Cancer-associated ischemic stroke: current knowledge and future directions

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ABSTRACT

Because cancer is a strong prothrombotic, there is an increased risk of thromboembolism, which includes ischemic stroke, especially in the first six to twelve months following a cancer diagnosis. The risk of ischemic stroke differs according to the location and stage of cancer. Given that the risk increases prior to a cancer diagnosis, stroke may be the initial sign of occult cancer. Although data on the risk, treatment, and outcomes of cancer-associated stroke are more limited than those on cancer-associated venous thromboembolism, the condition is still recognized as a thrombotic complication of cancer. Up to 10% of ischemic stroke patients also have a concurrent cancer diagnosis, and these patients seem to have higher short-term mortality and morbidity rates. With more people expected to survive longer after cancer treatment and an increasing number of cancer survivors, the burden of stroke among cancer patients is predicted to rise. This narrative review aims to provide an overview of the pathophysiologic mechanisms, treatment options, and epidemiology of ischemic stroke, including cancer screening for those who have cryptogenic (unexplained) stroke.

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Ischemic stroke in patients with cancer: burden of the problem

Cancer survivorship, "the process of living with, through and beyond cancer",[1] is increasing. Advances in the early detection and treatment of cancer, and population growth and aging have resulted in higher numbers of cancer survivors. In the United States, there are currently an estimated 15 million people living with a history of cancer, a number which is expected to reach 21 million by 2026.[2,3] Up to one-third of Europeans and one-half of Canadians are expected to develop cancer in their lifetime.[4,5] Over 60% of those diagnosed with cancer are expected to survive for 5 years or longer after a cancer diagnosis.

Cancer is highly thrombogenic and increases the risk of venous and arterial thromboembolism.[6,7] Unlike cancer-associated venous thromboembolism (VTE), data regarding the risk of cancer-associated stroke, its management, and outcomes are more limited. Approximately 4% to 10% of patients with ischemic stroke have a concurrent diagnosis of cancer.[8] Ischemic stroke appears to have higher morbidity and short-term mortality in patients with cancer and may interfere with the provision of optimal cancer therapies thereby impacting disease prognosis.[9,10] The burden of stroke among individuals with cancer is expected to grow due to the increasing number of cancer survivors and longer survival after cancer treatment.

In this narrative review, we describe the epidemiology of ischemic stroke in patients with cancer, summarize the existing evidence for treatment, and propose future directions for prevention and treatment. Table 1 reports a brief summary of previously released cohort studies that looked at cancer patients' risk of stroke.

Epidemiology of ischemic stroke in patients with cancer

Early evidence for an association between cancer and ischemic stroke was demonstrated in an autopsy study in which pathological evidence of cerebrovascular disease was found in 14.6% of patients with non-central nervous system cancer.[11] Subsequent analyses of data from the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute revealed a higher 6-month risk of ischemic stroke in individuals newly diagnosed with cancer when compared to those without cancer [3.0% *vs*. 1.6%, hazard ratio (HR) 1.9, 95% confidence interval (CI) 1.8-2.0] which decreases over time after diagno-

Table 1. Summary of previously published cohort studies that examined the risk of stroke in cancer patients.

