UNDERSTANDING AND IMPROVING THE RELATIONSHIP BETWEEN CANCER AND STROKE

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Preface

This thesis is an “article-based thesis”, composed of seven major chapters and five component articles. The primary author, Dr. Ronda Lun, was responsible for the conceptualization, design, and primary manuscript drafting of the entirety of its content. Statistical analysis was performed by Dr. Lun with supervision by Drs. Dowlatshahi, Ramsay, and Siegal. Proper ethics approval was obtained from each of the relevant regulatory committees for all datasets utilized. Where necessary, ethics approval documents were attached as appendices for each chapter. Dr. Lun takes responsibility for the integrity of the data and the accuracy of the analysis. The roles of other individual co-authors are listed within each component article.

Thesis Abstract

Cancer is an important risk factor for stroke, but the relationship between cancer and stroke is not well understood. Cancer patients with stroke often do not receive guideline-based treatments due to perceived higher risks, and experience worse outcomes than patients without cancer, including more recurrent strokes. The aim of this thesis is to expand our knowledge of the relationship between cancer and stroke by addressing five major objectives: 1) calculate the pooled one-year incidence of stroke after a new diagnosis of cancer by performing a systematic review and meta-analysis, 2) investigate if the risk for future stroke varies by a history of stroke prior to cancer diagnosis, 3) compare differences in treatment and outcomes between cancer patients with stroke and the general stroke population, 4) identify predictors for recurrent stroke in cancer patients, and 5) evaluate the utility of synthetic data for the purpose of cancer and stroke research.

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Glossary

aHR: adjusted hazard ratio

ALC: Alternative Level of Care

BMI: Body mass index

BTK: Bruton tyrosine kinase

CHF: Congestive heart failure

CI: Confidence interval

CIF: Cumulative incidence function

COPD: Chronic obstructive pulmonary disease

CRP: C-reactive protein

CNS: Central nervous system

DOAC: Direct oral anticoagulant

ED: Emergency department

ESUS: Embolic stroke of undetermined source

EVT: Endovascular thrombectomy

ICAD: Intracranial atherosclerotic disease

ICD: International Classification of Diseases

ICES: Institute for Clinical Evaluative Sciences

ICH: Intracerebral hemorrhage

IQR: Interquartile range

IS: Ischemic stroke

LDH: Lactate Dehydrogenase

LMWH: Low-molecular weight heparin

MRI: Magnetic resonance imaging

NETs: Neutrophil extracellular traps

NOS: Newcastle-Ottawa Scale

OR: Odds ratio

PFO: Patent foramen ovale

PRISMA: Preferred Reporting Items for Systematic Reviews

RCT: Randomized controlled trial

ROB: Risk of bias

SEER: Surveillance Epidemiology and End-Results

TIA: Transient ischemic attack

TOH: The Ottawa Hospital

tPA: tissue plasminogen activator

VIF: Variance inflation factor

VTE: Venous thromboembolism

Table of Contents

Chapter One: Thesis Overview

1.1 Primary Research Objectives:

Cancer and stroke are significant contributors to morbidity and mortality worldwide. Cancer is becoming an increasingly recognized risk factor for stroke, and stroke in cancer patients may differ significantly from stroke in the general population in terms of its epidemiology, pathophysiology, treatment options, and outcomes.

This thesis proposes to advance the current understanding of the relationship between cancer and stroke through four separate research projects, presented in five principal chapters:

1. A systematic review and meta-analysis of the incidence of stroke one year after a new diagnosis of cancer (chapters 3 and 4).
2. A retrospective, matched cohort study of a provincial administrative database looking at how a previous history of stroke affects the risk for future stroke after a diagnosis of cancer (chapter 5).
3. A retrospective cohort study of our local administrative database comparing cancer patients with ischemic stroke to ischemic stroke in the general population and identifying predictors for recurrent stroke in cancer patients (chapter 6).
4. A comparison study of synthetic data to real patient data in the context of cancer and stroke research (chapter 7).

These studies will contribute to our limited understanding of the relationship between stroke and cancer on an epidemiological level.

1.2 Overview of Chapters

Chapter 2 – Background

This introductory chapter summarizes our current understandings of the relationship between cancer and stroke. In this narrative review, we discuss the association between cancer and stroke, the unique pathophysiologic mechanisms underlying this phenomenon, treatment options including acute reperfusion therapies and secondary prevention strategies, compare outcomes between cancer-related stroke and stroke in the general population, and review new and emerging evidence in this field. This chapter is currently under review at the Journal of American Heart Association.

Publication: **Lun R,** Siegal D, Ramsay T, Dowlatshahi D. Stroke and Cancer: What do we Know and Where Do We Go? JAHA. Under Review (April 2022).

Chapters 3 and 4 – Systematic review and meta-analysis

These next two chapters address the question "what is the incidence of stroke at one year after a new diagnosis of cancer?" Chapter 3 is the protocol paper "Incidence of Stroke in the First Year After Diagnosis of Cancer – A Protocol for Systematic Review and Meta-Analysis", published in PLOS ONE in September 2021. The subsequent chapter is the meta-analysis titled "Incidence of Stroke in the First Year After a Diagnosis of Cancer – A Systematic Review and Meta-Analysis", currently under review at JACC: CardioOncology.

Publication: Lun R, Roy DC, Ramsay T, Siegal D, Shorr R, Fergusson D, et al. (2021) Incidence of stroke in the first year after diagnosis of cancer—A protocol for systematic review and meta-analysis. PLoS ONE 16(9): e0256825. https://doi.org/10.1371/journal.pone.0256825

Publication: Lun R, Roy DC, Hao Y, Deka R, Huang WK, B. Babak, Siegal DM, Ramsay T, Fergusson D, Shorr R, Dowlatshahi D. Incidence of Stroke in the First Year After Diagnosis of

Cancer – A Systematic Review and Meta-Analysis. JACC:CardioOncology. Under Review (April 2022).

Chapter 5 – Population-based matched cohort study

This chapter uses data from provincial administrative databases to address the question: "how does a previous history of stroke affect the risk for future stroke after a new diagnosis of cancer?" This manuscript is currently being prepared for submission.

Chapter 6 and 7 – Retrospective cohort study

Chapter 6 utilizes synthetic data to compares key differences in demographics, treatment, and outcomes between ischemic stroke patients with cancer and ischemic stroke patients without cancer. We also attempt to identify risk factors for recurrent stroke in cancer patients with ischemic stroke. Given the novelty of synthetic data in the context of cancer and stroke research, chapter 7 compares the key findings from chapter 6 between synthetic data and original health systems data. This manuscript is currently being prepared for submission.

Chapter Two: Background

2.1 Preface

This chapter is a narrative review of the current understanding between cancer and stroke. This study required no ethics approval. A condensed version of this manuscript is currently under submission at the Journal of the American Heart Association (JAHA). A confirmation of submission is available in Appendix I.

Authorship and contributions: Dr. Lun was responsible for drafting of the manuscript. All other authors contributed to revising the manuscript for intellectual content.

Appendix I. Submission confirmation of Chapter 2:
Publication: Lun R, Siegal D, Ramsay T, Dowlatshahi D. Stroke and Cancer: What do we Know and Where Do We Go? JAHA. Submitted April 2022.

2.2 Introduction

Cancer is the leading cause of mortality in Canada, accounting for approximately 30% of all deaths.[1] Stroke is the leading cause of disability worldwide, and the fourth leading cause of mortality in Canada.[2,3] With increases in global population, introduction of screening programs, and advances in diagnostic modalities, the incidence of cancer has increased in recent decades.[4,5] Earlier detection and improved cancer therapeutics have also prolonged cancer survival, resulting in a higher prevalence of active cancer patients and cancer survivors.[6] Given shared risk factors between cancer and stroke, there has been an increase in the number of cancer patients with stroke, particularly among the aging population.[7] However, stroke in cancer patients may be different from stroke in the general population in terms of pathophysiology, clinical presentation, treatment options, and outcomes.[8] Cancer patients may not receive guideline-recommended stroke care and the occurrence of stroke may also preclude patients from receiving optimal cancer treatments. Therefore, cancer patients with stroke represent an important population to study, as current stroke guidelines may not be generalizable to cancer patients. Due to the high degree of morbidity and mortality associated with both conditions, understanding the relationship between stroke and cancer is crucial.

The first report of the association between cancer and stroke was by Graus in 1985: an autopsy study of patients with cancer found approximately 15% of patients had pathologic evidence of cerebrovascular disease, with only 51% of those subjects having experienced clinical symptoms during their lifetime.[9] Hemorrhagic and ischemic lesions were found to be equal in frequency, although the rates of symptomatic stroke were higher with the hemorrhagic subgroup. However, while the association between ischemic stroke and cancer is now well established in the

literature, there is conflicting evidence as to whether or not patients with cancer have an elevated risk for spontaneous intracerebral hemorrhage (ICH), also known as primary hemorrhagic stroke.[10,11] This may be secondary to the inability to distinguish spontaneous ICH from cerebral bleed secondary to underlying metastasis on imaging, which is supported by the higher incidence of ICH among patients with renal cell carcinoma, melanoma, and choriocarcinoma – primary malignancies associated with a higher incidence of cerebral metastases.[11,12] Thus, this background chapter will focus primarily on the association between ischemic stroke and cancer.

In general, there are five major mechanisms by which ischemic stroke may occur: larger-artery atherosclerosis, cardioembolism, small vessel occlusion, stroke of other determined etiology, and cryptogenic stroke – referring to a stroke of undetermined etiology after appropriate investigations.[13] Ischemic stroke and cancer share many similar risk factors, such as older age, smoking, obesity, sedentary lifestyle, and atrial fibrillation, making cancer patients susceptible to conventional mechanisms for stroke as well.[14–16] Large vessel atherosclerosis was the most frequent cause of stroke in one of the earliest cohorts evaluating the relationship between the two conditions.[17] However, there are likely additional unique pathophysiological mechanisms that link cancer and stroke, which is supported by the higher incidence of stroke in the cancer population as compared to the general population, and the higher prevalence of "cryptogenic" stroke in the cancer population.[16,18] The term "cryptogenic stroke" refers to an ischemic stroke with no established mechanism after standard diagnostic evaluations.[19] In 2014, the term "embolic stroke of undetermined source" (ESUS) was proposed as a new clinical construct that refers to a non-lacunar (i.e. embolic) ischemic stroke remains cryptogenic after evaluation for

conventional mechanisms.[20] Among patients with ischemic stroke of undetermined etiology, approximately 5-10% are diagnosed subsequently with cancer during their workup.[21–23]

2.3 Unique Mechanisms for Cancer-Associated Stroke

Cancer may be directly related to stroke via multiple unique mechanisms: cancer-associated hypercoagulability, non-hypercoagulable mechanisms, direct tumour effects, and cancer-treatment related adverse effects.[11]

Hypercoagulability

Cancer induces a hypercoagulable state. A causal relationship between cancer and thrombosis was first proposed by Armand Trousseau in 1865, when he described the phenomenon of migratory thrombosis as the initial manifestation of occult gastric cancer.[24,25] However, the concept of "Trousseau's Syndrome" has evolved since its inception and is now used to describe any hypercoagulable state associated with cancer.[26] The presence of malignancy drives many unique pathways for hypercoagulability when compared to non-cancer thromboembolism, including the activation of coagulation cascades and platelets, as well as elevated circulating levels of procoagulant proteins.[27] Thrombocytosis and leukocytosis are often seen in many types of cancer, which increases the risk for thrombosis via the formation of neutrophil extracellular traps (NETs) or the release of tissue factor.[28] In addition to an elevated platelet count, biomarkers of platelet activation (such as soluble P-selectin, soluble CD40 ligand, platelet factor 4, and plasma von Willebrand factor) have been reported to be elevated in cancer patients and associated with the development of thrombosis.[27] P-selectin mediates the adhesion of leukocytes, platelets, and cancer cells in inflammation, thrombosis, and cancer growth; it has been found to

independently predict VTE in cancer patients.[29] Many tumours can also release high levels of procoagulant tumour proteins, such as plasminogen activator inhibitor 1, which inhibits fibrinolysis, and activators of the clotting cascade, such as factor XII and extracellular vesicles.[27] These unique biochemical anomalies suggest that cancer may be associated with a hypercoagulable state even in the absence of clinically overt thrombotic events.

While most studies of biomarkers for hypercoagulable state have been conducted in patients with venous thromboembolism, preliminary data in cancer patients with stroke suggest that hematologic markers such as D-dimer, P-selectin, thrombin-antithrombin complex, sICAM-1, and vlCAM-1 may also associated with the development of stroke.[30] Furthermore, cancer patients with solid tumours are known to have a higher prevalence of antiphospholipid antibodies, with one case series reporting that approximately 60% of cancer patients with thromboses tested positive for antiphospholipid antibodies.[31] A systematic review identified there was an increased risk for antiphospholipid antibodies to be detected for almost all solid tumours when compared to controls without cancer, with the highest risk observed in gastrointestinal, lung, and genitourinary cancers.[32] While the clinical significance of antiphospholipid antibodies in this context is still uncertain, it is speculated that these antibodies represent an acquired immune-mediated risk factor for thromboembolic events.[32]

The most common clinical manifestation of cancer-associated hypercoagulability is the development of venous thromboembolism (VTE), which includes deep vein thrombosis and pulmonary embolism; patients with cancer have a 5-7-fold increased risk for VTE compared to non-cancer patients.[33] The presence of VTE and a left-to-right cardiac shunt, such as a patent

foramen ovale (PFO) or pulmonary arteriovenous malformation, may result in paradoxical embolization causing stroke.[11] Other manifestations of cancer-associated hypercoagulability include development of superficial thrombophlebitis, hepatic/ splenic vein thrombosis, non-bacterial thrombotic endocarditis, and arterial thromboses such as cardioembolism causing acute limb ischemia or ischemic stroke.[28] Finally, cancer itself may produce a consumptive coagulopathy such as disseminated intravascular coagulation or thrombotic microangiopathy, which may manifest as excessive bleeding or thrombosis.[33]

Direct Tumour Effects

Direct tumour effects causing stroke are relatively rare compared to other mechanisms. Primary central nervous system (CNS) tumours or metastases to the brain may cause compression of intracranial vessels resulting in disruption of arterial flow and eventually ischemia in the distal territories.[11] CNS tumours may also mimic the appearance of spontaneous intracerebral hemorrhage in their clinical presentation and radiographic appearance.[34] Direct obstruction of blood vessels may result from malignant hematologic cells or direct tumour processes, such as intravascular lymphoma.[35] Rarely, embolic mechanisms of stroke may result from benign tumours of the heart (i.e. atrial myxoma), or metastases in the heart.[36]

Non-Hypercoagulable Mechanisms

In addition to the many hematologic and immune-mediated changes that promote hypercoagulability, other additional risk factors for thrombosis in cancer patients include vascular obstruction or invasion by tumour, surgery, chemotherapy, central venous catheter insertion, hospitalization and immobility. Immunosuppression is common among patients with

active cancer, which may be secondary to the cancer itself, reduced nutritional intake, or adverse effects of chemotherapy.[37] The incidence of sepsis and severe sepsis is significantly higher in the cancer population when compared to non-cancer controls, particularly in older individuals.[38] This predisposes cancer patients to complications such as infective endocarditis causing cerebral emboli, and disseminated intravascular coagulopathy. Dysregulation of the autonomic nervous system in sepsis may result in significant hypo- or hypertension with acute alterations in cerebral perfusion pressure, potentially causing ischemia or hypertensive crisis with intracerebral hemorrhage. Cardiomyopathy may occur as a result of systemic illness (i.e. Takutsubo cardiomyopathy) or cancer treatments (i.e. anthracycline based chemotherapy, thoracic radiation), which is also a risk factor for stroke. Certain cancer therapies (such as Bruton tyrosine kinase (BTK) inhibitors) may increase the risk for atrial fibrillation, predisposing patients to recurrent thromboembolism.[39] Finally, as mentioned at the beginning of this section, due to the shared risk factors between stroke and cancer (i.e. smoking, sedentary lifestyle), cancer patients may experience accelerated atherosclerosis of the arteries compared to non-cancer individuals. Cancer therapy-related arterial toxicity may also cause accelerated atherosclerosis, acute vasospasms, as well as acute thrombus formation.[40]

Cancer-treatment effects

Chemotherapeutic agents such as bevacizumab, platinum-based treatments and L-asparaginase can increase the risk of ischemic stroke via various mechanisms, including affecting the synthesis of natural anticoagulants such as antithrombin.[41] The presence of common stroke mimics (e.g. treatment-related neurotoxicity, seizures), and development of alternative diagnoses such as posterior reversible encephalopathy syndrome or cerebral venous sinus thrombosis

further complicate the evaluation of stroke.[42,43] Radiation treatment may result in radiation-induced vasculopathy, which often manifests in a delayed increased in the risk for stroke, sometimes decades later.[44] A systematic review found that the risk for severe stenosis of the extracranial carotid arteries was 7.5-fold higher in those that received radiation compared to controls.[45] In a population-based study of teenage and young adult survivors of cancer, survivors of central nervous system tumours and head and neck tumours (i.e. tumours that frequently require whole-brain or head and neck radiation for treatment) were at the greatest risk of future ischemic stroke.[46]

2.4 Recognizing Cancer-Associated Stroke

Early identification of cancer-associated stroke could direct appropriate investigations for stroke etiology and potential stroke treatments. A patient that does not have an identifiable conventional mechanism for stroke should be considered for age-appropriate cancer screening. Based on observational data, clinical features that should prompt a search for cancer include older age, history of smoking or active smoking, low body mass index (BMI), history of heavy drinking, or previous history of cancer.[47] In a cohort of stroke patients with active cancer, an elevated D-dimer and diffusion-weighted-imaging patterns on magnetic resonance imaging (MRI) demonstrating strokes in multiple vascular territories may be helpful in early identification of non-conventional stroke mechanisms such as coagulopathy.[48,49] Other biochemistry markers that may suggest cancer as the underlying mechanism for stroke include high C-Reactive Protein (CRP) > 20 mg/L, low hemoglobin, low albumin, elevated fibrinogen >600 mg/dL, and elevated Lactate Dehydrogenase (LDH).[23,47,50]

2.5 Treatment of Cancer-Associated Stroke

The treatment of acute ischemic stroke in any patient consists of two phases: reperfusion therapy for eligible patients during the first hours after symptom onset, and secondary prevention with antithrombotic therapy and targeted interventions based on the underlying etiology of stroke.[51]

Acute reperfusion therapies

The Canadian Stroke Best Practice Guidelines recommend that all eligible patients with disabling ischemic stroke should be offered intravenous alteplase. Detailed criteria in terms of inclusion/ exclusion criteria can be found in the acute stroke management practice guidelines.[51] However, these guidelines may not be generalizable to cancer patients, as bleeding complications are more common in cancer patients and use of anticoagulants further augments the risk for bleeding.[52,53] A survey of international stroke experts found that in hypothetical decision-making scenarios on the provision of thrombolytic therapy, patients with cancer had significantly lower odds of being offered thrombolysis.[54] These results are similar to those reported in a U.S. administrative database study that evaluated thrombolysis in routine clinical practice. Owusu-Guha et al found that the frequency of administration of thrombolytic therapy was significantly lower in cancer patients compared to non-cancer patients, despite no difference in intracranial bleeding, all-cause bleeding, or in-hospital mortality.[55] A recent systematic review found that there was no significant difference between cancer and non-cancer patients receiving thrombolysis in favourable outcomes, symptomatic ICH, hemorrhagic transformation, in-hospital and 3-month mortality.[56] Lower rates of thrombolysis administration in cancer patients may be due to their higher likelihood for having absolute or relative contraindications secondary to cancer-related treatments (i.e. major surgeries in the preceding 14 days, thrombocytopenia

secondary to chemotherapy, etc).[51] Furthermore, one study found that cancer patients have higher comorbidity indices compared to non-cancer patients at baseline, and treatment with acute therapies may not always be within their goals of care.[57] Ultimately, it is important to remember that a diagnosis of cancer itself is not contraindication to thrombolytic therapy, and each patient's bleeding risk should be weighed against the potential benefit to be gained from thrombolysis.[51]

Mechanical thrombectomy is effective for treating large vessel occlusions, with a pooled number needed to treat of 2.6 to prevent 90-day functional disability.[58] Thrombectomy has not been studied exclusively in cancer patients, and evidence for its efficacy and safety have come from retrospective cohort studies, case series, and subgroup analyses of large randomized trials.[59–63] The largest sample of cancer patients receiving endovascular thrombectomy (EVT) comes from a substudy of the MR CLEAN registry. In this study, Verschoof et al found that patients with active cancer had similar rates of successful reperfusion and symptomatic ICH, although the rates of 90-day recurrent stroke were more common in patients with cancer, and 90-day functional outcomes were worse.[63] Despite some conflicting evidence in terms of the rates of symptomatic ICH and 90-day functional outcomes across these studies, almost all studies found that thrombectomy does seem to be a feasible and effective reperfusion therapy for cancer patients.[59,61] However, despite technically successful procedures resulting in small post-treatment infarct volume, the presence of cancer is an independent risk factor for functional dependence or death at 3 months.[64] Therefore, while it is imperative to not withhold acute reperfusion therapies for an otherwise eligible stroke patient who has active cancer, treatments should be individualized and involve a multi-disciplinary discussion between the patient, their family

members, their oncologist, and the neurologist, with a focus on the patient's wishes and goals of care.

Secondary Prevention: Antithrombotic Therapy

All stroke patients should undergo investigations to determine their underlying stroke etiology, including vessel imaging, echocardiogram, and Holter monitor. If an indication to anticoagulate is found (i.e. atrial fibrillation, cardiac thrombus, free floating thrombus), the choice of anticoagulant should be individualized.[65] Otherwise, the Canadian Stroke Best Practice guidelines recommend all ischemic stroke or transient ischemic attack (TIA) patients be initiated on at least a single antiplatelet agent.[65] A short course of dual antiplatelet therapy may be considered for minor ischemic stroke/TIA, and for the treatment of large vessel atherosclerosis, including intracranial atherosclerotic disease (ICAD).[66–70] In addition to antithrombotic therapy, lifestyle behaviours (i.e. smoking cessation, regular exercise, healthy diet) and risk factor management should be assessed, with the goal of optimizing modifiable vascular risk factors.

Unfortunately, optimal antithrombotic agent for secondary prevention of ischemic stroke in the setting of cancer is unknown. There is limited evidence to guide whether cancer patients with stroke should be treated with a non-standard therapy such as anticoagulation and this decision should be individualized based on the etiology of the stroke.[71] However, for patients without an identifiable etiology – i.e. cryptogenic stroke or ESUS– some evidence exists for both antithrombotic strategies.

Multiple studies have found that endovascularly-retrieved thrombi in stroke patients with active cancer are fibrin and platelet-rich, suggesting they may respond better to antiplatelet medications.[72,73] Two large randomized controlled trials (RCT) failed to demonstrate the superiority of anticoagulation with a direct oral anticoagulant (DOAC) over antiplatelet therapy in individuals with ESUS.[74,75] However, cancer-associated ESUS may represent a separate entity within the ESUS construct. A subgroup analysis of the New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial versus ASA to Prevent Embolism in Embolic Stroke of Undetermined Source (NAVIGATE ESUS) trial restricted only to cancer patients demonstrated that there were similar rates of recurrent ischemic stroke between the rivaroxaban and aspirin groups, although there was a trend towards less recurrent stroke events with aspirin (5.4% for aspirin vs 7.7% for rivaroxaban).[76] Furthermore, there were significantly higher rates of major bleeding in the rivaroxaban group compared to the aspirin group (2.9% for rivaroxaban vs 1.1% for aspirin). These results may suggest that antiplatelet therapy is safer for cancer patients with ESUS, particularly given the higher risk for bleeding at baseline in cancer patients due to their malignancy. However, it should be noted that the major limitation of this study was the definition of cancer: cancer status was ascertained by asking patients if they have a "history of cancer", and only 9% of cancer patients had their cancer diagnosed in the year leading up to enrolment in the trial. As most of the stroke risk associated with cancer appears to occur around the time of cancer diagnosis,[77] these results may not be generalizable to newly diagnosed cancer patients.

The Canadian Stroke Best Practice Guidelines recommend patients with active malignancy who experience an arterial ischemic stroke or TIA secondary to a presumed cancer-associated

hypercoagulable state be considered for anticoagulation therapy over antiplatelet.[71] They further recommend the use of low-molecular weight heparin (LMWH) as the anticoagulant of choice. This received an "Evidence Level C" grade, meaning this recommendation was based on writing group consensus and/or was supported by limited research evidence. In a prospective cohort study, patients with acute ischemic stroke and active systemic cancer were recruited and hypercoagulability was assessed using plasma D-dimer levels as a surrogate marker of hypercoagulable state.[78] The authors found that patients with D-dimer levels in the third and fourth quartiles (i.e. above 9.06 ug/mL) were at higher risk for 1-year and overall mortality. Treatment with anticoagulation using LMWH or warfarin in patients with elevated D-dimer resulted in a significantly lower D-dimer level, which was independently associated with reduced risk for 1-year mortality, but not overall mortality. The rates of recurrent ischemic stroke were not reported in this study, but the authors concluded that hypercoagulability is associated with poor survival in cancer-related strokes, and that effective anticoagulation may be associated with better survival.[78] As for the choice of anticoagulant therapy, there are no studies that directly compare the efficacy and safety profiles of anticoagulants in this specific population; much of the evidence comes from expert opinions and extrapolation from the venous thromboembolism literature. The Randomized Comparison of Low-Molecular-Weight Heparin versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer (CLOT) trial compared patients with cancer and venous thromboembolism receiving either LMWH with dalteparin or dalteparin followed by warfarin, and found that the dalteparin group had lower rates of recurrent venous thromboembolic events.[79] Similar findings were confirmed in multiple subsequent studies.[80–83] While recent RCTs comparing anti-Xa DOACs to LMWH in cancer-associated VTE have demonstrated that these drugs (i.e.

Rivaroxaban, Apixaban, Edoxaban) may be reasonable alternatives to LMWH, this has not translated to similar recommendations in the treatment of cancer-associated ischemic stroke.[84–87]

The Trial of Enoxaparin versus Aspirin in patients with Cancer and Stroke (TEACH) trial is the only study that directly compares anticoagulation with low molecular weight heparin to aspirin in a group of cancer patients with ischemic stroke.[88] As this was a pilot trial with a primary outcome of feasibility, the results of the study were inconclusive in terms of treatment effects, although they reported a 40% crossover rate from the enoxaparin group to aspirin due to patients' discomfort with receiving injections. The authors concluded that future trials evaluating antithrombotic therapy in this patient population should compare DOACs to antiplatelet therapy, particularly in the context of the approval of anti-Xa inhibitors in the treatment of cancer-associated venous thromboembolism (VTE).[89,90] However, there are distinct differences in the pathophysiology and treatment between VTE and arterial thromboses, and how these will translate into differences in clinical efficacy and adverse events is unknown.

Currently, there are two planned/active randomized controlled trials with the objective of comparing various anticoagulant strategies in patients with active cancer and stroke. The authors of the TEACH trial are planning a multicenter, double-blind, randomized trial: Trial of Apixaban Versus Aspirin in Cancer Patients with Cryptogenic Ischemic stroke (TEACH2). This trial will compare anticoagulant therapy with a direct oral anticoagulant against monotherapy antiplatelet therapy with aspirin in patients with active cancer and deemed to have an ESUS etiology to their stroke. The second trial is a pilot trial in Korea: Edoxaban for the treatment of Coagulopathy in Patients with Active Cancer and Acute Ischemic Stroke (NCT03570281), which aims to compare

edoxaban against subcutaneous low-molecular weight heparin in patients with cancer and ESUS. The primary outcome of this trial is to assess the interval change in serum D-dimer after a week of initiating anticoagulant therapy. The trial is actively enrolling, although no updates have been provided from the study group since 2018. The results from both of these clinical trials in the near future will be hugely informative and may guide treatment on antithrombotic therapies for cancer patients.

2.6 Outcomes

Mortality and functional disability

In early large prospective studies of the general ischemic stroke population, cumulative mortality risks after first stroke were approximately 5% at 1 month, and 16% after 1 year.[91] With recent advances in acute stroke treatments, the proportion of patients experiencing death or severe disability have significantly decreased.[92] In large-vessel occlusion patients who received thrombectomy, 46% were functionally independent at 3 months, compared to 26.5% of patients who received medical therapy alone.[58] Compared to the general population, patients with cancer have significantly higher rates of mortality, with 30-day mortality reported in approximately 25-50% of patients.[63,93] As discussed above, despite technical successes in reperfusion therapies such as thrombectomy, the odds of achieving 3-month functional independence are approximately 50% less in cancer patients when compared to the general population.[63]

Recurrent Stroke

The rates of recurrent stroke are significantly higher in cancer patients when compared to the general population. At 3 months, 4.0% of cancer patients who underwent thrombectomy had

recurrent ischemic strokes compared to just 1.3% in the general population.[63] A large cohort study reported rates of recurrent thromboembolic events were as high as 37% at 6 months – a number that is approximately 3 times higher compared to the general ischemic stroke population.[94] The higher rates of recurrent thromboembolic events and ischemic stroke in cancer patients may be a reflection of the underlying hypercoagulability, and highlight the importance of identifying effective secondary prevention strategies in these patients.

2.7 Knowledge Gaps and Conclusion

This introductory chapter has reviewed the current understanding of the relationship between cancer and stroke. However, there are still many uncertainties and knowledge gaps in this field. For example, what is the risk of stroke after a new diagnosis of cancer? Which cancer patients are at the highest risk for an ischemic stroke after their diagnosis? Are there certain patient or disease characteristics that are predictive of stroke? Which cancer patients experience recurrent strokes? These are important questions to address, as they may help health care providers risk stratify cancer patients for stroke and provide an opportunity to implement prevention strategies. The subsequent five chapters of this thesis will attempt to address some of these knowledge gaps.

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Chapter Three: Incidence of Stroke in Newly Diagnosed Cancer Patients – Systematic Review Protocol

3.1 Preface

This chapter outlines our methodological protocol for a systematic review and meta-analysis looking at the incidence of stroke at 1 year after a new diagnosis of cancer. Ethics approval for this study was not required. A published PDF of this manuscript is available in Appendix II.

Authorship and contributions: RL, DS, TR, DF and DD designed the research question. RL, TR, DS, RS, DF and DD designed the eligibility criteria and the screening strategy. RL and DD designed the data extraction items. RL, DCR, and DF developed the data synthesis strategy. RL drafted the protocol manuscript and it was reviewed and approved by all authors.

RL and DD are the guarantors of this review.

Appendix II: Published PDF of Chapter 3:
Publication: Lun R, Roy DC, Ramsay T, Siegal D, Shorr R, Fergusson D, et al. (2021) Incidence of stroke in the first year after diagnosis of cancer—A protocol for systematic review and meta-analysis. PLoS ONE 16(9): e0256825. https://doi.org/10.1371/journal.pone.0256825

3.2 Abstract

Introduction

There is an increased risk of stroke in patients with cancer – this risk is particularly heightened around the time of cancer diagnosis, although no studies have systematically quantified this risk in the literature. Patients newly diagnosed with cancer without prior stroke represent a highly susceptible population in whom there is a window of opportunity to study and implement primary prevention strategies. Therefore, the objective of this systematic review and meta-analysis is to identify the cumulative incidence of ischemic and hemorrhagic strokes during the first year after a diagnosis of cancer.

Methods and Analysis

MEDLINE, EMBASE, and PubMed will be searched with the assistance from a medical information specialist, from 1980 until present. Eligible studies will include observational studies that have enrolled adult patients newly diagnosed with cancer and report outcomes of stroke during the first year of cancer diagnosis. We will exclude all randomized and non-randomized interventional studies. Data on participant characteristics, study design, baseline characteristics, and outcome characteristics will be extracted. Study quality will be assessed using the Newcastle-Ottawa Scale for cohort studies, and heterogeneity will be assessed using the I^2 statistic. Pooled cumulative incidence will be calculated for ischemic and hemorrhagic strokes separately using a random-effects model.

