Cancer-Associated Ischemic Stroke

The Bergen NORSTROKE Study

Henriette Aurora Selvik

Thesis for the Degree of Philosophiae Doctor (PhD)
University of Bergen, Norway
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Bergen Stroke Research Group

UNIVERSITY OF BERGEN

Contents

List of Abbreviations

AF Atrial fibrillation

ADL Activities of daily living

AUC Area under curve

BMI Body mass index

CNS Central nervous system

CVD Cardiovascular disease

CI Confidence interval

COPD Chronic obstructive pulmonary disorder

CAD Coronary artery disease

CRP C-reactive protein

CP Cancer procoagulant

CTC Circulating tumor cell

CT Computed tomography

CTA Computed tomography angiography

DIC Disseminated intravascular coagulation

DOAC Direct oral anticoagulant

DALY Diseases adjusted life year

DM Diabetes mellitus

DWI Diffusion-weighted imaging

DNT Door-to-needle time

ECG Electrocardiography

ED Emergency Department

EVs Extracellular vesicles

EVT Endovascular treatment

FDP Fibrinogen degradation product

GCS Glasgow coma scale

GBD Global burden of disease

Hb Hemoglobin

HT Hypertension

HL Hyperlipidemia

IA Intra-arterial

ICH Intracerebral hemorrhage

IS Ischemic stroke

IV Intravenous

IGF Insulin-like growth factor

IL Interleukin

LMWH Low molecular weight heparin

LMIC Low- and middle income countries

LVO Large vessel occlusion

MACI Multiple acute cerebral infarcts

MCA Middle cerebral artery

MI Myocardial infarction

MRI Magnetic resonance imaging

mRS Modified Rankin scale

NETs Neutrophil extracellular traps

NCD Noncommunicable Disease

NIHSS National Institutes of Health Stroke Scale

OR Odds ratio

PFO Patent foramen ovale

PAI Plasminogen activator inhibitor

ROC Receiver operating characteristic

SAH Subarachnoid haemorrhage

SES Socioeconomic status

TEE Thromboembolic event

TF Tissue factor

TNF Tumor necrotizing factor

TIA Transient ischemic attack

TOAST Trial of Org 10172 in Acute Stroke Treatment

tPA Tissue plasminogen activator

WHO World Health Organization

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Abstract

Background: Stroke and cancer are both leading causes of death and disability in the Western world. Cancer can lead to a hypercoagulable state that can cause ischemic stroke. Mechanisms include disturbance of the coagulation cascade, tumor substance secretion, infections and non-bacterial endocarditis. Many types of cancer also share a similar risk factor profile to that of ischemic stroke. The cancer-stroke connection has not previously been studied in Norway. Further knowledge on which subgroups of patients are at highest risk for both stroke and cancer, as well as on how to recognize a cancer-associated stroke is needed.

Methods and materials: The studies 1-3 are the foundation of the present thesis. All papers have used data from The Norwegian Stroke Research Registry (NORSTROKE). NORSTROKE is a comprehensive, prospective registry that since February 2006 has included all stroke patients admitted to the Stroke Unit at Haukeland University Hospital. For the present studies, the medical charts of all stroke patients were reviewed for collection of cancer diagnoses. Cancer data was quality assured through linking NORSTROKE to The Cancer Registry of Norway.

Results: From August 2006 through August 2011, 1511 patients with ischemic stroke were registered in NORSTROKE. In study I, patients with cancer post stroke were excluded. In study I, a total of 1456 patients were included, of whom 229 (15.7 %) had cancer prior to index stroke. The prevalence of stroke was higher in stroke patients compared to the general population below the age of 70.

In study II, patients with cancer pre stroke were excluded. In study II, a total of 1282 patients were included, of whom 55 (4.3 %) were diagnosed with cancer post index stroke. In study III, the inclusion period was extended and patients with inactive cancer were excluded. In study III, 1646 patients were included in the study, of whom 82 (5.0 %) had active cancer.

The most common cancer types overall were cancer of the; colon, prostate, breast, lung, bladder, uterus and ovaries as well as of unknown primary site. Patients with active cancer had similar risk factors to patients without a history of cancer. Active cancer in stroke patients was associated with smoking, age, increased D-dimer and

decreased hemoglobin. Active cancer was also associated with stroke of unknown etiology.

Conclusions: The prevalence of cancer was higher in stroke patients compared to the general population below the age of 70. Findings in patients with cancer-associated ischemic stroke were elevated D-dimer, signalling hypercoagulation, lower hemoglobin and a history of smoking. These factors may also be used to predict active cancer in stroke patients and thus indicate which stroke patients could be screened for underlying cancer.

List of publications

The thesis is based on the following papers:

Paper I: **Prior Cancer in Patients with Ischemic Stroke: The Bergen NORSTROKE Study**.

Selvik HA, Thomassen L, Logallo N, Naess H.

Journal of Stroke and Cerebrovascular Diseases, 2014.

Paper II: **Cancer-Associated Stroke: The Bergen NORSTROKE Study**.

Selvik HA, Thomassen L, Bjerkreim AT, Naess H.

Cerebrovascular Diseases Extra, 2015.

Paper III: **When to Screen Ischaemic Stroke Patients for Cancer.**

Selvik HA, Bjerkreim AT, Thomassen L, Waje-Andreassen U, Naess H, Kvistad CE.

Cerebrovascular Diseases, 2018.

Introduction

The brain as an organ is in many ways still a great mystery. Millions upon millions of neurons fire in an intricate network to shape our thoughts, our actions and our very sense of being. It can seem quite surreal that this grey, gelatinous matter is not only what gives us feelings, enables reason and reflections, gives us hopes and ambitions, creates the perception of our surroundings, but also what defines us as a species.
In neuroscience this is referred to as The Binding Problem;[1-5] the lack of explanation for how the electronic firings of the neurons all come together, shaping our consciousness.

There are endless unanswered questions regarding the brains workings, potential for rehabilitation and plasticity.[6-9] One thing is however certain; if the brain is damaged or impaired, it is often striking, and for a patient with functions temporarily or permanently lost, it can be life altering. The brain holds our personality and maintains our abilities. In order to uphold these defining functions, the brain requires constant blood flow for supply of oxygen and energy. Even brief disruptions in blood flow can have grave consequences, which is often the case in an ischemic stroke.

The foundation for the following thesis

While working in the Stroke Unit at Haukeland University Hospital, Professors Næss and Thomassen observed that a number of ischemic stroke patients had a medical history that included cancer. For some ischemic stroke patients, cancer was first diagnosed during the stroke work-up in the Stroke Unit. This founded the hypothesis for this project and thesis; cancer is a risk factor for ischemic stroke.
While cancer can cause hypercoagulability, leading to ischemic stroke, ischemic stroke and cancer also share a number of risk factors, increasing the risk for both diseases.[10]

Ischemic stroke

Definition of ischemic stroke

The classic definition of stroke from the World Health Organization (WHO) was "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin".[11] However, the definition is under constant review as stroke science, diagnostics and imaging techniques are changed and improved. Stroke has later been defined as neurological symptoms or deficit lasting >24 h or transient ischemic attacks where CT or MRI shows infarctions related to the clinical findings.[12]

The most recent consensus on defining stroke from the American Heart Association/American Stroke Association provides a broader definition and is shown in table 1.[13]

Table 1. Definition of stroke.

The term "stroke" should be broadly used to include all of the following definitions of:
Central Nervous System (CNS) infarction: CNS infarction occurs after brain, spinal cord, or retinal cell death attributable to ischemia, documented by
1. pathological imaging, or other objective evidence of cerebral, spinal cord, or retinal focal ischemic injury in a defined vascular distribution; or
2. clinical evidence of cerebral, spinal cord, or retinal focal ischemic injury based on symptoms persisting ≥24 hours or until death, and other etiologies excluded.
Ischemic stroke: An episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction.
Silent CNS infarction: Imaging or neuropathological evidence of CNS infarction, without a history of acute neurological dysfunction attributable to the lesion.
Intracerebral hemorrhage: A focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma.
Stroke caused by intracerebral hemorrhage: Rapidly developing clinical signs of neurological dysfunction attributable to a focal collection of blood within the brain parenchyma or ventricular system that is not caused by trauma.
Silent cerebral hemorrhage: A focal collection of chronic blood products within the brain parenchyma, subarachnoid space, or ventricular system on neuroimaging or neuropathological examination that is not caused by trauma and without a history of acute neurological dysfunction attributable to the lesion.
Subarachnoid hemorrhage: Bleeding into the subarachnoid space (the space between the arachnoid membrane and the pia mater of the brain or spinal cord).
Stroke caused by subarachnoid hemorrhage: Rapidly developing signs of neurological dysfunction and/or headache because of bleeding into the subarachnoid space (the space between the arachnoid membrane and the pia mater of the brain or spinal cord), which is not caused by trauma.
Stroke caused by cerebral venous thrombosis: Infarction or hemorrhage in the brain, spinal cord, or retina because of thrombosis of a cerebral venous structure. Symptoms or signs caused by reversible edema without infarction or hemorrhage do not qualify as stroke.
Stroke, not otherwise specified: An episode of acute neurological dysfunction presumed to be caused by ischemia or hemorrhage, persisting ≥24 hours or until death, but without sufficient evidence to be classified as one of the above.

Adapted from Sacco et al., Stroke, 2013.[13]

Stroke pathophysiology – time is of the essence

In an ischemic stroke (IS), the patient suffers a cerebral infarction as a result of the disruption of blood supply to a part of the brain. This disruption is caused by hypoperfusion or obstruction; either from local thrombosis, emboli, severe stenosis due to atherosclerosis, inflammation, dissection or other causes. Estimates show that 87 % of all strokes are ischemic, whereas 10 % are haemorrhagic strokes, the result of a spontaneous intracerebral haemorrhage (ICH), and approximately 3 % are caused by subarachnoid haemorrhage (SAH).[14] If a patient has clinical symptoms of a stroke that subside within 24 hours, imaging is normal and differential diagnoses have been ruled out, the patient has likely suffered a transient ischemic attack (TIA). In a TIA, the blood supply to part of the brain is temporarily obstructed. TIA can be an early warning sign of an ischemic stroke, and a comprehensive review study show that TIA patients have a risk from 0.9 to 11.0 % of suffering an ischemic stroke within one week, depending on access to emergency care and specialist stroke services, and should be treated urgently.[15] For the following year after TIA, the patients have a 5.1 % risk of stroke.[16] In contrast to a TIA, an IS causes permanent damage to the brain due to severe disruption of blood flow; an infarction is established. The term infarction is derived from the Latin word “infarctus”,[17] which means “stuff into”.

Ischemic tissue will through the disruption of blood supply have an oxygen deprivation, to the extent of metabolic demand no longer being feasible. The pathological lack of oxygen and nutrients will cause excitotoxicity, mitochondrial alterations, oxidative stress from free radicals and protein misfolding, as well as an inflammatory response.[18] Cells in the infarcted area will be unable to uphold cell homeostasis and affected neurons, endothelial cells and surrounding glia will be injured or die.

Even though our brain only constitutes about 2 % of our body weight, it requires approximately 20 % of total oxygen consumption.[19, 20] Within minutes without oxygen, neurons will start to die. Collateral circulation to the area with restricted blood supply will often determine the final size of the infarcted area.

However, collaterals may shut down as processes are dynamic; especially in the acute

phase after infarction. Also, the peripheral zone of the infarction, the penumbra, can survive the stroke if reperfusion is rapid. Predicting the exact size of the infarcted area is therefore quite difficult. Though time is indicative of the progression of pathophysiological processes, growth of the infarction in the acute phase is dynamic, and shows great inter-individual variability.[21, 22]

When a stroke occurs, the expression "time is brain" is used with due cause. Humans are born with an average of 90 billion neurons,[23] and in an untreated ischemic stroke, up to 2 million neurons die per minute.[24] Thus, after initiating acute stroke treatment and intervention, immediate transportation to a comprehensive stroke center is crucial, in order to ensure the best and fastest recanalization possible.

Acute stroke treatment and management

The main goal of stroke treatment is early recanalization. Penumbral tissue, still alive and within the threshold of cell homeostasis, is located in the peri-infarct area and is still salvageable.[25-27] Acute ischemic stroke treatment comprises intravenous (IV) thrombolysis with tissue plasminogen activator (tPA) and endovascular treatment (EVT). Thrombolytic agents convert plasminogen into plasmin, the primary fibrinolysin; thereby instigating lysis of the occluding thrombus (Figure 2).[28, 29]

The IV tPA alteplase, Actilyse ®, was approved for stroke treatment by the American Food and Drug Administration in 1996, whereas the Norwegian Medicines Agency first approved it as standard stroke treatment in 2003. Today, other tPAs, such as tenectaplase, Metalyse ®, have been tested for use in acute stroke with promising results. All stroke patients in the present thesis received the thrombolytic agent alteplase if thrombolysis was indicated.

The ground-breaking "National Institute of Neurological Disorders and Stroke rt-PA" (NINDS) and European Cooperative Acute Stroke Study (ECASS) trials in 1995 proved the benefit of thrombolytic treatment within 3 hours post stroke onset.[30] However, since ECASS III in 2008, 4.5 hours has been the accepted treatment window.[31, 32, 33] Even though IV tPA treatment can be administered up until 4.5 hours,

faster treatment leads to better clinical outcome.[32] Hence the focus on so-called door-to-needle time (DNT); the time from an IS patient's arrival to the Emergency Department (ED) to administration of IV tPA. Demonstrating just how time-critical thrombolysis treatment is, the thrombolysis review by Meretoja et al in Stroke from 2014 concluded with "save a minute save a day". They showed that for each minute the DNT was reduced, patients gained an average of 1.8 days of disability-free life.[34]

IV tPA alone is not always successful in obtaining recanalization, especially when a larger blood clot is located in a branch of a main artery. EVT can, when indicated, provide a more effective revascularization and better clinical outcome.[35-37] In 2015, the results of five major EVT-trials were published, proving EVT's efficacy and safety.[35] EVT consists of thrombectomy with or without intra-arterial (IA) thrombolysis, and thrombectomy is today the recommended standard of care for IS patients with large vessel occlusion (LVO) in the anterior circulation.[35, 38, 39] EVT is also performed for occlusions in the posterior circulation on a case by case basis. Posterior occlusions often entail fatal outcomes with or without EVT, and the chosen treatment is therefore varied.[40-42]

EVT procedures will likely increase dramatically in the coming years, as the recently published DAWN trial demonstrated an effect of EVT up to 24 hours after stroke onset in selected patients.[38, 43-45] After the implementation of EVT in stroke treatment, the consensus has turned into "save a minute save a week", since it has been shown that reducing the stroke onset to thrombectomy time by a minute could give a patient an extra 4.2 days of disability-free life.[46]

Ideally, all IS patients should be transported directly to a comprehensive stroke center that offers tPA, as well as EVT, when indicated. However, due to geographical and resource limitations, this is not always feasible. This is when the so-called "Drip and ship" method is used.[47] Thrombolytic treatment is then initiated, the drip, prior to transport to a stroke center for possible endovascular treatment, hereby using IV tPA as bridging and starting acute treatment with the aim of removing the clot.