First author	Title	Journal/year	Cancer population	Comparator	Outcome	Measure of association
Jang *et al.*	The long-term effect of cancer on incident stroke: a cohort study in Korea	Front Neurol 2019	New diagnosis of digestive organs, lip/oral/pharynx, respiratory, thyroid, others (breast and reproductive organs)	Individuals without cancer (propensity score matched)	Stroke within 7 years	Subdistribution hazard ratio: 1.13; 95% CI 1.02-1.26
Lun *et al.*	Previous ischemic stroke significantly alters stroke risk in newly diagnosed cancer patients	Stroke 2023	New diagnosis of cancer (non-melanoma skin cancer and primary central nervous system cancer excluded)	N/A	Ischemic stroke at 1 year	Incidence rate: 107.8 per 10,000 person-years
Navi *et al.*	New diagnosis of cancer and the risk of subsequent cerebrovascular events	Neurology 2018	New diagnosis of cancer (cutaneous basal cell or squamous cell carcinoma excluded)	N/A	Cerebrovascular events at 30 days	Hazard ratio: 6.1; 95% CI 2.7-13.7
Navi *et al.*	Risk of arterial thromboembolism in patients with cancer	J Am Coll Cardiol 2017	New diagnosis of breast, lung, prostate, colorectal, bladder, pancreatic, or gastric cancer or non-Hodgkin lymphoma	Individuals without cancer (matched)	Arterial thromboembolism at 6 months	Hazard ratio: 2.2; 95% CI 2.1 to 2.3
Navi *et al.*	Recurrent thromboembolic events after ischemic stroke in patients with cancer	Neurology 2014	Active systemic cancer (diagnosis of, or treatment for, systemic within the prior 6 months, or known recurrent or metastatic disease (local basal cell or squamous cell carcinoma of the skin and primary brain tumors excluded)	N/A	Recurrent thromboembolic events after ischemic stroke	Incidence 34%; 95% CI 28-40%
Navi *et al.*	Association between incident cancer and subsequent stroke	Ann Neurol 2015	New diagnosis of breast, colorectal, lung, pancreatic or prostate cancer	Individuals without cancer (matched)	Stroke at 3 months	Analyzed individually
Mulder *et al.*	Arterial thromboembolism in cancer patients	JACC: CardioOncology 2021	First-time diagnosis of all cancers (skin cancers excluded)	Individuals without cancer (matched)	Arterial thromboembolism at 12 months	Cumulative incidence of 1.50%; 95% CI 1.47-1.54% in cancer patients
Wei *et al.*	Stroke rate increases around the time of cancer diagnosis	Front Neurol 2019	New diagnosis of lung, colorectal, hepatocellular, urogenital, gastric, prostate, brain malignancy, esophageal, nasopharyngeal, breast, ovarian, thyroid, lymphoma, leukemia	Individuals without cancer (matched)	Stroke within 1 year after cancer diagnosis	Subdistribution hazard ratio 1.72; 95% CI 1.48-2.01
Zoller *et al.*	Risk of haemorrhagic and ischaemic stroke in patients with cancer: a nationwide follow-up study from Sweden	Eur J Cancer 2012	New diagnosis of cancer (all types)	N/A	Ischemic stroke	Standardized incidence ratio: 1.2; 95% CI 1.2-1.2

CI, confidence interval; N/A, not applicable.

sis.[6,12] The risk of arterial thromboembolism precedes cancer diagnosis with a 69% increase beginning about 5 months before the date of cancer diagnosis.[12] Canadian population cohort data similarly show that individuals with a new diagnosis of cancer have a 1.5-fold higher risk of ischemic stroke compared to matched cancer-free controls within 1.5 years (HR 1.40, 95% CI 1.34-1.47).[13] In a recent meta-analysis, the 1-year incidence of ischemic stroke after a new diagnosis of cancer was about 1.3% (95% CI 1.0-1.8%).[4]

Specific characteristics intrinsic to cancer including site, histology, and stage appear to play a role in reflecting unique pathophysiological mechanisms associated with stroke in this context.[5] Stroke risk varies across cancer sites; in a systematic review, survivors of pancreatic, hematologic, lung, head and neck, and stomach cancers had a higher risk for stroke compared to cancer-free controls, but not other cancer sites.[6] Other studies have shown excess risk after colorectal cancer as well.[13,14] Adenocarcinoma is a high-risk histology associated with circulating cancer-cell-derived extracellular vesicles and elevated biomarkers of hypercoagulability such as D-dimer.[7] Stroke risk increases with cancer stage and is highest among patients with stage 4 disease.[6]

Cardiovascular risk factors such as obesity, glucose intolerance, and smoking contribute to the increased stroke risk among patients with cancer.[15] Atrial fibrillation is more prevalent in the cancer population and confers a high 1-year risk of stroke of 3.3% (95% CI 2.4-4.6%).[4,8] A history of previous ischemic stroke increases the risk for stroke after a new diagnosis of cancer [aHR, 2.68 (95% CI, 2.41-2.98)], with events occurring within 1 year of diagnosis associated with the highest risk [aHR, 3.68 (95% CI, 3.22-4.22)].[9]