Ethics and Dissemination

No formal research ethics approval is necessary as primary data collection will not be done. We will disseminate our findings through scientific conference presentations, peer-reviewed publications, and social media/ the press. The findings from this review will inform clinicians

and patients regarding the risk of stroke in patients newly diagnosed with cancer by quantifying the cumulative incidence of each subtype of stroke during the first year after a diagnosis of cancer. This represents a window of opportunity to implement prevention strategies in a susceptible population.

Registration ID with Open Science Framework: osf.io/ucwy9

3.3 Background

Cancer remains the leading cause of mortality in Canada, accounting for approximately 30% of all deaths.(1) Comparatively, stroke is the fourth leading cause of mortality in Canada, but remains the leading cause of disability worldwide.(2,3) The combination of cancer and stroke accounts for significant morbidity and mortality, but the relationship between the two diseases is not well understood. While the association between cancer and increased risk for venous thromboembolism has been well established,(4) the risk of stroke in patients with cancer is under studied.(5)

Multiple registry-based studies have confirmed an increased risk for both ischemic and hemorrhagic stroke in patients with cancer.(6–9) The pathophysiology underlying this increased risk varies for ischemic versus hemorrhagic strokes, but are likely both multifactorial. Postulated mechanisms for ischemic stroke include hypercoagulability from the malignancy, treatment-related adverse effects, and overlapping risk factors (e.g. smoking).(5,8) Conversely, the most common etiologies responsible for intracerebral hemorrhage (ICH) in patients with cancer are coagulopathy, and hemorrhage of intracranial tumours, which may mimic the presentation and appearance of spontaneous ICH.(10)

The incidence of stroke and its temporal correlation with a diagnosis of cancer is variable in the literature. Multiple studies have acknowledged the increased risk for arterial thromboembolic events in the months leading up to a diagnosis of cancer.(6,8,9,11) Andersen et al reported that the risk for stroke tripled around time of diagnosis compared with controls without malignancy.(8) This risk may remain elevated when compared to the general population without

cancer, even up to 10 years after a diagnosis of cancer is made.(6) There is also an increased risk for hemorrhagic stroke around the time of cancer diagnosis.(8,10) While a new diagnosis of stroke in those without cardiovascular risk factors should prompt initiation of screening tests for malignancy,(12) identifying newly diagnosed cancer patients who have not yet experienced a stroke represents an important population in which primary prevention strategies should be studied. From a clinical perspective, quantifying the risk of stroke *after* a new diagnosis of cancer is important, as it represents a window of opportunity to implement prevention strategies in a susceptible population. A recent systematic review and meta-analysis reported an increased risk for stroke in cancer survivors, but the patient population examined in that study all had "a previous cancer diagnosis" and the temporal relationship between cancer and stroke is unclear.(13) Therefore, to better understand and quantify the relationship between a new diagnosis of cancer and the risk for stroke, the current study aims to examine the risk of stroke immediately following a new diagnosis of cancer – when the risk may be highest. We will conduct a systematic review and meta-analysis of the literature, with the primary objective of identifying the cumulative incidence of ischemic and hemorrhagic strokes during the first year after a diagnosis of cancer.

Primary Objective:

To determine the cumulative incidence of stroke (ischemic and hemorrhagic) during the first year after a diagnosis of cancer.

Secondary Objectives:

To determine the cumulative incidence of ischemic stroke in newly diagnosed cancer patients.

To determine the cumulative incidence of hemorrhagic stroke in newly diagnosed cancer patients.

To determine the temporal relationship between occurrence of ischemic/ hemorrhagic stroke and a new diagnosis of cancer.

3.4 Methods

Study Registration

This study has been registered with the Open Science Framework (osf.io/ucwy9) and will be conducted based on the guidelines of the Cochrane Handbook for Systematic Reviews.(14) This protocol was designed using the Preferred Reporting Items for Systematic Review Protocols (PRISMA-P) guidelines.(15) The final paper will be reported using the updated guideline for Preferred Reporting Items for Systematic Reviews (PRISMA).(16)

Eligibility Criteria:

Our comprehensive literature search will address the primary question, "what is the incidence of stroke (ischemic and hemorrhagic) within the first year after a new diagnosis of cancer"? Our search will be limited to adult human subjects (i.e. 18 years or older), since the pediatric population has significantly different risk factors for stroke.(17) We will include all forms of cancer except non-melanoma skin cancer, due to their favourable prognosis and relative inaccuracies in diagnostic coding, which is in line with existing interventional studies in the cancer population.(18,19) Due to the natural history nature of our research question, our search will focus on observational studies only and exclude all interventional studies (including randomized and non-randomized controlled trials), as they represent a different population – it is

estimated that less than 5% of adult cancer patients enroll in clinical trials,(20) and this population is comparatively much healthier and younger than the general cancer population.(21) A summary of our inclusion/ exclusion criteria are provided, and further broken down in terms of subject information vs study type.

Inclusion criteria:

1. Population:
    - Adult human subjects (≥ 18 years)
    - Patients with new diagnosis of cancer, including all cancer types except non-melanoma skin cancers
        i. For prospective cohort studies, "new diagnosis of cancer" will be defined as any cancer other than non-melanoma skin cancer that was diagnosed in the 12 months before study inclusion
        ii. For retrospective or registry-based studies involving cancer patients, we will only extract information on strokes that happened within 1 year after a diagnosis of cancer was recorded
2. Outcomes: need to have well-described and documented strokes as outcomes (including subtype of stroke – ischemic/ ICH):
    - For prospective studies:
        i. Ischemic stroke definition: neurologic dysfunction caused by focal cerebral infarction confirmed by neuroimaging or pathology (22)
        ii. Hemorrhagic stroke definition: neurologic dysfunction caused by a collection of blood within the brain parenchyma/ ventricles that is not caused by trauma and confirmed by neuroimaging or pathology (22)

- For retrospective/ registry based studies: registry-code based diagnosis for ischemic and hemorrhagic stroke will be used (i.e. International Classification of Diseases)
    i. We will record what type of diagnosis codes were utilized by studies. As an example, we have provided the relevant ICD-9 and ICD-10 codes of interest.
    ii. Ischemic stroke ICD codes:
        - ICD-9: 433x, 434x
        - ICD-10: I63x
    iii. Hemorrhagic stroke: ICD codes:
        - ICD-9: 431.x
        - ICD-10: I61.x
- However, our search will not be limited to studies using these codes. We will capture case definitions in our extraction form for each individual study.

3. For studies using repeat cohorts/ registries, we will assess the relevance of information reported in each publication in addition to the sample size – the study deemed to have the most complete set of variables of interest and largest sample size will be included for analysis
4. Study types:
    - Observational studies only
    - English language

Exclusion criteria:

1. Population:

- Predominant pediatric population (i.e. >50% of enrolled patients are under the age of 18)
- Cancer diagnosed > 12 months prior to enrollment in studies:

If a study includes a mix of newly diagnosed (≤12 months) cancer patients and patients that were diagnosed after 12 months, only those that were diagnosed ≤12 months prior to enrollment will be used for analysis

i. Retrospective or registry-based studies reporting cancer outcomes above the 1-year cutoff from cancer diagnosis will be included, but only stroke outcomes reported during the 1st year of cancer diagnosis will be included for analysis

2. Outcomes:
    - Subtypes of stroke other than ischemic or hemorrhagic stroke, including cerebral venous sinus thrombosis, aneurysmal or non-aneurysmal subarachnoid hemorrhage, epidural hematoma, subdural hematoma, and transient ischemic attacks
    - Non-descriptive definition of stroke (i.e. "stroke" without specifying the subtype)
3. Study types:
    - Conference abstracts, case reports, case series, editorials, narrative reviews
    - Interventional studies: randomized controlled trials, non-randomized controlled trials, cross-over trials
    - Non-English language

Information Sources:

Electronic searches will be conducted in MEDLINE and EMBASE via OVID and PubMed, and will include all relevant studies from 1980 until present. Articles published before 1980 are

likely to be irrelevant due to the lack of modern diagnostic imaging technologies used to diagnose stroke and cancer, and is in line with existing literature on similar topics.(23) Our search strategy will be limited to the English language, and studies involving human subjects only. All studies identified for full-text review will undergo further screening of their reference lists for potentially relevant studies.

Search Strategy:

Structured search strategies were formulated using MeSH terms for the OVID interface and Emtree terms for the Embase interface after meeting with a medical librarian with expertise in conducting systematic reviews. Full search strategies for all three databases are included in Supplemental Materials 1 as examples.

Study Records:

Data Management:

Database search results will be imported into Covidence Systematic Review Software (Covidence, Melbourne, VIC, Australia). After removing duplicate results, citation titles and abstracts will be screened by two independent reviewers.

Selection Process:

Two independent reviewers will screen the search results in two stages. The first will be a review of titles and abstracts. Potentially relevant articles will be brought forward for full-text review during the second stage. Discrepancies regarding inclusion of full-text articles will be resolved by a senior third reviewer (DD). A PRISMA flow diagram will be used to summarize the process of study selection.

Data Collection Process:

The two reviewers will independently collect data for each phase of the review, including screening, eligibility, and extraction. Once full-text articles are identified for inclusion, each reviewer will also evaluate the completeness, content, and quality of the studies. For any included full-text article that contains missing data, the reviewers will contact the investigators of the original study for clarification. If a same study has multiple reports, the data will be extracted separately but will be collated and linked together for analysis. Data will be extracted from full-text articles using an a priori data extraction form. After extraction has been individually completed, any discrepancies will be resolved via discussion with a senior author (DD) or consultation with a third party, if necessary.

Data items:

Information collected will include:

- Publication data: article title, journal of publication, authorship list, year of publication, country of origin
- Study population: proportion of males/females, average age, baseline vascular risk factors (proportion of patients with hypertension, diabetes, smoking status, dyslipidemia, previous stroke, atrial fibrillation, and heart failure)
- Exposure (cancer): stage, type, location, treatment-related factors (i.e. surgeries, radiotherapy, and use of chemotherapies by drug class)
- Outcomes (stroke): type of stroke, etiology of stroke (i.e. cardioembolic, atheroembolic, cryptogenic, small vessel disease) timing in relation to cancer diagnosis, method of diagnosis (i.e. registry code, imaging, pathology), mortality rates, functional outcomes

Outcomes and Prioritization:

The primary outcome we are interested in is stroke – specifically, the subtype of stroke and timing of stroke diagnosis in relation to a diagnosis of cancer. Transient ischemic attacks (TIA) were not included as an outcome of interest, due to low reliability and accuracy in diagnostic coding of TIA, particularly in a non-inpatient setting and when diagnosed by non-experts.(24) Furthermore, the definition of TIA has evolved over the years, which may result in additional heterogeneity.(25) Additional outcomes that may be gathered, if available, include mortality rates and functional outcomes (i.e. modified Rankin Scale).

Risk of Bias in Individual Studies:

Cohort studies will be assessed for methodological rigor at the study level using the Newcastle-Ottawa Scale (NOS),(26) which will be performed by two independent reviewers. Any discrepancies will be settled by consensus after reviewing with a senior author (DD). The NOS includes 3 main domains to assess the quality of observational cohort studies, including selection of study groups, comparability of the groups, and ascertainment of the outcome of interest. The NOS assigns up to a maximum of 9 points for assessment of risk of bias – lower NOS scores indicate greater risk of bias. We plan to perform a subgroup analysis stratified by level of risk of bias, based on the following thresholds for converting the NOS to the Agency for Healthcare Research and Quality (AHRQ) standards:

- Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

- Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain
- Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

Data Synthesis:

Heterogeneity across included studies for primary analysis will be assessed using visual inspection of forest plots and the I^2 statistic, as recommended by Cochrane Reviews.(27) This represents the percentage of total variation across studies. Heterogeneity is deemed considerable at a level of 50%. Between-study variance will be estimated using a random-effects meta-analysis to produce Tau^2 values.

We plan on performing sensitivity and subgroup analyses across the following prespecified factors to investigate potential sources of between study heterogeneity: study design (i.e. retrospective vs prospective cohort studies), year of publication, type and stage of cancer (if possible), and studies deemed to have high risk of bias.

Statistical Analysis:

Outcome analysis:

The primary outcomes in this review will be the type and timing of stroke in relation to a new diagnosis of cancer. Type of stroke will be reported as cumulative incidence (proportions) for hemorrhagic vs ischemic strokes. We will report the cumulative incidence of strokes at pre-specified timepoints during the first year after cancer diagnosis (i.e. 1 month, 3 months, 6 months, and 12 months) As this is an incidence study, there will be no comparator vs

intervention groups. If mortality data is available, the all-cause mortality rate will be calculated and subgroup analyses will be performed based on the subtype of stroke (i.e. ischemic vs hemorrhagic).

Meta-analysis:

For each study cohort, we will calculate the cumulative incidence of stroke by using the number of events divided by the total number of people at risk at multiple pre-specified time points during the first year after a diagnosis of cancer (i.e. 1 month, 3 months, 6 months, and 12 months). Due to anticipated heterogeneity in terms of the enrolled populations, we will use a random effects meta-analysis model to pool proportions (cumulative incidence and mortality) from appropriate studies, using generalized linear mixed models.(28) The upper and lower limits of the 95% confidence interval for the proportions at each time interval will be calculated.

All statistical analysis will be performed using Statistical Analysis System (SAS), version 9.4 (SAS Institute, Inc., Cary, North Carolina).

Meta-Biases:

For studies included in our primary analysis with an a priori study protocol, we will assess each study individually for potential selective reporting bias. For studies without a published protocol, we will compare the outcomes reported to what is stated in the Methods section. Publication bias will be assessed using funnel plots.

Confidence in Cumulative Evidence:

We will use Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to assess the quality of the evidence for our outcomes.(29) Since our planned

systematic review plans on looking at cumulative incidence and does not assess the effectiveness of an intervention, we will adapt GRADE methodology to produce a Summary of Findings (SoF) table, reporting a summary statement for each outcome of interest individually. This will include the number of studies pooled for each outcome, the measure of association with 95% confidence interval, and the certainty of evidence, as summarized using a 4-point scale from very low to high.(29) Patient-important outcomes will be prioritized, therefore, we will report our outcomes in the following order: pooled cumulative incidence of stroke (all subtypes) during the first year, pooled cumulative incidence of hemorrhagic stroke, followed by pooled cumulative incidence of ischemic stroke.

3.5 Ethics and Dissemination

The results of this study will help inform clinicians and patients regarding the risk of stroke in patients newly diagnosed with cancer by quantifying the risk of each subtype of stroke during the first year of diagnosis. The findings from this study will be disseminated via conference abstracts/ presentations, and the peer-reviewed journal publication process.

3.6 References

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3.7 Supporting Information

SUPPLEMENTAL MATERIALS 1 – SEARCH STRATEGY

EMBASE via OVID using EMTree search terms:

1 malignant neoplasm/ or neoplasm/ or solid malignant neoplasm/ or myeloproliferative neoplasm/ (567513)

2 (cancer or tumo?r* or neoplasms* or carcinoma or leuk?em* or myeloma* or melanoma or hodgkin* or lymphoma or malignanc* or oncology).tw. (5041168)

3 1 or 2 (5128557)

4 exp *brain hemorrhage/ (59384)

5 *cerebrovascular accident/ (84430)

6 brain ischemia/ (150108)

7 ((brain or cerebr*) adj3 (isch?em* or h?emorrhag* or bleed*)).tw. (94262)

8 stroke.ti. (167370)

9 ((isch?em* or h?emorrhag*) adj3 stroke*).tw. (117459)

10 cerebr* vascular accident*.tw. (2269)

11 or/4-10 (379118)

12 3 and 11 (17887)

13 incidence/ (442103)

14 incidence.tw. (1188620)

15 risk*.tw. (3427729)

16 *risk/ or *risk factor/ (150822)

17 13 or 14 or 15 or 16 (4322259)

18 12 and 17 (5883)

MEDLINE via OVID using MESH search terms:

1 exp Neoplasms/

2 (cancer or tumo?r* or neoplasms* or carcinoma or leuk?em* or myeloma* or melanoma or Hodgkin* or lymphoma or malignanc* or oncology).tw, kf.

3 1 or 2

4 *stroke/

5 stroke*.tw.

6 ((brain or cerebral) adj isch?em*).tw.

7 ((brain or cerebral) adj h*emorrhage*).tw.

8 Exp Intracranial Hemorrhages/

9 h*emorrhagic stroke*.tw.

10 incidence/ or incidence.tw,kf.

11 risk*.tw, kf

12 risk/ or risk assessment/ or risk factors/

13 10 or 11 or 12

14 4 or 5 or 6 or 7 or 8 or 9

15 3 and 13 and 14

16 case reports.pt.

17 randomized controlled trial.pt.

18 15 not (16 or 17)

19 limit 18 to (English language and humans and yr = “1980 – current”)

PubMed Search:

(((("Neoplasms"[MeSH Terms] OR ("cancer"[Title/Abstract] OR "tumor*"[Title/Abstract] OR "tumour*"[Title/Abstract] OR "neoplasm*"[Title/Abstract] OR "carcinoma"[Title/Abstract] OR "leukemia"[Title/Abstract] OR "myeloma"[Title/Abstract] OR "melanoma"[Title/Abstract] OR "hodgkins"[Title/Abstract] OR "lymphoma"[Title/Abstract] OR "malignanc*"[Title/Abstract] OR "leukaemia"[Title/Abstract] OR "oncology"[Title/Abstract])) AND ("Stroke"[MeSH Major Topic:noexp] OR "Stroke"[Title/Abstract] OR ("brain ischem*"[Title/Abstract] OR "brain ischaem*"[Title/Abstract] OR "cerebral ischem*"[Title/Abstract] OR "cerebral ischaem*"[Title/Abstract]) OR ("brain hemorrhag*"[Title/Abstract] OR "brain haemorrhag*"[Title/Abstract] OR "cerebral hemorrhag*"[Title/Abstract] OR "cerebral haemorrhag*"[Title/Abstract]) OR "Intracranial Hemorrhages"[MeSH Terms]) AND ("Incidence"[MeSH Terms] OR "Incidence"[Title/Abstract] OR ("Risk"[MeSH Terms] OR "Risk Assessment"[MeSH Terms:noexp] OR "Risk"[MeSH Terms:noexp] OR "Risk Factors"[MeSH Terms:noexp]) OR "risk*"[Title/Abstract])) NOT ("Animals"[MeSH Terms] NOT "Humans"[MeSH Terms])) AND ((english[Filter]) AND (1980:2021[pdat]))

Chapter Four: Incidence of Stroke in Newly Diagnosed Cancer Patients – Systematic Review & Meta-Analysis

4.1 Preface

This chapter is a systematic review and meta-analysis examining the incidence of stroke at one year after a new diagnosis of cancer. Ethics approval was not required for this study. A confirmation of submission is available in Appendix III.

Authorship Contribution Statement:

R. Lun: conceptualization, data curation, formal analysis, investigation, methodology, software, writing original draft, reviewing and editing. **D.C. Roy**: data curation, investigation, methodology, reviewing and editing. **Y. Hao**: data curation, investigation, reviewing and editing. **R. Deka:** data curation, investigation, reviewing and editing. **W.K. Huang:** data curation, investigation, reviewing and editing. **Babak B**: data curation, investigation, reviewing and editing. **D.M. Siegal:** conceptualization, methodology, supervision, reviewing and editing. **T. Ramsay:** conceptualization, data curation, methodology, supervision, reviewing and editing. **D. Fergusson:** data curation, formal analysis, investigation, methodology, resources, software, supervision, reviewing and editing. **R. Shorr:** data curation, methodology, reviewing and editing. **D. Dowlatshahi**: conceptualization, data curation, formal analysis, investigation, methodology, resources, supervision, reviewing and editing.

Acknowledgements: I would like to acknowledge the collaborators who shared their data with us for this systematic review and meta-analysis. This manuscript was a collaborative effort and could not have been possible without the participation of each of you.

Appendix III. Submission confirmation of Chapter 4:
Lun R, Roy DC, Hao Y, Deka R, Huang WK, B. Babak, Siegal DM, Ramsay T, Fergusson D, Shorr R, Dowlatshahi D. Incidence of Stroke in the First Year After Diagnosis of Cancer – A Systematic Review and Meta-Analysis. JACC: CardioOncology. Submitted April 2022.

4.2 Abstract

Background: Patients newly diagnosed with cancer represent a population at highest risk for stroke. The objective of this systematic review and meta-analysis was to estimate the incidence of stroke in the first year following a new diagnosis of cancer.

Methods: We searched MEDLINE and EMBASE from January 1980 – June 2021 for observational studies that enrolled adults with a new diagnosis of all cancers excluding non-melanoma skin cancer, and that reported the incidence of stroke at one year. PRISMA guidelines for meta-analyses were followed. Two reviewers independently extracted data and appraised risk of bias. We used the Dersimonian and Laird random effects method to pool cumulative incidences after logit transformation, and reported pooled proportions as percentages. Statistical heterogeneity was assessed using the I^2 statistic.

Results: A total of 12,083 studies were screened; 41 studies were included for analysis. Data from 2,552,121 subjects with cancer were analyzed. The cumulative incidence of total stroke at 1 year was 1.4% (95%CI 0.9% – 2.2%), while the pooled incidence of ischemic stroke was 1.3% (95%CI 1.0% – 1.8%) and 0.3% (95%CI 0. 1% – 0.9%) for spontaneous intracerebral hemorrhage (ICH), with consistently high statistical heterogeneity (>99% I^2).

Conclusion: The estimated incidence of stroke during the first year after a new diagnosis of cancer is 1.4%, with a higher risk for ischemic stroke than ICH. Cancer patients should be educated on the risk of stroke at the time of diagnosis. Future studies should evaluate optimal primary prevention strategies in this high-risk group of patients.

4.3 Introduction

Cancer is a well-known risk factor for stroke,[1] and both conditions are associated with a high degree of morbidity and mortality. There appears to be an increased risk for arterial thromboembolic events in the months preceding a diagnosis of cancer.[2–4] Many studies have found that the risk for stroke increases around the time of cancer diagnosis and that this elevated risk may persist for up to 10 years after diagnosis.[1] While this risk attenuates over time, it is hypothesized that the first year after a new diagnosis of cancer represents the period during which cancer patients have the highest stroke risk.[2] From a clinical care standpoint, identifying patients with a new diagnosis of cancer who have not yet experienced a stroke represents an opportunity to study and implement primary prevention strategies in order to maximize quality of life in cancer patients. Thus, the objective of this systematic review and meta-analysis was to examine the risk of stroke in the first year following a new diagnosis of cancer.

4.4 Methods

Data Availability Statement:

The data underlying this article will be shared on reasonable request to the corresponding author.

Study protocol and registration:

The protocol for this study was registered at the Open Science Framework (osf.io/ucwy9) and published in a peer-reviewed journal.[1] This study was conducted based on the guidelines of the Cochrane Handbook of Systematic Reviews.[2] It was reported using the updated guidelines for Preferred Reporting Items for Systematic Reviews (PRISMA).[3]

Inclusion Criteria:

Our systematic literature search was limited to studies in adults with a new diagnosis of cancer, encompassing all cancer subtypes except non-melanoma skin cancers (i.e. basal cell and squamous cell carcinoma) due to their favorable prognosis and treatment with local measures not requiring systemic therapy, resulting in inaccuracies in administrative diagnostic coding. Studies must report the incidence of ischemic stroke and/or spontaneous intracerebral hemorrhage (ICH) during the first year after cancer diagnosis. If a graphical representation of the data was provided without a corresponding numerical value, the incidence at one year was extracted using the Engauge Digitizer software.[4,5] As the primary objective of this systematic review was to synthesize the natural history (i.e. incidence) of stroke in the cancer population, our search was limited to only observational studies and we excluded any interventional studies, as they represent a different population – it is estimated that less than 5% of adult cancer patients enroll in clinical trials,[6] and this population is comparatively much healthier and younger than the general cancer population.[7] Further details on our inclusion/exclusion criteria can be found in our published protocol.[1]

Search Strategy:

Our search strategy was conducted with the assistance of a health science librarian with expertise in systematic reviews (R.S.). We searched MEDLINE and EMBASE via OVID and PubMed and included all relevant studies from January 1980 to June 2021. A sample search strategy can be found in Supplemental Materials eTable 1; detailed search strategies can be found in our published protocol.[1] We further searched the abstract databases from both the International Conference of Stroke and the European Stroke Organization Conference for the same time

period. Our search was restricted to human adult subjects, and the language was limited to English language only.

Article and Data Extraction:

Two reviewers (R.L. and D.C.R.) independently completed two-level screening for articles using the Covidence Systematic Review software. Any discrepancies were resolved by discussion with a third senior author (D.D.). Findings from the screening process were summarized using a flow diagram (Figure 1).

A standardized data extraction form was created a priori and piloted independently by the two reviewers. The data extraction form was separated into bibliographic information (i.e. study ID, authors, title, funding status, journal, country and year of publication, study type, and name of databased used [if applicable]), subject information (i.e. number of participants total, number of participants with cancer, sex, age, cancer type, stage, and prevalence of comorbidities), and outcomes (i.e. incidence of ischemic stroke and/or ICH at 1 month, 3 months, 6 months, and 1 year). Wherever information had to be extracted using the Engauge Digitizer, only information at 1 year was extracted.

Data Collection Process:

One reviewer (R.L.) performed primary data extraction from the included studies and a second reviewer (D.C.R.) peer reviewed the extracted information. Disagreements were resolved via discussion. For studies that met inclusion criteria but did not report the specific outcome we required, the corresponding author of the study was contacted for the data a minimum of two times.

Risk of Bias Assessment:

Risk of bias (ROB) of individual studies was assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies.[8] Two raters (R.L. and D.C.R.) independently implemented the tool for all included studies and any disagreements in the rating were resolved by discussion. The following thresholds for converting the NOS to the Agency for Healthcare Research and Quality (AHRQ) standards are:

• Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

• Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain

• Poor quality: 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain

Statistical Analysis:

Our primary outcome was the cumulative incidence of stroke (total, ischemic, and hemorrhagic) at one year after a new diagnosis of cancer, and defined as the proportion of events divided by the sample size. Given the low number of studies that reported the incidence of stroke at 1, 3, and 6 months, we only reported the incidence of total stroke at these timepoints after pooling ischemic and hemorrhagic stroke. The transformed incidences were pooled using the Dersimonian and Laird random effects method.[9] Between-study heterogeneity was assessed by the I^2 statistic. To explore potential sources of heterogeneity, we caried out pre-specified subgroup analyses, including stratification based on ROB assessments, year of publication,

location of primary cancer for studies that studied only one subtype of cancer, presence of atrial fibrillation, and study design (i.e. prospective vs retrospective cohorts). Univariate meta-regression analyses were carried out to test the influence of subgroup effects on heterogeneity. Sensitivity analyses were performed with the leave-one-out method to assess the influence of each study on the overall effect-size estimate. As this is a meta-analysis of pooled proportions from single cohorts (i.e. does not assess the effect of an intervention), publication bias was not assessed.[2]

All statistical analyses were performed using the OpenMeta-Analyst software.[10,11]

4.5 Results

Our search identified 12,083 studies across all databases searched. After removing duplicates, we screened 10,378 titles and abstracts and found 485 potentially eligible titles. During the second stage of full-text screening, we further excluded 444 studies (Figure 1), resulting in 41 full-text articles for data extraction and synthesis.

Study Selection and Characteristics:

The characteristics of included studies are listed in Table 1. The median year of publication was 2018 (interquartile range [IQR] 2015 – 2019). Of the 41 studies, 18 were from Asia, 12 were from the United States, and 11 were from Europe. In total, they contributed 10,637,699 subjects for analysis, and 2,552,121 subjects had a new diagnosis of cancer. The sample size of cancer patients in the included studies ranged from 48 to 820,491, with a median sample size of 7,479 (IQR 893 – 22,737). Overall, 46% of the patients were women. Three studies were prospective cohort studies,[12,13] and the remaining were retrospective cohort studies. There were 29 studies

that examined a single type of cancer (i.e. lung cancer), and the remaining studies included multiple types of cancer (Table 1).

Total stroke (ischemic stroke and ICH) after cancer diagnosis:

The total number of new stroke events at various timepoints throughout the first year of cancer diagnosis for the included studies are listed in Table 2. Of the included 41 studies, 22 reported the incidence of combined ischemic stroke and spontaneous ICH at 1 year.[12,14–34] For studies that reported the incidence of ischemic stroke and ICH separately, total stroke events were calculated by the sum of events. As shown in Figure 2, the pooled incidence of ischemic stroke and ICH at 1 year was 1.4% (95%CI 0.9% – 2.2%) with a high degree of statistical heterogeneity present (I^2=99.92%).

Due to the low number of studies that reported the incidence of ischemic stroke and ICH at 1, 3, and 6 months, we only evaluated the cumulative incidence of total stroke (i.e. sum of events) at these timepoints. Five studies reported the incidence of stroke at 1 month,[12,16,35–37] four reported the incidence of stroke at 3 months,[12,31,35,36] and eight reported the incidence of stroke at 6 months.[12,14,16,17,31,35,36,38] Their respective pooled incidences at 1, 3, and 6 months are 1.6% (95%CI 0.2 – 10.8%; I^2=99.78%), 1.0% (95%CI 0.3% – 2.8%; I^2=99.95%), and 1.3% (95%CI 0.6% - 2.9%; I^2=99.96%) (Supplemental Materials eFigure 1).

Ischemic stroke at one year after cancer diagnosis:

Of the 41 studies, 23 (N=1,972,059) reported the incidence of ischemic stroke events at 1 year after a diagnosis of cancer.[13–15,17,18,20,25,26,30,34–36,39–49] The pooled incidence of ischemic stroke

events during the first year after a new diagnosis of cancer (see Figure 3) was 1.3% (95%CI 1.0% – 1.8%) with a high degree of statistical heterogeneity present (I^2=99.72%).

Intracerebral hemorrhage (ICH) at one year after cancer diagnosis:

There were 11 studies (N=1,361,817) that reported the incidence of ICH at 1 year after a diagnosis of cancer.[14,15,17,18,20,25,26,30,34,50,51] The pooled incidences of ICH at one year after diagnosis was 0.3% (95%CI 0. 1% – 0.9%) with a high degree of statistical heterogeneity present (I^2=99.46%).

Subgroup Analyses:

Atrial fibrillation and Ischemic Stroke:

Three studies exclusively included cancer patients with atrial fibrillation.[34,52,53] Two of these studies specifically examined the use of anticoagulation in these patients,[53,54] while the third study reported approximately that 85% of their cohort was on anticoagulation.[52] In a subgroup analysis of studies that only included cancer patients with atrial fibrillation, the incidence of ischemic stroke was 3.3% at one year (95%CI 2.4% – 4.6%) with relatively low heterogeneity (I^2=29.70%), which was significantly higher than the incidence of ischemic stroke in 20 other studies (1.2% [95%CI 0.9% – 1.6%], I^2=99.76%) (Supplemental Materials eFigure 2).