The last stance of stroke treatment will for certain patients be a decompressive hemicraniectomy (DHC). When an MCA infarction causes edema, leading to

malignant increase of the intracerebral pressure, a malignant infarction with an ensuing 80 % mortality occurs. Of all stroke patients, about 10 % will suffer from the potentially fatal malignant infarction.[48] DHC avoids herniation and consequently reduces mortality in these patients.[49, 50]

No matter what acute stroke treatment is initially chosen by the on-call neurologist and intervention radiologist in the ED, all stroke patients admitted to Haukeland University Hospital are transferred to the Stroke Unit for observation and continued treatment to restore and maintain homeostasis. Stroke progression and symptoms are monitored by use of repeated scores with the National Institutes of Health Stroke Scale (NIHSS) according to the Stroke Unit`s standardized operating procedures.

Cardiovascular risk factors

Stroke and other cardiovascular diseases (CVD) have a high prevalence and incidence and are affected by several risk factors. CVD risk factors are dichotomized as modifiable and non-modifiable risk factors. Examples of non-modifiable risk factors are age, sex, genetic disposition and ethnicity. Modifiable risk factors are often affected by the environment and socioeconomic status (SES), but can be influenced through choices of lifestyle.[51] Some environmental, modifiable risk factors, such as air pollution,[52] are influenced by governmental policy more than the choices of the individual.[53] The traditional CVD risk factors are hypertension (HT), hyperlipidemia (HL), diabetes mellitus (DM), atrial fibrillation (AF), coronary artery disease (CAD), peripheral artery diseases (PAD) and carotid stenosis, obesity, physical inactivity, poor diet, and smoking. [54-56]

Risk factors that have not yet been documented as thoroughly are migraine, metabolic syndrome, heavy alcohol consumption, drug abuse, sleep-disordered breathing, hyperhomocysteinemia, inflammation and infection, and finally, hypercoagulability, including an acquired hypercoagulable state.[54]

Epidemiological studies have shown us that the risk of CVD increases with each added risk factor, and that risk factors not only appear in clusters, but also have the ability to potentiate each other.[57] For instance, for patients with DM type 2, the risk of cardiovascular complications is somewhere between 2- 4 times higher than in a healthy person.[58]

Stroke risk factors vary greatly between age strata and stroke etiologies.[59-61] Stroke is in no way a strictly geriatric disease, as also children may suffer stroke. Age nevertheless remains the most important risk factor for ischemic stroke in adults. Approximately 60 % of all stroke patients are above 75 years of age when they suffer their first stroke.[62]

A recent large-scale study comparing stroke risk factors globally, found that 90 % of all stroke cases are associated with ten modifiable risk factors.[63] Many of these are also risk factors for cancer.

Shared risk factors for CVD and cancer

Many risk factors are important in both ischemic stroke and cancer causality. These include risk factors on a macro level, such as air pollution,[64] to the micro level of the inflammatory response of our immune system to various stimuli.

Because CVD and cancer share risk factors, the WHO now recommends that we direct preventative efforts at CVD and cancer conjointly.[65] The four modifiable risk factors that have gained special attention are diet, sedentary lifestyle, tobacco use and obesity.[66] Recent evidence shows that CVD and cancer have pathophysiological factors in common and that these factors can cause both disease entities.[67] The shared biology of the risk factors is mainly through inflammation and oxidative stress.[10] Obesity, hyperglycemia, hyperlipidemia, hypertension, alcohol consumption, tobacco use, as well as other chronic diseases, all induce inflammation. [68] Inflammation mediates all stages of atherosclerosis, including thrombosis, and also promotes carcinogenesis and tumor progression.[10] Inflammation is also known to induce oxidative stress and reactive oxygen species, another biological factor shared by CVD and cancer.[69] Oxidative stress and its free radicals can alter lipids, proteins and DNA, and is seen in pathogenesis of cancers, atherosclerosis as well as inflammation.[70]

Tobacco use

Smoking is the primary cause of the most harmful non-communicable diseases (NCDs) globally; cancer, CVD, diabetes and chronic respiratory disorders.[53] Smoking was responsible for over 100 million deaths in the 20th century, and therefore has smoking cessation been a global public health target. Less smoking has resulted in an overall tobacco reduction in the past decade, also in Norway.[71] This will lower the risk of CVD and stroke, albeit, not with immediate effect. Smoking has a so-called delayed disease burden, thus in cancer epidemiology it takes three decades to see a reduction in lung cancer rates after smoking cessation.[66]

In the Nordic countries where snuff (smokeless tobacco) is in large replacing prior smoking, it can be speculated if we will see snuff use as a shared risk factor in the future. At present, the epidemiological studies of snuff and health outcomes have

found no increased risks for long-term morbidity or mortality connected to snus-use.[72] However, similar to smoking, snuff gives a temporary increase in blood pressure, and should therefore be used by caution by patients with known CVD.[73] Tobacco products in general contain nicotine that leads to a vasoconstriction of blood vessels and increases the blood pressure. Smoking is also proinflammatory.
The combustion reaction in smoking will also create carbon monoxide and nitrosamines, known carcinogens, and other oxidizing agents. Toxic to the cardio-respiratory system, they increase the risk of CVD and lung cancer, as well as the risk of other cancer types, such as cancer of the larynx, kidneys, esophagus, stomach, oral cavity and bladder, as well as acute leukemia.[53] Nicotine has also been shown to enhance angiogenesis and inhibit apoptosis.[74]

Obesity

Alarmingly, more than one third of the adult population is obese.[75] Obesity increases the risk for both cardiovascular and cancer, as well as mortality from both diseases. Epidemiological studies show that up to 20 % of all cancers are related to obesity,[76] and the risk of cancer increases with an increasing body mass index (BMI). Obesity has now been linked to cancer of the pancreas, colon, breast, liver, endometrial, kidneys, and esophageal adenocarcinoma.[10] The connection between obesity, CVD and cancer is especially intricate compared to other risk factors as obesity fosters other traditional CVD risk factors like metabolic syndrome, DM, HT, HL and hyperglycemia. Moreover, the other modifiable risk factors, such as physical activity and diet, greatly determine the degree of obesity and vice versa. Adipose tissue produces hormones and cytokines that may have altering effects on metabolic functions. Hormones, like leptin and insulin-like growth factor (IGF), and adipokines, cytokines from adipose tissue, can be proinflammatory and prothrombotic,[77] as well as have tumorigenic effects. The cytokine produced at the highest rate by adipose tissue is interleukin-6 (IL-6), which instigates hypertension. IL-6 also stimulates the liver to produce C-reactive protein (CRP). It has been shown that increased CRP is an independent risk factor for CVD events.[78]

Sedentary lifestyle

A sedentary lifestyle is a risk for cancer and CVD, as well as for other CVD risk factors like obesity, DM, HT and HL. Regular exercise can decrease the incidence of cancer, specifically, cancer of the colon, breast and endometrium, and reduce the risk of cardiovascular disease.[79] Exercise has many positive effects; from strengthening our skeleton to maintaining the functions of our vessel musculature. Again overlapping with the other risk factors, living a sedentary lifestyle disposes obesity and thus adipose tissue increase, with its production of proinflammatory and prothrombotic cytokines and hormones, insulin and leptin.

Diet and alcohol

The link between diet and CVD risk is well established, but the link is, like obesity, facilitated by other CVD risk factors such as BMI, HT and level of serum lipids. Consensus from the World Heart Federation is that a good diet, with the lowest risk of leading to CVD or cancer, is high in fruits, vegetables, whole grains, legumes, fish and nuts.[80] A diet often recommended is therefore the Mediterranean diet because it is low in sugar, saturated fats and sodium. A Mediterranean diet can decrease the risk of cancer, such as colon cancer, and also provide cardiovascular protection.[81] A linear relationship between red meat consumption and colon cancer has recently been shown,[82] while the colon cancer risk decreases with a diet high in fruits and fiber. The colon cancer risk is hypothesized to result from chronic inflammation. Low folate intake increases the risk of CVD and cancer, and lack of folate has been shown to contribute in the atherosclerosis pathogenesis. Intake of polyphenols, found in fruits and vegetables, have also been shown to protect against CVD and cancer.[83] Polyphenols are micronutrients with antioxidant properties.[84] Alcohol in moderate quantities, in otherwise healthy persons, has been postulated to be CVD-protective. This is also due to alcohol's polyphenol content and polyphenols' effect of decreased inflammation and antithrombotic capacities.[85, 86] Higher alcohol consumption is on the contrary associated with increased CVD and CVD mortality, as well as cancers of the entire gastrointestinal tract, liver, larynx and breast.[10] Alcohol has been associated

with triggering AF, inducing HT, increased triglycerides and polymorphisms in the genes; thus linking alcohol to both CVD and cancer. [87]

Diabetes mellitus

Diabetes mellitus (DM) is known as one of the traditional CVD risk factors because it effects the macro- and microvasculature. With the increasing incidence of obesity, the incidence of DM type II also increases. DM is linked to development of atherosclerosis through insulin resistance and hyperglycemia causing endothelial dysfunction and dyslipidemia.[10]

In the last decades, studies have also shown that DM is associated with cancer of the colon, breast, liver, pancreas, endometrium and bladder. [88] DM causes inflammation through hyperglycemia, hyperinsulinemia and IGF, which contributes to CVD pathogenesis and induces cell proliferation in tumors.

The cancer-stroke connection

Definition of cancer

Cancer is by definition an uncontrolled and continuous division of cells, from any tissue or place in the body.[89] In a healthy individual, cell functions, cell division included, are strictly regulated through cell signals; certain signals induce an action or process, others suppress it. A cancerous cell has become autonomous and is therefore no longer stimulated by the natural cell signals and regulations. The cancer cells have undergone multiple mutations increasing exponentially with every division. Often, these mutations provide the cancer cells with the ability to override any signal of apoptosis, the programmed cell death.[90] Avoiding apoptosis permits the uncontrolled growth.

When a solid cancer develops, it breaks through the basal membrane of the epithelium, no longer respecting its natural boundaries. First it becomes an invasive tumor which invades nearby tissue. Thereafter the invasive tumor will shed cancer cells that spread to distant sites through the lymph – or blood vessels. These shed cells may induce growth of new tumors, metastasize, depending on metastasis-progression genes and expression.[91] The development of solid cancer is portrayed in Figure 1. For cancers of the blood or bone marrow, the development is different, but still a result of a series of mutations.[92]

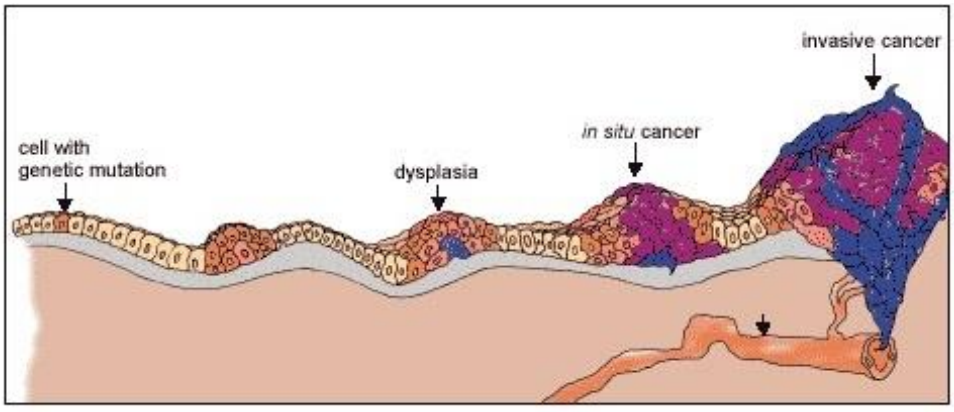
There are more than one hundred different types of cancer, yet some occur more frequently than others.[89] Globally, the cancers with the highest incidence are breast cancer, pulmonary cancer (including tracheal, bronchus and lung cancer), colorectal cancer, prostate cancer, stomach cancer, gynecological cancer (including ovarian, uterine and cervical cancer), liver cancer, Non-Hodgkin lymphoma and leukemia.[93] The incidence of each cancer type various greatly between countries, and depends both on genetics and risk factors.[94] Any incidence will also be contingent on the infrastructure of the local healthcare system; for example if registration of diagnoses is mandatory or voluntary.

Cancer can affect the body's homeostasis and organs in a many ways. Cancer cells may invade and physically impede the normal function if the tissue, or the presence of cancer cells can induce a cellular response from otherwise healthy cells as part of a host defense.[95]

Moreover, cancer cells can produce and secret substances, such as enzymes or cytokines. This may interrupt other natural processes and cycles, for instance by suppressing the immune system and defense. [96] Hence, an invasive cancer may cause multiple reactions in itself or through host-response, which in turn induces responding cascades that may lead to a malignant domino effect.

Cancer can also affect coagulation and lead to ischemic stroke, which is the scientific foundation of the present thesis.

Figure 1. The Development of Invasive Cancer.



Adapted from "3 Stages of Cancer Development", accessed Jan. 9, 2018.[97]

The pioneer in cancer-associated stroke

In 1865 Armand Trousseau (1801 – 1867) was the first to write about a connection between stroke and cancer.[98] Working at the hospital l`Hõtel-Dieu in Paris, France, Professor Trousseau noticed that cancer patients often suffered migratory thrombophlebitis; recurrent venous thrombosis.[99] These extraordinary findings were first presented in his lecture named "'Phlegmasia Alba Dolens".[100]

Most importantly, he discovered that thrombotic events often preceded the clinical manifestation and diagnosis of cancer, thus pioneering the thought of investigating for cancer in the presence of idiopathic thrombosis.[101] Trousseau Syndrome became the first term of cancer-associated thromboembolism. Professor Trousseau insisted that the thromboembolism was not due to mechanical obstruction in the blood vessel, but due to tumor-related alterations of the hemostatic system itself.[100] This is important because it provides the basis for cancer causing ischemic stroke; arterial thromboembolism, and also venous embolisms.