Individuals with cancer have unfavorable outcomes following ischemic stroke, characterized by high rates of recurrent stroke (11% to 16%), thromboembolic events (up to 37% within 6 months), increased mortality, and functional impairment.[16,17] Arterial thromboembolic events (including stroke) carry a 3-fold higher among patients with cancer compared to those without cancer.[18] In a small retrospective study, patients with cancer experienced high mortality rates (47%) and half of the survivors had a poor neurological outcome at 3 months post-stroke as measured by the modified Rankin scale.[16] Cryptogenic stroke (*i.e.*, no known stroke mechanism) is more common in cancer patients and portends poor survival [median 55 days (IQR 21-240 days) and an increased risk of death (HR 1.64, 95% CI 1.2-2.1].[19] However, these studies were limited by small sample size and clinically important outcomes such as bleeding were not captured.

Mechanism of ischemic stroke in patients with cancer

Multiple factors contribute to the risk of stroke in patients with cancer including but not limited to shared risk factors (*e.g.*, older age, smoking, obesity, alcohol), cancer-associated hypercoagulability, and the effects of cancer therapies (*e.g.*, systemic therapies, surgery, radiation-induced complications including vasculopathy, *etc*) (Figure 1).[20] A number of mechanisms that promote hypercoagulability have been implicated including activation of coagulation (*e.g.*, increased D-dimer, thrombin-antithrombin, tissue factor release), platelet function (P-selectin), and endothelial integrity (thrombomodulin, soluble intercellular adhesion molecule-1, and soluble vascular cell adhesion molecule-1) and formation of neutrophil extracellular traps.[21-24] Patients with cancer who experience stroke have a distinct blood mRNA expression profile and higher levels of cancer cell-derived extracellular vesicles compared to those without stroke and without cancer.[25,26] Antiphospholipid antibodies appear to be highly prevalent among patients with active cancer and are associated with the development of thrombotic events.[27-30] Diffusion-weighted-imaging patterns on magnetic resonance imaging showing the involvement of multiple vascular territories in individuals with cancer suggest a central embolic source, and may point to cancer-associated coagulopathy as the underlying mechanism.[31,32]

Cancer-associated hypercoagulability can manifest as stroke through unconventional mechanisms including non-bacterial thrombotic endocarditis (NBTE) and or paradoxical embolism through right-to-left intra-cardiac shunt (*i.e.*, patent foramen ovale). NBTE is a rare condition in the general population characterized by non-infectious organized thrombi on native cardiac valves and is associated with hypercoagulable states such as antiphospholipid antibody syndrome.[33] NBTE appears to be an underappreciated etiology of cryptogenic stroke in patients with cancer.[34] In an autopsy series, NBTE was present in 1.6% of individuals of whom 80% had concurrent cancer.[35] Venous thromboembolism is a frequent complication of cancer and can cause ischemic stroke via paradoxical embolism through right-to-left intra-cardiac shunt which is present in about 25-35% of individuals.[36] A prospective cohort study found a right-to-left intra-cardiac shunt in 18% of patients with ischemic stroke, 5% of whom had cancer.[37] The prevalence of right-to-left intra-cardiac shunt was higher among patients with cancer compared to those without (55% *vs*. 15%, P=0.001). All patients with cancer and right-