Cancer Subtype:

Out of 22 studies that reported the combined incidence of ischemic and hemorrhagic stroke at 1 year, eight were cohort studies that included multiple types of cancer (Supplemental Materials eFigure 3).[12,14,15,25,27,31,33,34] The remaining 14 studies were limited to specific cancer subtypes

including head and neck cancer (n=3),[16,24,28] hematologic malignancies (n=2),[19,29] breast cancer(n=2),[21,23] and thyroid cancer (n=2).[26,32] There was only one study for each of the following subtypes of cancer: pancreatic, cervical, prostate, colorectal, and hepatic.[17,18,20,22,30] Subgroup analyses based on cancer type found that the pooled incidence of stroke for the eight studies that enrolled multiple types of cancer had a similar incidence to our overall pooled incidence: 1.1% (95%CI 0.5% – 2.7%), with significant heterogeneity (I^2=99.97%). Studies that enrolled head and neck cancer patients exclusively appeared to have a higher incidence of stroke (5.3% [95%CI 0.8% –27.5%, I^2 = 99.83%]), although this difference was not statistically significant. Studies that enrolled hematologic cancer patients also reported a higher incidence of stroke: 3.9% (95%CI 2.4% - 6.3%), with moderate heterogeneity, I^2=63.64% (Supplemental Materials eFigure 3). Thyroid cancer appeared to have a non-significant lower risk of stroke: 0.6% (95%CI 0.1% - 4.8%), while breast cancer patients reported a lower risk of stroke that was statistically significant: 0.4% (95%CI 0.2% - 0.9%, I^2=95.10%). Based on results from a single study each, it appeared that pancreatic cancer, cervical cancer, prostate cancer, and hepatic cancer all had elevated risk of stroke compared to the overall pooled incidence of stroke (Supplemental Materials eFigure 3).

Sensitivity Analyses and Meta-Regression:

Sensitivity analyses were performed with the leave-one-out method to examine the stability of the results (Supplemental Materials eFigure 4). We found that no single study significantly altered the pooled effect measure – cumulative incidences ranged from 1.3% (95%CI 0.8% – 2.0%) to 1.6% (95%CI 0.010 – 0.025), which was not statistically different from the pooled estimate of 1.4% (95%CI 0.9% –2.2%). Subgroup analysis based on the geographic region of

enrolled patients found that the risk of stroke appeared to be highest in cohorts from the United States (4.1%, 95%CI 2.8% –5.3%) compared to cohorts from Asia (1.5%, 95%CI 1.8% –2.7%) or Europe (0.5%, 95%CI 0.1% – 0.9%) (Supplemental Materials eFigure 5). Between-study heterogeneity was statistically quantified with univariate meta-regression analyses, which identified that substantial heterogeneity originated from differences in cancer type (p=0.014), but not from year of publication, risk of bias, presence of atrial fibrillation, or study design (i.e. retrospective vs prospective).

Risk of Bias in Studies:

Using the NOS risk of bias tool, we found that 6/41 studies were "poor quality", one was "fair quality", and the remaining 34 were "good quality" (eTable 2, Supplemental Materials). Subgroup analysis stratified by the ROB ratings found that 20 of 22 studies that reported 1-year stroke outcomes were deemed "good quality",[12,14–28,30–33] while one received a "poor" rating[34] and one received a "fair" rating.[29] The studies that received a "good" rating had a similar pooled incidence of stroke at one year compared to the primary analysis (Supplemental Materials eFigure 6): 1.4% (95%CI 0.9% – 2.2%, I^2 = 99.92%). The study with a "poor" rating reported a slightly higher cumulative incidence of stroke at 1 year (2.7% [95%CI 1.2% – 5.8%]), although this difference was not statistically significant. The single study that received a "fair" rating similarly reported a slightly higher incidence of stroke at 1 year: 2.8% (95%CI 1.5 – 5.0%).

4.6 Discussion

Through our systematic literature search, we identified that the cumulative incidence of any stroke during the first year after a new diagnosis of cancer was 1.4%. The risk of ischemic stroke

was similar (1.3%), but the risk for spontaneous ICH was much lower comparatively, at 0.3%. The risk for ischemic stroke was particularly high in patients with cancer and atrial fibrillation, and in those with head and neck cancer and hematologic cancers. For context, the incidence of stroke in those aged 55 years or older has been reported to be approximately 5.3 per 1000 person-years, which translates to a cumulative incidence of approximately 0.53% per year for a single individual.[55] This suggests that compared to the general population, there is approximately a 2.6-fold increase in the risk for stroke during the first year after a new cancer diagnosis. This is slightly higher than the reported relative risk for stroke in a previous meta-analysis looking at the risk of stroke in cancer *survivors*: Zhang et al found that the risk for stroke was 1.66 times higher (95%CI 1.35 – 2.04) for cancer survivors compared to the cancer-free population over an unspecified follow-up period.[56] This is likely due to the difference in study population and follow-up time– by evaluating cancer survivors, the previous meta-analysis would have excluded malignancies with poor prognoses, and may have also excluded those who suffered a stroke already with consequent mortality. Additionally, the elevated risk for stroke in cancer patients is not also constant over time – previous studies have found that stroke risk increases during the months leading up to a diagnosis of cancer, and peaks around the time of diagnosis.[57,58] Therefore, the first year after a diagnosis of cancer may represent the period during which the risk is the highest, and this risk attenuates over time in cancer survivors. Our results are similar to those reported by a national Danish registry study evaluating the risk of arterial thromboembolic events in adult cancer patients (excluding skin cancers): Mulder et al reported that the 12-month cumulative incidence of ischemic stroke was 1.22% (95%CI 1.19% - 1.26%) in cancer patients during the first year after a new diagnosis of cancer.[59] As this study was

published in July 2021, it was not yet published at the time of conducting our systematic review, and therefore was not included in our meta-analysis.

Our meta-analysis identified that the combined risk of stroke varied by geographic location: the risk of stroke was significantly higher in cohorts from the United States compared to the Asia and Europe. This is different than previously reported numbers of stroke risk by geographic region in the general population: East Asia has been reported to have the highest lifetime risk of stroke, followed by Central and Eastern Europe.[60] The discrepancy reported in our study may reflect the heterogeneity that is present in baseline patient characteristics and cancer subtypes across studies. Using visual inspection of the forest plot, it is evident that the higher incidence of stroke in the United States cohort may be largely driven by three studies: Bigelow (study ID 420), Hong (study ID 2599) and B. Navi (2015; study ID: 2397) (Supplemental Materials eFigure 5).[16,24,31] Two of these studies (Hong and Bigelow) were specifically investigating the risk of stroke in elderly patients with glottic and oropharyngeal cancer – the respective median/mean ages of cancer subjects include in these two cohort studies were 72 (IQR 69 – 77) and 73.8 (no standard deviation reported).[16,24] The population from the 2015 study by Navi selectively included patients with breast, colorectal, lung, pancreatic, or prostate cancer from the Surveillance Epidemiology and End-Results (SEER) Medicare database – the authors chose these cancer types *a priori* because pancreatic cancer is the cancer type most commonly reported in association with thromboembolic events, and the remaining four represent the most common cancers reported in the United States population.[31] This may therefore represent a highly selected group of patients, as gastric, lung and pancreatic cancers are particularly associated with a higher risk for stroke.[56,61,62] These cancers are also more likely to be at advanced stages at the time of

diagnosis, which is an independent risk factor to increase the risk for thromboembolic events.[31] Unfortunately information regarding cancer stage was not available for this meta-analysis. Furthermore, the SEER-Medicare database restricts the study population to patients 65 and older so the higher rates of stroke may be partly driven by the older population – this is supported by the high rates of stroke seen in the matched control patients without cancer.[31]

Our subgroup analysis found that in patients with cancer and atrial fibrillation, there was an elevated risk for ischemic stroke compared to the general cancer cohort: 3.3% vs 1.3%, respectively. This is similar to what is reported in the literature – a large national registry-based cohort study reported that the annual incidence rate of ischemic stroke was 3.44% in those with atrial fibrillation and active or history of cancer.[63] This risk is stratified by the presence of comorbidities, including older age, and the presence of other vascular risk factors.[64,65] While current risk stratification tools for atrial fibrillation (i.e. CHADS2 or CHADS2-VASC) do not take cancer into account, when applied in a population of cancer patients with atrial fibrillation, they were still found to be predictive of ischemic stroke.[66] There is a higher prevalence of atrial fibrillation in patients with cancer compared to those without cancer – a relationship that persists regardless of surgery or cancer therapy.[67] The mechanism by which this occurs is postulated to be multifactorial, but may be related to higher incidences of post-operative atrial fibrillation, chemotherapy-related adverse effects, cancer-associated systemic inflammation which promotes atrial re-structuring, and autonomic dysregulation in patients with malignancy.[67–70] Thus, the co-occurrence of atrial fibrillation and cancer represents a highly susceptible population with the highest risk for ischemic stroke; these patients may require anticoagulation for primary prevention.

There are no randomized studies that evaluate the efficacy and safety of antithrombotic therapies specifically for the primary prevention of stroke in patients with new/active cancer. Initiation of antithrombotics in this population is challenging for multiple reasons. First, currently there is no risk stratification tool for accurately identifying patients with cancer at the highest risk for stroke. This represents the biggest challenge, as patients with cancer on antithrombotic therapy are also at increased risk for major bleeding compared to non-cancer patients, and therefore accurate patient selection is crucial.[71] Second, the choice of antithrombotic for primary prevention should be highly individualized. For example, anticoagulation is recommended for the prevention of stroke in patients with atrial fibrillation, and it is generally accepted that direct oral anticoagulants (DOAC) are preferred to warfarin.[72] While patients with cancer were excluded from the large DOAC trials comparing rivaroxaban, apixaban, dabigatran, and edoxaban to warfarin,[73–76] recent observational data suggests that DOAC is comparable to warfarin in terms of efficacy and safety profiles, and the Canadian Cardiovascular Society recommends the use of DOAC as first line anticoagulation therapy in patients with atrial fibrillation and active cancer [weak recommendation; low-quality evidence].[72] However, many DOACs are mainly metabolized via cytochrome P450 3A4 in the liver, and concomitant use of DOACs with drugs that regulate this pathway may be contraindicated, as many chemotherapeutic agents fall in this category.[77] This example highlights that the choice of antithrombotic therapy in cancer patients should be highly individualized due to multiple patient and treatment considerations, and therefore should be chosen under the guidance of an expert multidisciplinary team.[72]

In contrast, there is high-level evidence to support the use of reduced-dose DOACs in the setting of primary prevention for venous thromboembolism (VTE) in ambulatory cancer patients starting chemotherapy at intermediate to high risk for VTE (defined as Khorana Score ≥2).[78,79] In two large randomized controlled trials, reduced-dose apixaban and rivaroxaban lowered the risk for VTE compared to placebo with an acceptable risk of bleeding.[78,79] Although this indirect evidence generally supports the use of antithrombotic treatments to prevent cardiovascular events among newly diagnosed cancer patients, the low number of cerebrovascular events in both trials may limit the generalizability of these results.[78,79]

Our study reported a very high I^2 value, indicative of substantial between-study heterogeneity. Significant heterogeneity is a well-recognized statistical phenomenon for meta-analyses of single proportions, and interpretation of I^2 values in this context is challenging.[56,80] Extremely large sample sizes of single cohort studies result in very narrow confidence intervals, thereby I^2 for pooled estimates can be extremely high even in the presence of modest inconsistency between studies.[81] Moreover, despite the extreme values of heterogeneity, we feel these results are still valid and clinically informative, as the primary objective of this study was to provide a global estimate of the risk for stroke in newly diagnosed cancer patients – a heterogeneous population to begin with. Therefore, it may be reasonable to sacrifice statistical homogeneity for broad inclusion criteria encompassing different cancer subtypes, treatments, and settings to increase the generalizability of our results and statistical power.[82] Using univariate meta-regression analyses, we found that substantial heterogeneity could be attributed to differences in cancer type, which is known to influence the risk of stroke.[15] Residual heterogeneity likely also originates from differences in baseline patient characteristics which cannot be quantified in an aggregate-level

meta-analysis (i.e. patient age, sex, presence of vascular comorbidities, differences in cancer treatment, and use of antithrombotics). For example, Pardo Sanz et al examined a cohort of patients with breast cancer and atrial fibrillation, where 84.9% of patients were anticoagulated.[46] However, as not everyone in the study was anticoagulated, this study could not be included in our subgroup analysis looking at the use of anticoagulation. Therefore, significant heterogeneity remains despite our attempts at quantification of the sources of heterogeneity.

Our meta-analysis provides significant clinical implications for the risk of stroke in patients newly diagnosed with cancer. Our study confirms that the risk of ischemic stroke is high compared to the general population during the first year after a cancer diagnosis, and these patients should be considered for primary prevention strategies. At present, there isn't enough evidence to support the use of antithrombotic therapy empirically in these patients. However, patients should at least be educated that their stroke risk is high during this time period, and patient education regarding healthy lifestyle habits (i.e. healthy diet, regular exercise, smoking cessation, alcohol consumption reduction) should be provided. Furthermore, patient education around what to look for in terms of signs or symptoms of stroke should also be emphasized to minimize delays in access to acute treatments.

Our study has several strengths to note. This meta-analysis produced one of the largest pooled cohorts of newly diagnosed patients with cancer in which to characterize the risk of stroke. We believe our pooled results will provide patients and clinicians with an accurate estimation of the cumulative incidence of stroke during a high-risk period. Our statistical methodology was robust, with the publication of an a priori, peer-reviewed study protocol and a comprehensive search

strategy encompassing multiple databases.[1] However, our study is not without limitations. First, our pooled results reported significant heterogeneity among the included studies, which is likely due to differences in baseline patient characteristics (i.e. cancer subtype, age, sex, presence of vascular risk factors, ethnicity, treatment and prognoses), as discussed above. However, we believe that the increased statistical power we report due to our large sample size is also a strength of our study, and may result in increased generalizability of these results. Second, our meta-analysis only included observational cohort studies; we may have missed potential data from randomized/interventional studies and grey literature. This was intentional during the design of our study protocol, as we wanted to focus on the natural history of disease so the results are applicable to all cancer patients, and the clinical trial population is often highly selected in oncology literature. Finally, as this meta-analysis was conducted exclusively in the English language, we may have missed literature published in other languages, which might have introduced language bias, though previous studies found little to no effect on summary measures excluding non-English studies.[83]

4.7 Conclusion

We found that the estimated cumulative incidence of stroke during the first year after a new diagnosis of cancer is 1.4%, and the risk for ischemic stroke is higher than the risk for spontaneous ICH. Patients newly diagnosed with cancer require education around the risk of stroke at the time of their diagnosis, as well as signs and symptoms of stroke to watch out for to minimize delays in access to acute treatments. Healthcare providers should advocate for conservative primary prevention strategies in this group of high-risk patients.

4.8 Figures

Figure 1. PRISMA Flow Diagram

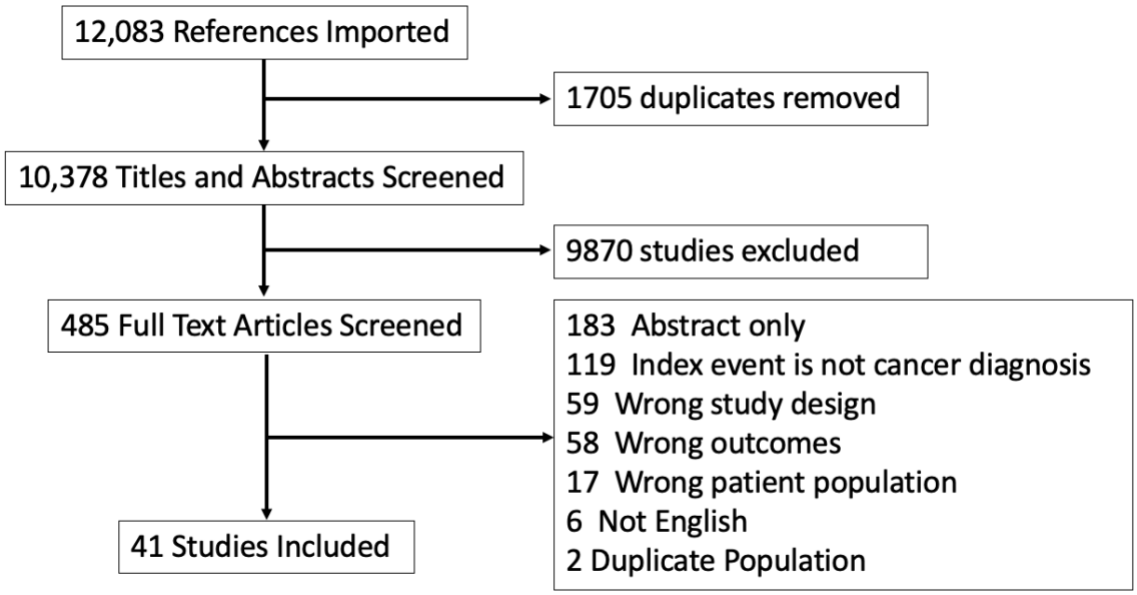


Figure 2. Forest plot of the pooled incidence of total stroke (ischemic and hemorrhagic) at 1 year after a diagnosis of cancer.

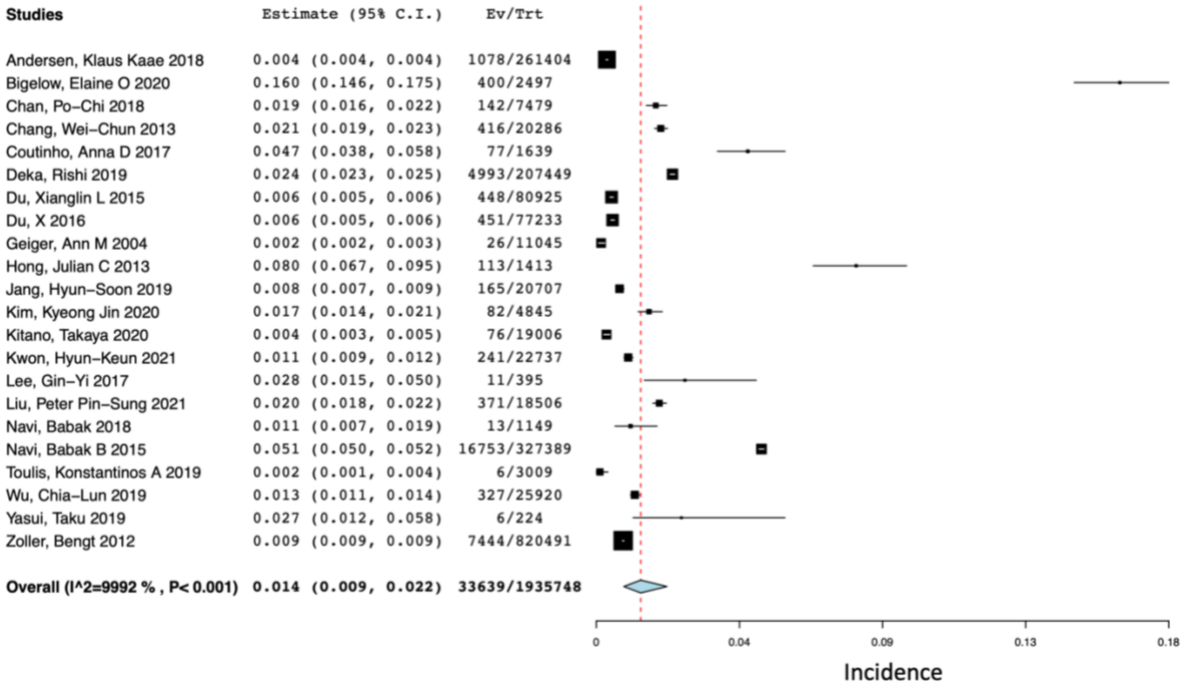


Figure 3. Forest plot of the pooled incidence of ischemic stroke at 1 year after a diagnosis of cancer.

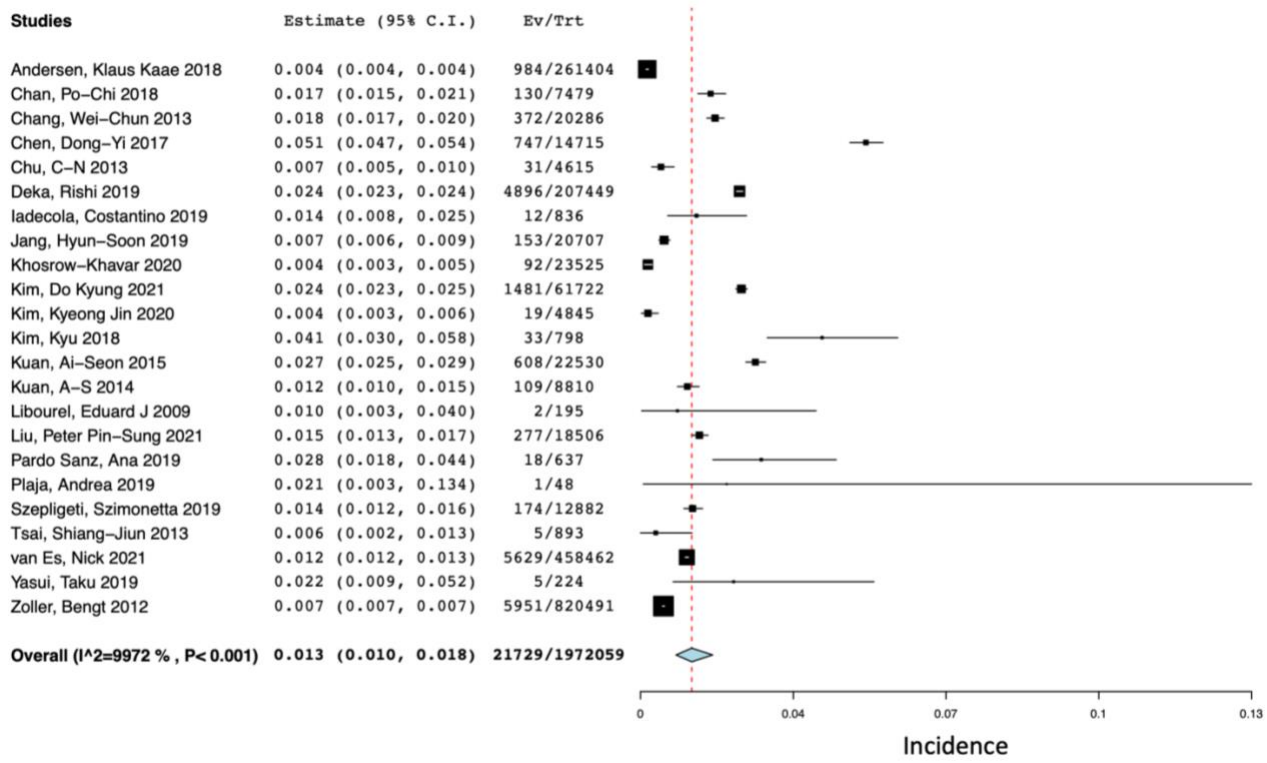
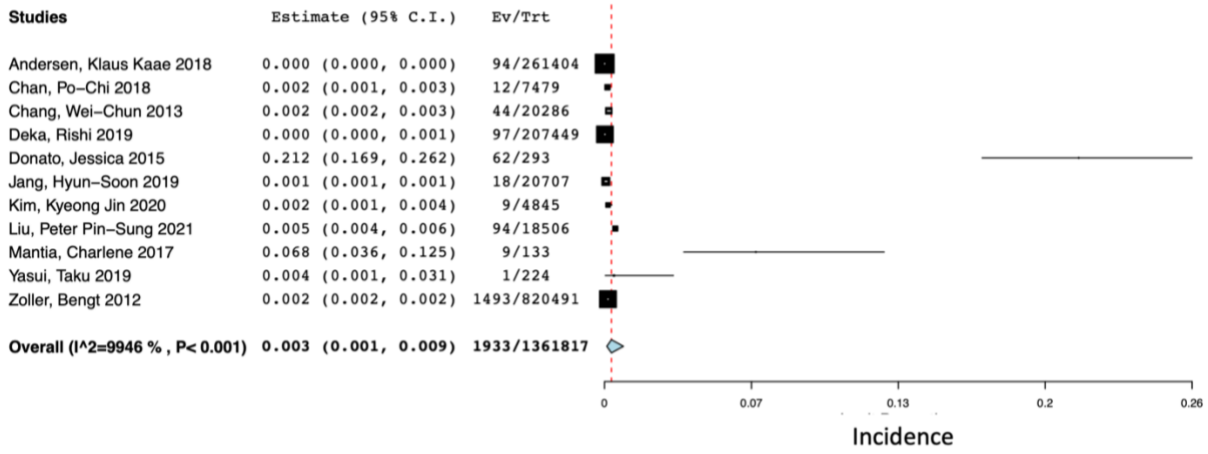


Figure 4. Forest plot of the pooled incidence of spontaneous ICH at 1 year after a diagnosis of cancer



4.9 Tables

Table 1. Included full-text articles for data extraction and meta-analysis

Study ID	First Author	Title	Journal	Year	Study Type	Cancer type Enrolled
1781	Andersen, Klaus Kaae	Risk of Ischemic and Hemorrhagic Strokes in Occult and Manifest Cancers	Stroke	2018	Retrospective case control	Multiple: 12.7% lung; 14.6% prostate, 2.3% CNS, 7.2% kidney & bladder, 3.9% urogynecologic, 2.7% pancreatic, 12.6% colorectal, 1.7% stomach, 5.1% melanoma, 2.5% head and neck, 3.1% myeloproliferative neoplasms
420	Bigelow, Elaine O	Burden of comorbidities is higher among elderly survivors of oropharyngeal cancer compared with controls.	Cancer	2020	Retrospective case control	Head & Neck
7128	Chan, Po-Chi	Higher stroke incidence in the patients with pancreatic cancer	Medicine	2018	Retrospective Cohort study	Pancreatic
2511	Chang, Wei-Chun	A nationwide population-based retrospective cohort study: decreased risk of stroke in cervical cancer patients after receiving treatment.	Archives of gynecology and obstetrics	2013	Retrospective Cohort study	Cervical
1319	Chen, Dong-Yi	Risk of Cardiovascular Ischemic Events After Surgical Castration and Gonadotropin-Releasing Hormone Agonist Therapy for Prostate Cancer: A Nationwide Cohort Study.	Journal of clinical oncology	2017	Retrospective Cohort study	Prostate
2077	Chu, C-N	Young nasopharyngeal cancer patients with radiotherapy and chemotherapy are most prone to ischaemic risk of stroke: a national database, controlled cohort study.	Clinical otolaryngology	2013	Retrospective case control	Head & Neck: 100% nasopharyngeal cancer
1265	Coutinho, Anna D	Elevated Cardiovascular Disease Risk in Patients With Chronic Myelogenous Leukemia Seen in	Clinical lymphoma, myeloma & leukemia	2017	Retrospective Cohort study	Hematologic: 100% chronic myelogenous leukemia

		Community-based Oncology Practices in the United States.				
552	Deka, Rishi	Stroke and thromboembolic events in men with prostate cancer treated with definitive radiation therapy with or without androgen deprivation therapy.	Prostate cancer and prostatic diseases	2019	Retrospective Cohort study	Prostate
2837	Donato, Jessica	Intracranial hemorrhage in patients with brain metastases treated with therapeutic enoxaparin: a matched cohort study	Blood	2015	Matched Cohort	Central Nervous System: 100% brain metastases
2721	Du, Xianglin L	Risks of Venous Thromboembolism, Stroke, Heart Disease, and Myelodysplastic Syndrome Associated With Hematopoietic Growth Factors in a Large Population-Based Cohort of Patients With Colorectal Cancer.	Clinical colorectal cancer	2015	Retrospective Cohort study	Colorectal
1107	Du, Xianglin L	Associations between hematopoietic growth factors and risks of venous thromboembolism, stroke, ischemic heart disease and myelodysplastic syndrome: findings from a large population-based cohort of women with breast cancer.	Cancer causes & Control	2016	Retrospective Cohort study	Breast
4405	Geiger, Ann M	Stroke risk and tamoxifen therapy for breast cancer.	Journal of the National Cancer Institute	2004	Nested Case Control	Breast
6733	Gurnari, Carmelo	Early intracranial haemorrhages in acute promyelocytic leukaemia: analysis of neuroradiological and clinico-biological parameters	British Journal of Hematology	2021	Retrospective Cohort study	Hematologic: 100% acute promyelocytic leukemia
2599	Hong, Julian C	Risk of cerebrovascular events in elderly patients after radiation therapy versus surgery for early-stage glottic cancer.	International journal of radiation oncology, biology, physics	2013	Retrospective Cohort study	Head & Neck: 100% glottic cancer

6104	Iadecola, Costantino	The risk of arterial thromboembolic events after cancer diagnosis	Research and Practice in Thrombosis and Hemostasis	2019	Prospective Cohort Study	Multiple: 21% prostate, 15% breast, 13% unknown primary, 11% lung, 8% colorectal, 5% bladder, 3% for leukemia, non-Hodgkin lymphoma and melanoma, 2% for kidney, head and neck, ovarian and primary brain, 1% for pancreas, multiple myeloma, uterine, gastric, esophageal, liver, and thyroid
7839	Jang, Hyun-Soon	The long-term effect of cancer on incident stroke: A nationwide population-based cohort study in Korea	Frontiers in Neurology	2019	Retrospective Cohort study	Multiple: proportions of subtypes not specified
845	Khosrow-Khavar, Farzin	Aromatase Inhibitors and the Risk of Cardiovascular Outcomes in Women With Breast Cancer: A Population-Based Cohort Study.	Circulation	2020	Retrospective Cohort study	Breast
6859	Kim, Do Kyung	Does androgen-deprivation therapy increase the risk of ischemic cardiovascular and cerebrovascular diseases in patients with prostate cancer? A nationwide population-based cohort study	Journal of Cancer Research and Clinical Oncology	2021	Retrospective Cohort study	Prostate
6222	Kim, Kyeong Jin	Effects of radioactive iodine treatment on cardiovascular disease in thyroid cancer patients: a nationwide cohort study	Annals of Translational Medicine	2020	Retrospective Cohort study	Thyroid
7134	Kim, Kyu	Effect of non-Vitamin K antagonist oral anticoagulants in atrial fibrillation patients with newly diagnosed cancer	Korean Circulation Journal	2018	Retrospective Cohort study	Multiple: proportions of subtypes not specified
600	Kitano, Takaya	The Effect of Chemotherapy on Stroke Risk in Cancer Patients.	Thrombosis and Haemostasis	2020	Retrospective Cohort study	Multiple: 12.9% breast, 10.9% uterus, 8.9% gastric, 7.8% for prostate, 7.8% for colorectal, 7.3% lung, 6.3% esophageal, 4.8% oropharyngeal, 4.2% hepatic, 3.3% pancreatic, 21.5%

						others, 4.4% hematopoietic cancers
2832	Kuan, Ai-Seon	Risk of Ischemic Stroke in Patients With Gastric Cancer: A Nationwide Population-Based Cohort Study.	Medicine	2015	Retrospective Cohort study	Gastric
2255	Kuan, Ai-Seon; Teng	Risk of ischemic stroke in patients with ovarian cancer: a nationwide population-based study	BMC Medicine	2014	Retrospective Cohort study	Ovarian
6476	Kwon, Hyun-Keun	The incidence of myocardial infarction and stroke in head and neck cancer patients	Scientific Reports	2021	Retrospective Cohort study	Head & Neck
1550	Lee, Gin-Yi	Risk of stroke in patients with newly diagnosed multiple myeloma: a retrospective cohort study	Hematological oncology	2017	Retrospective Cohort study	Hematologic
10377	Libourel, Eduard J	High incidence of arterial thrombosis in young patients treated for multiple myeloma: Results of a prospective cohort study	CLINICAL TRIALS AND OBSERVATIONS	2009	Prospective Cohort Study	Hematologic
6895	Liu, Peter Pin-Sung	High 1-year risk of stroke in patients with hepatocellular carcinoma: a nationwide registry-based cohort study	Scientific Reports	2021	Retrospective Cohort study	Hepatic
1379	Mantia, Charlene	Predicting the higher rate of intracranial hemorrhage in glioma patients receiving therapeutic enoxaparin.	Blood	2017	Matched Retrospective Cohort Study	Central Nervous System
1750	Navi, Babak B	New diagnosis of cancer and the risk of subsequent cerebrovascular events.	Neurology	2018	Prospective Cohort Study	Multiple: proportions of subtypes not specified
2397	Navi, Babak B	Association between incident cancer and subsequent stroke.	Annals of Neurology	2015	Retrospective matched cohort study	Multiple: 24.7% lung, 21.2% breast, 29.0% prostate, 5.1% pancreatic, 20.1% colorectal
151	Pardo Sanz, Ana	Current status of anticoagulation in patients with breast cancer and atrial fibrillation.	Breast	2019	Retrospective Cohort study	Breast
460	Plaja, Andrea	Thromboembolism and bleeding in patients with cancer and mechanical heart valves.	Journal of Thrombosis and Thrombolysis	2019	Retrospective Matched Cohort study	Multiple: 22% urogynecologic, 21% gastrointestinal, 21% other, 10% lung, 12% breast, 15% hematologic

7240	Szepligeti, Szimonetta	Vascular diseases in patients with chronic myeloproliferative neoplasms - Impact of comorbidity	Clinical Epidemiology	2019	Retrospective matched cohort study	Hematologic
554	Toulis, Konstantinos A	Risk of incident circulatory disease in patients treated for differentiated thyroid carcinoma with no history of cardiovascular disease.	Clinical Endocrinology	2019	Retrospective Matched Cohort Study	Thyroid
2479	Tsai, Shiang-Jiun	Increased risk of ischemic stroke in cervical cancer patients: a nationwide population-based study.	Radiation Oncology	2013	Retrospective Cohort study	Cervical
6920	van Es, Nick	Arterial Thromboembolism in Cancer Patients: A Danish Population-Based Cohort Study	JACC: CardioOncology	2021	Retrospective Matched Cohort study	Multiple: 18.7% breast, 16.4% lung, 16.9%, 14.9% prostate, colorectal, 9.3% hematologic, 7.0% gynecological, 4.0% esophageal/stomach, 3.5% pancreatic, 3.5% bladder, 2.7% renal, 1.9% brain, 1.3% hepatic
2569	van Herk-Sukel, Myrthe P P	Pulmonary embolism, myocardial infarction, and ischemic stroke in lung cancer patients: results from a longitudinal study.	Lung	2013	Retrospective Matched Cohort study	Lung
7874	Wu, Chia-Lun	Stroke rate increases around the time of cancer diagnosis	Frontiers in Neurology	2019	Retrospective Cohort study	Multiple: 15.0% lung, 15.0% colorectal, 13.0% hepatic, 7.5% urogenital, 6.7% gastric, 6.5% prostate
506	Yasui, Taku	Oral Anticoagulants in Japanese Patients with Atrial Fibrillation and Active Cancer.	Internal Medicine	2019	Retrospective Cohort Study	Multiple: 44.2% gastrointestinal, 24.1% lung, 11.2% urogynecologic, 9.8% head & neck, 4.0% breast, 3.1% hematologic, 3.6% others
1254	Zhang, Qiaolei	Risk factors and clinical characteristics of non-promyelocytic acute myeloid leukemia of intracerebral hemorrhage: A single center study in China.	Journal of Clinical Neuroscience	2017	Retrospective Cohort study	Hematologic
3788	Zoller, Bengt	Risk of haemorrhagic and ischaemic stroke in patients with cancer: a nationwide	European Journal of Cancer	2012	Retrospective Cohort study	Multiple: proportions of subtypes not specified

		follow-up study from Sweden.				