As fate would have it, Professor Trousseau later diagnosed himself with Trousseau Syndrome upon discovering that he himself suffered from gastric cancer.[100, 102] Upon diagnosis of thromboembolism in his left arm, he famously said to his medical students: "I am lost; I have no doubt about the nature of my disease". He passed away from his cancer at the age of 66 years.

Graus et al. break new ground

Two English doctors, Matheson and James, published a cohort study in 1935, confirming Professor Trousseau's findings.[100] However, further research on the cancer-stroke connection was scarce until Graus et al. published an extensive autopsy study on the topic in 1985.

In this study, they completed 3426 autopsies of patients with non-CNS cancer. The results demonstrated that 15% of cancer patients suffered cerebrovascular disease during the course of their cancer disease. However, only about 50% of these patients had documented and diagnosed clinical symptoms of stroke during their lifetime. [103]

Graus et al. suggested retrospectively that this was because the clinical symptoms of stroke in cancer patients were more diffuse, and less often focal.

Stroke is the second most common neurological disease in cancer patients, surpassed in numbers only by cancer metastasis to the nervous system.[103, 104] As such, we know that systemic cancer provides an increased risk of stroke.[105, 106]

Cancer itself, as well as cancer treatment, may lead to a hypercoagulable state, causing ischemic stroke.[105, 107-111] In a hypercoagulable state the patient has an abnormal and increased tendency to create blood clots or thromboemboli, as well as reduced fibrinolysis.[112, 113] A hypercoagulable state has been defined as "any prothrombotic condition caused by a specific disorder of blood coagulation".[114]

There are numerous causes to hypercoagulable states, some are genetic while others are acquired. Cancer is one of the most common causes of an acquired hypercoagulable state.[115, 116] Mechanisms include disturbance of the coagulation cascade, tumor mucin secretion, infections and non-bacterial endocarditis.[104, 117-120]

Causes of cancer-associated stroke

Another benchmark study in the field of cancer-associated hypercoagulation and subsequent stroke, is the review by Grisold et al. from 2009.[118] They presented the following main causes of cancer-associated stroke:

- Coagulation disorders; including hypercoagulable state, disseminated intravascular coagulation (DIC; most often in metastatic and hematological cancer), Non-bacterial Thrombotic Endocarditis and reduced fibrinolysis.
- Tumor related factors; including direct tumor effect (tumor embolism, vessel infiltration or compression), intravascular lymphoma (a diagnosis most often made on autopsy) and hyper-viscous obstructions due to hematological cancer.
- Infections (sepsis can be associated with DIC).
- Therapy-related; including chemotherapy, surgical complications and post-radiation vasculopathy (especially in relation to head- and neck cancer).

The latest major review on cancer-associated strokes was published in 2014.[109] In this review, Dearborn et al. presented the most common mechanisms of cancer-related stroke published in recent years (table 2).
Of the above mentioned main causes, the focus in this thesis is on that of hypercoagulability.

Table 2. Potential Mechanisms of Cancer-Related Stroke.

Mechanism	Causal factor	Associated tumors	Stroke Characteristics
Hypercoagulability	Tumors secrete mucin; tumors activate coagulation; release pro-coagulant cytokines	Adenocarcinoma of breast, lung, prostate, colon. Also brain, kidney or hematologic malignancies	Embolic appearing infarcts, end vessels
Venous-to-arterial embolism	PFO, right-to-left shunt	Likely similar to tumors of hypercoagulable state	Embolic appearing
Non-bacterial thrombotic endocarditis	Sterile vegetations, clumps of platelets and fibrin develop on aortic valve	Adenocarcinoma is most common	Multiple widely distributed small and large infarcts
Direct tumor compression of vessel	Tumor growth and edema compress intracranial vessel	Glioblastoma multiforme, metastasis to brain	Large vessel
Tumor embolism	Cardiac tumor with embolization of malignant cells	Atrial or aortic valve myxoma, metastatic tumors to heart	Embolic appearing
Hyperviscosity	"Thickened" blood causes obstruction of small end vessels	Polycythemia vera, multiple myeloma, Waldenstrom's macroglobulinemia, leptomeningeal carcinomatosis	End-vessel strokes
Angioinvasive/infiltrative	Hematologic malignancies infiltrate blood vessel wall, causing irregularities that predispose to embolism	B-cell lymphoma	Multiple vascular territory infarcts
Post-radiation vasculopathy	Radiation causes accelerated atherosclerosis, vessel wall irregularities and embolism	Squamous cell carcinoma, other head and neck tumors	Embolic infarcts
Chemotherapy associated	Unknown	Associated with cisplatin, methotrexate, L-aspariginase, thalidomide, lenalidomide, bevacizumab	Varied

Adapted from Dearborn et al., J Neurol Transl, 2014.[109]

Hypercoagulability- the pathogenesis

Despite more than a century passing since Trousseau discovered cancer-associated thrombosis, the pathophysiology behind the hypercoagulable state is still poorly understood.[121] Thereby is also the pathway from cancer-induced hypercoagulation to ischemic stroke remaining unclear. However, certain factors have been unveiled. Cancer cells can express procoagulant factors themselves,[122, 123] or they can stimulate healthy cells to secrete procoagulant factors.[124] This means that tumor cells affect homeostasis and the coagulation cascade from different target points; both directly, by producing for instance thrombin (factor II), and indirectly through affecting healthy cells.

The two cancer cell substances with prothrombotic abilities that have been isolated and sufficiently characterized are cancer procoagulant (CP) and tissue factor (TF).[125-130] CP is a Vitamin K-dependent cysteine protease that activates factor X of the coagulation cascade directly (Figure 2). CP has also been shown to activate platelets in a similar fashion to that of thrombin.[131] CP is, unlike TF, not found in normal, differentiated tissue.[132]

TF is a transmembrane glycoprotein found on the surface of many cells, both normal and tumor cells, and is also known as coagulation factor III. TF is a primary initiator of clotting by way of the coagulation cascade (Figure 2). TF will, through the so-called extrinsic pathway of the coagulation cascade, form a complex together with factor VII. This complex will activate factors IX and X; coagulation has been initiated. The expression of TF on the tumor cell surface has been shown to be linearly correlated with the malignancy and histological grade of tumors.[133] Higher histological grades have a higher TF expression.

Circulating tumor cells (CTCs) produce TF and procoagulant factors like other tumor cells, but they can also cause formation of coagulation factor-complexes on their cell surfaces, another way of activating coagulation.[134] Circulating microparticles are small fragments shed from endothelial cells, leucocytes or tumor cells. They are often saturated with TFs, and are known to initiate both inflammation and thrombosis.[134] Cancer cell-derived extracellular vesicles (EVs), a form of microparticles, also

contribute to the cancer-induced hypercoagulable state. Recently it was shown that EV-induced coagulopathy can be independent of TF, though both TF and EV are often found in high quantitates in the same cancer patients.[135]

Malignancies also have another indirect way of affecting coagulation; i.e. by inhibiting endogenous anticoagulation. Tumor cells cause endothelial cells and platelets to upregulate their production of plasminogen activator inhibitor-1 (PAI-1). PAI-1 is a protein that functions as our main physiological inhibitor of tPA. Upregulation of PAI-1 therefore inhibits fibrinolysis. Inflammation can also induce PAI-1generation by stimulating monocytes and endothelial cells.[136]
Cancer can induce a systemic response in the body, similar to that in inflammatory disease or infection, causing release of cytokines (TNF, interleukins and interferons) and acute phase reactants, such as CRP. Inflammatory cytokines are thus paramount to the pathophysiology of cancer-associated thrombosis.[137]
TF is often expressed in response to tumor necrotizing factor (TNF), interleukins (IL-1, IL-2 and IL-6), interferons and plasmin. Also monocytes and endothelial cells can become procoagulant under the influence of cancer-mediated cytokine release.[138]
TNF can also suppress the fibrinolytic activity of the endothelium, meanwhile cytokines in general can also cause inflammation of the endothelial lining creating a prothrombotic surface, triggering thromboembolic events.[139]

Another immune response that affects cancer-associated thrombosis and coagulation is that of neutrophil extracellular traps (NETs).[140] NETs are components of the innate immune system, produced by neutrophils to trap microbes. Tumor cells can stimulate neutrophils to release NETs,[141] where they in turn will cause platelet aggregation and activation of other coagulation factors.[142] NETs were only first discovered in 2004, but will remain important as they now have been shown in ischemic stroke thrombi.[143]

Worthy of note is the fact that IL promote procoagulant secretion from endothelial cells, and the endothelial cells will in turn respond to this stimulus by secreting IL, thus creating continuous stimuli for inducing an inflammatory response. This is seen

throughout the studies on cancer-thrombosis pathophysiology; indefinite circuits of prothrombotic stimuli are created.[138]

This is also the instance for selectins; cell adhesion molecules. Selectins are normally expressed by healthy cells, but they are expressed at a higher rate under tumor cell stimulation. Selectins will in turn increase TF-expression on endothelial cells and monocytes.[144] Selectins on tumor cell surfaces can moreover cause platelet activation and aggregation. As such, it has been hypothesized that an increase in selectins is associated with risk of thromboembolic events in cancer patients.[145] Also endothelial cells can be stimulated to produce "platelet activating factor".

We do not yet fully understand the intricate factors of hypercoagulation, nor do we know which factors are the most important. The induction of hypercoagulability probably also differs from tumor cell type, to cancer stage and other innate factors.[146] Though, in summary, what has been recognized, is that hypercoagulation is mediated by 1) prothrombotic factors from tumor cells; solid or CTCs, 2) prothrombotic factors from healthy cells after tumor cell stimuli, 3) decreased level of inhibitors of coagulation and/or 4) through a systemic inflammatory response to tumor cells. Lastly, it should be mentioned that tumor-secreted and induced procoagulant factors are also promoters of tumor metastasis and tumor angiogenesis.[132]

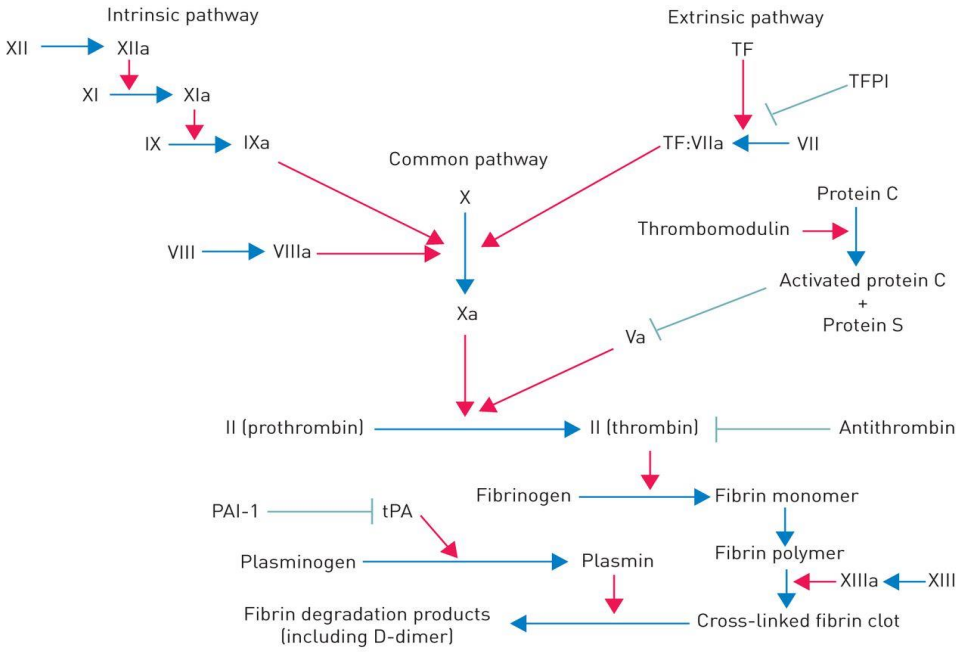
Hypercoagulability - clinically

Although many of the coagulation factors are difficult to measure, there are two that can be used as signs of activated coagulation: elevated D-dimer and fibrinogen. Fibrinogen is an acute phase reactant, and therefore increases in response to inflammation. Elevated fibrinogen has been linked to an increased risk of thrombotic disease,[147] and is studied in the patients included in studies I-III.
D-dimer is a fibrin degradation product (FDP), a small protein fragment present in the blood after a blood clot has been broken down through fibrinolysis; the body's own clot-dissolving mechanisms. It is named D-dimer because it contains two cross-linked D-fragments of the fibrin protein. In a healthy person D-dimer is normally not present

in the blood, therefore D-dimer presence suggests the presence of clot-formation or thrombosis. Since it often used as a sign of hypercoagulability, D-dimer measurements were vital in the included studies.

TF, CP and CTCs have been suggested as biomarkers for both cancer activity and degree of hypercoagulability in cancer patients, but this is not yet in clinical use.[148, 149]

Figure 2. The Coagulation Cascade.



