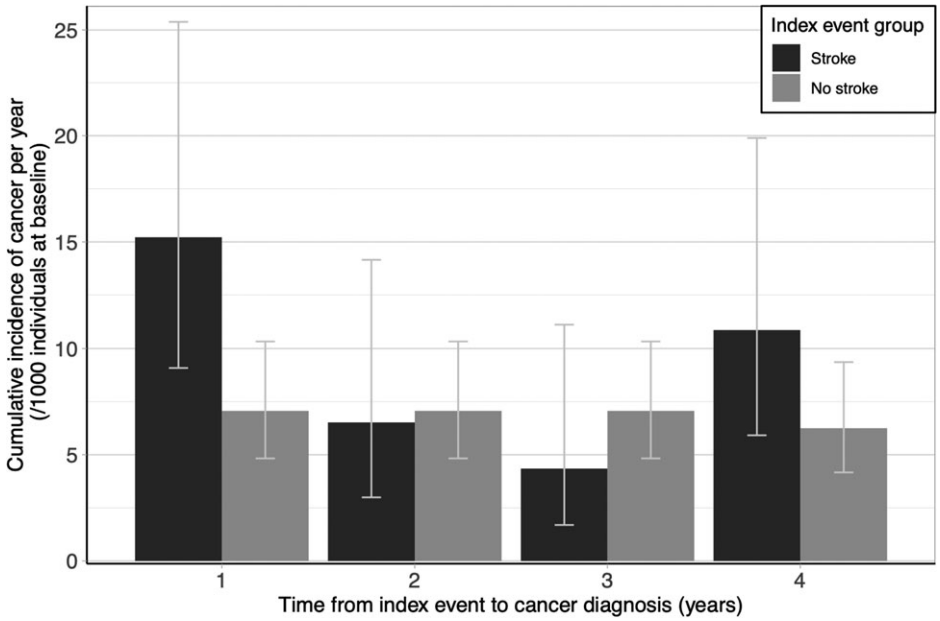

Figure 1: *Cumulative incidence of cancer per year by index event group. This figure shows the cumulative incidence of cancer (per thousand individuals at baseline) per year after the index event, with 95% confidence intervals.*

(up to 5%).[26] Second, the relative distribution of cancer types observed in our study needs to be interpreted with caution. The retrospective design of the study likely led to a depletion of aggressive malignancies with a higher mortality and may explain the absence of pancreas adenocarcinomas in both study groups. Third, a recent stroke or TIA increases the likelihood of a medical contact that may lead to a diagnosis of cancer unrelated to stroke. This surveillance bias would manifest as an increased proportion of cancers diagnosed after stroke. Participants of the CLSA comprehensive cohort, however, report higher socioeconomic status overall than the general population, which is associated with greater cancer screening utilization in the community and lowers the potential effect of a surveillance bias in our study.[27,28] Fourth, diagnoses were all self-reported and therefore prone to errors in classification. A diagnostic accuracy study of the QVSFS, however, found a high specificity (99%) and a moderate sensitivity (79%) for self-reported strokes as compared to history and examination by an experienced neurologist.[5] Self-reported TIAs also had a high specificity (97%), but a lower sensitivity (45%).[5] When compared to medical records, the combination of self-reported strokes and TIAs has a high specificity (99%) and a moderate sensitivity (78%) for ischemic cerebrovascular events.[29] The effect of this bias on our results was likely small as the hazard ratio point estimates were similar after excluding TIAs, although the few participants left in the analyses yielded non-significant results.

Conclusion

In this retrospective cohort study from the CLSA, we found that the one-year risk of a new cancer diagnosis is about 2.4 times

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Table 3: Sensitivity analyses for the cumulative incidence and hazard ratios of cancer diagnosis after stroke

	Exclusion of cognitively impaired participants					Exclusion of transient ischemic attacks				
Index event	**Cancer, n (%)**	**Hazard ratio, simple model* (95% CI)**	**p-value**	**Hazard ratio, adjusted model† (95% CI)**	**p-value**	**Cancer, n (%)**	**Hazard ratio, simple model* (95% CI)**	**p-value**	**Hazard ratio, adjusted model† (95% CI)**	**p-value**
One year after the index event										
Stroke	13 (1.5)	2.08 (1.06, 4.06)	**0.032**	2.21 (1.12, 4.39)	**0.023**	6 (2.0)	2.20 (0.81, 5.95)	0.120	2.35 (0.84, 6.60)	0.104
No stroke	25 (0.7)	Reference		Reference		11 (0.9)	Reference		Reference	
Four years after the index event										
Stroke	32 (3.8)	1.33 (0.89, 1.98)	0.162	1.35 (0.90, 2.02)	0.144	13 (4.2)	1.86 (0.97, 3.57)	0.062	2.08 (1.07, 4.05)	**0.032**
No stroke	97 (2.9)	Reference		Reference		30 (2.5)	Reference		Reference	
Any time after the index event										
Stroke	97 (11.4)	1.12 (0.90, 1.40)	0.309	1.15 (0.92, 1.44)	0.221	35 (11.4)	1.21 (0.83, 1.74)	0.323	1.26 (0.86, 1.83)	0.230
No stroke	392 (11.6)	Reference		Reference		149 (12.2)	Reference		Reference	

*Matched for age. †Matched for age and adjusted for sex, ethnicity, alcohol use, smoking, hypertension, and diabetes mellitus. Bold characters indicate a p-value <0.05. Abbreviation: CI = confidence interval.

higher in people with an incident ischemic stroke as compared to those without a history of stroke. Additional research is needed to determine whether cancer screening tests after ischemic stroke are warranted, and in which sub-populations these may apply.

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Disclosures

BR reports no potential conflicts of interest. MRK reports unrestricted educational grants from UCB and Eisai and research grants from UCB and Eisai. LCG reports speaker fees and advisory board honoraria from Bayer, BMS Pfizer, and Servier and investigator-initiated funding from Servier.

Statement of Authorship

All authors contributed to the design, data preparation, analyses, interpretation, and writing of the manuscript.

Statement of Ethics

Subjects involved in the CLSA study have given their written informed consent, and our institutional Research Ethics Board approved this secondary analysis.

Disclaimer Statement

The opinions expressed in this manuscript are the authors' own and do not reflect the views of the CLSA.

Data Availability Statement

Data are available from the CLSA (www.clsa-elcv.ca) for researchers who meet the criteria for access to deidentified CLSA data.

Supplementary Material

To view supplementary material for this article, please visit https://doi.org/10.1017/cjn.2021.55.

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