Table 2. Extracted Outcomes of Various Stroke Events at Different Timepoints for Included Studies

Study ID	First Author & Publication Year	Total Participants with Cancer	Number of Ischemic Stroke Events				Number of ICH Events				Number of Combined Stroke Events			
			1-mo	3-mo	6-mo	12-mo	1-mo	3-mo	6-mo	12-mo	1-mo	3-mo	6-mo	12-mo
1781	Andersen, Klaus Kaae 2018	261,404				984				94				1,078
420	Bigelow, Elaine 2020	2497									200		350	400
7128	Chan, Po-Chi 2018	7479			109	130			10	12			119	142
2511	Chang, Wei-Chun 2013	20,286				372				44				416
1319	Chen, Dong-Yi 2017	14,715				747								
2077	Chu, C-N 2013	4615				31								
1265	Coutinho, Anna 2017	1639												77
552	Deka, Rishi 2019	207449				4,896				97				4,993
2837	Donato, Jessica 2015	293								62				
2721	Du, Xianglin L 2015	80,925												448
1107	Du, Xianglin L 2016	77,233												451
4405	Geiger, Ann M 2004	11045												26
6733	Gurnari, Carmelo 2021	95					13							
2599	Hong, Julian C 2013	1,413												113
6104	Iadecola, Costantino 2019	836	4	6	8	12								
7839	Jang, Hyun-Soon 2019	20707				153				18				165
845	Khosrow-Khavar, Farzin 2020	23525				92								

6859	Kim, Do Kyung 2021	61722				1,481								
6222	Kim, Kyeong Jin 2020	4845				19				9				82
7134	Kim, Kyu 2018	798				33								
600	Kitano, Takaya 2020	19,006												76
2832	Kuan, Ai-Seon 2015	22,530				608								
2255	Kuan, Ai-Seon; Teng 2014	8,810				109								
6476	Kwon, Hyun-Keun 2021	22,737												241
1550	Lee, Gin-Yi 2017	395												11
10377	Libourel, Eduard J 2009	195				2								
6895	Liu, Peter Pin-Sung 2021	18,506				277				94				371
1379	Mantia, Charlene 2017	133								9				
1750	Navi, Babak B 2018	1,149									6	8	9	13
2397	Navi, Babak B 2015	327,389										9,042	12,734	16,753
151	Pardo Sanz, Ana 2019	637				18								
460	Plaja, Andrea 2019	48				1								
7240	Szepligeti, Szimonetta 2019	12,882				174								
554	Toulis, Konstantinos A 2019	3,009												6
2479	Tsai, Shiang-Jiun 2013	893				5								
6920	van Es, Nick 2021	458,462	1,567	2,847	3,975	5,629								
2569	van Herk-Sukel, Myrthe P P	3,717			6									

	2013													
7874	Wu, Chia-Lun 2019	25,920												327
506	Yasui, Taku 2019	224				5				1				6
1254	Zhang, Qiaolei 2017	1467					90							
3788	Zoller, Bengt 2012	820,491			3,708	5,951			965	1,493			4,673	7,444

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4.11 Supplemental Materials

eTable 1. Search strategy using EMBASE via the OVID interface:

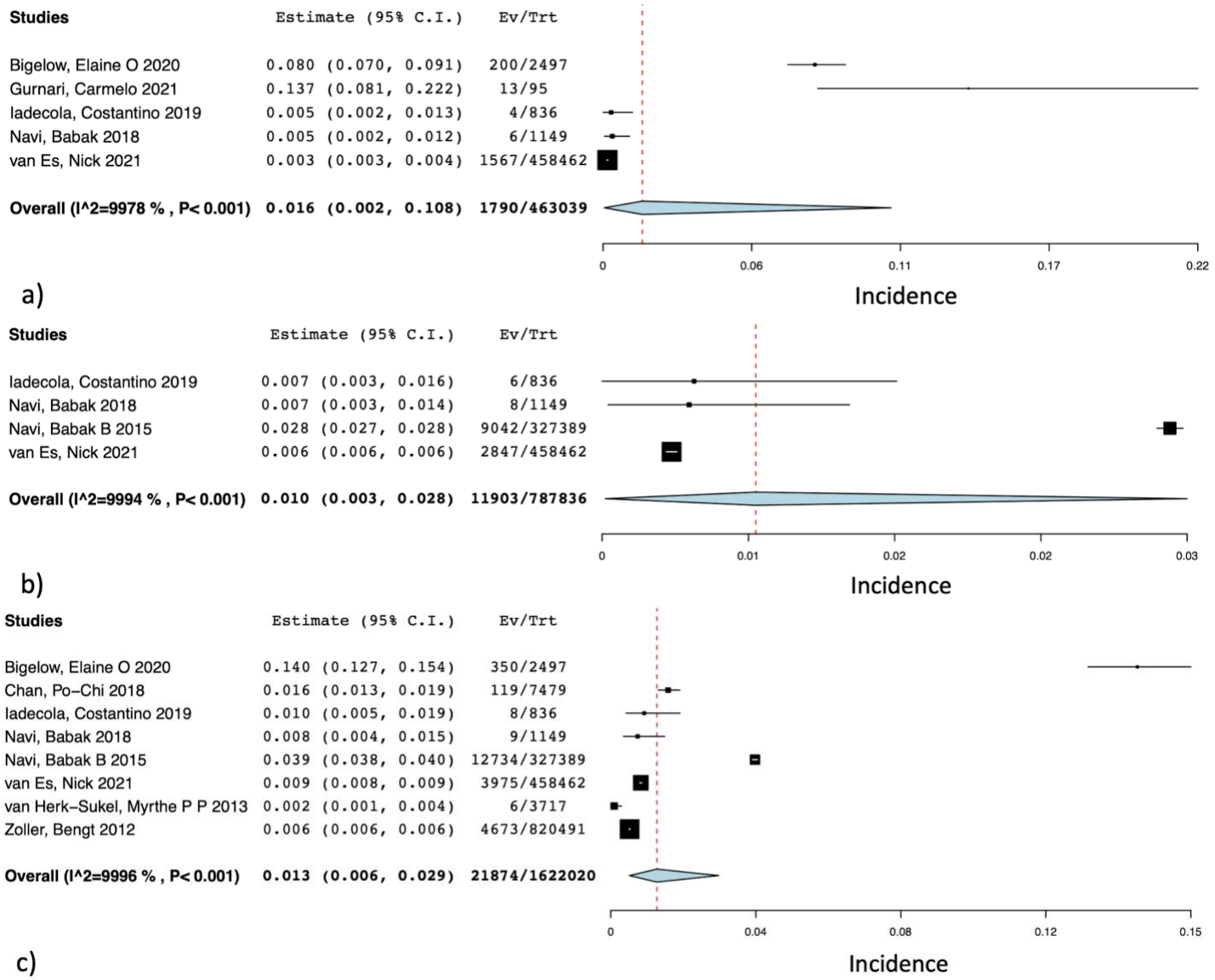
1 malignant neoplasm/ or neoplasm/ or solid malignant neoplasm/ or myeloproliferative neoplasm/ (567513)
2 (cancer or tumo?r* or neoplasms* or carcinoma or leuk?em* or myeloma* or melanoma or hodgkin* or lymphoma or malignanc* or oncology).tw. (5041168)
3 1 or 2 (5128557)
4 exp *brain hemorrhage/ (59384)
5 *cerebrovascular accident/ (84430)
6 brain ischemia/ (150108)
7 ((brain or cerebr*) adj3 (isch?em* or h?emorrhag* or bleed*)).tw. (94262)
8 stroke.ti. (167370)
9 ((isch?em* or h?emorrhag*) adj3 stroke*).tw. (117459)
10 cerebr* vascular accident*.tw. (2269)
11 or/4-10 (379118)
12 3 and 11 (17887)
13 incidence/ (442103)
14 incidence.tw. (1188620)
15 risk*.tw. (3427729)
16 *risk/ or *risk factor/ (150822)
17 13 or 14 or 15 or 16 (4322259)
18 12 and 17 (5883)

eTable 2. Risk of bias assessments using the Newcastle-Ottawa Scale for the included articles for meta-analysis.

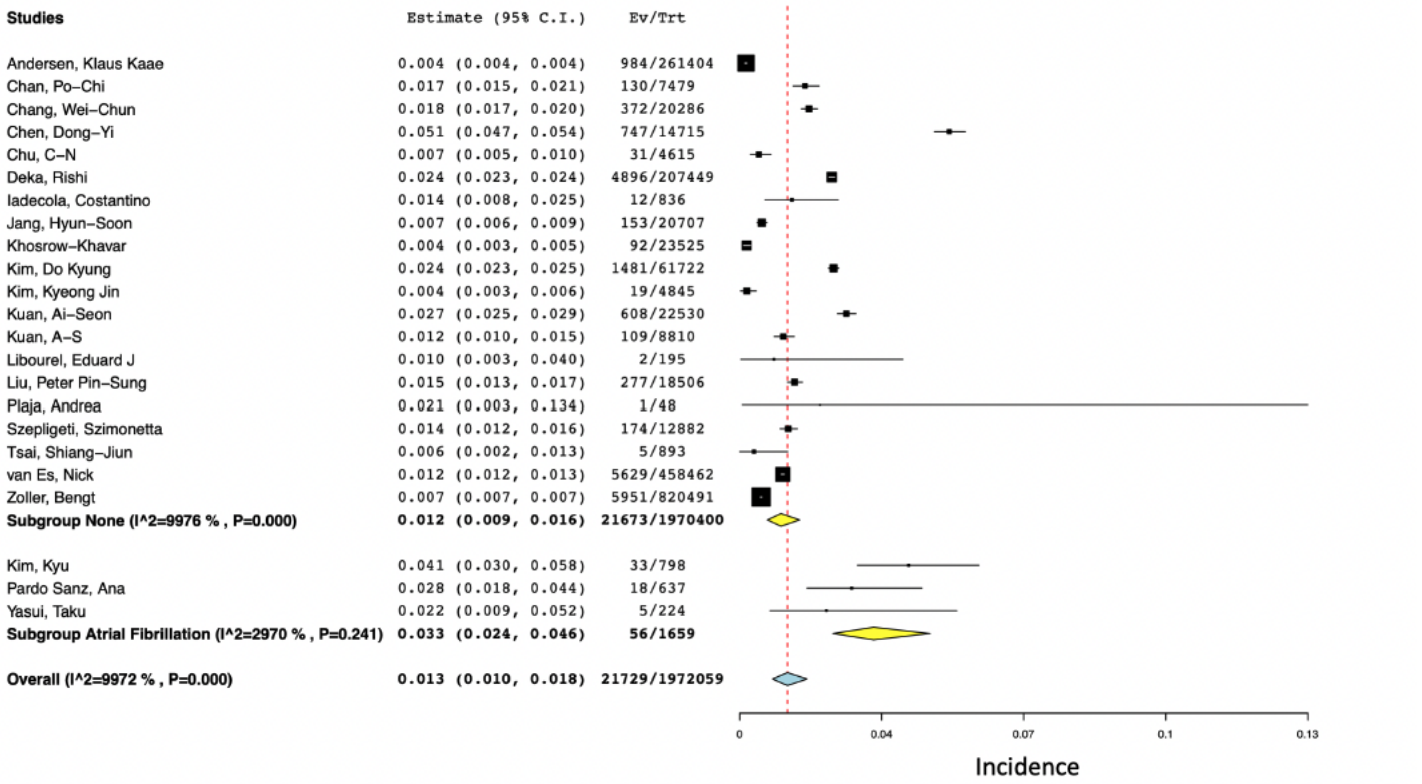
Study ID	First Author	Year	ROB Domain Selection	ROB Domain Comparability	ROB Domain Outcome	ROB Overall
1781	Andersen	2018	3	2	3	Good
420	Bigelow	2020	3	2	2	Good
7128	Chan	2018	4	2	2	Good
2511	Chang	2013	4	2	2	Good
1319	Chen	2017	3	2	2	Good
2077	Chu	2013	4	2	2	Good
1265	Coutinho	2017	3	2	2	Good
552	Deka	2019	3	2	2	Good
2837	Donato	2015	3	2	3	Good
2721	Du	2015	4	2	3	Good
1107	Du	2016	4	2	3	Good
4405	Geiger	2004	3	2	2	Good
6733	Gurnari	2021	2	0	2	Poor
2599	Hong	2013	4	2	2	Good
6104	Iadecola	2019	4	2	3	Good
7839	Jang	2019	4	2	2	Good
845	Khosrow-Khavar	2020	3	2	3	Good
6859	Kim	2021	4	2	2	Good
6222	Kim	2020	3	2	3	Good
7134	Kim	2018	3	2	3	Good
600	Kitano	2020	3	2	3	Good
2832	Kuan	2015	4	2	3	Good
2255	Kuan	2014	4	2	3	Good
6476	Kwon	2021	4	2	2	Good
1550	Lee	2017	2	2	1	Fair
10377	Libourel	2009	3	2	2	Good
6895	Liu	2021	4	2	2	Good
1379	Mantia	2017	3	2	2	Good
1750	Navi	2018	3	2	2	Good
2397	Navi	2015	4	2	2	Good
151	Pardo Sanz	2019	2	2	1	Poor
460	Plaja	2019	3	2	1	Poor
7240	Szepligeti	2019	3	2	3	Good
554	Toulis	2019	4	2	2	Good
2479	Tsai	2013	4	2	2	Good
6920	van Es	2021	3	2	1	Poor

2569	van Herk-Sukel	2013	4	2	2	Good
7874	Wu	2019	4	2	2	Good
506	Yasui	2019	3	2	1	Poor
1254	Zhang	2017	2	2	1	Poor
3788	Zoller	2012	3	2	2	Good

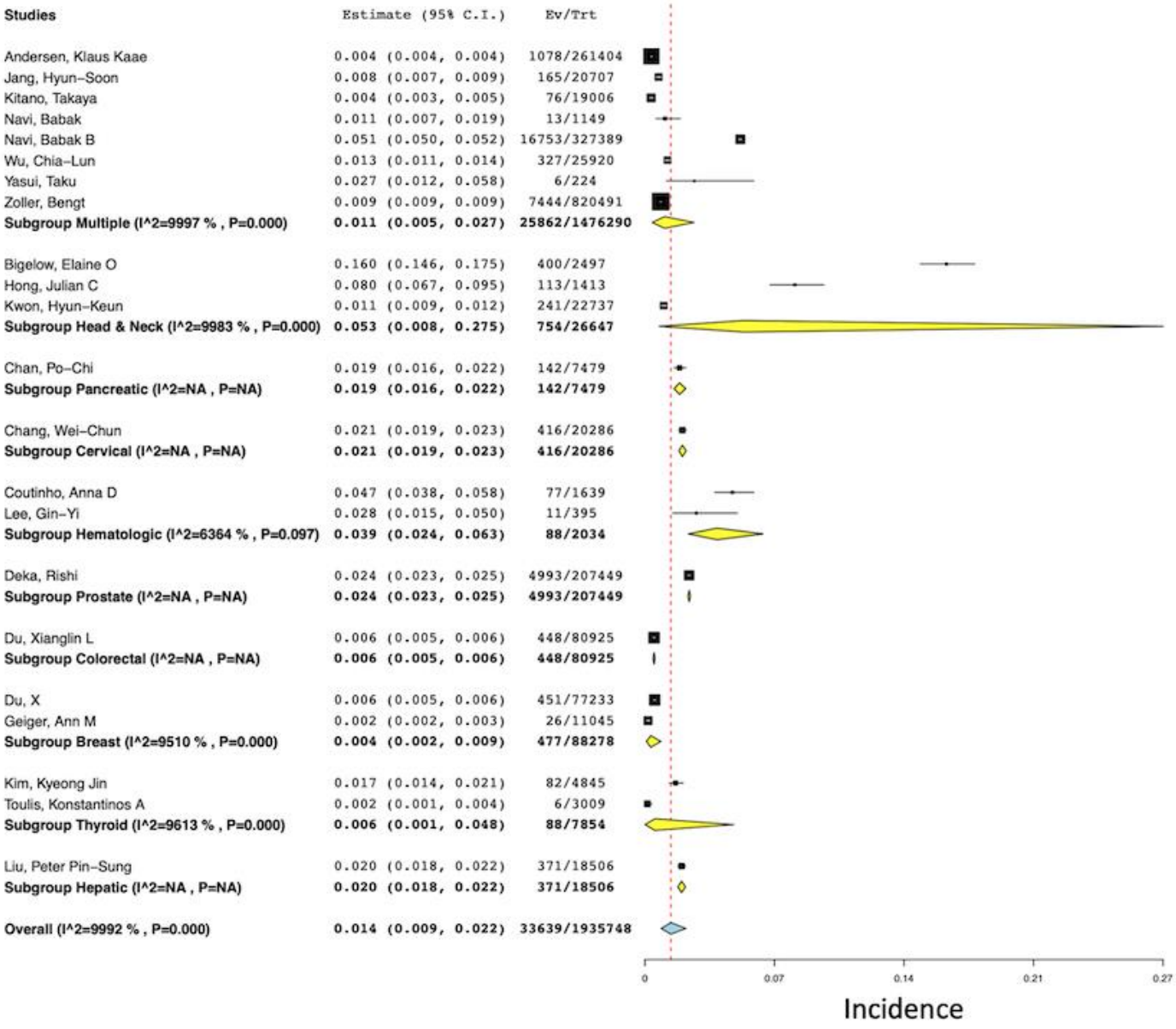
eFigure 1. Pooled incidence of total strokes (ischemic and intracerebral hemorrhage) at 1 month (a), 3 months (b), and 6 months (c).



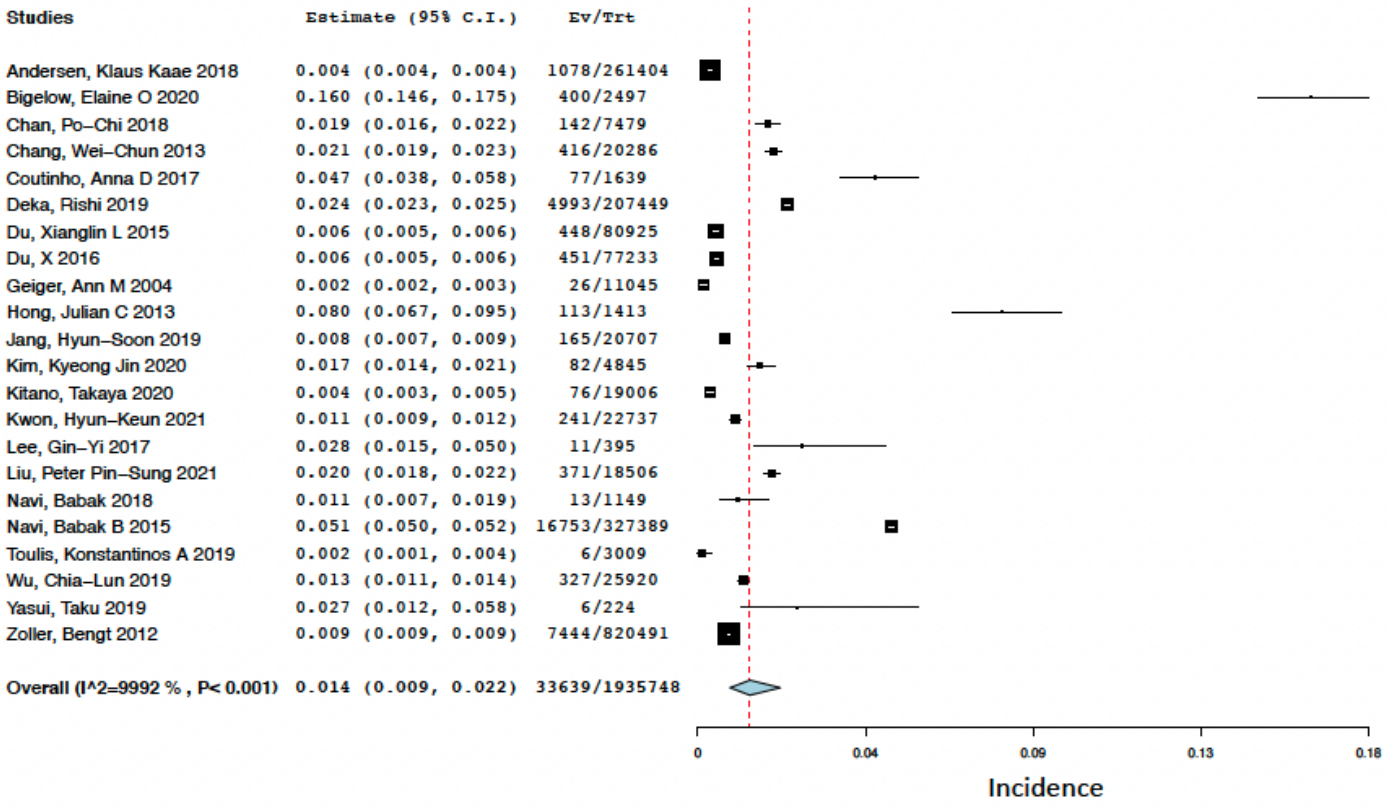
eFigure 2. Subgroup analysis of the incidence of ischemic stroke at 1 year, stratified by exclusive enrollment of cancer patients with atrial fibrillation.



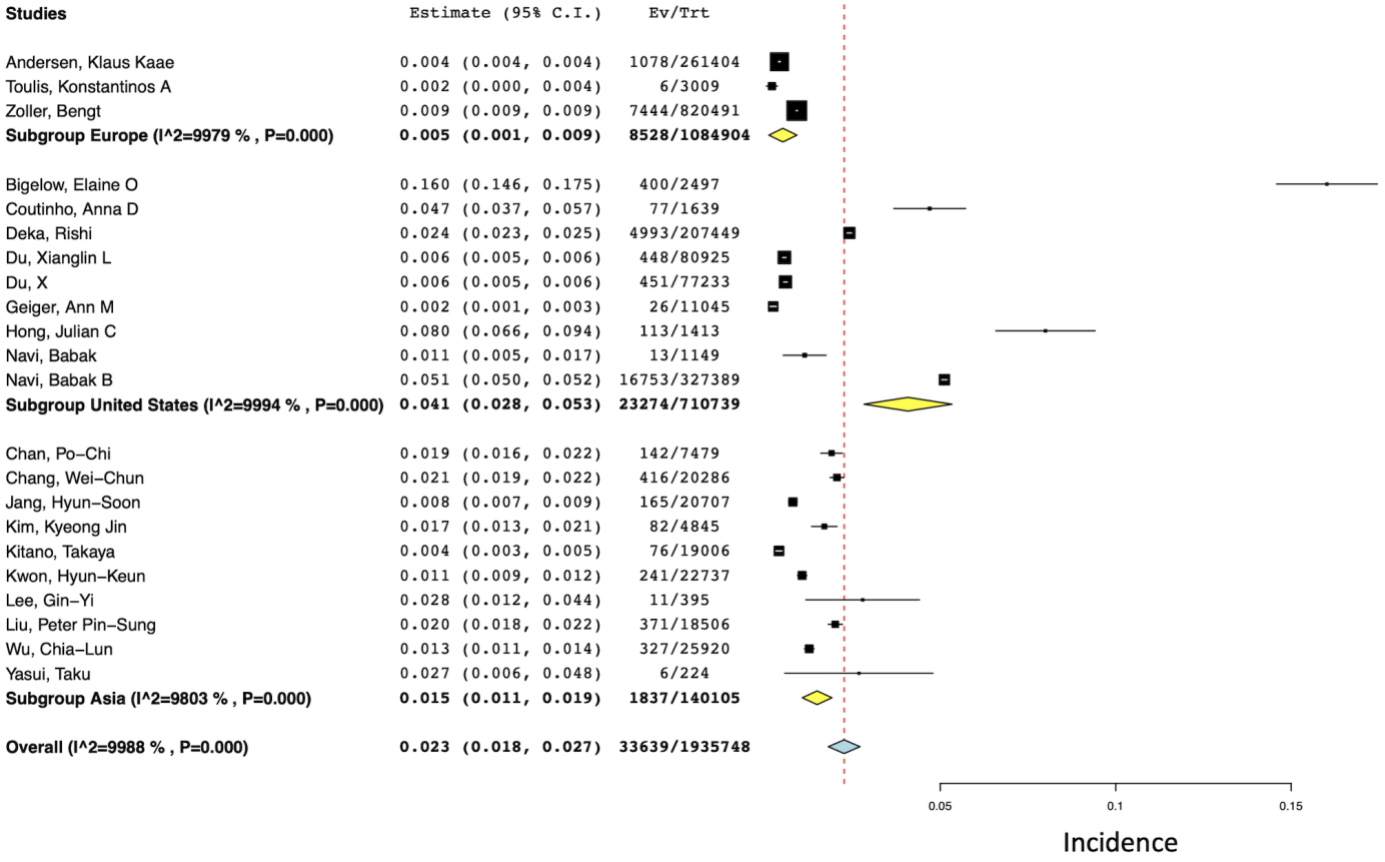
eFigure 3. Subgroup analysis of the incidence of total stroke at 1 year, stratified by cancer subtype.



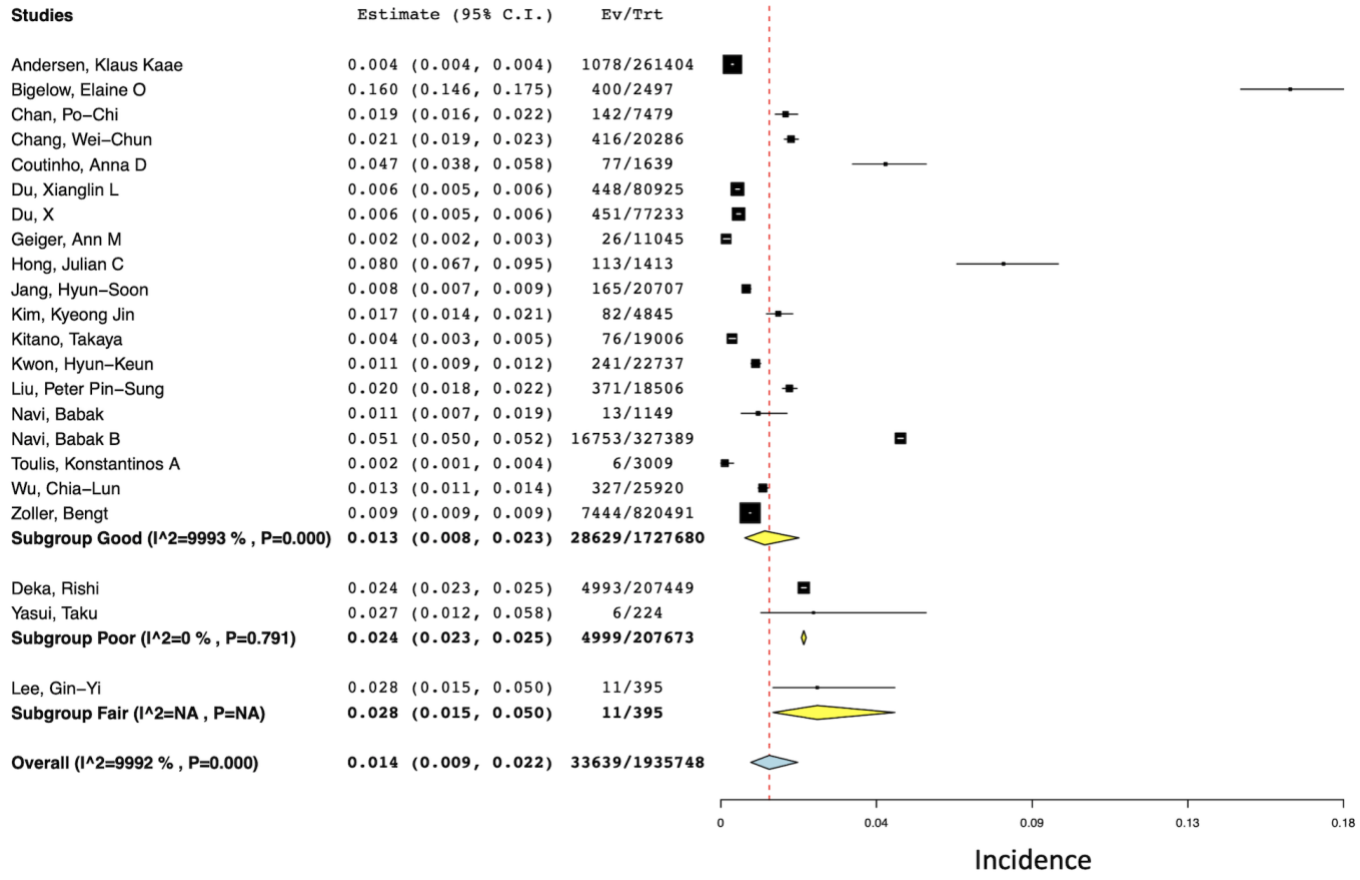
eFigure 4. Sensitivity analysis with leave-one-out method. Outcome assessed is the cumulative incidence of ischemic and hemorrhagic stroke.



eFigure 5. Subgroup analysis of the risk for stroke (ischemic and hemorrhagic) based on geographic location.



eFigure 6. Subgroup analysis stratified by risk of bias assessments using the Newcastle Ottawa Scale.