Adapted from Crooks et al., European Respiratory Review, 2016 [150]

Deciphering the risk of a cancer-associated stroke

Cancer is in itself an independent risk factor for ischemic stroke.[151] The risk can be potentiated by other, classical cardiovascular risk factors, but not necessarily.[106]

For a cancer patient, the risk of ischemic stroke is reportedly higher shortly after diagnosis.[106] A large-scale study from Sweden showed that risk of stroke post cancer is the highest in the first six months, however, the risk remains increased for a decade.[152] [127, 144] Increased stroke risk is also seen in cancer patients with metastasis.[152] Historically, mucin-producing adenocarcinomas were found to be the strongest inducers of cancer-associated hypercoagulability and thus thromboembolism.[139, 144, 153] This is still consistent with studies showing that the cancer types most commonly associated with stroke are lung cancer, colorectal cancer, breast cancer, pancreatic cancer, gynaecological cancer and gastric cancer; often adenocarcinomas.[110, 117, 154, 155] However, today there are theories on non-mucin producing tumours also inducing hypercoagulable states. Supporting this belief is the fact that no study has been able to prove the procoagulant activity of, or procoagulant factor in, mucin.[127]

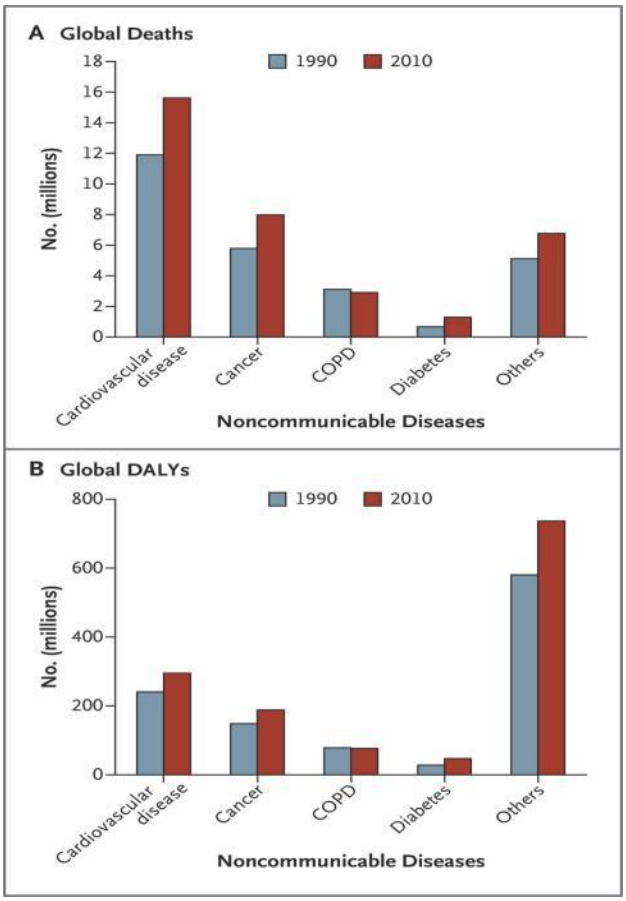
Stroke and cancer epidemiology

A global perspective

Stroke and cancer are both leading causes of death in the Western world. Stroke alone is the leading cause of disability globally.[156] CVD, including stroke, is one of the main types of the "non-communicable diseases" (NCDs), in addition to cancer, DM and chronic respiratory disorders. NCDs are induced and affected by both modifiable and non-modifiable risk factors.[157]

Figure 3, panel A, shows that stroke and cancer are the leading causes of death globally, studying NCDs, and that this has increased in the last decades.[158] Figure 3, panel B, shows that stroke and cancer are responsible for the highest number of Disease Adjusted Life Years (DALYs) lost globally.

Figure 3. Non-Communicable Diseases and Global Deaths.



(COPD: Chronic Obstructive Pulmonary Disorder, DALYs: Disease Adjusted Life Years)

Adapted from Hunter et al., NEJM, 2013. [158]

To measure the global burden of specific diseases, the Global Burden of Disease (GBD) study was launched in 1991 by the WHO and the World Bank. The GBD study integrates data on prevalence, incidence, and mortality to portray the true global cardiovascular burden. The most recent results from the "GBD 2015" showed once more that CVD is responsible for major loss of health globally.[159]

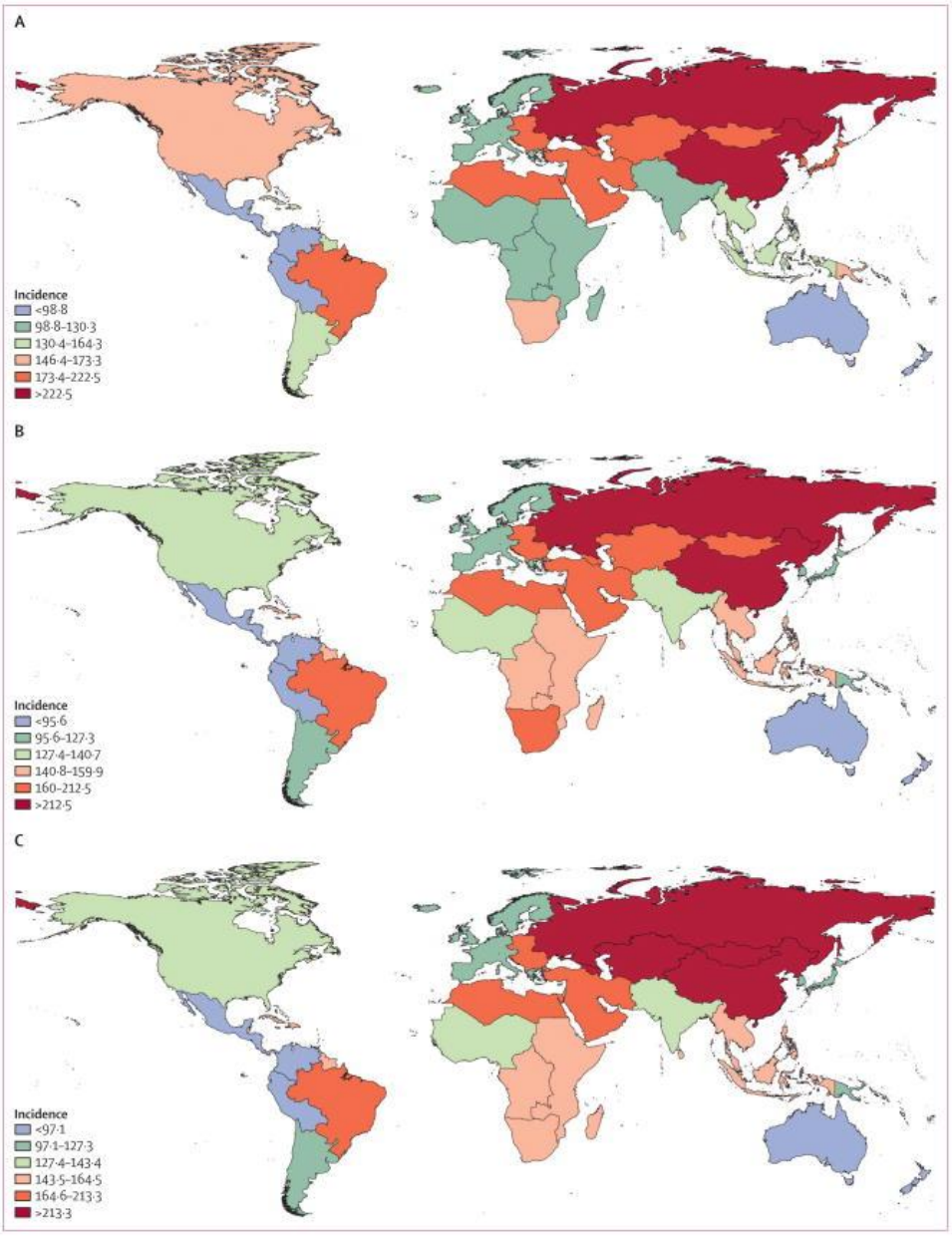
There are great disparities in ischemic stroke incidence, mortality and burden between high-income countries and the low- and middle-income countries (LMIC).[156]

According to the WHO, approximately 80% of all CVD occurs in LMIC.[53] Stroke incidence has decreased in high-income countries. The same countries have also seen a reduction in stroke mortality due to better treatment.[160]
However, total stroke incidence has increased globally in the last two decades; especially in LMIC has the incidence of first-ever ischemic stroke increased significantly (Figure 4, panels A-C).[161]
The NCD burden is one of the biggest health threats of this century, with the potential to increase health inequalities globally.[65] Therefore it became a goal of the American Heart Association/ American Stroke Association to lower CVD morbidity and mortality by 20 % from 2010 to year 2020.[162]

Economic burden

Based on today's numbers, predictions for the next couple of decades show that the stroke incidence will increase by 50 % in our ageing population.[163] This will certainly have a global economic impact. A study instigated by the World Economic Forum estimated that the cost of all NCDs over the next 20 years could total 47 trillion United States Dollars (USD). The rise of NCDs in LMIC is worrisome, as the increase can greatly affect a country's gross domestic product (GDP) as they often are costly to treat, and often disables the patients permanently. The loss of labor in the most productive years of life can in turn cause great loss of capital.

Figure 4. Incidence of first-ever ischemic stroke per 100.000 person-years for the years A: 1990, B: 2005, and C: 2010.



Adapted from Krishnamurthi et al., The lancet , 2013 [164]

Stroke in Norway

Estimates of stroke incidence in Norway are sparse, and vary depending on geographic location and the form of data registration.[165-167]

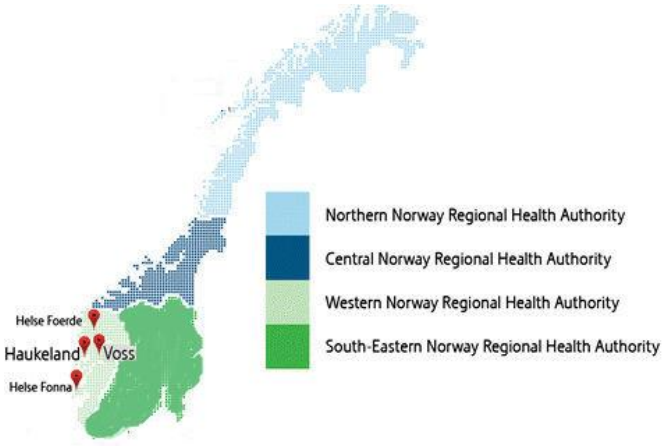
Gaging the true stroke incidence has been difficult for many reasons. Firstly, stroke diagnosis and treatment is handled differently depending on the proximity to a stroke center. Secondly, certain stroke patients will suffer a stroke while in a healthcare facility, for instance in end-of-life-care or in palliative care, where a capable physician will know that treatment or further stroke diagnostics are not warranted. Also, there are some patients in nursing homes with recurrent stroke where, again, diagnosis will not implicate treatment, and they are therefore not transferred to a stroke center. This means that not every stroke diagnosis has been registered through the hospitals' International Coding of Diseases (ICD-10) system.

However, the accuracy of the monitoring of stroke diagnoses and stroke care is improving as Norway now has a national stroke registry with mandatory inclusion.[168] Latest consensus is that each year approximately 12.000 Norwegians suffer an acute stroke.[169] These figures include all types of stroke, and recent reports show that ischemic stroke still constitutes about 85 % of all strokes.[166]

Haukeland University Hospital, home of NORSTROKE, is the biggest hospital of the Western Norway Regional Health Authority and serves a well-defined area of approximately 250.000 inhabitants (Figure 5). It also serves as one of the two of the region's EVT centra. Here, the incidence of ischemic stroke has been shown to be 105 per 100,000 citizens per year.[170]

The annual costs associated with acute strokes are in Norway about 8 billion Norwegian Kroner (NOK).[171] A stroke victim may suffer permanent neurological deficits and need increased or full-time care at great expense of the public health care system. Of the patients that survive their stroke, around 50 % of them will have some form of permanent neurological deficit, many of them requiring long-term rehabilitation or care services for activities of daily living (ADL).[172]

Figure 5. Map of the Regional Health Authorities in Norway.



Adapted from Soerensen et al., 2014 [173]

The cancer-stroke connection in Norway

The cancer-stroke connection has not been studied in Norway previously. Worldwide, stroke and cancer are leading causes of death, which is also true in Norway. According to the Norwegian Cause of Death Registry and the Norwegian Cardiovascular Disease Registry, cancer has now surpassed CVD as the leading cause of death in all age groups below 80 years. Cardiovascular disease is the most common cause of mortality in those above 80 years.[174]

Due to public health improvements, such as a reduction in tobacco use and less hypertension, the overall incidence of stroke and cardiovascular disease is declining.[174] However, the post-war generation is ageing, there is general population growth and other risk factors such as obesity are on the incline. Furthermore, a higher number of patients survive their cancer, stroke and heart attack, as treatment options are increased and improved. Consequently the prevalence of both stroke and cancer is rising. As such, cancer-associated strokes will also become more prevalent. [16,57]

Further knowledge on what subgroups of patients are at highest risk for both stroke and cancer is needed. This could lead to implementation of new treatment options or lead to specific diagnostic investigations in patient groups at risk for cancer-associated stroke. We know that cancer patients who suffer a stroke have poorer outcomes,[175] and both diseases are associated with large economic burdens for society. Therefore, preventing a stroke in a cancer patient or detecting an occult cancer in a stroke patient is beneficial.

Note

The review of literature for the present thesis was completed within February 2018.

Aims of the thesis

The primary aim of the study was to investigate the associations between cancer and ischemic stroke within the NORSTROKE registry. Three studies provide investigation into the associations within distinct study populations.

1. To assess the prevalence of cancer in ischemic stroke patients compared to the general population. To assess what cancer types are the most common in stroke patients and what are their stroke etiologies as well as risk factors. This is discussed in paper I.

2. To assess the frequency of cancer in patients who had recently suffered ischemic strokes and to investigate whether certain strokes should be classified as “cancer-associated” due to underlying malignancy at the time of ictus. To assess whether undetermined stroke etiology predicts underlying malignancy, and whether routine screening for cancer is warranted in every patient with ischemic stroke. This is discussed in paper II.

3. To assess how to detect active cancer in ischemic stroke patients and best decide which stroke patients to screen for occult cancer. This is discussed in paper III.

Materials and methods

The Bergen NORSTROKE Study

Data for the present thesis was obtained from The Bergen NORSTROKE Study. The Bergen NORSTROKE Study prospectively registers all patients admitted to the Stroke Unit at Haukeland University Hospital diagnosed with IS, ICH and TIA. Haukeland University Hospital serves an area of about 250.000 inhabitants and has a comprehensive Stroke Center that, as one of five centers in Norway, provides state-of-the-art endovascular stroke treatment.

Data collection for the Norwegian Stroke Research Registry (NORSTROKE) was commenced in February of 2006 and will continue indefinitely. Data registration comprises a standardized form, which today is integrated in the routines in the Stroke Unit and prospectively filled out during treatment and follow-up.

NORSTROKE includes all key patient data; demographics, medical history, clinical findings and vital parameters during hospital stay, blood samples, radiological findings, treatment prior to – and during admission, and finally short-term outcome. Medications used prior to admission are also registered.

Risk factor definitions

Risk factors are registered in NORSTROKE upon admission. They are defined according to current protocol in the Stroke Unit and include hypertension (HT), diabetes mellitus (DM), paroxysmal or chronic atrial fibrillation (AF), prior stroke, transitory ischemic attack (TIA), angina pectoris (AP), coronary artery disease (CAD), myocardial infarction (MI), peripheral artery disease (PAD), hyperlipidemia (HL), intermittent claudication and smoking.

DM was defined by diagnosis or treatment with any glucose lowering - medication or diet prior to hospital admission, or if revealed on admission for index stroke (HbA1c > 6.4%).[176, 177] HT was also defined as diagnosis or treatment prior to hospital admission. AF was defined as paroxysmal or chronic AF confirmed by electrocardiogram (ECG) before the stroke. Smoking was categorized as active smokers (if smoking at least 1 cigarette per day), previous smokers (if quitting smoking at least 1 year prior to index stroke) and never smoker.