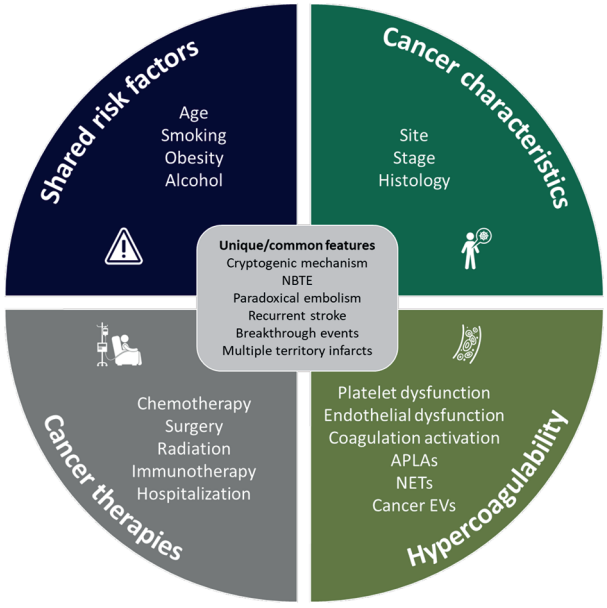

Figure 1. Factors contributing to ischemic stroke in patients with cancer. APLAs, antiphospholipid antibodies; NETs, neutrophil extracellular traps; EV, extracellular vesicles; NBTE, non-bacterial thrombotic endocarditis.

to-left shunt also had venous thromboembolism (*i.e.*, lower extremity deep vein thrombosis or pulmonary embolism).

Cryptogenic ischemic stroke and undiagnosed cancer

Cryptogenic stroke refers to ischemic stroke with no known pathogenic mechanism after standard diagnostic evaluation. The term "embolic stroke of undetermined source" (ESUS) was coined in 2014 to describe a non-lacunar (*i.e.*, embolic) ischemic stroke that remains cryptogenic after evaluation.[38] Cryptogenic stroke accounts for 10% to 40% of all ischemic strokes.[39-42]

Given that the risk of arterial thromboembolism increases before cancer diagnosis, ischemic stroke may be the first clinical manifestation of underlying cancer possibly reflecting prothrombotic effects of occult cancer. Patients without known cancer who present with cryptogenic ischemic stroke are at increased risk of cancer diagnosis within the subsequent year. In a recent meta-analysis, the 1-year incidence of cancer diagnosis after cryptogenic stroke was 6.2% (95% CI 1.4 to 13.9).[43] Therefore, detection of occult cancer after cryptogenic stroke may lead to earlier cancer diagnosis and treatment, and possibly improved survival.

Although cancer may underlie unexplained thrombosis, for patients with cryptogenic stroke there are no high-quality data regarding the potential benefits and harms of cancer screening and the optimal screening strategy is unknown. Although expert guidance endorses consideration of underlying cancer as an etiology of cryptogenic stroke, specific recommendations beyond cancer screening according to sex, age and risk for the general population are lacking.[44,45] This approach may be inadequate for the cryptogenic stroke population at higher risk of occult cancer and younger age. Professional guidelines (*e.g.*, American Heart Association/American Stroke Association Guidelines 2021, Canadian Stroke Best Practice Guidelines 2022) do not make specific recommendations as to how and when to screen for occult cancer after cryptogenic stroke which likely reflects the paucity of data regarding the utility of screening approaches.[46,47]

A systematic review evaluating the frequency and predictors of cancer after ischemic stroke found that the cumulative incidence of a new cancer diagnosis in a general ischemic stroke population was low: 13.6 per thousand (95% CI 5.6-24.8).[43] However, studies restricted to the cryptogenic stroke population had a higher cancer incidence as compared to those including all stroke subtypes (62.0 per thousand; 95% CI 13.6-139.3 *vs*. 9.6 per thousand; 95% CI: 4.0-17.3; P=0.02). The most predictive clinical factors for occult cancer in ischemic stroke patients were older age, a history of smoking, cryptogenic etiology, and involvement of multiple vascular territories on brain imaging. Laboratory indices associated with cancer were lower hemoglobin levels, higher C-reactive protein, higher D-dimer, and higher fibrinogen. Given the burden of financial, time-related, and healthcare resource costs associated with cancer screening, an evidence-based approach to screening is needed.