Chapter Five: Does the Incidence of Stroke Vary According to Previous History of Stroke in Cancer Patients?

5.1 PREFACE

This chapter examines whether the risk for ischemic stroke in cancer patients varies according to a previous history of stroke. This is a population-based, retrospective, matched cohort study using linked clinical and health administrative databases in Ontario, Canada. The use of data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board.

Mr. Cerasuolo, along with Drs. Lun, Sutradhar and Siegal were responsible for study conception, design, and statistical analyses. Drs Lun and Siegal were responsible for drafting the manuscript. All other authors participated in critical revisions of the manuscript for intellectual content.

5.2 ABSTRACT

Background: The objective of this study is to examine the association between previous stroke and risk for future stroke in individuals with newly diagnosed with cancer.

Methods: Using linked clinical and administrative databases, we conducted a population-based matched cohort study of adults in Ontario, Canada, from 2010-2019. Individuals with a new diagnosis of cancer and a history of ischemic stroke were matched (1:4) by age, sex, year of cancer diagnosis, cancer stage, and cancer site to those without a history of ischemic stroke. Individuals were followed until stroke, death, or March 31, 2021. Cumulative incidence function (CIF) curves were created to estimate the incidence of stroke (primary outcome), with the date of cancer diagnosis as the index and death as a competing event. Sub-distribution adjusted hazard ratios (aHR) and 95% confidence intervals (CI) were calculated, where death was treated as a competing event. We further stratified those with a history of stroke by the timing prior to index: 0-1 years, 1-2 years, 2-5 years, or 5-10 years. Regression analyses were adjusted for baseline characteristics that were imbalanced between groups.

Results: We examined 65,525 individuals with a new diagnosis of cancer, including 13,070 with a history of ischemic stroke and 52,280 without; the overall incidence of ischemic stroke following cancer diagnosis was 261.3 over 10,000 person-years in the cohort with prior stroke and 75.3 over 10,000 person-years in the cohort without prior stroke. Individuals with a prior history of ischemic stroke had an increased risk for ischemic stroke after cancer diagnosis compared to those without a history of stroke (aHR 2.68 95%CI [2.41-2.98]). The highest risk of ischemic stroke was seen among individuals with ischemic stroke diagnosed less than 1 year before their cancer diagnosis (aHR 3.68, 95%CI 3.22-4.22 compared to those without a history of stroke).

Conclusion: Among individuals with newly diagnosed cancer, those with a history of ischemic stroke were almost 3 times more likely to experience a stroke after cancer diagnosis, especially if the pre-diagnosis stroke occurred less than 1 year before the cancer diagnosis. This finding has important implications for advancing strategies to prevent stroke in patients with cancer.

5.3 INTRODUCTION

Cancer is a leading cause of morbidity and mortality worldwide, with over 19 million new cases diagnosed in 2020 alone.[1] In Canada, nearly 1 in 2 individuals are expected to develop cancer during their lifetime.[2] With advancements in cancer therapeutics, cancer survivorship is increasing, and over 60% of those with cancer are expected to survive for 5 years or longer after their diagnosis.

Cancer is a well-recognized risk factor for thrombosis, and its association with venous thromboembolism (VTE) has been extensively studied and characterized.[3–5] While the identification of risk factors for VTE has led to risk prediction models that guide the use of prophylactic anticoagulation,[4,6] the relationship between cancer and arterial thromboembolism, such as ischemic stroke, is relatively understudied.[7] Previous retrospective data suggest that cancer patients are at a higher risk for ischemic stroke, particularly around the time of cancer diagnosis.[7–10] Identifying risk factors for ischemic stroke in cancer patients is important as it may identify individuals at high risk who may benefit from strategies to prevent stroke-related morbidity and mortality. Clinical outcomes appear to be worse after stroke among patients with cancer compared to those without cancer, and the resulting disability can contribute significantly to morbidity in cancer survivors.[11]

Although there are likely shared risk factors for ischemic stroke between people with cancer and those in the general population, the magnitude of risk may vary due to the incremental thrombotic risk of active cancer. For example, a history of previous ischemic stroke or transient ischemic attack (TIA) is the greatest risk factor for recurrent stroke in the general population

(pooled relative risk [RR] 2.5, 95%CI 2.1 – 3.1).[12] However, it is unknown how a prior history of stroke or TIA affects future stroke risk in the presence of cancer. In a large, administrative database-based cohort of patients with cancer without a previous ischemic stroke, the risk for ischemic stroke was almost double compared to patients without cancer (hazard ratio 1.9; 95%CI 1.8 – 2.0).[7] Another small retrospective study showed that patients with active cancer diagnosed with acute ischemic stroke have a high risk for recurrent thromboembolism (incidence of 34% [95%CI 28 – 54]), including ischemic strokes. Nevertheless, the results of this single-center study may not be generalizeable.[13] Furthermore, these studies did not specifically examine those with a history of ischemic stroke prior to their diagnosis of cancer, nor did it assess the impact of a prior stroke history.

The objective of this large, population-based matched cohort study was to measure and compare the risk of ischemic stroke among newly diagnosed cancer patients with and without a prior history of stroke. Our secondary objectives were to explore the impact of timing of prior stroke on future stroke risk, and to examine the risk of stroke within various cancer subtypes.

5.4 METHODS

Study Design and Setting

We conducted a population-based, retrospective matched cohort study using linked clinical and health administrative databases in Ontario, Canada which has a population of 14.6 million. Ontario has a single payer healthcare system, whereby all publicly funded healthcare services, physician visits, hospital visits, and demographic information for residents are recorded in these databases. We obtained data on cancer diagnoses and staging from the Ontario Cancer Registry,

inpatient hospitalizations from the Discharge Abstract Database (DAD), emergency department visits from the National Ambulatory Care Reporting System (NACRS), physician billings from the Ontario Health Insurance Plan database (OHIP), and demographic and vital status information from the Registered Persons Database (RPDB). Furthermore, DAD, NACRS, Same Day Surgery database (SDS), and Cancer Activity Level Reporting (ALR) were used to extract information on cancer treatment, including surgery, radiation, and chemotherapy. Data sources were linked via unique encoded identifiers and analyzed at ICES.

Participants and Study Size

We included all Ontario residents aged 18 years or older with an incident diagnosis of cancer in the Ontario Cancer Registry from April 1, 2010 to March 31, 2020 (inclusive). Cancer diagnoses were determined using the International Classification of Diseases for Oncology, third edition (ICD-O-3). Individuals with diagnoses of squamous or basal cell carcinoma, primary central nervous system tumours, and those with cancer diagnoses made at death or autopsy were excluded. If more than one cancer diagnosis was present, individuals were classified based on the earliest primary site. A history of ischemic stroke was defined as a diagnosis of ischemic stroke in hospitalization or emergency department records [determined using validated ICD-9 (433, 434, and 436) or ICD-10 diagnostic codes (I63, I64, and H34.1)][14] within 10 years preceding the index cancer diagnosis date. Individuals with a new diagnosis of cancer and a history of ischemic stroke were matched to those without a history of ischemic stroke (1:4) based on calendar year of birth, sex, year of cancer diagnosis, cancer stage, and cancer site. The index date was the date of cancer diagnosis. All participants were followed until stroke, death, loss of OHIP eligibility, five years following cancer diagnosis, or March 31, 2021 – whichever occurred first.

Outcomes

The primary outcome was the incidence of ischemic stroke following the index date (i.e., date of cancer diagnosis), determined using validated ICD-10 diagnostic codes (I63, I64, and H34.1) from hospitalizations (most responsible diagnosis) or emergency department visits (main problem). All-cause mortality was treated as a competing event for the primary analysis. Secondary outcomes included subgroup analysis based on cancer type.

Statistical analysis

Standardized differences were used to compare the distributions of baseline characteristics between exposed (pre-cancer diagnosis of ischemic stroke) and control (no pre-cancer diagnosis of stroke) groups. A standardized difference (SD) greater than 0.1 reflected significant imbalance at baseline. We reported continuous variables as means with standard deviation, or medians with interquartile ranges (IQR); categorical variables were reported as proportions. Cumulative incidence function (CIF) curves were generated for ischemic stroke with all-cause mortality handled as a competing event. This was done for the cohort, overall, and by exposed and controls groups. To quantify the association between our exposure (history of ischemic stroke) and risk of stroke after cancer diagnosis, competing risk Fine-Gray regression models were used to calculate sub-distribution adjusted hazard ratios (aHR) and 95% confidence intervals (CI) for ischemic stroke, where death was treated as a competing event. The regression models adjusted for baseline characteristics that were imbalanced. Once these primary methods were completed, the main binary exposure (i.e., prior ischemic stroke vs no prior ischemic stroke) was then further divided into a 5-level measure to examine the relationship between the timing of stroke prior to

the index date and risk for future stroke: 0-1 years, 1-2 years, 2-5 years, 5-10 years, vs no prior ischemic stroke. The CIF curves and Fine-Gray regression methods mentioned above were then repeated with this revised 5-level main exposure.

Ethics and Study Approval

The use of data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board.

Data Sharing

The dataset from this study is held securely in coded form at ICES. While data sharing agreements prohibit ICES from making the dataset publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at www.ices.on.ca/DAS. The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

5.5 RESULTS

Patient Characteristics

The cohort included 65,350 individuals with an incident cancer diagnosis, which included 13,070 with prior ischemic stroke and 52,280 without prior ischemic stroke (Table 1).

Cardiovascular risk factors and comorbidities were more prevalent at baseline among individuals with prior stroke compared to those without prior stroke, including diabetes (42.5% vs 30.3%,

SD=0.25), congestive heart failure (CHF; 22.7% vs 12.5%, SD=0.27), hypertension (88.2% vs 71.0%, SD=0.44), chronic obstructive pulmonary disease (COPD; 36.9% vs 29.9%, SD=0.15), dementia (14.7% vs 6.6%, SD=0.26), vascular disease (12.6% vs 2.6%, SD=0.38), dyslipidemia (14.5% vs 4.4%, SD=0.35) and atrial fibrillation (19.7% vs 7.6%, SD=0.36). The degree of baseline comorbidity was also higher among those with prior stroke as reflected by Elixhauser comorbidity index of ≥4 (30.9% vs 14.1%, SD=0.41). The proportion of patients who underwent surgery and radiation during the six months following the index cancer diagnosis was similar between individuals with and without prior stroke (35.1% vs 39.9% for surgery [SD=0.10] and 22.7% vs 24.4% for radiation [SD=0.04]) whereas a higher proportion of patients without prior stroke received chemotherapy (24.7% v 17.9%, SD=0.17).

Out of the 13,070 individuals with a history of ischemic stroke within the 10 years prior to cancer diagnosis, the most recent stroke occurred 1 year before cancer diagnosis in 35.4%, 1 to 2 years in 11.8%, 2 to 5 years in 26.6%, and 5 to 10 years in 26.2% (Table 1).

Primary outcome

The incidence rate of ischemic stroke following cancer diagnosis was 261.3 over 10,000 person-years in the cohort with prior stroke and 75.3 over 10,000 person-years in the cohort without prior stroke. In univariate analyses where death was treated as a competing event, prior ischemic stroke was associated with an increased risk for ischemic stroke (aHR 3.00, 95%CI 2.73 – 3.31) after a new cancer diagnosis. After adjusting for imbalanced baseline covariates (use of chemotherapy within 6 months of diagnosis, age, sex, diabetes, CHF, COPD, hypertension, heart disease, vascular disease, dyslipidemia, atrial fibrillation, dementia, and Elixhauser comorbidity

index), the adjusted HR for the primary outcome of ischemic stroke comparing exposed against controls was 2.68 (95%CI 2.41 – 2.98) (Figure 1, Table 2). Baseline characteristics associated with the occurrence of ischemic stroke included female sex, a history of diabetes, hypertension, dyslipidemia, and Elixhauser comorbidity index of ≥4 (Table 2).

When lag time between prior ischemic stroke and the cancer diagnosis was incorporated into the multivariable Fine-Gray regression models, patients with a prior ischemic stroke within 1 year preceding their cancer diagnosis had the highest risk of future stroke compared to controls (i.e. no previous history of ischemic stroke): aHR 3.68 (95%CI 3.22 – 4.22) (Table 3). Compared to controls, the risk of ischemic stroke was higher within all lag time categories (Figure 2) with a decreasing trend in the strength of association with increasing lag time from cancer diagnosis (aHR 2.44 [95%CI 1.93 – 3.09] for stroke 1-2 years prior, and aHR 2.13 [95%CI 1.79 – 2.54] beyond 2 years prior).

5.6 DISCUSSION

In a previous analysis we conducted, we found that compared to cancer-free controls, the risk of ischemic stroke in subjects with a new diagnosis of cancer depended on the presence or absence of prior history of ischemic stroke.[15] In this follow-up study, we found that individuals with newly diagnosed cancer and a history of ischemic stroke were almost 3-fold more likely to be diagnosed with ischemic stroke compared to matched individuals without a history of ischemic stroke. The duration of time elapsed from prior stroke to cancer diagnosis influenced the magnitude of this risk; individuals with strokes less than 1 year before cancer diagnosis had the highest risk (almost 4-fold), while those with strokes more than 2 years before had the lowest

risk (approximately 2-fold). To our knowledge, this is the first study that examined previous ischemic stroke as a risk factor for future stroke in cancer patients. Female sex, the presence of baseline vascular risk factors (history of diabetes, hypertension, and dyslipidemia), and an Elixhauser comorbidity index of ≥4 were associated with a higher risk for future ischemic strokes.

Our findings confirmed that a higher number of pre-existing comorbidities and vascular risk factors were predictive of future ischemic stroke.[16] We also found that female sex was associated with a higher risk for stroke after cancer diagnosis. In a meta-analysis conducted in the general population, sex was not found to be predictive of recurrent ischemic stroke.[17] Similarly, a post-hoc analysis of the Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trial demonstrated no sex difference for recurrent stroke in the short-term period.[18] We speculate that the higher risk for recurrent stroke in females observed in our current analysis may be secondary to a combination of longer cancer survival in females and a higher lifetime risk of stroke in females.[19,20]

We found that the risk for future stroke was highest if the previous stroke occurred in the preceding year. This is similar to studies examining stroke as a risk factor in the general population: the risk for recurrent stroke has been found to be highest immediately following first-time stroke: a registry-based study found that patients with a history of stroke had a persistently elevated risk for future stroke compared to those without a history of stroke: this risk was found to be 15.3 times higher in the first year, and only 2.0 times in the 5th year.[21] We believe the lower magnitude of risk during the first year in our study may be related to higher rates of mortality in

our cohort: mortality rates were 32.6% at one year and 56.7% at five years in the current study, compared to 17% at one year and 56% at ***ten*** years in the general population.[22] Thus, the cancer population represents a group that is at high risk for both all-cause mortality and recurrent stroke events.

Although traditional vascular risk factors, such as hypertension, dyslipidemia, diabetes, smoking, and atrial fibrillation increase the risk of stroke among individuals with cancer, we found a persistently higher risk of stroke after adjusting for these factors, especially among those with stroke in the year prior to cancer diagnosis, suggesting that occult cancer may contribute to the development of stroke through non-conventional stroke mechanisms.[23,24] Hypercoagulability associated with occult and newly diagnosed cancer may contribute to the development of thromboembolic complications even before a diagnosis of cancer is made.[25,26] Navi et al found a 70% increase in the risk of arterial thromboembolic events in the year prior to a cancer diagnosis.[9] It is possible that subjects with ischemic stroke during the year preceding cancer diagnosis represents a group with malignancies that are more hypercoagulable, thus contributing to a higher risk of future stroke following cancer diagnosis.

An association between cancer and stroke has been proposed since early autopsy studies.[27] However, risk factors for stroke among newly diagnosed cancer patients have not been well defined. Currently there are no risk prediction models to stratify patients with cancer according to stroke risk and existing risk stratification tools developed in the general may not be directly applicable. For example, atrial fibrillation is a well-known risk factor stroke, and is responsible for 36% of all stroke in individuals older than 80 years of age.[28] While the $CHADS_2$ and

CHA_2DS_2VASc scores are well validated and commonly utilized tools for predicting the risk for future ischemic stroke in the general population, its applicability in the cancer population is controversial.[29–31] One retrospective cohort validated the CHADS2 and CHADS-2VASc scores in cancer patients as a way of predicting stroke and mortality,[32] but other similar studies have found varying efficacies of these risk scores in predicting thromboembolism in active or recent cancer patients.[33,34] This example highlights the fact that there are likely unique mechanisms that contribute to the development of stroke in cancer patients (i.e. hypercoagulability) and that new risk stratification tools with specific predictors are needed in this high-risk population.

Other risk prediction models that have been extrapolated to predict the risk for stroke in cancer patients include models predicting venous thromboembolism (VTE). The Khorana score is a validated prediction model used to identify ambulatory cancer patients starting chemotherapy who are at intermediate to high risk of VTE, for whom the net clinical benefit favours prophylactic anticoagualtion.[4,35–37] However, when extrapolated to predict recurrent thromboembolism in cancer patients with ischemic stroke, the Khorana score was found to have poor discriminatory abilities.[38] This may reflect key differences in pathophysiology and risk factors for arterial vs venous thromboembolism in cancer patients. We believe the findings from our study will help advance knowledge in the field of predictive modeling for ischemic stroke in cancer patients, as we demonstrated that a previous history of ischemic stroke was the most predictive factor for subsequent stroke after cancer diagnosis. This may be incorporated into future prediction models, although our findings will require external validation.

The strengths of our study include the use of a large, well characterized population-level cohort with competing risk analyses. However, our study is not without limitations, such as misclassification bias, which is a potential risk for any study using retrospectively collected administrative data. For example, in patients with advanced cancer, intracranial metastases may mimic stroke and be wrongly diagnosed and classified. It may also be challenging to differentiate whether repeat use of a single diagnostic code (i.e. I63 for ischemic stroke) is related to a new clinical event or complications related to their initial stroke (i.e. recrudescence of chronic stroke symptoms in the context of acute illness). To mitigate this potential risk, we used validated ICD codes in conjunction with hospital admissions or emergency department visits to minimize misclassification and increase the specificity of ICD codes for stroke events. Using this approach, we may have missed minor ischemic strokes diagnosed in clinics, although this number is low – in Ontario, approximately 89% of all strokes were initially diagnosed in the emergency department.[39]

5.7 CONCLUSION

Individuals who have a history of stroke prior to a diagnosis of cancer were more likely to suffer stroke after cancer diagnosis, especially if that stroke had occurred within the year preceding the cancer diagnosis. This finding has potentially important implications for advancing strategies to prevent stroke in patients with cancer.

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5.9 TABLES

Table 1. Baseline characteristics of patients with cancer, stratified by absence or presence of a history of ischemic stroke.

Characteristics	No ischemic stroke history (N=52,280)	Ischemic stroke history (N=13,070)	Standardized Difference
Age (Mean, SD)	74.97 ± 10.13	74.96 ± 10.11	0
Sex (Female)	21,508 (41.1%)	5,377 (41.1%)	0
Past Medical History (n, %)			
• **Diabetes**	15,846 (30.3%)	5,551 (42.5%)	0.25
• **Congestive heart failure**	6,511 (12.5%)	2,971 (22.7%)	0.27
• **Hypertension**	37,137 (71.0%)	11,529 (88.2%)	0.44
• **COPD**	15,648 (29.9%)	4,826 (36.9%)	0.15
• **Dementia**	3,471 (6.6%)	1,926 (14.7%)	0.26
• **HIV**	73 (0.1%)	28 (0.2%)	0.02
• **Asthma**	7,153 (13.7%)	1,897 (14.5%)	0.02
• **Heart disease**	5,582 (10.7%)	2,669 (20.4%)	0.27
• **Vascular disease**	1,375 (2.6%)	1,650 (12.6%)	0.38
• **Atrial fibrillation**	3,968 (7.6%)	2,572 (19.7%)	0.36
• **Dyslipidemia**	2,303 (4.4%)	1,900 (14.5%)	0.35
Elixhauser Comorbidity Index >=4 (n, %)	7,352 (14.1%)	4,036 (30.9%)	0.41
Cancer Treatment 6 months following diagnosis (n, %)			
• **Surgery**	20,867 (39.9%)	4,589 (35.1%)	0.1
• **Radiation**	12,759 (24.4%)	2,966 (22.7%)	0.04
• **Chemotherapy**	12,890 (24.7%)	2,339 (17.9%)	0.17
Lag time from previous ischemic stroke to index date (n, %)			
• **≤ 1 year**	--	4621 (35.4%)	--
• **1 – 2 years**	--	1538 (11.8%)	--
• **2 – 5 years**	--	3484 (26.6%)	--
• **5 – 10 years**	--	3427 (26.2%)	--

Table 2. Multivariable adjusted Fine-Gray competing risk regression model for the effect of a previous history of ischemic stroke on the risk of recurrent ischemic stroke after a diagnosis of cancer. Effect measures are displayed as sub-distribution adjusted hazard ratios (aHR) with 95% confidence intervals (95% CI).

Model parameter	P-value	aHR (95% CI)
Primary exposure		
Ischemic stroke hx (ref: no hx)	<.0001	**2.68 (2.41-2.98)**
Demographics		
Age group 45-65y (ref: 18-44y)	0.20	0.64 (0.33-1.25)
Age group >65y (ref: 18-44y)	0.69	0.87 (0.45-1.69)
Sex (ref: male)	0.0062	1.15 (1.04-1.27)
Cancer treatment		
Chemotherapy, 6m post-index (ref: no chemo)	0.49	1.04 (0.93-1.18)
Past medical history		
Diabetes (ref: no hx)	0.049	1.11 (1-1.23)
CHF (ref: no hx)	0.45	0.95 (0.82-1.09)
COPD (ref: no hx)	0.081	0.91 (0.82-1.01)
Hypertension (ref: no hx)	0.00020	1.3 (1.13-1.49)
Heart disease (ref: no hx)	0.36	1.07 (0.93-1.23)
Vascular disease (ref: no hx)	0.39	1.09 (0.9-1.31)
Dyslipidemia (ref: no hx)	0.0019	1.29 (1.1-1.51)
Atrial fibrillation (ref: no hx)	0.13	1.13 (0.97-1.32)
Dementia (ref: no hx)	0.25	0.91 (0.77-1.07)
Elixhauser >=4 (ref: <4)	0.035	1.15 (1.01-1.31)

Table 3. Multivariable adjusted Fine-Gray competing risk regression model for the effect of previous history of ischemic stroke and lag time to index date on the risk of recurrent ischemic stroke after a diagnosis of cancer. Effect measures are displayed as sub-distribution adjusted hazard ratios (aHR) with 95% confidence intervals (95% CI).

Model parameter	P-value	aHR (95% CI)
Primary exposure		
Isc. stroke <=1y (ref: no hx)	<.0001	**3.68 (3.22-4.22)**
Isc. stroke 1-2y (ref: no hx)	<.0001	**2.44 (1.93-3.09)**
Isc. stroke 2-5y (ref: no hx)	<.0001	**2.13 (1.79-2.54)**
Isc. stroke 5-10y (ref: no hx)	<.0001	**2.13 (1.78-2.54)**
Demographics		
Age group 45-65y (ref: 18-44y)	0.2107	0.65 (0.33-1.27)
Age group >65y (ref: 18-44y)	0.7440	0.9 (0.46-1.74)
Sex (ref: male)	0.0087	1.14 (1.03-1.26)
Cancer treatment		
Chemotherapy, 6m post-index (ref: no chemo)	0.5086	1.04 (0.92-1.17)
Past medical history		
Diabetes (ref: no hx)	0.0379	1.11 (1.01-1.23)
CHF (ref: no hx)	0.6993	0.97 (0.84-1.12)
COPD (ref: no hx)	0.1096	0.92 (0.83-1.02)
Hypertension (ref: no hx)	0.0001	1.31 (1.14-1.51)
Heart disease (ref: no hx)	0.2939	1.08 (0.94-1.24)
Vascular disease (ref: no hx)	0.5057	1.07 (0.88-1.28)
Dyslipidemia (ref: no hx)	0.0050	1.26 (1.07-1.47)
Atrial fibrillation (ref: no hx)	0.1078	1.14 (0.97-1.33)
Dementia (ref: no hx)	0.2708	0.91 (0.78-1.07)
Elixhauser >=4 (ref: <4)	0.4786	1.05 (0.92-1.2)

5.10 FIGURES

Figure 1. Cumulative incidence function (CIF) curves for ischemic stroke (solid line) and mortality (dashed line), stratified by the presence/ absence of a previous history of ischemic stroke prior to cancer diagnosis.

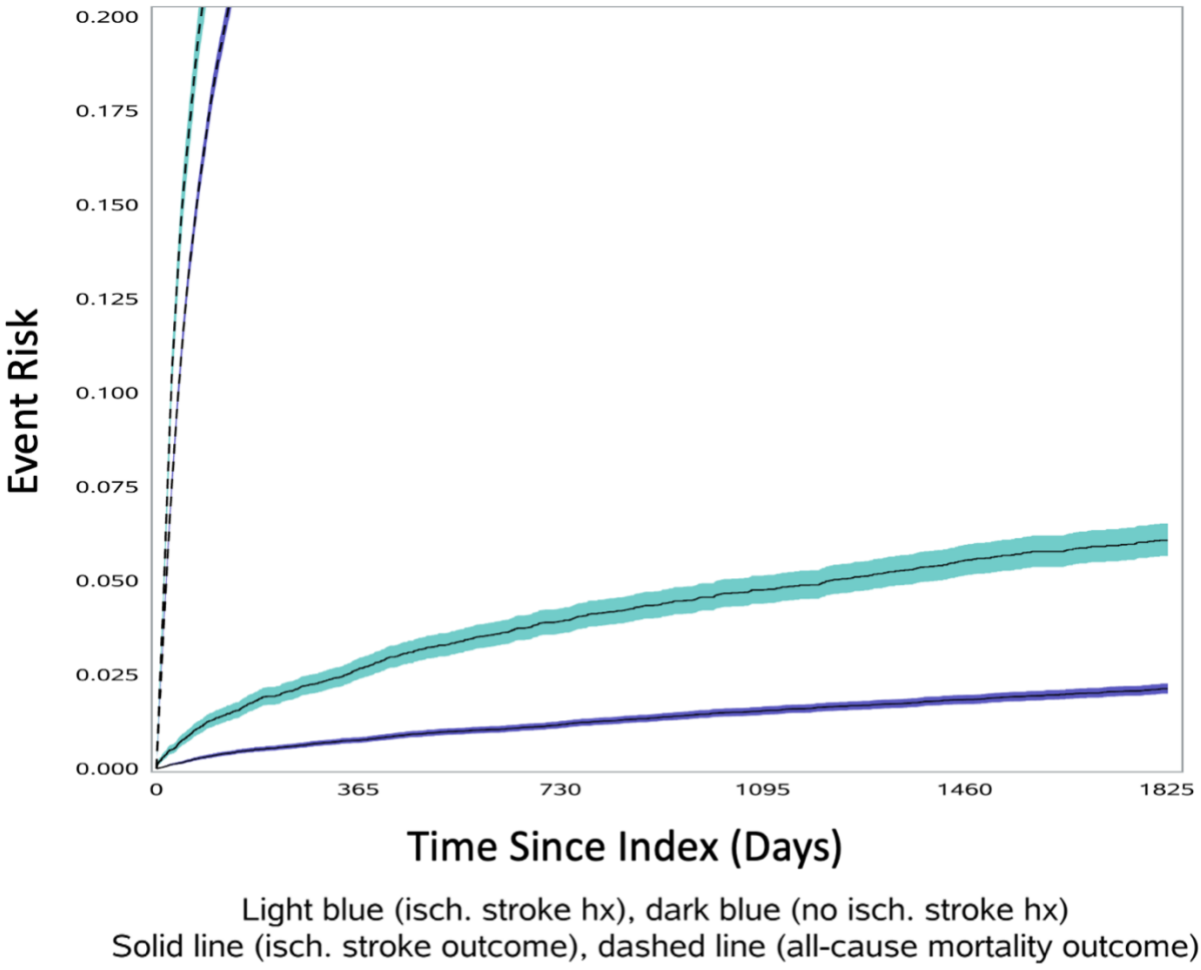
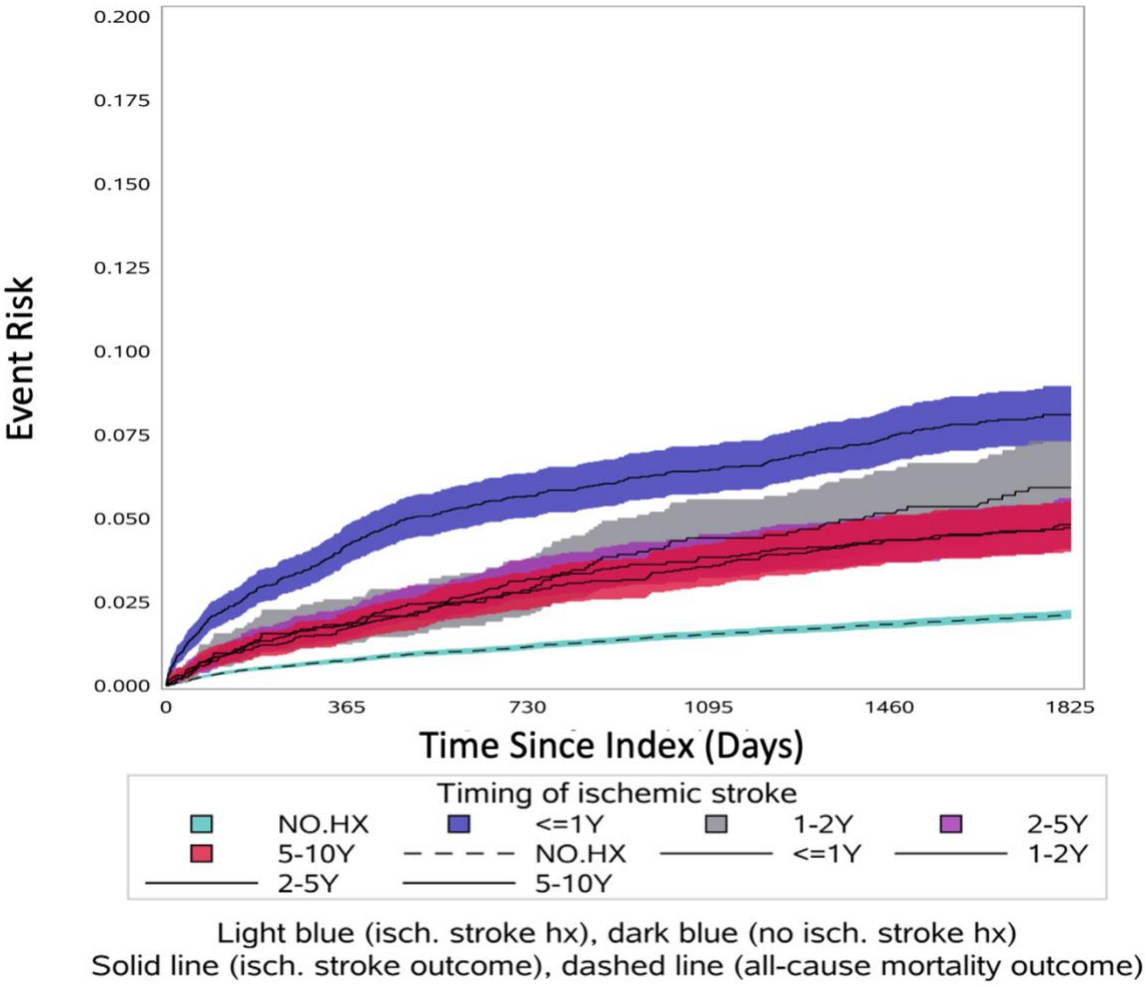


Figure 2. Cumulative incidence function (CIF) curves for ischemic stroke, stratified by lag time from a diagnosis of previous ischemic stroke prior to cancer diagnosis. Death is treated as a competing event.