Stroke diagnostics and imaging

All stroke patients underwent urgent cerebral CT (computed tomography) on admission. Patients admitted within 6 hours of ictus also underwent CT angiography (CTA), which was performed using an IV contrast medium to visualize the arterial tree; both the neck- and the intracranial vessels. This enabled assessment of possible occlusions and to ascertain whether EVT would be feasible. In addition, CTA represents a mean to radiologically determine the severity of the stroke in the acute phase, as large vessel occlusion seen on CTA has a worse prognosis than small vessel occlusion.[178, 179]

Cerebral CT was repeated throughout the acute phase if indicated by clinical worsening of the stroke patient; noticed either by an increase in the NIHSS score or reductions of the GCS score.

Routinely, all stroke patients underwent magnetic resonance imaging (MRI) within the first day post stroke ictus, unless contraindicated. All MRI investigations were performed using 1.5 Tesla Siemens Magnetom (Symphony). A Diffusion Weighted Imaging (DWI)-sequence was performed as part of the stroke patient MRI protocol. The DWI-sequence used was ep2d_diff_3scan_trace, with the following specifications of parameters: field of view (FOV) 230 mm, slice thickness 5 mm, TR 3200 ms, TE 94 ms. Additional sequences were t2_flair_tra and ep2e_diff_3scan_trace_ADC. All MRI scans were reviewed by a neuro-radiologist as well as by a stroke neurologist (HN).[180] “Multiple acute cerebral infarcts” (MACI) on

DWI was defined as having lesion(s) in a minimum of two different arterial territories (right or left anterior or posterior cerebral circulation).[181] This equaled involvement of 1) bilateral anterior circulation, 2) unilateral anterior and posterior circulation or 3) bilateral anterior and posterior circulation. The anterior vascular territory included the anterior cerebral artery (ACA), the middle cerebral artery (MCA), the leptomeningeal branches of the MCA and ACA, the anterior choroidal artery (AchA) as well as the perforating branches of ACA, MCA and AchA. The posterior vascular territory included the vertebral artery, the basilar artery, the superior cerebellar artery, the posterior inferior cerebellar artery, the anterior inferior cerebellar artery and the posterior cerebral artery as well as perforating branches.[182]

ECG was obtained in all patients and Holter monitoring was done in selected patients with embolic stroke of unknown etiology. Trans-esophageal or trans-thoracic echocardiogram was performed in the Cardiology Ward if indicated. Duplex-sonography and color-coded sonography of the carotid arteries was performed in all stroke patients. The sonography was performed by a resident or attending neurologist from the Stroke Unit.

Cancer data & The Cancer Registry of Norway

All new cancer diagnoses are to be registered in the Cancer Registry of Norway by the treating physician. Any physician is obliged to register cancer diagnoses within a specific time frame, and this has been common practice since 1951. Due to Norwegian personal identification numbers, a public health care system and the mandatory registering, the Cancer Registry is one of the oldest and most comprehensive cancer registries globally. It is estimated that it contains at least 98.8% of all cancer diagnoses in Norway.[183]

The present study used data from the Cancer Registry through linking the personal identification numbers from NORSTROKE with the Cancer Registry. This enabled quality assurance of the cancer data registered in NORSTROKE.

There were 42 separate cancer diagnoses identified in the Cancer Registry that were not registered in NORSTROKE.

Extracting and matching data in this manner was a careful process, completed in 2012. The Cancer Registry informs that the interpretation and reporting of these data are the complete responsibility of the researcher. Endorsement by the Cancer Registry of Norway was not intended and should not be inferred.

For the studies included in the present thesis, date of cancer diagnosis was set as the date of the pathology report stating a cancer diagnosis. If missing, the diagnosis date used was the date of the first hospitalization for cancer treatment. In the final paper, active cancer was studied. Active cancer was defined as 1) new cancer diagnosis, 2) metastasis of known cancer, 3) recurrent cancer or 4) receiving cancer treatment, all within 12 months before or after the index stroke.

Stroke etiology

To assess the cause of the ischemic stroke, the stroke etiology, criteria from the Trial of Org 10172 in Acute Stroke Treatment (TOAST) were used.[184] Inter-observer agreement has been found satisfactory.[185]

The etiology by use of TOAST criteria was classified as follows:[184]

- Large-artery atherosclerosis (embolus/ thrombosis)
- Cardioembolism (high-risk / medium-risk)*
- Small-vessel occlusion (lacune)
- Stroke of other etiology (i.e. cancer or dissection)
- Stroke of undetermined etiology (i.e. competing etiologies or cryptogenic stroke)
    - Two or more causes identified
    - Negative evaluation
    - Incomplete evaluation

* Possible or probable depending on results from other examinations

The treating physician and/or a senior stroke physician in the Stroke Unit, determine the stroke etiology based on results from a series of routine investigations. In the present studies, all stroke etiologies were determined by neurologist and stroke specialist Professor Halvor Næss. As indicated in the TOAST overview, a stroke may have more than one probable etiology and still be classified as stroke of undetermined etiology.

A large-scale study of European stroke patients estimated that about 30% of ischemic stroke patients have cardioembolic etiology, 15% large-artery atherosclerosis, 25% small-vessel occlusion and 20% other determined etiology.[186] The etiological distribution does vary somewhat between different reports and study populations.[185, 187-189] Consensus is that about 40% of all ischemic stroke patients are classified with undetermined etiology.[184, 188] This is similar to the etiological distribution in the NORSTROKE registry patients. The number of stroke patients with undetermined etiology remains quite high, but also includes patients with two or more potential causes that are equally likely to have caused the stroke.

Stroke severity and the National Institutes of Health Stroke Scale

To determine stroke severity, the National Institutes of Health Stroke Scale (NIHSS) was used. This is the standard tool for quantifying neurological deficits and stroke severity. It has also become important in acute stroke treatment as it is often used as an aid to determine which patients get thrombolytic treatment and which do not; no findings on the NIHSS, a score of zero, equals no IV tPA in many cases. As such it functions as the primary selection method in acute stroke. Although it was first intended for use solely in clinical trials of stroke patients,[190] it is today an integral part of stroke treatment, observation and outcome prediction.[191]

The score ranges from 0 - 42, where a score of 42 is the most severe and 0 is no functional or clinical neurological deficits.[192] The stroke patient is scored with NIHSS immediately upon arrival to the hospital, after 1 hour and subsequently at standardized intervals by a stroke nurse in the Stroke Unit to monitor improvement,

stability or progression. This serial assessment with the NIHSS score also helps clinicians to catch early deterioration after thrombolytic treatment; most importantly stroke in progression, for example caused by progressing occlusion of an artery or its collaterals, increasing intracranial edema or intracerebral haemorrhage.

It has been noted that the NIHSS score is biased in its sensitivity towards symptoms from the anterior circulation,[193] and that it is heavily weighted towards detecting weakened motor function, as opposed to cognitive impairment.[194] The NIHSS score does not, for instance, pick up apraxia or a loss of fine motor skills, which can both be debilitating for the affected patient.

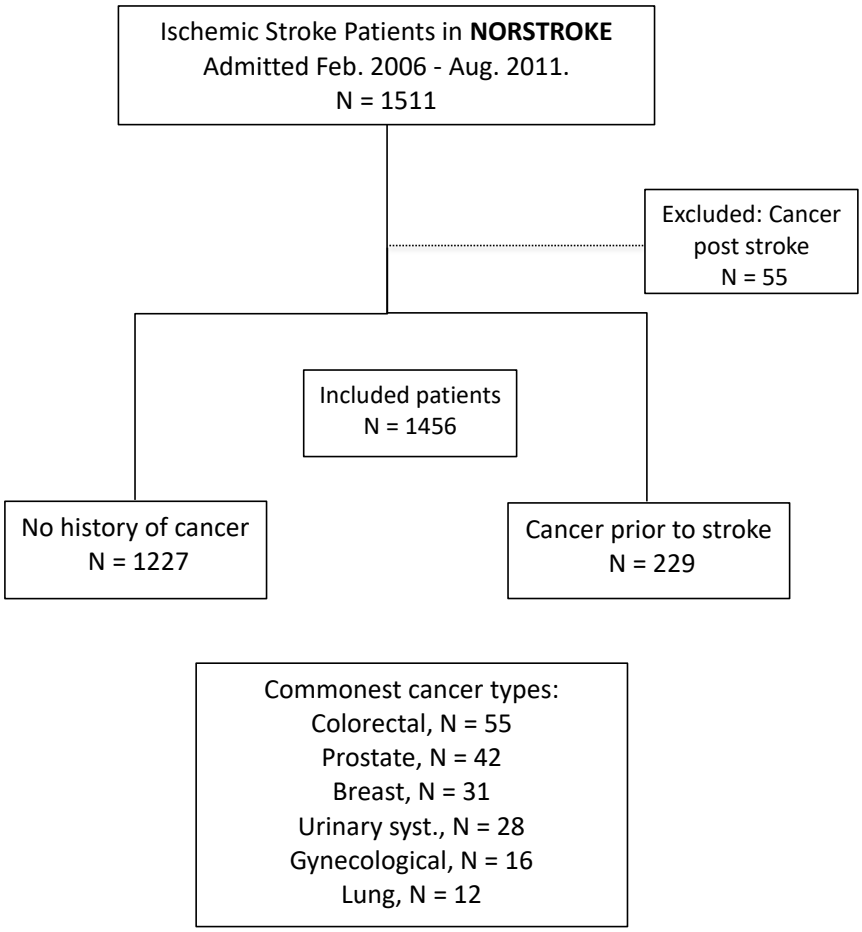
Another weakness of the NIHSS score is that it predicts arterial occlusion more accurately if the stroke patient is assessed shortly after debut of symptoms.[195] Nevertheless, the NIHSS score used globally and its validity has been deemed more than satisfactory, both in the acute phase and the serial assessment.[196] It has even been shown that the NIHSS score can be predicted quite accurately retrospectively based on clinical findings.[197]

Short-term functional outcome and the modified Rankin Scale

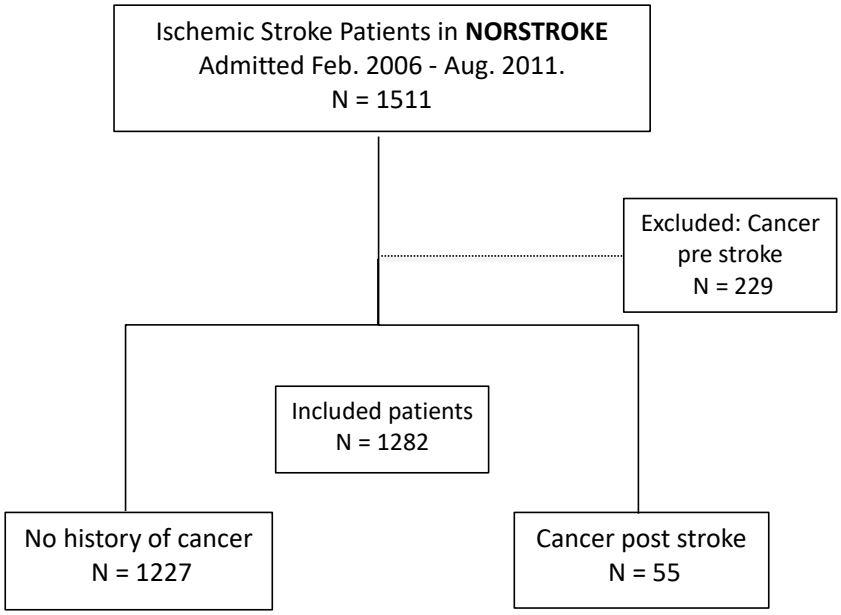
On day 7 or on the day of discharge from the Stroke Unit, the short-term functional outcome of the stroke patient is determined by use of the modified Rankin Scale (mRS). This score is a valid method commonly used in stroke units to determine the stroke patients' disability or dependence and the functional outcome.[198] The score ranges from 0-6, where 0 is no symptoms at all, and 6 is dead. Score 0-2 indicates that the patient is independent, while score 5 indicates need for fulltime care. Premorbid mRS is also used when discussing stroke symptoms and potential for treatment.

Study populations

Paper I studied cancer prior to ischemic stroke. Between February 2006 and August 2011, 1511 ischemic stroke patients were submitted to NORSTROKE. The study in Paper I included all patients with ischemic stroke in NORSTROKE who were not diagnosed with cancer post index stroke, as these 55 patients were excluded from the study. Of the 1456 patients included, 229 (15.7%) had one or more cancer diagnoses prior to their index stroke. In this study, cancer prevalence in our study population was compared to that of the general population of Norway. For this purpose, prevalence rates from the NORDCAN database, which provides cancer statistics for all the Nordic countries, was used.[199]



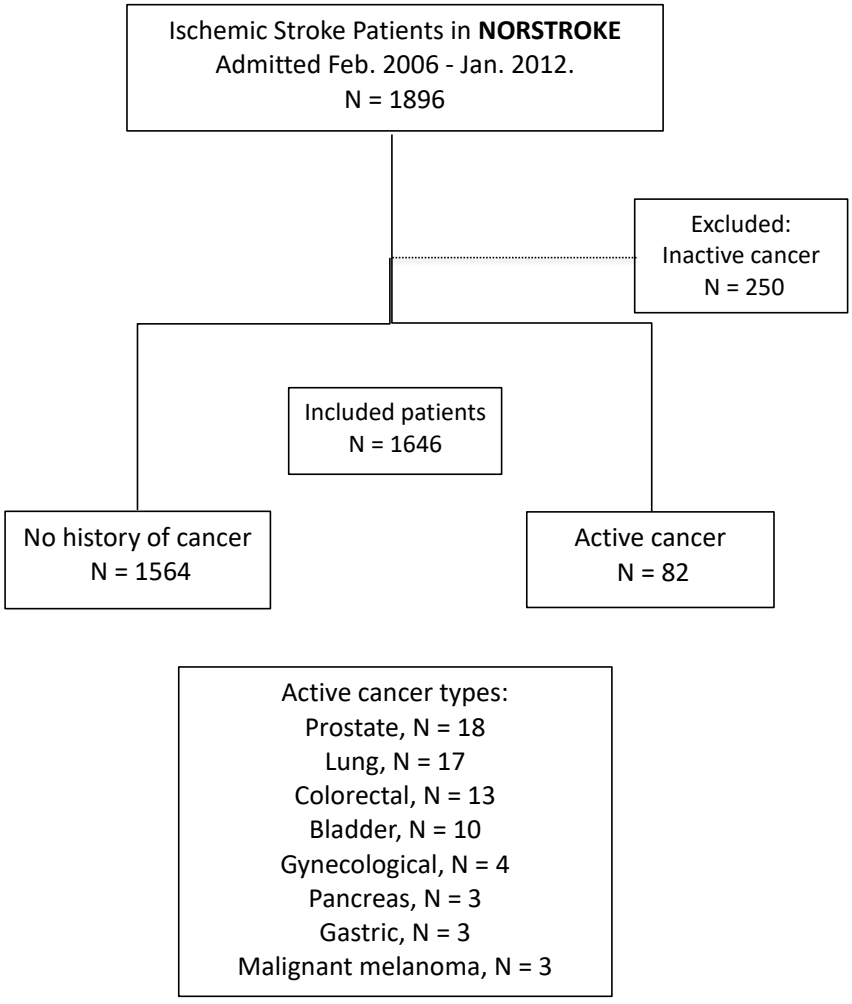
Paper II studied cancer diagnosed post stroke in the patients from the same inclusion period as study I (February 2006- August 2011). However, in this study, patients with cancer prior to stroke were excluded. After excluding patients with a history of cancer, 1282 ischemic stroke patients were included. Of these, 55 patients were diagnosed with cancer after their stroke within the study's end-point; September 15th, 2011 or date of death if prior to study end-point. The 55 patients were diagnosed with a total of 64 diagnoses, of 13 different cancer types. Twenty-three of the patients were diagnosed with cancer within one year post stroke, while median time from stroke to cancer diagnosis was 14 months. The follow-up time, however, varied between patients, and therefore, some patients only had a three week window to be diagnosed with cancer post stroke.