A recent registry and population-based study of 390,398 patients in the Netherlands that was published after the above-mentioned meta-analysis found that the cumulative incidence of new cancer at 10 years after a first-ever stroke was 3.7% (95% CI 3.4-4.0%) among patients aged 15-49, and 8.5% (95% CI 8.4-8.6%) among those 50 years or older.[48] However, when compared with age-matched peers from the general population, patients aged 14-49 were more likely to receive a diagnosis of new cancer after ischemic stroke (standardized incidence ratio 2.6, 95% CI 2.2-3.1). These results suggest that patients younger than 50 were about 3 times more likely to receive a new diagnosis of cancer compared to peers from the general population, and this risk remained elevated for 8 years after ischemic stroke. Among younger adults aged 15-49 years, the three most common cancers diagnosed were breast cancer (22.2%), gastrointestinal cancer (20.0%), and lung cancer (19.8%). Conversely, among older adults, the most common cancers were gastrointestinal (28.5%), urogenital (24.3%), and lung cancer (18.8%).

A risk prediction model was developed to identify patients at the highest risk for occult cancer diagnosis after ischemic stroke.[49] The incidence of a new occult cancer diagnosis was 3% at 1 year (34/1157) and 5% at 3 years (55/1158). The independent predictors of cancer included levels of white blood cells >9,600/µl [subdistribution (SHR) 3.68, P=0.014, platelets >400,000/µl (SHR 7.71, P=0.001), and D-dimer ≥3 mg/l (SHR 3.67, P=0.007); ischemic strokes in ≥2 vascular territories not attributed to a cardioembolic etiology was associated with cancer diagnosed within 1 year after stroke only in univariate analysis (SHR 3.69, P=0.001). A score of 2 or higher had a sensitivity of 43% and a specificity of 92% for prediction of new cancer diagnosis within 1 year after stroke. However, given its retrospective nature and low number of outcomes (*i.e.*, only 34 patients were diagnosed with cancer within 1 year after stroke), this study requires external validation.

In a survey of 138 physicians who manage stroke in patients with cancer, approximately half of respondents indicated they defer cancer screening investigations to primary care providers. (Poirier *et al*. manuscript embargo). Less than a third of physicians ordered tests that are commonly used for screening such as body imaging, mammograms or fecal occult blood tests even guideline-directed age-, sex- and risk-appropriate screening tests.

Given the clinical equipoise about screening and a lack of evidence-based guidelines to inform clinical practice, the Intensive Cancer Screening After Cryptogenic Stroke (INCOGNITO) Randomized Pilot Trial is evaluating to evaluate whether fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) in addition to usual care screening increases the number of occult cancers detected in patients with cryptogenic ischemic stroke compared to usual care alone (NCT05733416).[18] FDG PET/CT, which is an established imaging technique used for the diagnosis, staging and restaging of cancers, is a promising candidate for occult cancer screening in this setting. It is a non-invasive, whole-body test with acceptable diagnostic accuracy. In patients with unexplained venous thrombosis, there was a lower rate of missed cancer among patients who had screening that included FDG-PET/CT compared to those who did not (0.5% *vs*. 4.6%).[50]

Antithrombotic treatment considerations

Guidelines regarding antithrombotic therapies for acute reperfusion and secondary prevention of ischemic stroke may not be generalizable to patients with cancer who are at a

uniquely high risk of both bleeding and thrombosis, especially given the predominance of alternative stroke mechanisms.

Intravenous (systemic) thrombolysis is the mainstay of treatment for acute ischemic stroke, the benefit of which is time-dependent. Patients with cancer and acute ischemic stroke appear less likely to be offered and to receive systemic thrombolysis which may reflect the presence of absolute or relative contraindications (*e.g.*, thrombocytopenia, renal/hepatic dysfunction, surgery, brain metastases).[51,52] For example, thrombocytopenia with platelets of $<100\acute{}10^9$/L is a contraindication to systemic thrombolysis.[53] Although timely administration of thrombolysis is crucial, if there is a high suspicion for thrombocytopenia (*e.g.*, patients with cancer receiving myelosuppressive chemotherapy) it may be reasonable to wait for initial laboratory tests prior to administration. Given concerns regarding bleeding complications, mechanical endovascular thrombectomy (EVT) appears to be feasible and effective for the management of acute ischemic stroke in this setting based on limited data. In a substudy of the MR CLEAN EVT registry, patients with active cancer who underwent EVT had similar rates of successful reperfusion and symptomatic intracerebral hemorrhage, but higher rates of recurrent stroke and worse functional outcomes compared to those without cancer.[9] Although there are limited data regarding optimal acute management, a diagnosis of cancer *per se* should not exclude patients from receiving thrombolysis or EVT given the substantial mortality and life-altering functional impairments of ischemic stroke. Decisions regarding acute reperfusion therapy should be individualized with multidisciplinary input if possible and shared decision-making with patients/caregivers.