Chapter Six: Differences Between Cancer and Non-Cancer Patients with Ischemic Stroke and Predictors of Recurrent Stroke in Cancer Patients

6.1 Preface:

This chapter evaluates the differences in baseline patient characteristics, treatments, and outcomes between cancer and non-cancer patients with ischemic stroke using synthetic data produced from the MDClone interface. We also attempt to identify predictors of recurrent ischemic stroke in cancer patients by building a logistic regression model. Local research ethics board approval was obtained from the Ottawa Health Science Network Research Ethics Board on May 31, 2021. An amendment to the original protocol was approved on Dec 23, 2021. A copy of the research ethics approval is available in Appendix IV.

Authorship and Contribution: Drs. Lun, Siegal, Ramsay, and Dowlatshahi were responsible for study conception, design, and statistical analysis. Drs Lun and Dowlatshahi were responsible for drafting the manuscript. All authors participated in critical revisions of the manuscript for intellectual content.

Appendix IV. Ethics approval from Ottawa Health Science Network Research Ethics Board for Chapter 6 and 7.

Appendix V. Manuscript embargo from MSc Epidemiology course work (EPI5340 and EPI5341 – referenced in the current chapter):
Publication: Lun R, Shaw JR, Roy DC, Siegal D, Ramsay T, Chen Y, Dowlatshahi D. Effect Modification of Age on Cancer & Prevalence of Self-Reported Stroke – A Cross-Sectional Study. Cancer Medicine. Submitted March 2022.

6.2 Abstract

Background: Patients with cancer are at an increased risk for ischemic stroke (IS) compared to those without cancer. The objectives of this study are 1) to examine risk factors for stroke in cancer and non-cancer patients, and 2) to identify predictive factors for recurrent IS in cancer patients.

Methods: We performed a retrospective cohort study using MDClone, a platform that produces synthetic datasets based on real health system data from the Ottawa Hospital Data Warehouse. We analyzed all subjects with a diagnosis of cancer (excluding non-melanoma skin cancer or primary central nervous system malignancies) and IS within a 2-year period preceding and following their stroke diagnosis, and all IS patients without cancer, from the same time period (2000-2019). Patients were followed until May 2019. A backward selection, stepwise multivariable logistic regression model was used to assess the association between recurrent IS after 14 days (primary outcome) and baseline characteristics. A sensitivity analysis was performed with only survivors in the cancer cohort.

Results: We analyzed 10,900 subjects with IS: 1,275 had cancer and 9,625 did not. In cancer subjects, there was a higher prevalence of chronic obstructive pulmonary disease (8.4% vs 4.7%), previous IS (1.9% vs 0.1%), and previous venous thromboembolism (VTE) (8.3% vs 1.5%); the prevalence of atrial fibrillation and vascular risk factors was similar between the two groups. The most frequent cancer type identified was lung (19.0%). The primary outcome occurred in 11.0% of the cancer subjects and 12.1% of the non-cancer subjects. Using the definition “recurrent ischemic stroke after 14 days”, we did not identify any predictors of recurrent ischemic stroke in the cancer cohort.

Conclusion: We found cancer patients with IS have a higher prevalence of COPD, previous IS and VTE than the general IS population. Future studies identifying predictors of recurrent stroke in the cancer population may require larger samples with well-defined covariates.

6.3 Introduction

Cancer is the leading cause of mortality in Canada, accounting for approximately 30% of all deaths.[1] In addition to the direct oncologic effects of cancer and cancer-associated treatments, patients with cancer are at an increased risk for thrombotic complications, including ischemic stroke.[2–4] While conventional stroke mechanisms may contribute to the development of ischemic stroke in cancer patients, there are additional unique pathophysiologic mechanisms in cancer that may further heighten the risk for ischemic stroke, including cancer-associated hypercoagulability, cancer-treatment-related adverse effects, and direct tumour effects.[5] Cancer-associated stroke has been proposed to be a separate entity from stroke in the general population, and identifying key differences in risk factors for development, treatment patterns, and outcomes is crucial in these patients.[6]

Guidelines on the acute treatment of ischemic stroke with intravenous thrombolysis or endovascular thrombectomy may not be generalizable to cancer patients.[7] Rates of bleeding-related complications are more common in cancer patients than age-matched controls, and cancer patients are also more likely to have relative contraindications to thrombolysis, including recent surgeries, thrombocytopenia, anemia, and coagulopathies.[8,9] Cancer patients may also have higher comorbidity indices compared to non-cancer patients, and may be denied acute reperfusion therapies due to poor functional baseline or shortened life expectancy.[10,11] An American administrative database study found that the frequency of administration of thrombolytic therapy was significantly lower in cancer patients compared to non-cancer patients, despite no difference in rates of bleeding or in-hospital mortality.[12] A large sample of patients with active cancer in the MR CLEAN registry had high rates of technical success with

endovascular thrombectomy, with similar rates of successful reperfusion and symptomatic intracranial hemorrhage, although cancer patients had worse 3-month functional outcomes.[13] It is unclear if these treatment patterns are similar in the Canadian population, and whether these decisions translate into longer lengths of stay, lower costs, or poor patient outcomes.

Cancer patients who experience ischemic stroke are also at higher risk for recurrent events after their initial stroke. A large cohort evaluating recurrent events in cancer patients with ischemic stroke reported a rate of recurrent thromboembolism of 37% at six months, despite a median survival of only 84 days.[14] Cancer types reported to be associated with a higher risk for recurrent stroke include brain tumours and adenocarcinoma histopathology.[15,16] However, predictors for recurrent ischemic stroke have not been studied extensively in cancer patients; there is speculation that recurrent events are more common in those with advanced stages of their malignancy, given a higher association with hypercoagulable mechanisms.[16,17]

The main objectives of this study are to: 1) describe the differences in baseline demographics between cancer patients with ischemic stroke and non-cancer patients with ischemic stroke; 2) describe differences in acute treatments, systemic costs, and patient outcomes between the two cohorts; and 3) identify risk factors for recurrent ischemic stroke in cancer patients.

6.4 Methods

Standard Protocol Approvals and Patient Consents:

We analyzed data through the MDClone platform. MDClone is an interactive platform that produces synthetic data from real health systems data for research purposes. It synthesizes

existing data from the Ottawa Hospital Data Repositories and produces an imitation dataset that no longer contains data from individual patients, but rather a collection of observations which maintain the statistical properties of the original dataset.[18] The advantages to using MDClone and synthetic data include reducing barriers to access by bypassing privacy and confidentiality controls surrounding clinical data, and to improve the ability to share informative datasets between researchers at various institutions. Real-patient data was obtained from the Ottawa Hospital Data Repositories for comparison; a comparison between synthetic data to real-patient data can be found in the subsequent chapter of this thesis report. The current study was approved by the Ottawa Health Science Network Research Ethics Board. Informed consent from patients was not required as this was a retrospective chart review.

Data Availability Statement:

This study used data from The Ottawa Hospital (TOH) Data Repositories. TOH Data Repositories contain administrative and clinical data for all patients seen at The Ottawa Hospital in addition to financial and human resource data for the organization.

Inclusion/Exclusion Criteria:

We included all patients meeting inclusion criteria for either cohort from April 1, 2002 – May 31, 2019. We created two separate cohorts: the first cohort included all patients with a diagnosis of cancer (excluding non-melanoma skin cancer or primary central nervous system [CNS] malignancies) and a diagnosis of ischemic stroke within a 2-year window before and after their cancer diagnosis. The list of cancer subtypes searched for are outlined in Supplemental Materials eTable 1. Patients with non-melanoma skin cancers were excluded due to their favourable

prognoses (i.e. squamous or basal cell carcinoma), often requiring local excision only with no systemic treatments, resulting in low accuracy of their administrative coding. The exclusion of primary CNS malignancies was chosen because of the potential for misdiagnoses of acute vascular events in the context of tumours on neuroimaging.[19] The two-year window was chosen because there appears to be an elevated risk for arterial thromboembolism in patients with cancer up to 24 months after a new diagnosis of cancer; the cumulative incidence curves for ischemic stroke start to cross over at 24 months.[20] There is also an increased risk for stroke as early as two years before a cancer diagnosis, peaking around the time of diagnosis.[21] Therefore, the two-year period immediately preceding and subsequent to a diagnosis of cancer was broadly chosen to be comprehensive and inclusive of all potential strokes related to a cancer diagnosis. The second patient cohort consisting of ischemic stroke patients without a history of cancer was created using administrative coding for "ischemic stroke". The list of included ICD-10 codes for the study can be found in Supplemental Materials eTable 2. All patients with ischemic stroke and no record of any malignancy documented in their chart were included for analysis.

Outcomes:

Covariates included for analysis include baseline patient demographics including age, sex, Charlson Comorbidity Index, presence of vascular risk factors, history of ischemic and hemorrhagic stroke, and history of venous thromboembolism. We also included biochemical information such as blood glucose at time of stroke presentation. Outcomes of interest included the proportion of patients receiving intravenous thrombolysis and the proportion of patients who underwent thrombectomy. We also analyzed the total cost associated with each stroke encounter, which was broken down into total cost as well as direct and indirect costs. Direct costs were

defined as all expenses in direct functional centers related to patient care, including salaries, supplies, and equipment amortization. Indirect costs included overhead allocation based on the percentage of the activity in the functional center, and consisted of costs not directly related to the patient, such as human resources, finance, health records, administration fees, building maintenance, etc. Information regarding costs were available for all inpatient encounters from April 2002, and for ED encounters, from April 2011. Mortality was captured from documented deaths in our administrative database. The primary outcome of interest for the cancer cohort was recurrent ischemic stroke, which we defined using three different methods: first ischemic stroke after reference event, recurrent ischemic stroke at least 14 days after the reference event, and recurrent ischemic stroke at least 30 days after the reference event. These definitions were chosen because exploratory analyses conducted using the definition "any recurrent ischemic stroke" demonstrated erroneously high rates of recurrent stroke in both cohorts, likely a reflection of error in administrative coding; this is discussed further in the discussion section of this manuscript, paragraph 4.

A unique challenge to using the MDClone platform is the censoring function, which the platform performs automatically if information requested from the administrative database is unable to be altered and therefore potentially identifiable to the real patient that the synthetic information is based on. When generating the dataset, the user must be cognizant of what percentage of information is censored, as this may significantly impact the usefulness of the data. Variables with too many censored variables may be inadequate for analysis. To avoid censoring of information across covariates, we searched for the presence/ absence of covariates by converting such dichotomous variables into continuous variables: this was done by requesting the date that a

medical condition was documented in the patient's chart, represented as the number of days from the reference event, as MDClone does not censor numeric variables. Other ways of avoiding information being censored included requesting the least granular information possible. For example, for cancer subtype, if "source diagnosis" is requested, about 40% of the dataset will be censored for protection of patient confidentiality. However, when the level of information is changed to "ICD-10 Category" (i.e. malignant melanoma of the skin), only 5% of the variable is censored.

Statistical Analysis:

We described the two cohorts using descriptive statistics. Normality of distribution was assessed using histograms; results with a normal distribution were compared using parametric tests for between-group comparisons (i.e. t-test for continuous outcomes and chi-squared test for dichotomous outcomes). Non-parametric tests were performed for values with non-normal distribution, as appropriate.

We used a binary logistic regression model to identify risk factors for recurrent stroke in cancer patients. Charlson comorbidity index was dichotomized at <4 or ≥ 4. We first performed exploratory univariate analyses to determine associations between candidate variables and the primary outcome, using the three definitions outlined in the "outcomes" section above. We then used a backwards selection, stepwise approach to evaluate the importance of individual covariates for inclusion in the final multivariable logistic regression model using the likelihood ratio test, set at a p value of <0.10 for covariate inclusion. Important collinearity was assessed

with variance inflation factor (VIF) values. A sensitivity analysis was conducted in only survivors in the cancer cohort.

All statistical analyses were performed using SPSS v27.0, (IBM, Armonk, NY).

6.5 Results

Comparison of cancer cohort to non-cancer cohort

In total, we included 10,900 patients for analysis, with 1,275 subjects in the cancer cohort and 9,625 in the non-cancer cohort. The baseline patient characteristics and demographics are listed in Table 1. There was no difference between the two cohorts in the age of presentation at the time of their ischemic stroke: 73.6±12.0 in the cancer cohort vs 73.6±12.6 in the non-cancer cohort. There was a higher proportion of males in the cancer cohort (55.2% vs 44.7%). We found no substantial difference in the proportion of patients with hypertension, diabetes, dyslipidemia, history of hemorrhagic stroke, transient ischemic attack (TIA), atrial fibrillation, or coronary artery disease (see Table 1). However, there was a higher prevalence of chronic obstructive pulmonary disease (COPD: 8.4% in the cancer cohort vs 4.7% In the non-cancer cohort), prior ischemic stroke (1.86% vs 0.1%), and prior venous thromboembolism (VTE: 8.3% vs 1.5%). The median Charlson Comorbidity Index in both cohorts was 1.0.

The distribution of cancer types included in the cancer and ischemic stroke cohort are outlined in Table 2. The most frequent cancer diagnosis was lung cancer, which was present in 242/1275 patients (19.0%). The next most frequent cancer type were secondary malignancies, defined as any malignancy that has emerged as a consequence of prior treatment for another primary

malignancy (i.e. chemotherapy/ radiation).[22,23] Together with colorectal cancer (152/1275), bladder cancer (95/1275), and immunoproliferative disease (87/1275), these five subtypes of cancer made up 59.5% of the included patients. Of note, there were 6.2 of patients whose primary cancer site was unspecified, and 6.3% of patients that had their cancer type censored by MDClone. Only 5.0% of information from our dataset was censored, and censoring occurred exclusively for the "cancer types" variable.

There were similar proportions of patients that received acute treatments for their ischemic stroke between the cancer and non-cancer cohorts (Table 3): 1.4% of patients in the cancer cohort received IV thrombolysis compared to 1.7% in the non-cancer cohort. Similarly, 2.0% of patients in the cancer cohort underwent endovascular thrombectomy compared to 2.5% in the non-cancer cohort; these differences were not statistically significant. The median length of stay was noted to be longer in the cancer cohort: 8 days (IQR 3 – 16) vs 6 days (IQR 3 – 13), but the median number of days spent in Alternative Level of Care (ALC) designation was no different. Overall, costs associated with the stroke encounter was significantly higher for cancer patients compared to non-cancer patients: $11,498 (IQR $4,440 – $20,668) vs $8,084 (IQR $3,947 – $16,706), respectively. The differences in costs were significantly higher in the cancer cohort for both direct costs ($6,819 [95%CI $3,214 – $14,074] for cancer cohort vs $5,896 [95%CI $2,862 – $12,302] for non-cancer cohort), as well as indirect costs ($2,865 [95%CI $4,886 – $1,186] for cancer cohort vs $2176 [95%CI $1,044 – $4,180] for non-cancer cohort).

There was a higher proportion of patients who died in the cancer cohort: 36.5% compared to 13.6% in the non-cancer cohort (Table 3). The rates of recurrent ischemic stroke, when defined

as any ischemic stroke that happens a minimum of 14 days after their initial stroke, was similar between the two cohorts: 11.0% in the cancer cohort and 12.1% in the non-cancer cohort. There were no differences between the rates of recurrent ischemic stroke using the definition "recurrent ischemic stroke after 30 days" or "recurrent ischemic stroke after 14 days". However, using the definition "any recurrent ischemic stroke", the cancer cohort had a lower rate of recurrent stroke: 32.2% compared to 41.1% in the non-cancer cohort ($p<0.0001$). The timing of when recurrent ischemic stroke events happened also varied based on the definition of the outcome: recurrent stroke events appeared to happen earlier in the non-cancer cohort if using the definition "any recurrent ischemic stroke", but there was no difference between the two groups in terms of timing of stroke if 14-day or 30-day definitions are used (Table 3).

Predicting Recurrent Ischemic Stroke in Cancer Patients

Table 4 summarizes the unadjusted (univariate) versus adjusted odds ratios (ORs) for the association between covariates of interest and the various definitions of the primary outcome of recurrent ischemic stroke in the cancer cohort: any timing, after 14 days, and after 30 days from initial stroke (reference event). For selection of covariates, we evaluated age, sex, vascular risk factors (i.e. diabetes, coronary artery disease, hypertension, dyslipidemia, atrial fibrillation), previous stroke, previous venous thromboembolism, and the Charlson comorbidity index. Cancer subtype was not included in regression analyses due to the number of different levels for this categorical variable (i.e. 17 total), including some unspecified cancer types (i.e. censored or unspecified primary site).

We used a backwards stepwise binary logistic regression model to select covariates for inclusion in our final model. Table 4 shows the crude, unadjusted ORs for each covariate's association with the outcome, as well as the adjusted ORs for the full model with all covariates included (i.e. step 1 of the backward stepwise selection model). The final model with only significant covariates included is outlined in Table 5. Using the definition of "recurrent ischemic stroke after 14 days", we found that none of the covariates we assessed were significantly associated with prediction of recurrent stroke.

A sensitivity analysis was conducted in survivors only in the cancer and stroke cohort. Table 6 displays the final logistic regression models for all 3 definitions of the primary outcome, including only predictors that met inclusion criteria based on the likelihood ratio test ($p<0.10$). Using the definition of "any recurrent ischemic stroke", we identified that a history of coronary heart disease was a negative predictor of future recurrent events (aOR 0.52, 95%CI 0.30 – 0.90), while a previous history of ischemic stroke (aOR 3.93, 95%CI 1.42 – 10.91) and dyslipidemia (aOR 2.26, 95%CI 1.07 – 4.78) were positive predictors of future stroke. We were unable to identify any significant predictors of future stroke using the other two definitions of recurrent stroke.

6.5 Discussion

Using synthetic data, we were able to demonstrate that cancer patients with stroke have a higher prevalence of baseline COPD, previous ischemic stroke, and prior venous thromboembolism (VTE) than non-cancer patients. While their rates of receiving acute reperfusion therapies were similar compared to non-cancer patients with ischemic stroke, the cancer and stroke cohort had a

significantly longer length of stay and higher costs than non-cancer individuals with stroke. Mortality was higher in the cancer and stroke cohort, but rates of recurrent ischemic stroke after 14 days from the initial event were similar. Using the definition "recurrent ischemic stroke after 14 days", we did not identify any predictors of recurrent ischemic stroke in the cancer cohort.

Similar to previously published cohorts of stroke in cancer patients, lung cancer was the most common type of cancer identified in our cancer cohort.[24] This may be related to shared risk factors between stroke and cancer, such as smoking; we also identified a higher prevalence of COPD in our cancer cohort – a disease that is almost exclusive to smokers.[21] Other imbalanced covariates at baseline included a higher prevalence of prior ischemic stroke and VTE in the cancer cohort. Other studies have reported similar findings in cancer patients with ischemic stroke when compared to age and sex matched non-cancer stroke patients, which may speak to the various manifestations of hypercoagulability associated with cancer.[25] There is conflicting evidence regarding the prevalence of traditional vascular risk factors in cancer vs non-cancer patients with ischemic stroke, with some studies reporting a higher prevalence in non-cancer patients, and others not finding a difference.[25–27] We believe that these differences may reflect the effect modification of age on the relationship between cancer and stroke and the variations in age across these study populations. In a large cross-sectional study of 86,809 adult patients, we demonstrated that the association between cancer and stroke was only significant in younger adults (defined as <40 years of age), and the association was stronger in those without conventional risk factors such as hypertension (Lun et al, unpublished data, manuscript embargo [Appendix V]). In this current study, the average age at time of stroke diagnosis was 73 for both

the cancer and non-cancer cohorts, with similar proportions of vascular risk factors reported, likely reflecting the increased prevalence of these conditions with age.

The rates of reperfusion therapy provided in Ontario were reported to be 15% in 2019/2020: 12% of ischemic stroke patients received IV thrombolysis with tissue plasminogen activator (tPA) and 5% underwent endovascular thrombectomy (EVT).[28] The higher proportion of patients receiving acute reperfusion therapies compared to our study period (i.e. 2001 – 2019) is likely a reflection of the recently implemented guidelines for endovascular thrombectomy and the extended time window for reperfusion.[29–32] Evidence for thrombectomy did not come out until 2015, when five randomized controlled trials demonstrated overwhelming efficacy of thrombectomy for large vessel occlusions, with a pooled number to treat of 2.6 to prevent functional disability.[31] In the current study, we did not find a difference in the rates of acute reperfusion therapies provided between the cancer and non-cancer cohorts, and this is disparate from previously published studies that found cancer patients are less likely to get reperfusion therapies than non-cancer patients.[13,33] We believe our results should be interpreted cautiously given the low number of patients receiving reperfusion therapies, particularly in the cancer cohort.

Overall, costs were significantly higher for the cancer cohort compared to the non-cancer cohort; this was true for both direct and indirect costs associated with the stroke encounter. For patients with known cancer, this increased cost may be related to more investigations pursued for the purpose of cancer staging, which may guide conversations around goals of care and prognosis. It is also possible that cancer was diagnosed during the workup for stroke, which may also contribute to higher costs in this cohort. In patients with embolic stroke of undetermined

significance (ESUS), between 5-10% of patients go on to receive a diagnosis of cancer from their workup.[34–36] Cancer patients are also at higher risk for in-hospital complications, including bleeding, development of venous thromboembolism, and infections.[9,37] Furthermore, those with limited life expectancies related to their cancer diagnosis may not be a candidate for rehabilitation services related to their stroke, which may also contribute to a longer length of stay and higher costs.

Using the definition "any recurrent ischemic stroke", we found that the incidence of recurrent ischemic stroke in the cancer cohort was 32.2% with a median of 8 days after the initial reference event. In the non-cancer cohort using the same definition, the incidence of recurrent stroke was 41.1% with a median of 7 days after the reference event. We know from large, population-based studies of the general population that the 1-year incidence rate of recurrent ischemic stroke after a first stroke is approximately 4-14%, and these numbers have been declining in recent decades.[38–40] In cancer patients, one of the largest cohort studies examining recurrent ischemic stroke reported a recurrence rate of 15.7% at 6 months.[16] We suspect that the extremely high numbers of recurrence in our study may be a reflection of errors and biases associated with the use of our particular administrative database rather than true recurrence. We used histograms to visualize when these recurrent stroke events were happening in relation to the reference event and found that in the non-cancer cohort, 6.7% of these recurrent ischemic stroke encounters occurred within 24 hours of the reference event, and 38.4% of these events occurred within the first 5 days after the reference event; similar incidences were found in the cancer cohort. This likely reflects an error in diagnostic coding rather than true recurrent ischemic stroke events documented as a separate encounter. For example, it is possible that a patient who presented to

the emergency department (ED) as a stroke code and subsequently got admitted to the inpatient service had two separate encounters created for the same event: the first encounter in the ED being their reference event, and their subsequent inpatient admission was erroneously counted as their "recurrent ischemic stroke". This would be the most likely explanation for the relatively high proportion of patients with "recurrent events" during the first 24 hours of presentation, rather than a new stroke that resulted in the creation of a new encounter in our medical records system. However, since approximately 90% of stroke inpatients are admitted from the emergency department at the Ottawa Hospital, it is unlikely that this was a systematic error affecting all encounters. Another possible explanation for the high rates of recurrent stroke events would be patient transfers between units being documented as separate encounters (i.e. intensive care unit to the neurologic acute monitoring area to the inpatient ward). Since "stroke" would be the primary diagnosis for each of these encounters, any encounter after the reference event may be inaccurately classified as a recurrent event. We chose two other definitions of recurrent ischemic stroke to potentially mitigate this misclassification bias: any new ischemic stroke encounter that happens at a minimum of 14 or 30 days after the reference event. We chose two weeks as our first reference point because only the majority of patients will have been discharged by this point – only 25% of patients had an inpatient stay of longer than 16 days. At thirty days, 90% of patients will have been discharged from their inpatient stay, however, with this definition, we are likely also missing patients who may have had a true recurrent ischemic stroke event. From population-based studies, the 30-day rate of recurrent events after minor stroke/TIA is approximately 10%.[41] Ultimately, we chose to use any recurrent ischemic stroke event after 14 days as our main definition since 75% of patients would be discharged by 14 days, thus any recurrent event documented after this timepoint is felt to be more likely to represent a

truly new event. Our results highlight the difficulties in using administrative databases for examining recurrent events, and these findings warrant further investigations.

We suspect that the reason we could not identify predictors of our primary outcome is multifactorial. First, it is possible that our covariates are not well defined. As previously discussed in the methods section, presence of baseline comorbidities was ascertained by requesting the date of diagnosis (i.e. a continuous variable) in MDClone to minimize any potential for data censoring. This may result in inaccuracies in variable creation, as the positive predictive value for identifying true positive cases will be high, but if a patient does not have a date of diagnosis recorded for the variable of interest, we are uncertain whether the patient truly did not have the condition or whether it's due to incomplete data entry. For the purpose of logistic regression modeling, we had to assume that all patients who did not have a date of diagnosis documented for the covariates of interest did not have the disease – this may have resulted in inaccuracies in the definitions of covariates. Next, using the definition of any recurrent ischemic stroke at least 14 days after the reference event, there were only 138 events out of our initial sample size of 1275 (11.0%). It is possible that this sample size was too small to be able to accurately build a prediction model. This theory is partly supported by the fact that when our primary outcome was defined as "any recurrent ischemic stroke", we were able to identify multiple significant predictors, including age, dyslipidemia, diabetes, and previous ischemic stroke. Atrial fibrillation and presence of VTE were identified as negative predictors, possibly because these conditions are often treated with anticoagulation when identified in hospital, thereby reducing the risk for future stroke. However, given the limitations of using the definition "any recurrent ischemic stroke" as outlined above, it may be that our dataset does not

have enough power to sufficiently build an accurate prediction model using the definitions set at 14 and 30 days. Lastly, it's possible that the covariates we chose are simply not predictive of recurrent ischemic stroke in cancer patients. One of the largest published cohorts evaluating recurrent thromboembolism (and specifically ischemic stroke) in cancer patients similarly also found that age, sex, and hypertension were not predictive of recurrent stroke.[16] The authors of that study found the only variable associated with recurrent thromboembolic events was adenocarcinoma histology. It may be that predictors of recurrent ischemic stroke in cancer patients are different than that in the general population: previously identified predictors in the general population such as older age, atrial fibrillation without anticoagulation, diabetes and use of antihypertensives have not been found to be predictive in cancer patients.[16,38] Prior ischemic stroke is an important risk factor for recurrent stroke in the general population, and in Chapter 3, we demonstrated that individuals with a history of stroke prior to a diagnosis of cancer were more likely to suffer stroke after a new diagnosis of cancer.[42] We may require a dataset with sufficient power to adequately assess other predictors of recurrent ischemic stroke in cancer patients.

The strengths of our study include our large sample sizes with minimal censored information, a prespecified study protocol, and careful selection of covariates with regards to the logistic regression modeling. The major limitations to our study include the lack of well-defined variables, including potentially erroneous coding related to our outcome of interest, as discussed extensively above. The definitions used to obtain baseline characteristics of interest may also be subject to high rates of false negatives, although this was necessary to obtain the most complete dataset possible due to the censoring function in MDClone. Next, a limitation specific to the

MDClone platform and the use of synthetic data is the inability to reproduce identical synthetic cohorts. If additional variables need to be requested after a dataset has already been generated by MDClone, the program will create a new synthetic cohort, with a slightly different size and numeric values, for the purpose of patient confidentiality. For example, the first cohort we generated had a patient sample size of 1250 patients; our final cohort had 1275 patients, and any exploratory analyses that were performed on the initial cohort had to be repeated with the new dataset.

6.6 Conclusion

Cancer patients with stroke have a higher prevalence of COPD, previous ischemic stroke, and previous VTE than stroke patients without cancer. They also have a longer average length of stay and higher costs associated with their stroke encounter. Larger epidemiological studies with reliable definitions of covariates and outcomes may be required to identify predictors of recurrent ischemic stroke in cancer patients with stroke. The next chapter of this thesis discusses the comparison of synthetic data to real-patient data.

6.7 Tables

Table 1. Baseline demographics, treatment characteristics, and outcomes for cancer patients who were diagnosed with ischemic stroke within a 2-year period around diagnosis of cancer (2 years before and 2 years after) compared to patients with ischemic stroke and no documented history of malignancy.

	Cancer Patients with ischemic stroke	**Non-Cancer Patients with ischemic stroke**
Number of patients	N=1275	N=9625
Demographics		
Age at cancer diagnosis (mean ± SD)	72.9±12.0	N/A
Age at stroke diagnosis (mean ± SD)	73.0±12.0	73.6±12.6
Male sex (n, %)	704 (55.2%)	4304 (44.7%)
Medical History		
Hypertension (n, %)	663 (52.0%)	5556 (57.7%)
Diabetes (n, %)	354 (27.8%)	2787 (29.0%
Hyperlipidemia (n, %)	61 (4.8%)	584 (6.1%)
COPD (n, %)	108 (8.5%)	455 (4.7%)
Ischemic Stroke (n, %)	22 (1.7%)	13 (0.1%)
Hemorrhagic Stroke (n, %)	23 (1.8%)	234 (2.4%)
Atrial Fibrillation (n, %)	289 (22.7%)	1945 (20.2%)
Coronary Artery Disease (n, %)	157 (12.3%)	1434 (14.9%)
Previous Venous Thromboembolism (n, %)	105 (8.2%)	143 (1.5%)
Charlson Comorbidity Index (median, IQR)	1.0 (0.0 – 2.0)	1.0 (1.0 – 1.0)
Bloodwork at Presentation		
Initial Glucose (mmol/L) (median, IQR)	6.4 (5.7 – 7.8)	6.8 (5.6 – 8.6)

Table 2. Distribution of the types of cancer in cohort #1: ischemic stroke patients with cancer

Cancer Type	**Frequency**	**Percentage**
Lung	242	18.98%
Secondary malignancies	183	14.35%
Colorectal	152	11.92%
Bladder	95	7.45%
Immunoproliferative disease	87	6.82%
Censored	80	6.27%
Unspecified	79	6.20%
Prostate	78	6.12%
Esophageal + upper GI	56	4.39%
Breast	49	3.84%
Pancreatic	43	3.37%
Urogynecologic	38	2.98%
Kidney	30	2.35%
Head and neck cancer	22	1.73%
Bone and cartilage	18	1.41%
Hepatobiliary	14	1.10%
Melanoma	9	0.71%

Table 3. Comparison of ischemic stroke patients with cancer to ischemic stroke patients without cancer in terms of acute treatments and patient outcomes.

Acute Treatment	**Cancer Cohort (N=1275)**	**Non-Cancer Cohort (N=9625)**	**P-Value**
Received Intravenous tPA (n, %)	17 (1.4%)	162 (1.7%)	0.40
Received Thrombectomy (n, %)	25 (2.0%)	244 (2.5%)	0.14
Length of stay (days; median, IQR)	7.65 (3.11 – 15.86)	6.09 (2.81 – 12.75)	**0.033**
Days in ALC (days; median, IQR)	0 (0.00 – 0.00)	0 (0.00 – 0.00)	0.64
Total cost of encounter (CAD; median, IQR)	$11,497.78 (4439.85 – 20,668.41)	$8084.24 (3947.40 – 16,706.04)	**0.011**
Direct cost of encounter (CAD; median IQR)	$6,819.40 (3214.30 – 14073.89)	$5895.69 (2861.88 – 12301.50)	**0.040**
Indirect cost of encounter (CAD; median IQR)	$2864.87 (4886.40 – 1185.75)	$2175.59 (1044.33 – 4180.32)	**0.038**
Outcomes			
Recurrent ischemic stroke after 30 days (n, %)	64 (5.0%)	505 (5.2%)	0.76
Recurrent ischemic stroke after 14 days (n, %)	138 (11.0%)	1163 (12.1%)	0.19
Recurrent ischemic stroke, any (n, %)	402 (32.2%)	3951 (41.1%)	**<0.0001**
Timing of recurrent IS after 30d (days; median, IQR)	69.7 (35.9 – 268.2)	91.28 (40.60 – 769.46)	0.40
Timing of recurrent IS after 14d (days; median, IQR)	25.4 (18.8 – 25.4)	26.4 (18.5 – 64.5)	0.34
Timing of any recurrent IS (days; median, IQR)	8.4 (3.9 – 20.8)	7.04 (3.24 – 16.53)	**0.00098**
Deaths (n, %)	465 (36.5%)	1313 (13.6%)	**<0.0001**

Table 4. Multivariable logistic regression models for prediction of recurrent ischemic stroke in cancer patients who suffered an ischemic stroke. Results are shown for crude, unadjusted odds ratios (ORs) between each covariate and the outcomes assessed, and adjusted ORs (aOR) for the full model.