Commonest cancer types:
Lung, N = 12
Prostate, N = 10
Colorectal, N = 7
Breast, N = 7
Gynecological, N = 5
CUP,* N = 4
Lymphoma, N = 4

*Cancer of unknown primary site

Paper III studied how to predict if an ischemic stroke patient had active cancer. This study had a longer follow-up time of the patients than paper I-II. Patients were included from February 2006 until January 2012, and follow-up was through August 2012. After excluding 250 patients with inactive cancer, 1646 patients were included, and of these, 82 had active cancer as defined on page 45 of the present thesis. In this study, the data from patients with active cancer and ischemic stroke was compiled and analysed to form a predictive score for clinical use. The aim of the score was to be a tool for deciding which ischemic stroke patients should be screened for cancer.



Statistics

Two-sample Student's t-test was used for continuous variables with a normal distribution, while Mann-Whitney U test was used for the variables not normally distributed. Chi-square analysis was used for categorical variables. Cox regression analysis was used to investigate survival. The study populations were dichotomized as ischemic stroke patients with active- , prior - or post-stroke- cancer and stroke patients with no history of cancer (never cancer), with never cancer serving as the control group. Logistic regression analysis with the cancer group versus never cancer as the dependent factor was used to determine variables independently associated with active cancer, prior cancer or cancer post stroke. Regression analyses were performed stepwise by backward elimination.

For paper III, variables independently associated with active cancer were chosen as clinical markers and dichotomized. The clinical markers were based on cut-off levels and entered in a clinical score. Different scores were compared using the area under the receiver operating characteristic (AUC-ROC) curves. Area Under the Curve (AUC) determined the strength of the score; 0.7- 0.8 was considered a fair AUC. [200]

Bayes' theorem was used to calculate post-test probabilities of active cancer in paper III. All p-values of < 0.05 were considered statistically significant. Analyses were executed using statistical software Stata 14.0 (Stata Corp College Station, TX).

Ethical considerations

The NORSTROKE registry is based upon written consent and informed consent was obtained from all patients or legal guardians included in the studies.

The study of cancer-associated stroke by use of NORSTROKE data was approved by the Regional Committee for medical and health research ethics (REK Vest) in 2012. All data in possession of the author from the Cancer Registry of Norway was deleted by December 31st, 2017 as per the written agreement. This was to ensure that cancer data cannot be used for other than the studies' intended purposes.

Summary of the included papers

Paper I:

Prior Cancer in Patients with Ischemic Stroke: The Bergen NORSTROKE Study. Selvik HA, Thomassen L, Logallo N, Naess H. ***J Stroke Cerebrovasc Dis 2014 May-Jun; 23(5):919-25***

Background: It has been shown that ischemic stroke occurs more frequently in cancer patients than in the general population. The aim of this study was to compare the prevalence of prior or on-going cancer in patients with ischemic stroke and in the general population. We hypothesized that cardioembolic stroke is the most common stroke etiology in patients with prior cancer and that the outcome for ischemic stroke patients (ISP) with prior cancer is poor.

Methods: All ISP registered in the Norwegian Stroke Research Registry (NORSTROKE) as part of the ongoing Bergen NORSTROKE Study were included. Stroke etiology was determined by the Trial of Org 10172 in Acute Stroke Treatment criteria, and the severity of the stroke was defined from the National Institutes of Health Stroke Scale score. Information about prior or ongoing cancer disease and type was retrospectively obtained from the medical patient record and The Cancer Registry of Norway. The prevalence of cancer among stroke patients was compared with the prevalence of cancer in the general population.

Results: Among 1456 ISP, 229 (15.7%) patients had 1 or more cancer diagnoses before the stroke. The prevalence of cancer was higher among stroke patients compared with the general population (P = .001). The most common cancer types were colorectal cancer (20.2%), prostate cancer (15.6%), breast cancer (12.7 %), cancer of the urinary tract system (10.3%), gynecological cancer (6.2%), and lung cancer (4.5%). Logistic regression analysis showed that patients with prior cancer had cardioembolic strokes at a higher rate (P = .03).

Conclusions: The prevalence of prior cancer is higher in ISP than in the general population. ISPs with prior cancer are more prone to cardioembolism.

Paper II:

Cancer-Associated Stroke: The Bergen NORSTROKE Study. Selvik HA, Thomassen L, Bjerkreim AT, Naess H. ***Cerebrovasc Dis Extra 2015 Oct 13; 5(3):107-13***

Background: Underlying malignancy can cause ischemic stroke in some patients. Mechanisms include the affection of the coagulation cascade, tumor mucin secretion, infections and nonbacterial endocarditis. The release of necrotizing factor and interleukins may cause inflammation of the endothelial lining, creating a prothrombotic surface that triggers thromboembolic events, including stroke. The aims of this study were to assess the occurrence of cancer in patients who had recently suffered an ischemic stroke and to detect possible associations between stroke and cancer subtypes.

Methods: All ischemic stroke patients registered in the Norwegian Stroke Research Registry (NORSTROKE) as part of the ongoing Bergen NORSTROKE study were included. Patients with a history of cancer were excluded from the study. Blood samples were obtained on admission. Stroke etiology was determined by the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria, and the severity of stroke was defined according to the National Institute of Health Stroke Scale score. Information about cancer disease after stroke was obtained from patient medical records and The Cancer Registry of Norway.

Results: From a total of 1,282 ischemic stroke patients with no history of cancer, 55 (4.3%) patients were diagnosed with cancer after stroke. The 55 patients were diagnosed with a total of 64 cancer diagnoses; of 13 different cancer types. The median time from stroke onset to cancer diagnosis was 14.0 months (interquartile range 6.2-24.5). Twenty-three (41.8%) patients were diagnosed with cancer within 1 year and 13 (23.6%) within 6 months. The most common cancer type was lung cancer (19.0%). By Cox regression analysis, cancer after stroke was associated with elevated D-dimer levels on admittance ($p < 0.001$), age ($p = 0.01$) and smoking ($p = 0.04$).

Conclusions: Cancer-associated stroke is rare, and routine investigation for cancer seems unwarranted in acute ischemic stroke. However, in stroke patients with elevated levels of blood coagulation factors, C-reactive protein, higher age and a history of smoking, underlying malignancy should be considered. Our study suggests that an unknown stroke etiology does not predict malignancy.

Paper III:

When to Screen Ischaemic Stroke Patients for Cancer. Selvik HA, Bjerkreim AT, Thomassen L, Waje-Andreassen U, Naess H, Kvistad C.E. ***Cerebrovasc Dis. 2018 Jan 9;45(1-2):42-47***

Background: Ischemic stroke can be the first manifestation of cancer and it is therefore important to ascertain which stroke patients should be considered for cancer-diagnostic investigations. We aimed to determine the frequency of active cancer in patients with acute ischemic stroke and to compare clinical findings in stroke patients with active cancer to ischemic stroke patients with no history of cancer. Finally, we aimed to develop a predictive and feasible score for clinical use to uncover underlying malignancy.

Methods: All ischemic stroke patients admitted to the stroke unit in the Department of Neurology, Haukeland University Hospital were consecutively included in the Norwegian Stroke Research Registry (NORSTROKE). Stroke etiology was determined by the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria. Data on cancer diagnoses was obtained from patients' medical records and the Cancer Registry of Norway. Active cancer was defined as cancer diagnosis, metastasis of known cancer, recurrent cancer or receiving cancer treatment, all within 12 months before or after the index stroke. Based on variables independently associated with active cancer, a predictive score was developed using the area under the receiver operating characteristic (AUC-ROC) curves. Bayes' theorem was used to calculate post-test probabilities of active cancer.

Results: Of the 1,646 ischemic stroke patients included, 82 (5.0%) had active cancer. Increased D-dimer (OR = 1.1, 95% CI: 1.1-1.2, p = <0.001), lower Hb (OR = 0.6, 95% CI: 0.5-0.7, p = <0.001), smoking (OR = 2.2, 95% CI: 1.2-4.3, p = 0.02) and suffering a stroke of undetermined etiology (OR = 1.9, 95% CI: 1.1-3.3, p = 0.03) were factors independently associated with active cancer. These were included in the final predictive score which gave an AUC of 0.73 (95% CI: 0.65-0.81) in patients younger than 75 years of age. Assuming the prevalence of cancer to be 5%, the score

shows that if a patient fulfills all 3 score points, the probability of active cancer is 53%.

Conclusions: Active cancer was found in 5% of our ischemic stroke patients. We found that a clinical score comprising elevated D-dimer ≥3 mg/L, lower Hb ≤12.0 g/dL and previous or current smoking is feasible for predicting active cancer in ischemic stroke patients.

General Discussion

Age and other risk factors

Age matters

In Norway, about 70 % of all strokes take place in persons above the age of 75 years.[167] The age demographics of our study populations were quite similar to what one would expect of a stroke population, but it differed between stroke patients with and without cancer. In paper I, the mean age was higher in patients with cancer prior to their stroke than in patients with no history of cancer (76.1 years versus 69.5 years). In the same study we found that the cancer prevalence was significantly higher in our NORSTROKE population than the general population of Western Norway, for all persons below 70 years. This finding suggests that cancer is an independent risk factor for ischemic stroke or associated with common risk factors for both stroke and cancer. In this study we also analyzed each cancer type separately, comparing the patients with the 7 most common cancer types to patients with no history of cancer. The age of the lung cancer group stood out as they were much younger than the other groups as well as the control group with no cancer, with their mean age of 67.2 years.

In paper II patients with cancer after stroke also had a higher mean age than patients with no history of cancer, 72.7 years versus 69.5 years, but this was not statistically significant.

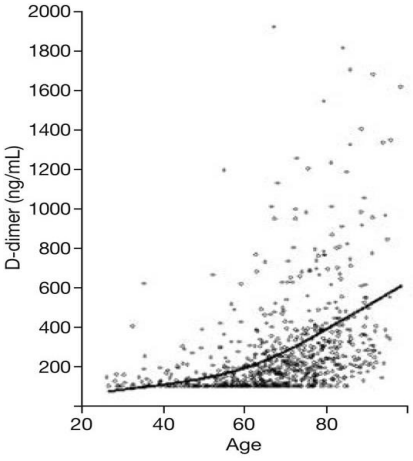
In paper III, a score was developed to screen stroke patients for active cancer. Again, patients with active cancer were older than stroke patients with no history of cancer; 73.7 years versus 69.5 years. The score included blood levels of hemoglobin (Hb) and D-dimer on admission, as well as smoking habits. Using AUC to assess the best score, the final score was only feasible for patients below 75 years of age. In patients above 75 years the sensitivity was too low, indicating that Hb and D-dimer were not viable markers for differentiating between a stroke patient with and without active cancer at this age. Anemia, defined by WHO as Hb < 13 g/dL and < 12 g/dL for men

and women respectively, is more common in the elderly.[201]

After the age of 65, around 5 - 10 % of the general population has anemia, and the prevalence increases with age.[202] The prevalence in those above 85 years is reported at 20 %,[203] and in populations with high comorbidity, such as inhabitants of nursing homes, even as high as 48 %.[201] Certainly the anemia prevalence will vary depending on factors such as genetics and diet. However, even if the above mentioned prevalence of anemia is an overestimate, it provides an explanation for why anemia, specifically low Hb, becomes less discriminate with age and why the score is only feasible for those below 75 years.

Similarly, the diagnostic value of D-dimer in the elderly has been discussed. As D-dimer can increase with age, Righini et al. suggested using different cut-off values of D-dimer for predicting pulmonary embolism, especially in patients above 75 years.[204] Idiopathic increase in D-dimer in the elderly may diminish the specificity of D-dimer as a marker of coagulation.[205] This is important to keep in mind as we used D-dimer as one of the point-giving factors in our predictive score. Nevertheless, we used D-dimer above 3000 ng/mL as the cut-off value, a high value, outside the range of what is considered normal (Figure 6), even in elderly patients.

Figure 6. The relationship between D-dimer and age measured in ng/mL.



Adapted from Tita-Nwa et al., Aging Clin Exp Res. 2010 [205]

Both cancer incidence and prevalence rise steeply with age. Age is the single most important risk factor for both stroke and cancer, and cogently the cancer prevalence increases with age, both in a stroke population as well as a general population.

In papers I and II, prostate cancer was the second most common cancer type in the patients with stroke and cancer, and in paper III it was the most common cancer type. As prostate cancer is one of the least aggressive types of cancer, it is believed to less likely induce a hypercoagulable state and is thus only weakly associated with an increased risk of ischemic stroke.[206] Its high prevalence in our studies might be due to its high incidence and prevalence in the general population.[206] Furthermore, as the patients in paper I were significantly older, they had a higher risk of getting both stroke and cancer simply by living longer and ageing.

Risk factors – conventional or distinctive?

Risk factor distribution is a highly disputable topic when discussing cancer-associated stroke. The question remains: do patients with stroke and cancer have the same conventional stroke risk factors as stroke patients without cancer, or do they have distinctive risk factor patterns with fewer conventional stroke risk factors?