The optimal antithrombotic regimen for secondary stroke prevention is not known. Antithrombotic choice in this setting is complicated by a paucity of data including limited studies comparing antithrombotic regimens. Anticoagulation is often favored for cancer-associated stroke based on the role of hypercoagulability in its pathogenesis and indirect extrapolation from cancer-associated VTE literature. In the general (non-cancer) population, large, randomized trials failed to demonstrate benefit of direct oral anticoagulants (DOACs) compared to aspirin for patients with ESUS.[54,55] However, anticoagulants may be preferred for cancer-associated stroke given that the pathophysiologic mechanisms appear to be distinct with a greater role of hypercoagulability contributing to cryptogenic etiology. In a NAVIGATE ESUS sub-study limited to participants with a history of cancer, the rates of recurrent stroke were similar among participants receiving rivaroxaban (7.7%) and those receiving aspirin (5.4%), while the rate of major bleeding was higher in the rivaroxaban group (2.9%) compared to the aspirin group (1.1%).[56] Given that only 9% of participants were diagnosed with cancer in the previous year, these results may not be generalizable to individuals with a recent diagnosis of cancer which is the highest risk time for cancer-associated stroke.

In a non-randomized study of patients with active cancer and acute ischemic stroke, anticoagulation with low molecular weight heparin or warfarin was associated with lower D-dimer levels and 1-year mortality, although methodological limitations preclude firm conclusions.[57] Another non-randomized study showed that patients treated with antiplatelet therapy had similar odds of recurrent stroke compared to those receiving anticoagulation.[17] The pilot trial of Enoxaparin *vs*. Aspirin in patients with cancer and stroke (TEACH) was designed to assess feasibility and showed that 40% of participants crossed over from enoxaparin to aspirin suggesting that anticoagulation with DOACs may be a more feasible approach.[58] The Edoxaban for the Treatment of Coagulopathy in Patients with Active Cancer and Acute Ischemic Stroke (ENCHASE) pilot trial is evaluating edoxaban *vs*. enoxaparin for cancer-associated ESUS (NCT03570281).

Given the role of coagulation and platelets in the pathogenesis of cancer-associated thrombosis and stroke, dual pathway inhibition with anticoagulants and antiplatelet therapy is a potential candidate for evaluation in this setting. The combination of very low dose rivaroxaban (2.5 mg twice daily) in addition to aspirin has been studied in patients with stable peripheral artery and coronary artery disease, and acute limb ischemia resulting in cardiovascular benefit at a cost of more major bleeding events.[59,60]

Conclusion and future directions

While acute ischemic stroke is a known complication of cancer, particularly within the first year after diagnosis, significant uncertainty remains with respect to prevention and treatment. First, there are no clinically available risk prediction models to identify patients at high risk who may benefit from prevention strategies. For example, the Khorana score is used to identify ambulatory cancer patients starting chemotherapy at high risk for VTE who are candidates for thromboprophylaxis based on the results of randomized trials.[61-63] Similarly, ischemic stroke risk assessment at cancer diagnosis may be used to evaluate prevention strategies in randomized trials for patients at high risk. Second, outcomes after cancer-associated stroke are not well characterized including bleeding which limits the use of antithrombotics and is key for establishing the net clinical benefit of therapies. Third, because of the uniquely high thrombotic and bleeding risk associated with cancer, antithrombotic data from non-cancer populations may not be generalizable and dedicated randomized trials are needed. Finally, cryptogenic ischemic stroke is associated with undiagnosed cancer, but there are no evidence-based strategies for cancer screening. Age-, sex-, and risk-directed screening may not be adequate in younger, high-risk populations. Like unprovoked VTE, randomized trials are needed to evaluate the benefits and harms of occult cancer screening strategies among patients with cryptogenic stroke.

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