Predictors	**Any recurrent ischemic stroke**		**Recurrent ischemic stroke after 14 days**		**Recurrent ischemic stroke after 30 days**	
	Unadjusted, crude OR (95%CI)	Adjusted OR* (95%CI)	Unadjusted, crude OR (95%CI)	Adjusted OR* (95%CI)	Unadjusted, crude OR (95%CI)	Adjusted OR* (95%CI)
Sex: Female	1.12 (0.89 – 1.42)	1.19 (0.92 – 1.53)	1.09 (0.78 – 1.53)	1.13 (0.79 – 1.63)	0.78 (0.47 – 1.31)	0.87 (0.50 – 1.49)
Age	**1.01 (1.00 – 1.02)**	**1.02 (1.01 – 1.03)**	1.00 (0.99 – 1.02)	1.00 (0.99 – 1.02)	0.99 (0.98 – 1.02)	1.00 (0.98 – 1.03)
Hypertension	0.93 (0.74 – 1.18)	0.82 (0.63 – 1.07)	0.74 (0.53 – 1.04)	0.69 (0.47 – 1.00)	0.98 (0.59 – 1.62)	0.96 (0.55 – 1.70)
Coronary Artery Disease	1.04 (0.73 – 1.49)	0.91 (0.60 – 1.37)	0.76 (0.43 – 1.33)	0.74 (0.39 – 1.40)	0.73 (0.31 – 1.71)	0.79 (0.31 – 2.00)
COPD	0.88 (0.57 – 1.35)	0.90 (0.57 – 1.44)	0.83 (0.43 – 1.58)	0.77 (0.37 – 1.59)	1.35 (0.60 – 3.04)	1.11 (0.42 – 2.91)
Diabetes Mellitus	1.09 (0.84 – 1.42)	**2.10 (1.17 – 3.76)**	1.23 (0.85 – 1.78)	1.40 (0.94 – 2.07)	**1.84 (1.10 – 3.08)**	**1.92 (1.09 – 3.37)**
Dyslipidemia	**1.84 (1.10 – 3.09)**	**2.10 (1.17 – 3.76)**	1.30 (0.63 – 2.69)	1.67 (0.75 – 3.74)	0.63 (0.15 – 2.64)	0.76 (0.17 – 3.43)
Previous Ischemic Stroke	**3.10 (1.32 – 7.32)**	**2.75 (1.13 – 6.67)**	1.17 (0.34 – 4.00)	1.20 (0.34 – 4.25)	0.00 (0.0 - .)	0.00 (0.0 - .)
Atrial Fibrillation	0.77 (0.58 – 1.03)	**0.69 (0.50 – 0.95)**	0.75 (0.48 – 1.15)	0.78 (0.48 – 1.24)	0.54 (0.27 – 1.12)	0.62 (0.29 – 1.31)
Venous thromboembolism	**0.47 (0.28 – 0.77)**	**0.51 (0.31 – 0.86)**	0.51 (0.23 – 1.11)	0.54 (0.24 – 1.22)	0.17 (0.02 – 1.23)	0.17 (0.02 – 1.24)
Charlson Comorbidity Index ≥4	1.00 (0.70 – 1.50)	1.08 (0.71 – 1.63)	0.79 (0.42 – 1.47)	0.77 (0.41 – 1.45)	0.82 (0.32 – 2.09)	0.75 (0.29 – 1.94)

*Adjusted for sex, age, hypertension, CAD, COPD, DM, DLD, previous IS, AF, VTE, and Charlson Comorbidity ≥4

Table 5. Final logistic regression models for the association between covariates and primary outcome of recurrent stroke in the cancer and stroke cohort. Results are displayed for all 3 definitions of the primary outcome as adjusted Odds Ratios (aOR) with 95% confidence intervals (95%CI).

Predictors	**Any recurrent ischemic stroke**	**Recurrent ischemic stroke after 14 days**	**Recurrent ischemic stroke after 30 days**
Age by decade (reference: <50 years)	**1.16 (95%CI 1.04 – 1.30)**	---	---
Ischemic stroke	**2.57 (95%CI 1.07 – 6.18)**	---	---
Atrial fibrillation	**0.67 (95%CI 0.49 – 0.91)**	---	---
Venous thromboembolism	**0.51 (95%CI 0.31 – 0.85)**	0.51 (95%CI 0.23 – 1.12)	0.18 (95%CI 0.02 – 1.28)
Dyslipidemia	**1.89 (95%CI 1.09 – 3.27)**	---	---
Diabetes	---	---	**1.83 (95%CI 1.07 – 3.14)**
Hypertension	---	0.73 (95%CI 0.51 – 1.03)	---

Table 6. Final logistic regression models for the association between covariates and primary outcome of recurrent stroke, in survivors only from the cancer and stroke cohort. Results are displayed for all 3 definitions of the primary outcome as adjusted Odds Ratios (aOR) with 95% confidence intervals (95%CI).

Predictors	**Any recurrent ischemic stroke**	**Recurrent ischemic stroke after 14 days**	**Recurrent ischemic stroke after 30 days**
Coronary Artery Disease	**0.52 (95%CI 0.30 – 0.90)**	---	---
Ischemic stroke	**3.93 (95%CI 1.42 – 10.91)**	---	---
Dyslipidemia	**2.26 (95%CI 1.07 – 4.78)**	---	---
Hypertension	---	0.65 (95%CI 0.42 – 1.01)	---

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6.9 Supplemental Materials

Supplemental Materials eTable 1. Search terms utilized for identifying cancer subtypes for Cohort 1: Cancer and Ischemic Stroke cohort

- Carcinoma in situ of breast
- Carcinoma in situ of cervix uteri
- Carcinoma in situ of middle ear and respiratory system
- Carcinoma in situ of oral cavity, oesophagus and stomach
- Carcinoma in situ of other and unspecified digestive organs
- Carcinoma in situ of other and unspecified genital organs
- Carcinoma in situ of other and unspecified sites
- Malignant immunoproliferative diseases
- Malignant neoplasm of accessory sinuses
- Malignant neoplasm of adrenal gland
- Malignant neoplasm of anus and anal canal
- Malignant neoplasm of base of tongue
- Malignant neoplasm of bladder
- Malignant neoplasm of bone and articular cartilage of limbs
- Malignant neoplasm of bone and articular cartilage of other and unspecified sites
- Malignant neoplasm of breast
- Malignant neoplasm of bronchus and lung
- Malignant neoplasm of cervix uteri
- Malignant neoplasm of colon
- Malignant neoplasm of corpus uteri
- Malignant neoplasm of eye and adnexa
- Malignant neoplasm of floor of mouth
- Malignant neoplasm of gallbladder
- Malignant neoplasm of gum
- Malignant neoplasm of heart, mediastinum and pleura
- Malignant neoplasm of hypopharynx
- Malignant neoplasm of kidney, except renal pelvis
- Malignant neoplasm of larynx
- Malignant neoplasm of lip
- Malignant neoplasm of liver and intrahepatic bile ducts
- Malignant neoplasm of nasal cavity and middle ear
- Malignant neoplasm of nasopharynx
- Malignant neoplasm of oesophagus
- Malignant neoplasm of oropharynx
- Malignant neoplasm of other and ill-defined digestive organs
- Malignant neoplasm of other and ill-defined sites
- Malignant neoplasm of other and ill-defined sites in the lip, oral cavity and pharynx

- Malignant neoplasm of other and ill-defined sites in the respiratory system and intrathoracic organs
- Malignant neoplasm of other and unspecified female genital organs
- Malignant neoplasm of other and unspecified major salivary glands
- Malignant neoplasm of other and unspecified male genital organs
- Malignant neoplasm of other and unspecified parts of biliary tract
- Malignant neoplasm of other and unspecified parts of mouth
- Malignant neoplasm of other and unspecified parts of tongue
- Malignant neoplasm of other and unspecified urinary organs
- Malignant neoplasm of other connective and soft tissue
- Malignant neoplasm of other endocrine glands and related structures
- Malignant neoplasm of ovary
- Malignant neoplasm of palate
- Malignant neoplasm of pancreas
- Malignant neoplasm of parotid gland
- Malignant neoplasm of penis
- Malignant neoplasm of peripheral nerves and autonomic nervous system
- Malignant neoplasm of placenta
- Malignant neoplasm of prostate
- Malignant neoplasm of pyriform sinus
- Malignant neoplasm of rectosigmoid junction
- Malignant neoplasm of rectum
- Malignant neoplasm of renal pelvis
- Malignant neoplasm of retroperitoneum and peritoneum
- Malignant neoplasm of small intestine
- Malignant neoplasm of stomach
- Malignant neoplasm of testis
- Malignant neoplasm of thymus
- Malignant neoplasm of thyroid gland
- Malignant neoplasm of tonsil
- Malignant neoplasm of trachea
- Malignant neoplasm of ureter
- Malignant neoplasm of uterus, part unspecified
- Malignant neoplasm of vagina
- Malignant neoplasm of vulva
- Malignant neoplasm without specification of site
- Malignant neoplasms of independent (primary) multiple sites
- Multiple myeloma and malignant plasma cell neoplasms
- Other and unspecified malignant neoplasms of lymphoid, haematopoietic and related tissue
- Secondary and unspecified malignant neoplasm of lymph nodes
- Secondary malignant neoplasm of other and unspecified sites

- Secondary malignant neoplasm of respiratory and digestive organs

eTable 2. List of codes used to select patients with ischemic stroke using the International Classification of Diseases (ICD) 10th revision.

	ICD-10 coding
Ischemic Stroke	I63.00, I63.01x, I63.02, I63.03x, I63.09, I63.10, I63.11x, I63.12, I63.13x, I63.19, I63.20, I63.21x, I63.22, I63.23x, I63.29, I63.30, I63.31x, I63.32x, I63.33x, I63.34x, I63.39, I63.40, I63.41x, I63.42x, I63.43x, I63.44x, I63.49, I63.50, I63.51x, I63.52x, I63.53x, I63.54x, I63.59, I63.6, I63.8, I63.9

Chapter Seven: A Comparison of Synthetic vs Real Patient Data

7.1 Preface

Computationally derived data is a new concept that has not been explored in cancer or stroke research. This chapter is a retrospective cohort study that compares synthetic data produced by MDClone to original health-system data from the Ottawa Hospital Data Repository. Local research ethics board approval was obtained from the Ottawa Health Science Network Research Ethics Board (Protocol #20210399-01H). The ethics approval document can be found in Appendix IV.

Drs. Lun, Siegal, Ramsay, and Dowlatshahi were responsible for study concept, design, and statistical analysis. Drs Lun and Dowlatshahi were responsible for drafting the manuscript. All other authors participated in critical revisions of the manuscript for intellectual content.

Appendix IV. Ethics approval from Ottawa Health Science Network Research Ethics Board for Chapter 6 and 7.

Appendix VI. Synthetic file comparison report produced by MDClone for Chapter 7.

7.2 Abstract

Background:

Synthetic data is computationally derived from real health systems data and does not contain any real patient information but maintains statistical properties similar to the original real data. Its use has not been extended to cancer or stroke research previously, and its performance compared to original data in this context is unknown.

Methods:

We analyzed synthetic data produced by the MDClone platform and compared it to original data from the Ottawa Hospital Data Repository. All adult subjects with a diagnosis of non-melanoma skin cancer that suffered an ischemic stroke within a two-year period around the time of their cancer diagnosis were included. Statistical properties of covariates and outcomes were summarized using descriptive statistics. Predictors for recurrent ischemic stroke were identified using binary logistic regression models and the results were compared between synthetic and original datasets.

Results:

MDClone generated a synthetic dataset of 1,275 patients compared to 1,246 patients from original data. The frequencies and distributions of all demographic information, treatments, and outcomes were similar between the two datasets, except in the context of high missingness or continuous variables with many outliers. The two binary logistic regression models had similarly poor performances, with low R^2 values for both final models: 0.026 for synthetic and 0.017 for original.

Conclusion:

Synthetic data produced similar patterns and results compared to the original data, except in the context of high missingness and for continuous variables with multiple outliers. Our results support the use of synthetic data in cancer and stroke research, particularly during the hypothesis-generating stage of a research inquiry.

7.3 Introduction

Administrative health data are routinely collected data from interactions with the healthcare system for the purpose of payment, monitoring, planning, priority setting, and evaluation of health service provision.[1] Sources of administrative data can come from hospitalizations, emergency department visits, clinic visits, physician billings, procedure billings, and pharmacy records. There has been increasing interest in the use of administrative data for the purpose of clinical research, given the abundance of data collected over a prolonged period of time.[2] In the last decade, the number of PubMed results for "administrative databases" has almost tripled: from 493 publications reported in 2010 to 1739 publications in 2021. This wealth of data can be used for disease modeling, risk analysis, quality improvement, and much more. However, in real-life practice, obtaining access to administrative data for the purpose of research can be time consuming and significant issues exist surrounding patient confidentiality, allocation of internal resources, delays due to ethics approval, and privacy concerns surrounding data sharing.

A novel concept in epidemiological research is the use of synthetic data, which is artificially manufactured from real health systems data, and does not contain any real patient information. For synthetic data to be useful in healthcare research, statistical properties would ideally be nearly identical to original data and could be analyzed as such.[3] The advantages to using synthetic data include reducing barriers to access by bypassing privacy and confidentiality controls, improving the ability to share informative datasets between researchers at different institutions, reducing timing delays in obtaining data, and decreasing the utilization of internal resources, such as information technology (IT) teams. MDClone (Beer Sheva, Israel) is a data synthesis platform that uses computational derivation methods to produce such deidentified,

synthetic datasets based on real health systems data. Previous studies using MDClone have demonstrated its utility and efficiency, particularly when rapid access to big data are required to make informative decisions regarding public health policies and interventions, such as during the COVID-19 pandemic.[4,5] Furthermore, they have been shown to have consistent statistical properties compared to the original administrative data they were derived from.

In February 2020, the Ottawa Hospital became the first center in Canada to partner with MDClone. The objectives for this thesis chapter are to evaluate the performance of MDClone at our center via comparison of synthetic data to original health systems data from the Ottawa Hospital Data Repository. We will 1) explore and compare the distributions of covariates and outcomes in both synthetic and real datasets, 2) explore the statistical correlations and properties of both datasets via the building of a predictive model for recurrent ischemic stroke in cancer patients with stroke, and 3) summarize our experience in using the MDClone platform and synthetic data.

7.4 Methods

Standard Protocol Approvals and Patient Consents:

We analyzed data through the MDClone platform. With each user query, MDClone will produce a new, deidentified synthetic dataset that preserves the statistical properties of the original data from the Ottawa Hospital Data Repositories.[3] During the data acquisition stage, MDClone will censor categorical values that are unique to few patients by removing the value and replacing it with the word “censored” in the synthetic dataset. Extreme numerical values also do not appear in the synthetic dataset, which ensures preservation of deidentified patient data and confidentiality.[5] Real-patient data was subsequently obtained from the Ottawa Hospital Data

Repositories for comparison. The current study was approved by the Ottawa Health Science Network Research Ethics Board. Informed consent from patients was not required as this was a retrospective chart review.

Data Availability Statement:

This study used data from The Ottawa Hospital (TOH) Data Repositories. TOH Data Repositories contain administrative and clinical data for all patients seen at The Ottawa Hospital in addition to financial and human resource data for the organization. Data can be made available upon reasonable request to the Ottawa Hospital Data Repository team.

Inclusion/Exclusion Criteria:

We analyzed the synthetic and original datasets for the cancer and stroke cohort from the previous thesis chapter. Detailed description of the inclusion/exclusion criteria for the creation of this cohort can be found in the Methods section of the preceding chapter. Briefly, patients must have a diagnosis of cancer (excluding non-melanoma skin cancer or primary central nervous system [CNS] malignancies) and a diagnosis of ischemic stroke within a 2-year window before and after their cancer diagnosis (reference event). We included all patients meeting inclusion criteria from April 1, 2002 – May 31, 2019.

Derivation of Variables/Outcomes:

Covariates included for analysis include basic demographic information including sex, age of cancer and stroke diagnosis, and the presence of vascular risk factors (i.e. hypertension, dyslipidemia, chronic obstructive pulmonary disease [COPD], coronary artery disease,

dyslipidemia, atrial fibrillation), a history of stroke, previous venous thromboembolism, and Charlson Comorbidity Index. Key characteristics about acute treatment and outcomes were also collected, including the proportion of patients who received thrombolysis, endovascular thrombectomy, lengths of stay, cost of stroke encounter, and outcomes including recurrent ischemic stroke and mortality. For the logistic regression model, we chose a primary outcome of "any recurrent ischemic stroke" – since the objective of this chapter was to compare the performance of synthetic of data against real-patient data, we chose to use the raw outcome data produced by both datasets.

Due to the censoring function in MDClone, direct request of categorical variables may result in variables with many "censored" values, rendering statistical analysis challenging due to incomplete/missing information. To minimize censoring, the user may either 1) request the least granular information possible for that variable, or 2) request a continuous variable instead of categorical wherever possible. For example, instead of requesting the presence/ absence of hypertension, the user can request the date that hypertension was documented in the patient's chart, displayed as the number of days before/after the reference event. If a patient has a date of diagnosis encoded for the covariate of interest, they are assumed to have the condition (encoded as 1 for the presence of the condition). However, if no date of diagnosis is available, the patient is assumed to not have the covariate of interest (encoded as 0).

Statistical Analysis:

Key characteristics of a cohort of patients with stroke and cancer were extracted from MDClone and compared to original data. We summarized the synthetic dataset and real-patient dataset

using descriptive statistics. Normality of distribution was assessed using histograms; we calculated mean and standard deviation (SD) for normally distributed continuous variables, and medians with interquartile ranges (IQR) for non-normally distributed continuous variables. Categorical variables were reported as counts and proportions.

The second objective of this study was to evaluate whether synthetic data would perform similarly to real patient data for the purpose of building a predictive model for recurrent ischemic stroke in cancer patients. We discussed the building of the logistic regression model extensively in the previous chapter of this thesis report (Chapter 6). Briefly, we used a binary logistic regression model to identify risk factors for recurrent stroke in cancer patients. Variables assessed for inclusion in the model included: sex, age, hypertension, coronary artery disease, chronic obstructive pulmonary disease, diabetes mellitus, dyslipidemia, history of ischemic stroke, atrial fibrillation, venous thromboembolism, and Charlson Comorbidity Index (CCI). Age was an ordinal variable that we recategorized into 5 subgroups: <50, 50-59, 60-69, 70-79, and ≥80. We first performed exploratory univariate analyses to determine associations between candidate variables and the primary outcome, using “any recurrent ischemic stroke” for the purpose of comparing synthetic data to real patient data. We then used a backwards selection, stepwise approach to evaluate the importance of individual covariates for inclusion in the final multivariable logistic regression model using the likelihood ratio test, set at a p value of <0.10 for covariate inclusion. Important collinearity was assessed with variance inflation factor (VIF) values. All statistical analyses were performed using SPSS v27.0, (IBM, Armonk, NY).

7.5 Results

MDClone generated a synthetic dataset of 1,275 patients with cancer and ischemic stroke, compared to 1,246 patients from the Ottawa Hospital Data Repository. Table 1 summarizes the clinical variables obtained from both the synthetic and original datasets. The mean age at cancer diagnosis in the synthetic dataset was 72.9±12.0 years, compared to 72.4±12.1 in the original dataset; the mean age at stroke diagnosis was similar also (73.0±12.0 vs 72.6±12.0, respectively). Figure 2 displays the histograms of the frequencies of age at cancer diagnosis. While the distributions were relatively normal in both datasets, there were visibly less outliers in the synthetic dataset; the resulting histogram has a slight left-sided skew (Figure 2a). There was a similar proportion of male sex: 55.2% in both cohorts. The distribution of comorbidities at baseline was similar, with no difference greater than 0.2% between the synthetic and original datasets (Table 1). The median CCI was 1 (IQR 0-2) in both datasets. Similar proportions of patients received acute treatments including intravenous thrombolysis and endovascular thrombectomy. The median length of stay was similar: 7.7 days (IQR 31. – 15.9) in synthetic dataset vs 7.6 days (IQR 3.6 – 15.9) in the original dataset. Outcomes between the two datasets did not differ: the proportion of patients with recurrent ischemic stroke was 32.2% in the synthetic dataset and 32.3% in the original dataset; mortality rates were 36.5% and 36.0%, respectively (Table 1).

Table 2 displays the percentage of data censored by MDClone if a direct request is made for categorical variables compared to a work-around request (i.e. requesting the date of diagnosis for each categorical variable, displayed as number of days from reference event). When “source diagnosis” was requested for information regarding cancer type, 99.4% of data was censored. Information regarding cancer type could not be converted to a continuous variable, but by

requesting International Classification of Disease-10th edition (ICD-10) classifications, only 6.27% of data was censored (see Chapter 6, Table 2). For all categorical variables, requesting data as a continuous variable eliminated censoring of data completely. For variables with a small sample size (i.e. proportion of patients that received thrombolysis and thrombectomy), more than half of the data was censored with the direct request approach, and none of those who received acute treatments were identified as such (Table 3). Variables requested as a continuous variable demonstrated similar proportions compared to real patient data.

Using the synthetic dataset produced by MDClone, we identified 5 predictors of the primary outcome "recurrent ischemic stroke after the reference event" with a binary logistic regression model. Older age, a history of ischemic stroke, and dyslipidemia were found to be positive predictors of the outcome, while atrial fibrillation and a history of venous thromboembolism were negative predictors (Table 3). Using the original dataset, we identified 3 predictors of recurrent stroke: atrial fibrillation and venous thromboembolism were consistently found to be negative predictors of the outcome, with similar adjusted odds ratios compared to synthetic data (aOR 0.67 [95%CI 0.49 – 0.91] from synthetic data compared to 0.71 [95%CI 0.52 – 0.97] from original data for atrial fibrillation; aOR 0.51 [95%CI 0.31 – 0.85] from synthetic data compared to 0.43 [95%CI 0.25 – 0.72] from original data for venous thromboembolism). Dyslipidemia was similarly identified as a positive predictor of the outcome (aOR 1.89 [95%CI 1.09 – 3.27] from synthetic data compared to 1.82 [95%CI 1.06 – 3.13] for original data). However, there was no statistically significant association between age or prior ischemic stroke with the outcome – in exploratory analyses, the p-values from their likelihood ratio tests were >0.1, and therefore they were not included in the final regression model. The Cox & Snell R^2 value for both final logistic

regression models were low: 0.026 for the synthetic dataset and 0.017 for the original dataset; suggesting that only approximately 2% of the variation in our primary outcome can be attributed to the predictors in our model.

The MDClone platform produces a synthetic file comparison report upon for each query, which compares the synthetic distribution of each variable in both the original and synthetic datasets. This report can be found in Appendix VI. Comparison of the distribution of variables between synthetic and original datasets can be found on pages 2-4 of Appendix VI. Out of the 28 variables assessed, 23 had missing data in more than 50% of the patients. While the median values did not differ significantly between the synthetic and original datasets for all of the variables, the IQR was consistently smaller in the synthetic dataset due to the program's automatic elimination of outliers for continuous variables. The Spearman's correlation graph comparing the correlation between all pairs of variables can also be found in Figure 2: it compares the correlation in the original dataset with the correlation of each pair of variables in MDClone's synthetic data. There was a higher number of numeric variables on the diagonal of the graph, suggesting better preservation of statistical properties for numeric variables compared to non-numeric variables or variables with more than 50% missing data (Figure 1).

7.6 Discussion

We demonstrated that variables derived from synthetic data were comparable to real-patient data in terms of basic statistical properties. However, 23/28 variables assessed had missing data for more than 50% of the population studied, and there were slight differences in the distributions of frequencies for numeric data, likely due to MDClone's automatic removal of outliers from the synthetic dataset. When categorical variables were requested directly, we encountered a high

frequency of variables with censored information, although we were able to overcome this by requesting substitute numeric values. Our prediction model for recurrent ischemic stroke in cancer patients with stroke had similarly poor performances using synthetic and original data, with low R^2 for the final models. Five predictors were identified using synthetic data, three of which were also identified using original data and all had similar adjusted odds ratios. Overall, synthetic data produced similar patterns and results compared to the original data, except in the context of high missingness and for continuous variables with multiple outliers.

In recent years, several studies have been published using synthetic data produced by MDClone, suggesting the growing recognition and support for its use amongst the scientific community.[4,6] However, these early studies did not compare the reliability of synthetic data to real health systems data. From our literature search, we were able to find three studies that compared synthetic data produced by MDClone to original data.[3,5,7] All three studies found that results derived from synthetic data were representative of real data in terms of basic descriptive statistical properties. For variables with large patient numbers, there were highly accurate and strongly consistent results observed compared to original data, but in the context of large missingness of data or small patient numbers, the results of synthetic data were less reliable.[3,7] One study found that for smaller population studies that evaluated confounders and effect modifiers in multivariate regression models, clear trends were still correctly observed with synthetic data, although the predictions were of moderate accuracy compared to original data.[7] This is in line with the findings from our current study – we believe that the reason previous ischemic stroke was found to be a predictor with synthetic data but not the real dataset is related to the low proportion of patients with this diagnosis: only 22 patients were identified to have a

history of ischemic stroke in both the synthetic and original datasets. The high missingness of data would render this covariate unreliable, which is further supported by the wide confidence interval for its adjusted odds ratio (aOR 2.57, 95%CI 1.07 – 6.18). The other covariate that was identified with the synthetic dataset but not original was age categorized by decades, which may be related to skewing of data related to the automatic removal of outliers by MDClone (Figure 1). A previous study also found that low sample size, highly irregular distributions, and high sparsity of data can all affect the data synthesis process and the interpretability of synthetic data.[3]

From our experience, we believe that MDClone is a useful adjunctive tool for clinical research using administrative databases. The advantages to this synthetic data platform are particularly evident during the early stages of a research inquiry, as it allows the investigator to easily explore project feasibility. This includes being able to predict the scope of a study population, generating hypotheses, and exploring relationships between covariates before applying for ethics approvals. Its deidentified nature also allows for data sharing between institutions. However, this platform is not without limitations. We were able to demonstrate that while most properties of descriptive statistics were maintained between original and synthetic data, significant proportions of missing data and automatic elimination of outliers may affect results, particularly during multivariable regression analyses. Categorical variables may be subject censoring if an indirect request for numeric values cannot be made, rendering statistical analysis challenging due to a high proportion of missing data. Therefore, we believe that the utility of MDClone may be during the early, hypothesis-generating stage of a research project; a robust and complete dataset with reliable variable derivation methods may require access to original data. Lastly, the accuracy of synthetic data is only as reliable as the administrative database it derives its

information from. Pitfalls related to the use of administrative data for healthcare research are beyond the scope of this report, but common criticisms pertaining its use include misclassification bias (see previous thesis chapter), coding inaccuracies, lack of reliable, timed follow-up, and lack of quality control of data.[1,2,8]

7.7 Conclusion

Variables derived from synthetic data were comparable to real-patient data in terms of basic statistical properties, although data reliability decreases for variables with considerable proportions of missing data or continuous variables with significant outliers. We would support the use of MDClone as a tool during the hypothesis-generating stage of a research inquiry.

7.8 Tables

Table 1. A comparison of the baseline characteristics and outcomes between the synthetic dataset and real patient dataset for a cohort of stroke patients with a diagnosis of cancer at the Ottawa Hospital.

	Synthetic Dataset	Real Patient Dataset
Number of patients	N=1275	N=1246
Demographics		
Age at cancer diagnosis (mean ± SD)	72.9±12.0	72.4±12.1
Age at stroke diagnosis (mean ± SD)	73.0±12.0	72.6±12.0
Male sex (n, %)	704 (55.2%)	688 (55.2%)
Medical History		
Hypertension (n, %)	663 (52.0%)	654 (52.5%)
Diabetes (n, %)	354 (27.8%)	347 (27.9%)
Hyperlipidemia (n, %)	61 (4.8%)	61 (4.9%)
COPD (n, %)	108 (8.5%)	105 (8.4%)
Ischemic Stroke (n, %)	22 (1.7%)	22 (1.8%)
Hemorrhagic Stroke (n, %)	23 (1.8%)	23 (1.9%)
Atrial Fibrillation (n, %)	289 (22.7%)	283 (22.7%)
Coronary Artery Disease (n, %)	157 (12.3%)	155 (12.4%)
Venous Thromboembolism (n, %)	105 (8.2%)	104 (8.4%)
Charlson Comorbidity Index (median, IQR)	1 (0 – 2)	1 (0 – 2)
Bloodwork at Presentation		
Initial Glucose (mmol/L) (median, IQR)	6.4 (5.7 – 7.8)	6.4 (5.5 – 8.2)
Acute Treatment		
Received Intravenous tPA (n, %)	17 (1.4%)	17 (1.4%)
Received Thrombectomy (n, %)	25 (2.0%)	23 (1.9%)
Length of stay (days; median, IQR)	7.7 (3.1 – 15.9)	7.6 (3.6 – 15.9)
Days in ALC (days; median, IQR)	0.0 (0.0 – 0.0)	0.0 (0.0 – 1.0)
Total cost of encounter (CAD; median, IQR)	$11,498 ($4,440 – $20,668)	$11,426 ($4,361 – $21,939)
Outcomes		
Recurrent Ischemic Stroke (n,%)	402 (32.2%)	402 (32.3%)
Timing of Recurrent Ischemic Stroke (days; median, IQR)	8.4 (3.9 – 20.8)	8.4 (3.6 – 21.7)
Death (n, %)	465 (36.5%)	449 (36.0%)

Table 2. Distribution of synthetic data produced by MDClone if a direct request is made for categorical variables compared to requesting a continuous variable as a substitute. Original data is displayed also for comparison.

	Synthetic Data from direct variable request (i.e. yes vs no)	**Synthetic data from continuous variable request (i.e. date of diagnosis) request**	**Original data**
Cancer Type	Source Diagnosis Requested: 99.4% censored Prostate cancer 0.3% Lung cancer 0.3%	N/A	N/A
Received thrombolysis	53.8% data censored 0% received thrombolysis	1.4% received thrombolysis	1.4% received thrombolysis
Received thrombectomy	53.2% data censored 0% received thrombectomy	2.0% received thrombectomy	1.9% received thrombectomy
Hypertension history	52.6% censored 19.9% history of hypertension	52.4% history of hypertension	52.5% history of hypertension
Venous thromboembolism (VTE) history	46.1% censored 3.0% history of VTE	8.3% history of VTE	8.4% history of VTE
Coronary artery disease (CAD) history	44.8% censored 2.2% history of CAD	12.5% history of CAD	12.4% history of CAD
Chronic obstructive pulmonary disease (COPD) history	41.6% censored 3.0% history of COPD	8.5% history of COPD	8.4% history of COPD
Diabetes mellitus (DM) history	34.9% censored 15.3% history of DM	27.8% history of DM	27.9% history of DM
Dyslipidemia history	25.6% censored 1.4% history of dyslipidemia	4.9% history of dyslipidemia	4.9% history of dyslipidemia
Atrial fibrillation	17.8% censored 16.6 % history of atrial fibrillation	22.9% history of atrial fibrillation	22.7% history of atrial fibrillation

Table 3. Final logistic regression model for the association between covariates and primary outcome of recurrent stroke in the cancer and stroke cohort using both the synthetic dataset as well as the real patient dataset. Only covariates meeting requirement for inclusion with likelihood ratio test ($p<0.10$) are included. Measures of association are reported as adjusted Odds Ratios (aOR) with 95% confidence intervals (95%CI).