When discussing risk factors for stroke, we think of the CVD risk factors such as age, HT, AF (chronic or paroxysmal), smoking, DM, PAD, known CVD and HL as well as others (see "Cardiovascular risk factors" in the Introduction).

In papers I-III we found little discrepancy in CVD risk factor distribution between patients with and without cancer. In paper I there was actually a higher frequency of patients with risk factors in the patients with cancer prior to stroke. Although these patients had a higher rate of hypertension and heart disease, this is probably a result of the patients being older and not indicative of a general increase in CVD risk factors for cancer patients. Smoking is the only risk factor that is distinctive in papers I-III. In paper I and II patients with stroke and cancer were more often smokers, and smoking is associated with long-term mortality for stroke patients with cancer pre – and post stroke. In paper III, smoking was independently associated with active

cancer as well as increased post-test probability of cancer by including smoking in the clinical score.

Several studies have also reported a similar CVD risk factor profile in stroke patients with and without suspected cancer-related stroke.[105, 109, 207-212] Others, such as Schwarzbach et al., have argued that stroke patients with cancer-related stroke have fewer conventional risk factors such as hypertension and hypercholesterolemia.[103, 107, 213]

Given the heterogeneity of cancer patients, perhaps this discussion has a scope that is too broad. Kim et al. studied the risk factor distribution on an etiological level. Instead of comparing patients with cancer-related stroke to other stroke patients, they compared patients with cancer-related stroke with different stroke etiologies, meaning they compared those of stroke of undetermined cause with the other etiologies.[214] In doing this, Kim et al found that cancer patients with stroke of undetermined etiology had fewer conventional risk factors.

The question of risk factors in cancer-related stroke might be moot. This is because the presence of conventional risk factors in stroke patients does not exclude the possibility of underlying cancer having contributed to the stroke. The reasoning for this is twofold. Firstly, a patient with for instance atherosclerosis from smoking can at random suffer both stroke and cancer. Secondly, a patient with atrial fibrillation and cancer can have an increased stroke risk from a hypercoagulable state, leading to stroke through amplification of the already present risk factor.

Accepting the hypothesis that stroke patients with underlying cancer have fewer conventional risk factors could be harmful. In doing so, physicians could be led to wrongly categorize a patient a patient where conventional risk factors mask an underlying cancer's involvement in stroke etiology.

Finally, both stroke patients with no cancer and occult cancer can suffer strokes despite having no known risk factors. Analyzing our own database, NORSTROKE, 19.3% of all ischemic stroke patients had no known traditional risk factors at the time of ictus.

Stroke etiology

Should cancer-related stroke be its own etiology?

Stroke etiology is also debated in relation to cancer-associated stroke.
Several questions have been raised; what is the most common stroke etiology in cancer patients? Do they suffer strokes of all etiologies, or are they often cryptogenic strokes of undetermined etiology? Moreover, some have even suggested "cancer-related stroke" as its own etiological classification.[109] The most common viewpoint is that cancer-related stroke often remains of undetermined cause and that stroke patients with stroke of undetermined cause are more likely to have an underlying malignancy than other etiologies.[213]
In paper I, we hypothesized that ischemic stroke patients with prior cancer had a higher rate of cardioembolic strokes. This was because a cancer-induced hypercoagulable state was believed to cause strokes of embolic cause and appearance.[105] We found cardioembolic strokes of a higher rate in patients with prior cancer on logistic regression. Also, as this paper was a study of prevalence over a given time, we did not distinguish the patients according to time from cancer to ictus, which could have affected the findings.

In paper II we studied stroke patients who were diagnosed with cancer post stroke, hypothesizing that some patients had underlying cancer at the time of stroke. Also in this population the stroke etiology was somewhat inconclusive. There was not one etiology that was significantly more common in patients with suspected cancer-associated stroke. It would have been interesting to see which etiology the patients with the shortest time from stroke ictus to cancer diagnoses had. A recent study by Quintas et al. with identical study design to that in paper II, also showed a similar distribution of etiologies between patients diagnosed with cancer post stroke and patients with no history of cancer.[212] They diagnosed approximately 3.4 % of their ischemic stroke patients with cancer within 6 months of stroke, yet, the distribution of etiologies was still the same; undetermined etiology was not more common in any cancer group than in patients with no history of cancer.

The inconclusive findings in paper II were part of what led us to the next study; only including patients with active cancer. In paper III with patients with active cancer, we found that undetermined etiology indeed predicted active cancer. Of the 82 patients with active cancer, 42 (50.6 %) had etiology of undetermined cause.

In recent literature, the main focus on cancer-associated stroke is often on those of undetermined etiology.[215] Not only have many studies concluded that undetermined cause is the most common in patients with stroke and cancer, but some have now even used etiology as a selection criteria for study participation, only including patients with undetermined etiology.[216, 217]

However, as discussed in terms of how finding conventional risk factors does not exclude cancer, similarly, does known stroke etiology not exclude cancer.
In fact, Aarnio et al., found that for stroke in the young, the cancer-associated strokes were especially not of undetermined cause.[218] Aarnio's young stroke patients with cancer had determined etiologies distributed similarly to the stroke patients with no cancer in the control group.[218] Although it did not reach statistical significance, the young stroke patients had a higher rate or cardioembolic strokes, also after adjusting for patent foramen ovale (PFO).[218]

Furthermore, Finelli et al. portrayed DWI-findings in patients with stroke and cancer, where 75 % of the patients with embolic appearing infarctions actually had emboli of no detected source.[219]
Clinically, if patients have embolic appearing strokes and report symptoms that indicate a possible AF such as palpitations, even without ECG findings, they might be classified as cardioembolic. Thus, if one were to only include patients with undetermined etiology in the search for underlying cancer, one might lose patients in the classification.

In our three studies we used the TOAST criteria to determine stroke etiology. The category of "stroke of undetermined etiology" includes both strokes of truly unknown cause, but also those with two or more possible etiologies, where either etiology is just as likely as the other. It would have been interesting to study the etiological

group of undetermined cause more in depth in papers I-III, dividing this etiological group in those of “no cause found” and “two or more possible” etiologies.
Of the 42 patients with active cancer classified as “stroke of undetermined cause” in paper III, 5 also had AF, which could have been one contributing factor to their stroke, despite it being classified as undetermined, and not cardioembolic.

Determining the aftermath

Functional outcome

As described in the Methods section, the mRS was used to assess functional outcome after stroke; on day 7 or on discharge from hospital if sooner. It is known that patients with stroke and cancer have a poorer functional outcome after stroke compared to stroke patients in general.[220] Even with acute stroke treatment, cancer patients with stroke fare poorly, with as many as 75 % of patients dependent on help or dead after three months.[221] This is not surprising as both are serious diseases to be inflicted with. Cutting et al. showed that the stroke severity is the most important factor in determining the functional outcome; even more important than cancer type or stage.[221]

In paper I we saw a poorer short-term outcome for patients with prior cancer as a group. Studying the separate groups of the most common cancer types, patients with prior colorectal- or lung cancer, had the poorest short-term outcome. Interestingly, these were also the two cancer groups that had a significantly higher NIHSS score on admission.

In paper II we saw no significant mRS score differences in the patients diagnosed with cancer post stroke, neither when we assessed the separate cancer types. In this study, however, the cancer-group only included 55 patients.

Also, in paper III, the active cancer patients had a poorer outcome than stroke patients with no history of cancer. Table 3 shows the mRS scores for the most common cancer types (paper I) or the patients with cancer (paper II and III) compared to the patients with no history of cancer.

It is noteworthy that in the global stroke community, the mRS score is often the only outcome measure used, both in clinical practice and for research purposes. Within each mRS category there is room for a large variation of ADL management and thus quality of life. Although the mRS has been found reliable, it can overlook persistent problems such as light cognitive impairments or depression, important factors for quality of life. For example, a recent study by Kapoor et al. showed that among

patients who recovered from stroke and had an mRS score 0-1, more than half of the patients were cognitively impaired, and one third was depressed.[222]

Given that Kapoor's dire results were from a study of a general stroke population where stroke was the only diagnosis for many of his study subjects, it is certainly plausible that the findings would be similar or worse in a population of patients suffering from both stroke and cancer.

Functional outcome as measured by mRS is important to measure post stroke. However, the pre-stroke mRS score may also be relevant in the acute phase. Discussing EVT, mRS 0-2 after thrombectomy is often considered a meaningful and satisfactory result or outcome. If a stroke patient is admitted with a pre-existing mRS of 4, this patient might not be considered for invasive treatment. It could be argued that premorbid mRS status should not be a considering factor however. For example, for the patient with a pre-stroke mRS score of 4, receiving EVT and thus remaining mRS 4, and not ending up with a post-stroke mRS score of 5, could pose huge potential for difference in quality of life. Another aspect of this is that the patients with a remaining mRS score of 4 would cost society significantly less by needing less assistance. Therefore it is arguably important that acute stroke treatment, including EVT, remains a top priority of funding and expansion in the years to come.

Mortality

Given the strong association between cancer-related stroke and poor clinical outcome, it is not surprising that the same patients also have an increased mortality.[105, 218]

In paper I we found that stroke patients with prior cancer had a double risk of death compared to other stroke patients. In paper III we did not study the mortality of the patients, but we saw that the patients with active cancer had a lower mean cholesterol level. Because statin use is associated with lower cancer-related mortality,[223] as well as stroke mortality[224], it would have been interesting to study the overall medications used in our cancer population.

According to Cutting et al., 50 % of patients with stroke and cancer die within three months, regardless of cancer stage or type.[221] Recent results from the OASIS-CANCER Study in South Korea indicated that the degree of hypercoagulability is a factor in cancer-stroke mortality.[225] This could possibly explain why the NIHSS score on admission was significantly higher only in patients with certain cancer types.

Table 3. mRS on day 7 or discharge for stroke patients with prior, post or active cancer compared to stroke patients with no history of cancer.

	Median mRS (IQR)
Paper I:	
Patients with prior cancer vs. patients with no history cancer	
Never cancer, n = 1227	2 (1-4)
Colorectal, n = 55	3 (1-4)*
Prostate, n = 42	2 (1-3)
Breast, n = 31	3 (2-4)
Urinary system, n = 28	2 (1-4)
Gynecological cancer, n = 16	3 (1.5-4)
Lung, n = 12	4 (2-4.5)*
Paper II:	
Patients with cancer post stroke vs. patients with no history cancer	
Never cancer, n = 1227	2 (1-4)
Cancer post stroke, n = 55	2 (1-4)
Paper III:	
Patients with active cancer vs. patients with no history cancer	
Never cancer, n = 1564	2 (1-4)
Active cancer, n = 82	2 (1-4) *

mRS: modified Rankin Scale. IQR: Interquartile Range.
* $P \leq 0.05$ comparing the various cancer groups to patients with no history of cancer.

Cancer aspects

Cancer prevalence

In paper III, the prevalence of *active* cancer in NORSTROKE was 5 %.
This was based on the follow-up time for all patients, where the active cancer diagnoses were registered during an interval of 12 months pre-stroke or 12 months post-stroke. This prevalence is not comparable to the cancer prevalence in a general stroke population, counting all cancer diagnoses.
The prevalence of cancer in the general population of Norway was reported at 5.0 % in 2016 according to The Cancer Registry of Norway. The prevalence for the general population, however, includes all patients either living with active cancer or having survived a cancer diagnosis. Therefore, the prevalence of *active* cancer would likely be lower in the general population, as the prevalence of active cancer in NORSTROKE was based on the total 24-month interval pre and post stroke diagnosis, and thus did not include someone who had inactive cancer.
Still, given the higher incidence of stroke in a cancer population, we would have expected that the active cancer prevalence was higher in an ischemic stroke population due to the shared risk factor burden. As recent reports have shown, patients with risk factors that increase both stroke and cancer risk may have a biology that predisposes them to both diseases.[10] Therefore, one could have expected an increased *active* cancer prevalence in a stroke population.
As seen in paper I, the prevalence of cancer is higher in the NORSTROKE population than in the general population of Western Norway in those below the age of 70. Last year, a comparable study from Germany also showed an increased cancer prevalence, especially of lung cancer, in their stroke population compared to the general population in Germany.[226]

In our studies the most common cancer types were colorectal cancer, prostate cancer, lung cancer, breast cancer, cancer of the urinary system, gynecological cancer, lymphoma and cancer of unknown primary site. This is comparable to the most common cancer types in other studies.[212] Still, these findings may reflect, and be affected by, the cancer prevalence in the general population. Thus do they not

necessarily reflect which cancers are the strongest inducers of hypercoagulability. As discussed by Lee et al. in one of the major studies on cancer and venous thromboembolic events, when adjusting for prevalence in the general population, the cancer types with the strongest effect on coagulation are lung cancer, cancer of unknown primary origin, pancreas cancer, brain cancer and ovarian cancer.[121] Also gastric cancer, often adenocarcinoma, has been mentioned frequently in the literature as especially prothrombotic.[227]

In our studies, there is a potential for underrepresentation of cancer-associated stroke prevalence. This is because not all stroke diagnoses are necessarily registered, as not all patients with stroke are hospitalized. In addition, even hospitalized cancer patients might suffer strokes that go untreated and thus unregistered. If a patient in palliative care suffers a stroke, this will likely be treated less acutely than if a healthy person suffers acute stroke, as other aspects may be more important in the end-of life phase.

Defining active cancer

In a study with an inclusion criteria of active cancer, such as paper III, the definition of active cancer will greatly impact the observed prevalence. We defined active cancer as 1) new cancer diagnosis, 2) metastasis of known cancer, 3) recurrent cancer or 4) receiving cancer treatment, all within *12 months before or after the index stroke*. The more common way to define active cancer is the three points above, but all within *6 months before or after the index stroke.* We performed preliminary analyses comparing the patients meeting the criteria for the 12-month definition to the patients in the 6-months definition. We found no significant differences between the groups and therefore chose to use the 12-month definition.
A recent study by Guo et al. also used the 12-month definition,[228] though the 6-month definition remains the one widely used.[107, 229] Yet another definition used is active cancer within *12 months before index stroke or cancer diagnosis while in the stroke unit*.[230]

This brings up another aspect of the active cancer definition. At what point does a cancer, solid or not, affect a patient negatively, and when could it affect coagulation? To answer this, one also has to answer the question of how long it takes for a cancer to proliferate. These are not easy questions to answer.