Predictors	**Synthetic Dataset**	**Real Patient Dataset**
Age by decade (reference: <50 years)	**1.16 (95%CI 1.04 – 1.30)**	**---**
Ischemic stroke	**2.57 (95%CI 1.07 – 6.18)**	**---**
Atrial fibrillation	**0.67 (95%CI 0.49 – 0.91)**	**0.71 (95%CI 0.52 – 0.97)**
Venous thromboembolism	**0.51 (95%CI 0.31 – 0.85)**	**0.43 (95%CI 0.26 – 0.72)**
Dyslipidemia	**1.89 (95%CI 1.09 – 3.27)**	**1.82 (95%CI 1.06 – 3.13)**

7.9 Figures

Figure 1. Histograms of the distribution of age at cancer diagnosis in the synthetic dataset (A) and the original dataset (B).

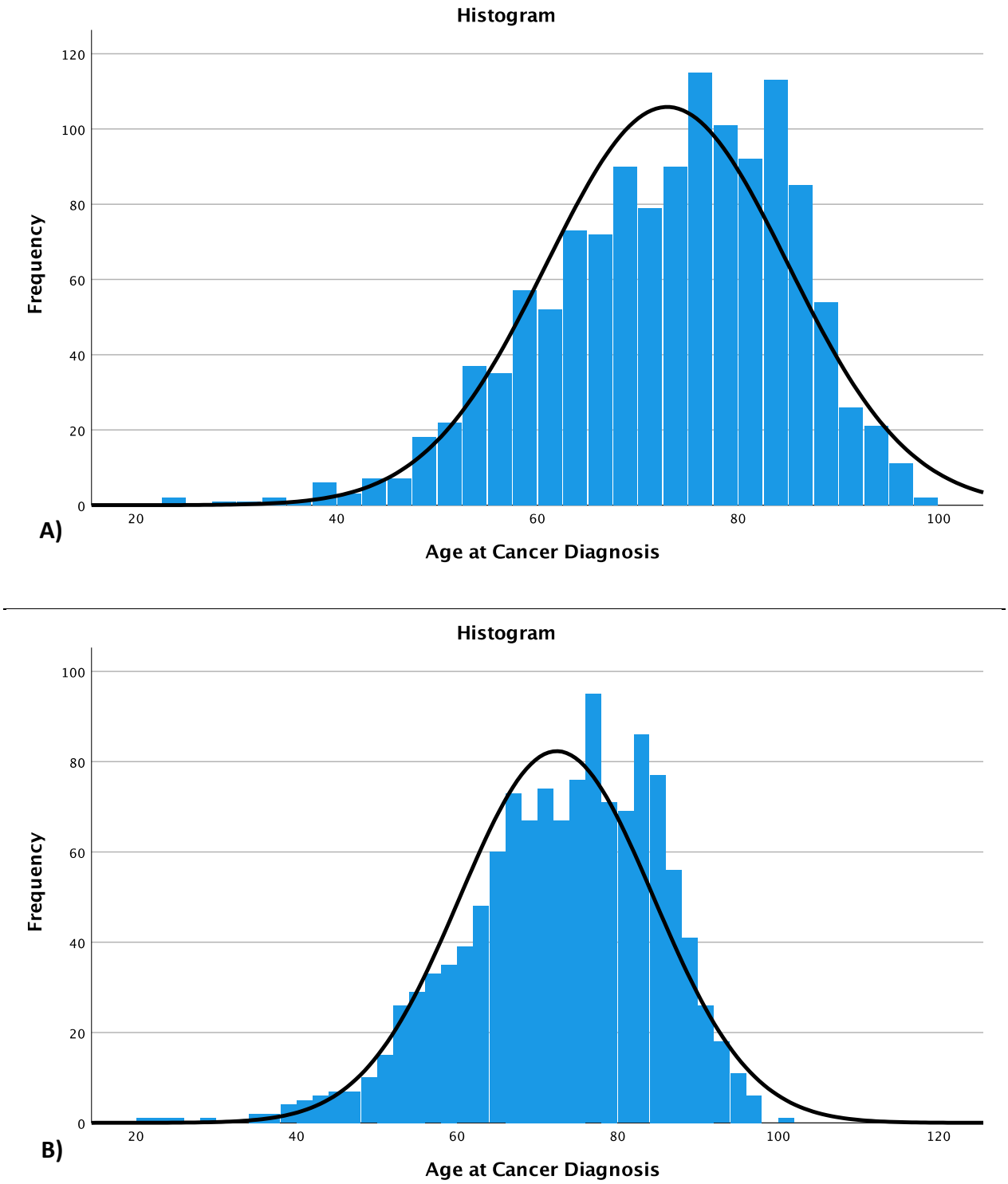
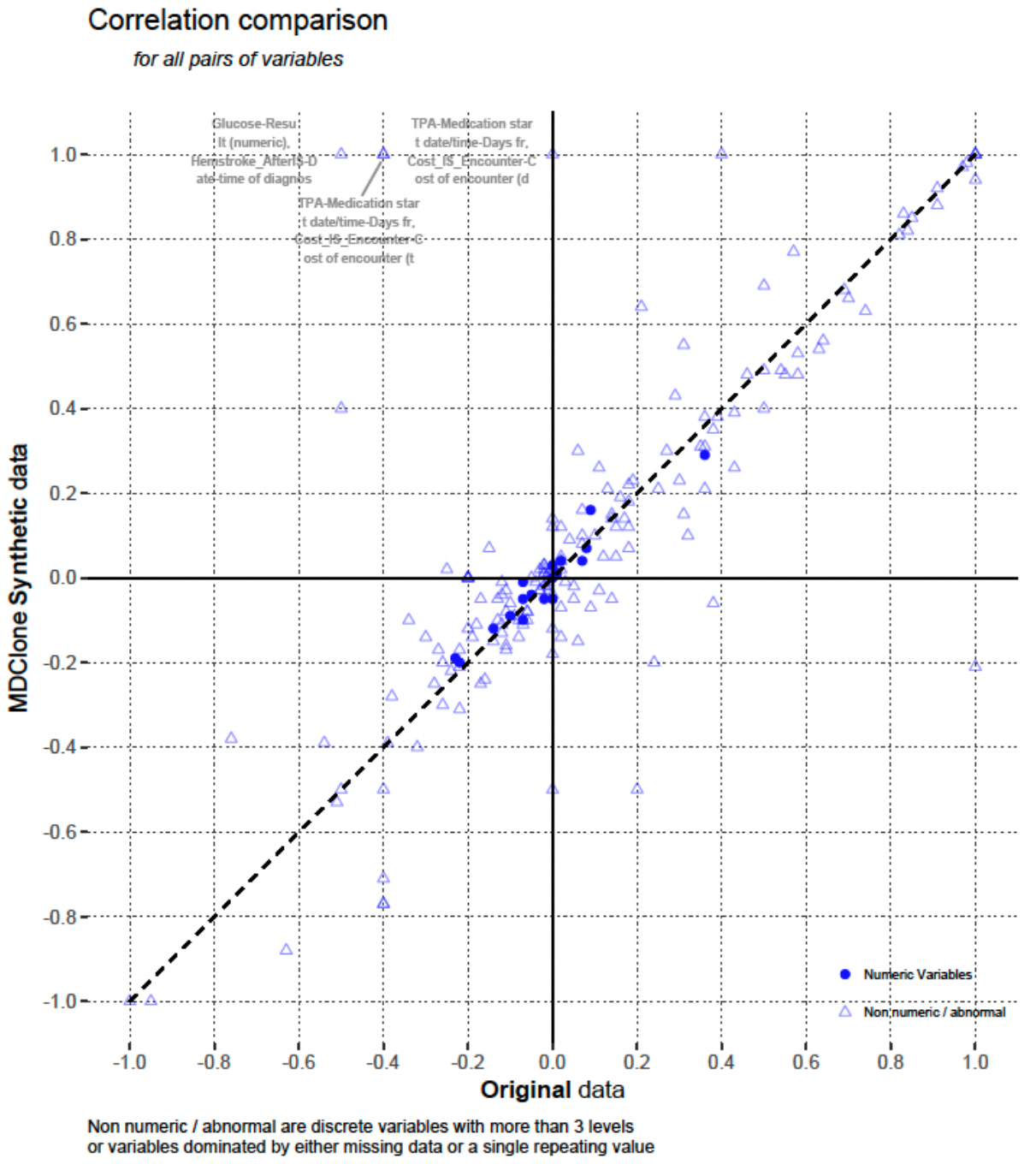


Figure 2. Spearman's correlation between all pairs of variables, comparing the correlation in the original dataset with the correlation of each pair in the synthetic dataset.



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APPENDICES

Appendix I. Submission confirmation of Chapter 2:
Lun R, Siegal D, Ramsay T, Dowlatshahi D. Stroke and Cancer: What do we Know and Where Do We Go? Journal of Thrombosis. Revisions ongoing.

Appendix II. Publication (PDF) of Chapter 3:
Lun R, Roy DC, Ramsay T, Siegal D, Shorr R, Fergusson D, et al. (2021) Incidence of stroke in the first year after diagnosis of cancer—A protocol for systematic review and meta-analysis. PLoS ONE 16(9): e0256825. https://doi.org/10.1371/journal.pone.0256825

Appendix III. Submission confirmation of Chapter 4:
Lun R, Roy DC, Hao Y, Deka R, Huang WK, B. Babak, Siegal DM, Ramsay T, Fergusson D, Shorr R, Dowlatshahi D. Incidence of Stroke in the First Year After Diagnosis of Cancer – A Systematic Review and Meta-Analysis. Frontiers in Neurology. Revisions Submitted.

Appendix IV. Ethics approval from Ottawa Health Science Network Research Ethics Board for Chapter 6 and 7.

Appendix V. Submission confirmation of manuscript from MSc Epidemiology course work (EPI5340 and EPI5341) (embargo):
Lun R, Shaw JR, Roy DC, Siegal D, Ramsay T, Chen Y, Dowlatshahi D. Effect Modification of Age on Cancer & Prevalence of Self-Reported Stroke – A Cross-Sectional Study. Cancer Medicine. Submitted March 2022.

Appendix VI. Synthetic file comparison report produced by MDClone for Chapter 7.

Appendix I. Submission confirmation of Chapter 2:
Lun R, Siegal D, Ramsay T, Dowlatshahi D. Stroke and Cancer: What do we Know and Where Do We Go? Journal of Thrombosis. Revisions ongoing.

Dear Dr. Lun,

Your submission entitled "Cancer and Stroke: What do we know and where do we go?" has been assigned the following manuscript number: TR-D-22-00566.

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Lun R, Roy DC, Ramsay T, Siegal D, Shorr R, Fergusson D, et al. (2021) Incidence of stroke in the first year after diagnosis of cancer—A protocol for systematic review and meta-analysis. PLoS ONE 16(9): e0256825. https://doi.org/10.1371/journal.pone.0256825

PLOS ONE

STUDY PROTOCOL

Incidence of stroke in the first year after diagnosis of cancer—A protocol for systematic review and meta-analysis

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Competing interests: The authors have declared that no competing interests exist.

Abstract

Introduction

There is an increased risk of stroke in patients with cancer–this risk is particularly heightened around the time of cancer diagnosis, although no studies have systematically quantified this risk in the literature. Patients newly diagnosed with cancer without prior stroke represent a highly susceptible population in whom there is a window of opportunity to study and implement primary prevention strategies. Therefore, the objective of this systematic review and meta-analysis is to identify the cumulative incidence of ischemic and hemorrhagic strokes during the first year after a diagnosis of cancer.

Methods and analysis

MEDLINE, EMBASE, and PubMed will be searched with the assistance from a medical information specialist, from 1980 until present. Eligible studies will include observational studies that have enrolled adult patients newly diagnosed with cancer and report outcomes of stroke during the first year of cancer diagnosis. We will exclude all randomized and non-randomized interventional studies. Data on participant characteristics, study design, baseline characteristics, and outcome characteristics will be extracted. Study quality will be assessed using the Newcastle-Ottawa Scale for cohort studies, and heterogeneity will be assessed using the I^2 statistic. Pooled cumulative incidence will be calculated for ischemic and hemorrhagic strokes separately using a random-effects model.

Ethics and dissemination

No formal research ethics approval is necessary as primary data collection will not be done. We will disseminate our findings through scientific conference presentations, peer-reviewed publications, and social media/the press. The findings from this review will inform clinicians and patients regarding the risk of stroke in patients newly diagnosed with cancer by

Appendix III. Submission confirmation of Chapter 4:
Lun R, Roy DC, Hao Y, Deka R, Huang WK, B. Babak, Siegal DM, Ramsay T, Fergusson D, Shorr R, Dowlatshahi D. Incidence of Stroke in the First Year After Diagnosis of Cancer – A Systematic Review and Meta-Analysis. Frontiers in Neurology. Revisions Submitted.

Dear Dr Lun,

The interactive review of your manuscript "Incidence of Stroke in the First Year After Diagnosis of Cancer -A Systematic Review and Meta Analysis" submitted to Frontiers in Neurology, section Stroke has now been activated.

Please respond by 14 Aug 2022 to all comments raised by the reviewers and editor in the online review forum. If a reviewer has finalized the review and discussion on the Reviewer tab is closed, you should submit a reply to pending comments in a new thread in the Editor tab. If necessary, you can also submit a revised version of your manuscript at that time. We encourage you to submit your documents with tracked changes to highlight the revisions.

To access the review forum and respond to the reviewers, please click on the following link:
[redacted]

Best Regards,
Your Frontiers in Neurology Team

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Manuscript title: Incidence of Stroke in the First Year After Diagnosis of Cancer -A Systematic Review and Meta Analysis
Manuscript ID: 966190
Authors: Ronda Lun, Danielle Carole Roy Bsc, Yu Hao, Rishi Deka Phd, Wen-Kuan Huang, Babak Navi, Deborah M Siegal, Tim Ramsay, Dean Fergusson, Risa Shorr and Dar Dowlatshahi
Journal: Frontiers in Neurology, section Stroke
Article type: Systematic Review
Submitted on: 10 Jun 2022

Appendix IV. Ethics approval from Ottawa Health Science Network Research Ethics Board for Chapter 6 and 7.

Ottawa Health Science Network Research Ethics Board (OHSN-REB) / Conseil d'éthique de la recherche du réseau de science de la santé d'Ottawa (CÉR-RSSO)
Civic Campus, Box 675, 725 Parkdale Avenue, Ottawa, Ontario, K1Y 4E9 613-798-5555 extension 16719 Fax: 613-761-4311
http://www.ohri.ca/ohsn-reb

Thursday, December 23, 2021

Dr. Dariush Dowlatshahi
The Ottawa Hospital - Civic Campus
Department of Medicine
Division of Neurology, C2182b
1053 Carling Avenue
Ottawa, ON K1Y 4E9

Dear Dr. Dowlatshahi:

RE: Protocol #20210399-01H - Ischemic Stroke in Patients with Cancer Compared to Ischemic Stroke in Patients Without Cancer – a Cohort Study Using MDClone Synthetic Data

Thank you for the email of December 21, 2021 from Zeinab Daham. I am pleased to inform you that your Amendment Request was reviewed by the Ottawa Health Science Network Research Ethics Board (OHSN-REB) and is approved.

Approval is for the following:
- Amendment form dated October 20, 2021.

Approval is effective as of: December 23, 2021.

Ethics approval remains in effect until May 28, 2022.

The OHSN-REB operates in compliance with, and is constituted in accordance with, the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations; or with the definition in the Interim Order Respecting Clinical Trials for Medical Devices and Drugs Relating to COVID-19; and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. OHSN-REB is qualified through the CTO REB Qualification Program and is registered with the U.S. Department of Health and Human Services (DHHS) Office for Human Research Protection (OHRP).

Appendix V. Manuscript embargo from MSc Epidemiology course work (EPI5340 and EPI5341):

Lun R, Shaw JR, Roy DC, Siegal D, Ramsay T, Chen Y, Dowlatshahi D. Effect Modification of Age on Cancer & Prevalence of Self-Reported Stroke – A Cross-Sectional Study. Cancer Medicine. Submitted March 2022.

CAUTION: External Mail. Do not click on links or open attachments you do not trust.
ATTENTION: Courriel externe. Ne cliquez pas sur des liens et n'ouvrez pas de pièces jointes auxquelles vous ne faites pas confiance.

26-Mar-2022

Dear Dr. Lun:

Your manuscript entitled "Effect Modification of Age on Cancer & Prevalence of Self-Reported Stroke – A Cross Sectional Study" by Lun, Ronda; Shaw, Joseph; Roy, Danielle; Siegal, Deborah; Ramsay, Tim; Chen, Yue; Dowlatshahi, Dar, has been successfully submitted online and is presently being given full consideration for publication in Cancer Medicine.

The submitting author is the contact author for this paper, as such all further correspondence will be sent to Dr. Ronda Lun.

Co-authors: Please contact the Editorial Office as soon as possible if you disagree with being listed as a co-author for this manuscript.

Your manuscript ID is CAM4-2022-03-1250.

Please mention the above manuscript ID in all future correspondence or when calling the office for questions. If there are any changes in your street address or e-mail address, please log in to ScholarOne Manuscripts at https://can01.safelinks.protection.outlook.com/?

[redacted]

information as appropriate.

You can also view the status of your manuscript at any time by checking your Author Center after logging in to https://can01.safelinks.protection.outlook.com/?

[redacted]

Thank you for submitting your manuscript to Cancer Medicine.

PLEASE NOTE: the Editorial office is currently experiencing a delay in receiving emails sent via Manuscript central/ScholarOne. To ensure your email is seen, we ask that if you have any queries to please contact cancermed@wiley.com directly. Thank you for your patience whilst we work to fix this.

Appendix VI. Synthetic file comparison report produced by MDClone for Chapter 7.

MDCLONE

MDClone Synthetic file comparison report

This report compares the quality of MDClone's synthetic data you have produced with the original data. If you are not familiar with the report please read the guide explaining how to read and understand the report.

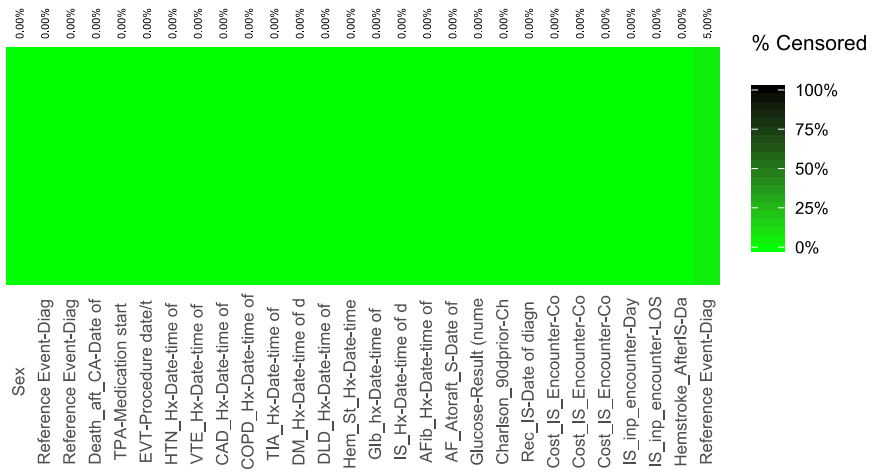
General

Comparison was created at Monday, March 28, 2022 15:58

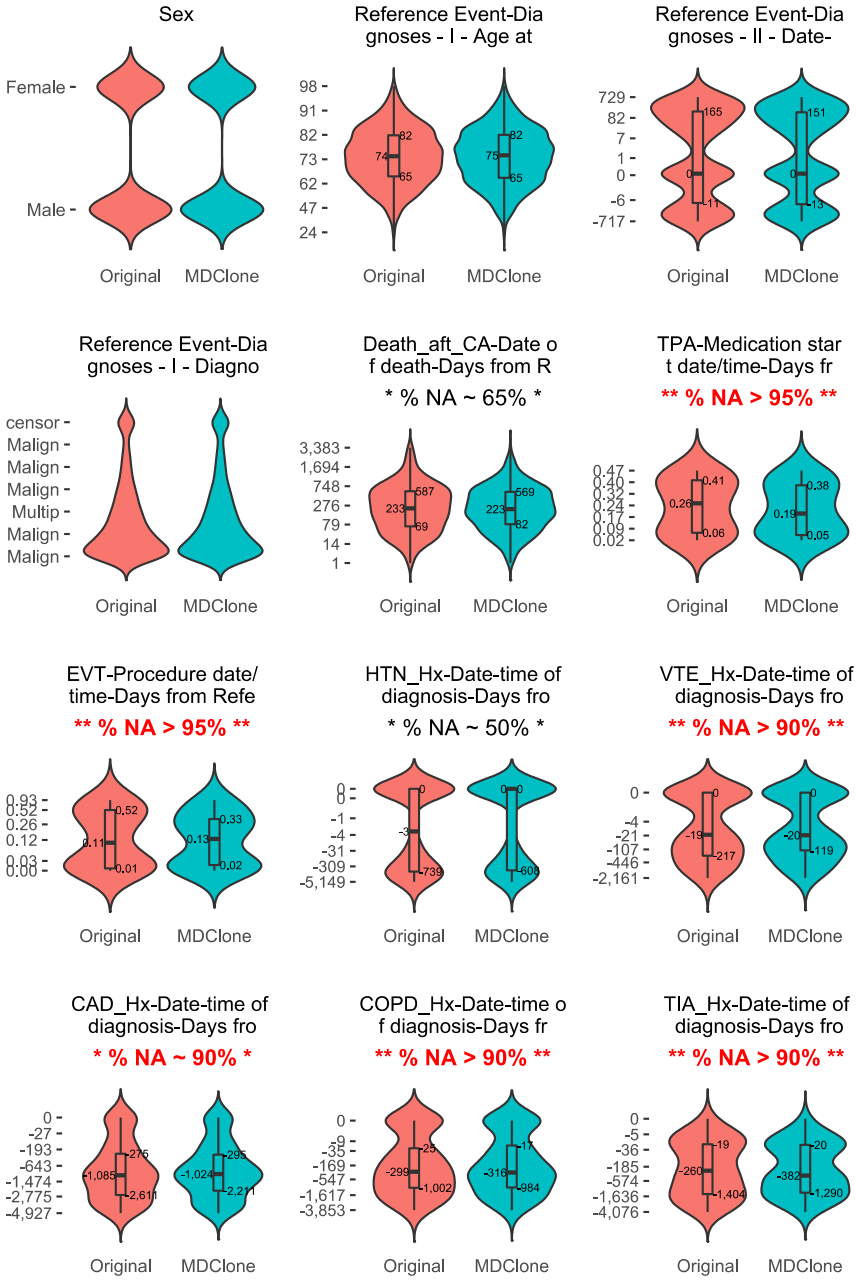
This file includes three parts: this page includes general information about the data and the comparison, followed by figures comparing the distribution of each variable in both original and synthetics data sets. Last there is a comparison of the correlations between each pair of variables.

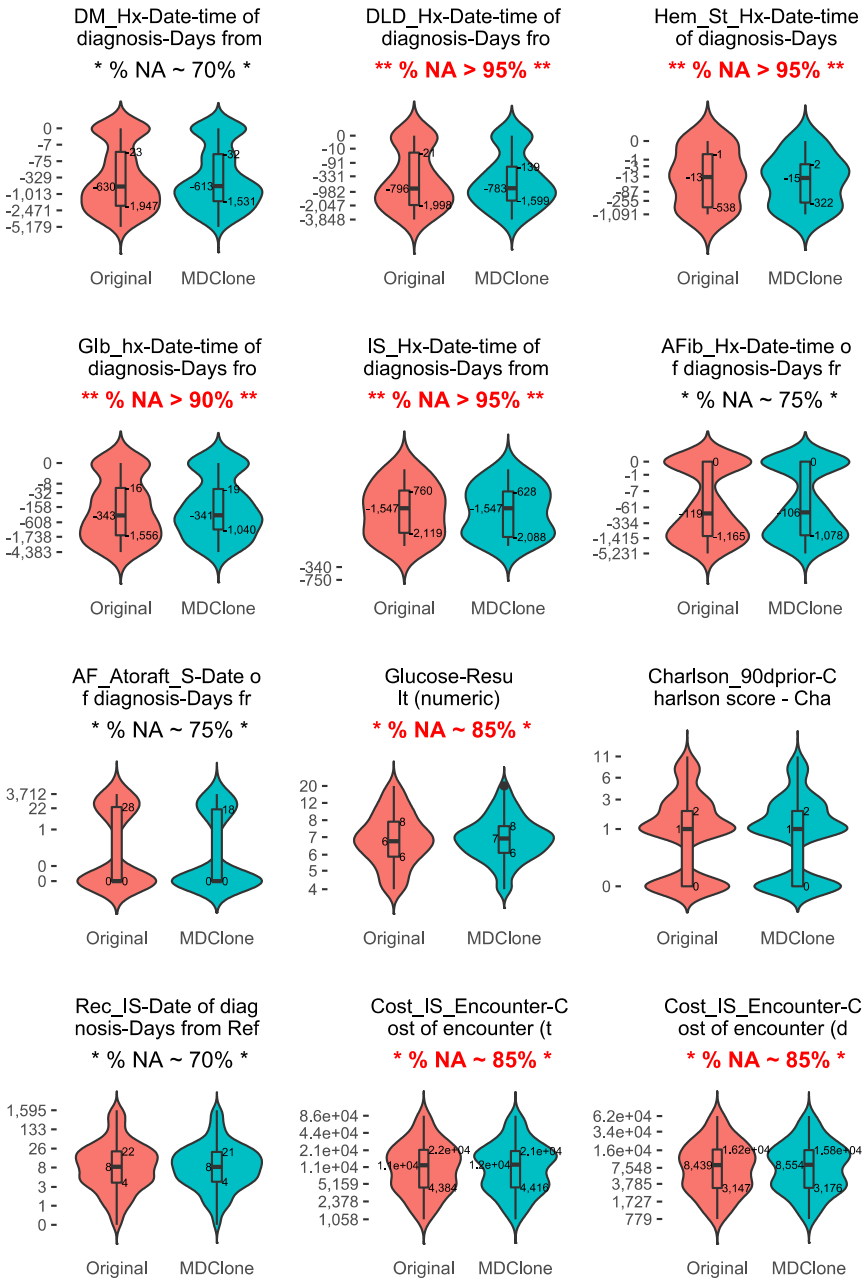
Synthetic Data includes 1,275 rows of data.

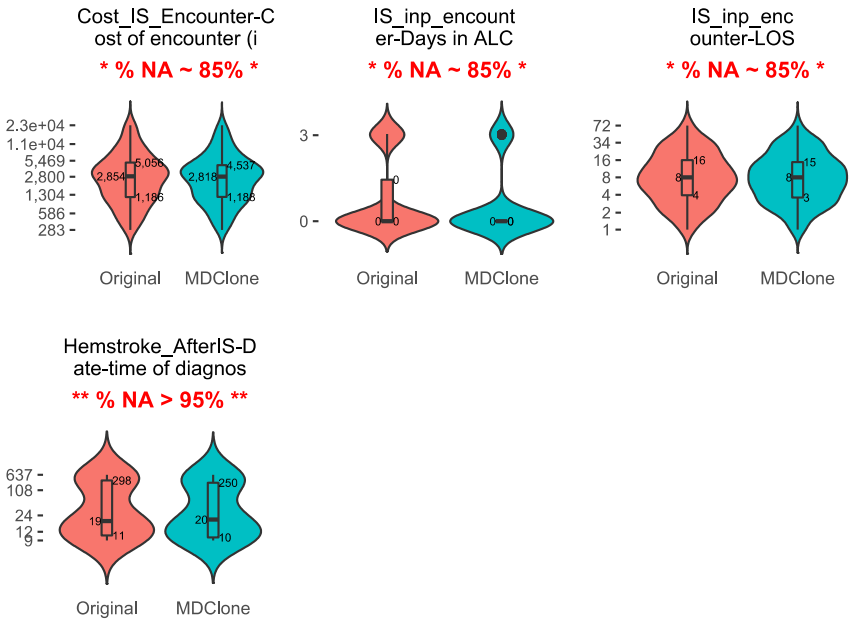
Approximately ~6.00% of the rows have some censoring. The following figure shows how much censoring occurs for each variable. A light green means no censoring (using the full original data) and black means heavy censoring.



Variables' distribution




DM_Hx-Date-time of diagnosis-Days from
* % NA ~ 70% *
0
-7
-75
-329
-1,013
-2,471
-5,179
33
-630
1,947
32
-613
1,531
Original
MDClone
DLD_Hx-Date-time of diagnosis-Days fro
** % NA > 95% **
0
-10
-91
-331
-982
-2,047
-3,848
21
-796
1,998
139
-783
1,599
Original
MDClone
Hem_St_Hx-Date-time of diagnosis-Days
** % NA > 95% **
0
-1
-13
-87
-295
-1,091
1
-13
538
2
-15
322
Original
MDClone
Glb_hx-Date-time of diagnosis-Days fro
** % NA > 90% **
0
-8
-32
-158
-608
-1,738
-4,383
16
-343
1,556
19
-341
1,040
Original
MDClone
IS_Hx-Date-time of diagnosis-Days from
** % NA > 95% **
-340
-750
760
-1,547
2,119
628
-1,547
2,088
Original
MDClone
AFib_Hx-Date-time of diagnosis-Days fr
* % NA ~ 75% *
0
-1
-7
-61
-334
-1,415
-5,231
0
-119
1,165
0
-106
1,078
Original
MDClone
AF_Atoraft_S-Date of diagnosis-Days fr
* % NA ~ 75% *
3,712
22
1
0
0
28
0
0
18
0
0
Original
MDClone
Glucose-Result (numeric)
* % NA ~ 85% *
20
12
8
7
6
5
4
8
6
6
8
7
6
Original
MDClone
Charlson_90dprior-Charlson score - Cha
11
6
3
1
0
2
1
0
2
1
0
Original
MDClone
Rec_IS-Date of diagnosis-Days from Ref
* % NA ~ 70% *
1,595
133
26
8
3
1
0
22
8
4
21
8
4
Original
MDClone
Cost_IS_Encounter-Cost of encounter (t
* % NA ~ 85% *
8.6e+04
4.4e+04
2.1e+04
1.1e+04
5,159
2,378
1,058
2.2e+04
1.1e+04
4,384
2.1e+04
1.2e+04
4,416
Original
MDClone
Cost_IS_Encounter-Cost of encounter (d
* % NA ~ 85% *
6.2e+04
3.4e+04
1.6e+04
7,548
3,785
1,727
779
1.62e+04
8,439
3,147
1.58e+04
8,554
3,176
Original
MDClone


Cost_IS_Encounter-Cost of encounter (i
* % NA ~ 85% *
2.3e+04
1.1e+04
5,469
2,800
1,304
586
283
5,056
2,854
1,186
2,818
1,537
1,186
Original
MDClone
IS_inp_encounter-Days in ALC
* % NA ~ 85% *
3
0
0
0
0
0
Original
MDClone
IS_inp_encounter-LOS
* % NA ~ 85% *
72
34
16
8
4
2
1
16
8
4
15
8
3
Original
MDClone
Hemstroke_AfterIS-Date-time of diagnos
** % NA > 95% **
637
108
24
12
9
298
19
11
250
20
10
Original
MDClone

Correlations

Finally, here is a graph of Spearman's correlation between all pairs of variables, comparing the correlation in the original data set with the correlation of each pair in MDClone's synthetic data.
When the correlations in the synthetic data are identical to the correlations in the original data they are on the diagonal.