A study of the time from first symptom to diagnosis of lung cancer in England showed that if a patient`s first symptom was worsening of a cough, or persistent cough > 3 weeks, median time to diagnosis was about 4.2 months.[231] One can suspect that a cancer causing clinical symptoms has had an effect on the body's homeostasis or coagulation for a weeks or months. As mentioned in paper III; a study of Trousseau syndrome showed that patients with idiopathic thromboembolic events had an increase in occult cancer prevalence from 6.1 % at the thromboembolic event to 10.0 % at 12 months.[232] This gives ample reason to believe that the occult cancer was present in the body, although not diagnosed, at time of event. This justifies including patients for up to 12 months post stroke as active cancer patients.

Cancer risk and screening

Risk stratification and ROC curves

In the 1950s, the idea of clinical prediction by use of a statistical method emerged. Much thanks to clinical psychologist Paul Meehl's book "Clinical vs. Statistical Prediction: A Theoretical Analysis and a Review of the Evidence" published in 1954,[233] the ideal of the close to omnipotent doctor was questioned in terms of being the only one able to predict disease. Meehl suggested that algorithms and scores could be used to predict a patient's combined risk of disease over time.
In cardiovascular research especially, there has been a desire to stratify the risk of suffering acute events, such as stroke or heart attacks. In order to do so, scores to predict levels of risk at separate thresholds, as well as diagnostic tests, have been developed. The so-called C-statistic, or the Area Under the ROC Curve (AUC-ROC) is one of the frequently used statistics for prediction. The AUCROC will provide the researcher with a measurement of the accuracy of a score or diagnostic test.

In paper III, we used AUCROC to develop a clinical score to predict active cancer in ischemic stroke patients. In a Circulation paper by Nancy Cook, a Harvard T. H. Chan School epidemiologist, the wide use of ROC curves was criticized.[234] She argued that relying solely on the ROC curve is unwise because it does not portray the true risk.
Certainly, no test or score can ever truly reflect the complex reality of nature and individual differences will always remain.
As any diagnostic test, using a score from AUCROC is a function based on the sensitivity and specificity of each measure included in the model. This means that there inherently will be false negative, as well as false positive outcomes. The question is then how many false outcomes we are willing to endure in order to reveal the true outcomes, here active cancer. How do we screen for cancer in a way that maintains our ethical standard, costs, and the well-being of the patient?
In paper III we constructed a score that may be used with caution in the clinical setting. In this study we argued that the score threshold of 2, with a 0.81 specificity and 13% post-test probability of cancer warranted screening.

Theories for cancer screening in ischemic stroke patients

In paper II, we conclude that underlying occult cancer is too rare in ischemic stroke patients to warrant screening of all ischemic stroke patients. Others have also supported this conclusions.[235] Therefore, a selection of high-risk patients to screen must be made. This was also our aim in paper III.
For the purpose of screening stroke patients for underlying cancer, various factors have been suggested; laboratory tests, specific DWI findings or a combination of these.

Laboratory tests studied as cancer-screening in ischemic stroke patients:

- CRP > 20 [210]
- Fibrinogen > 600 [19, 210]
- D-dimer > 5.5 mg/dL [228]
- Hemoglobin < 12.8 g/dL[236]

Increased D-dimer level is a direct measure of activated coagulation and has been used and seen as a sign of hypercoagulability in patients suffering both stroke and cancer.[217]

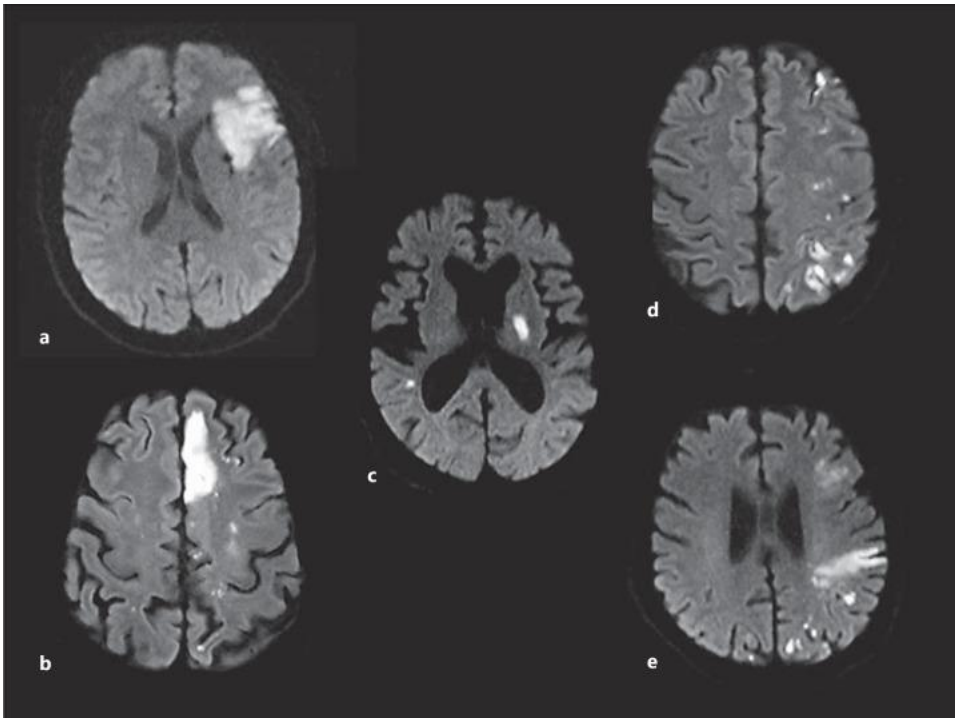
The basis for increased CRP as a predictor is that cancer activates release of cytokines and other pro-inflammatory substances. Similarly, long-term inflammation as a result of underlying cancer is a cause of decreased Hb.

MRI-DWI lesions:

Suffering multiple acute cerebral infarctions (MACI) is associated with cancer.[219, 228] In NORSTROKE, 11.0 % of all patients with active cancer had acute DWI lesions in multiple vascular territories, while only 5.4 % of stroke patients with no history of cancer had multiple vascular territories affected.

It has also been postulated that certain MACI patterns on DWI-MRI, or MACI in correlation with laboratory tests can be used to screen for occult cancer.[228] MACI are associated with strokes form embolic sources, which can be a result of cancer-induced hypercoagulability.

Imaging example 1. DWI patterns in stroke patients with cancer



Images from Schwarzbach et al., with permission under the Creative Commons Attribution-Non Commercial-No Derivatives 4.0 International License, Cerebrovasc Dis Extra, 2015.[216] The final, published version of this article is available at https://doi.org/10.1159/000439549

Schwarzbach et al. show common DWI patterns in stroke patients with cancer (Imaging example 1); picture MACI with and without scattering of emboli as compared to single acute lesions (a). **a** Single acute lesion. **b** Multiple acute lesions in one vascular territory with (micro-) embolic scattering of infarction**. c** Multiple acute lesions in >1 vascular territory (bihemispheric anterior circulation lesions) without (micro-) embolic scattering of infarction. **d** Multiple acute lesions in >1 vascular

territory (bihemispheric anterior circulation lesions) with (micro-) embolic scattering of infarction. **e** Multiple acute lesions in >1 vascular territory (anterior and posterior circulation lesions) with (micro-) embolic scattering of infarction.[216]

While MACI can result from a number of etiologies like endocarditis, PFO, myxoma and others, it is often occurs in relation to both AF and cancer. Therefore, Ito et al., suggested using concomitant D-dimer above 2.0 μg/mL and MACI to indicate cancer-associated stroke, despite presence of AF.[237]
Also Kassubek et al. suggested using laboratory results in combination with MACI to detect active cancer. However, by use of AUC-ROC curves their decided screening involved increased CRP, granulocytosis, increased lactate dehydrogenase and presence of MACI.[226]

CT thorax:

Lung cancer is one of the cancer types believed to have an especially strong association with hypercoagulability. Therefore, Bentsen et al. investigated whether all ischemic stroke patients should be screened for lung cancer with a CT thorax during the stroke work-up. They concluded that the incidence of occult lung cancer in their stroke population was 1.1 % and that this did not warrant CT screening of all stroke patients.[235] They included all patients, similar to the method used in our paper II.

Management of thromboembolic events in patients with active cancer

Secondary prophylaxis

We know that cancer is an independent risk factor for ischemic stroke, a thromboembolic event (TEE). Thus it is tempting to ask if cancer patients should be prophylactically treated with anticoagulants. However, the use of anticoagulants in cancer patients is a continuous balancing act between the risk of hemorrhage and the risk of thromboembolism.[238] Nevertheless, TEEs in cancer patients are strongly associated with increased mortality and remain the second most common cause of death in oncological patients,[239] thus preventing TEE can be crucial.

For prevention of venous TEEs in cancer patients, such as DVT and pulmonary embolism, low-molecular weight heparin (LMWH) has been the recommended treatment.[240, 241] Jang et al. compared enoxaparin, a LMWH, to warfarin for secondary prevention of cancer-associated strokes specifically, and found that LMWH was more effective in TEE prevention.[242]

At Haukeland University Hospital, primary prophylaxis with anticoagulation is not common in cancer patients (unless AF is known or diagnosed). As per guidelines, the LMWH agent Fragmin (Dalterparin), is instigated as secondary prophylaxis if a TEE occurs.

Treating cancer patients with oral anticoagulants is difficult due to their changed metabolism and interactions with other drugs.[229] Warfarin is therefore undesirable, especially as it takes time to reverse the effect in case of a hemorrhagic event.

As Fragmin is administered subcutaneously by use of syringes, it affects the quality of life. Therefore, oncologists believe that the threshold for anticoagulation in cancer patients might be lowered if medications could be administered orally.

The Direct Oral Anticoagulant (DOAC) Apixaban, (Eliquis ®), is now investigated for use in cancer patients in a multi-center trial in Norway. Previous, smaller studies have shown that DOACs in cancer patients lead to fewer hemorrhages while remaining efficient in preventing TEE.[240, 243]

A recent New England study also showed that edoxaban, (Lixiana ®), a novel direct factor Xa inhibitor, is non-inferior to Fragmin in preventing cancer-associated venous

TEE,[244] signaling that we will likely see increased use of DOACs in cancer patients in the future.

Intravenous thrombolysis for cancer patients with acute stroke

The guidelines for treatment of cancer patients with intravenous (IV) tPA are unclear. This is because many of the major trials investigating tPA-efficacy excluded patients with cancer.[245]

To date, the largest study on IV tPA in cancer patients is a brief report by Murthy et al. published in Stroke in 2013.[246] This report was a retrospective study based on ICD-10 codes and included 150.000 stroke patients, where the use and safety of IV tPA in cancer patients was studied. This study concluded that there was no increase in IV tPA complications (ICH) for patients with cancer-associated stroke. However, another finding was that there were significantly fewer cancer patients that received treatment with IV tPA compared to other stroke patients.[246]

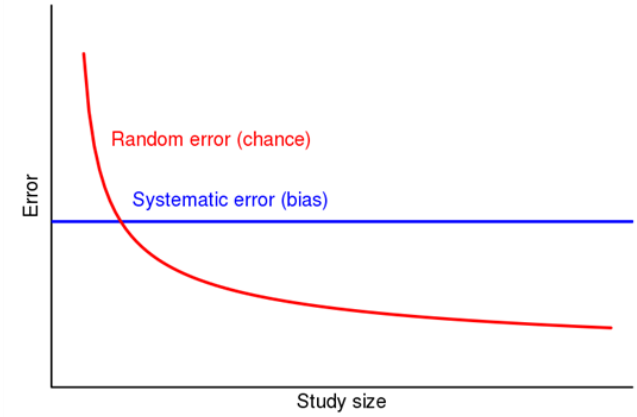
In the NORSTROKE population included in paper III, only 4.0 % of the patients diagnosed with cancer prior to stroke received IV tPA treatment for their acute stroke. In the control group of patients with no history of cancer, 16.7 % were treated with IV tPA. This discrepancy could be indicative of physicians being hesitant to treat cancer patients due to risk or fear of hemorrhage. Graus et al. postulated that cancer patients generally have strokes with more diffuse symptoms,[103] however, this was not the case for the NORSTROKE patients, where the median NIHSS on admission was similar in patients with and without cancer. On the contrary, in paper I we saw that patients with colorectal – and lung cancer had a significantly higher NIHSS on admission. These analyses were not adjusted for age or other potential confounders.

Despite the high number of patients, the short report by Murthy et al. should be interpreted with caution given its retrospective nature. A more recent study showed that ischemic stroke patients with active cancer treated with IV tPA had a poorer clinical outcome than non-cancer stroke patients treated, especially if they had cryptogenic strokes. This study, however, only included 12 patients.[247]

Methodological considerations

Handling the Inevitable Errors

In any epidemiological study, two types of error have to be kept in mind: "systematic errors" and "random errors". The random errors are the factors that are hard to adjust for as they naturally occur in any sample or population by chance. Random errors are diminished with an increase in study size. Nevertheless, one would need an infinitely large study size to completely eliminate them.



The term systematic error is often used interchangeably with the term bias. The bias can lie within the researcher or be a systematic error, such as selection bias when selecting study subjects.

In our studies, the size of the study population varied through studies I-III. In study III where the group of patients with active cancer was quite low, the chance of random errors affecting the results is quite high. This warrants caution when transferring the findings on to other study populations, or in our study specifically, to implement the findings in clinical use. Selection bias in determining study subjects was avoided by default, as the study hypotheses were not shared with the clinicians collecting and registering the NORSTROKE data. One could however suspect that there is a "healthy worker effect"[248] in certain factors that are investigated. For instance, in study III, the number of infarctions shown on DWI MRI is compared between stroke patients with active cancer at the time of ictus and stroke patients with no cancer. In cases where CT shows massive infarction at the time of admittance, or the patients has a non-compatible pacemaker for MRI, MRI is not performed. In such an instance, one

might miss large or multiple infarctions in the MRI data of the sickest patient group. If so, the control group is thereby healthier than the analyses can portray.

The confounders of CVD risk factors

Another factor to be kept in mind in epidemiological studies is that of confounding.[249] In the present study we were, inter alia, searching for associations between cancer and subsequent stroke, aiming to uncover independent risk factors of cancer-related stroke to use for prediction. A confounder is a hidden factor that can lead to misleading results through correlation with both the dependent and the independent variable being studied.[250]

In our papers, age can be a confounder in the analyses of cancer-related stroke. Age is associated with both the exposure, cancer, and the outcome of ischemic stroke. To prevent this confounder distorting our results, we adjusted for age in all multivariate analyses. Smoking is also a shared risk factor of stroke and cancer, therefore this was also forced into all regression models in papers I-III.

To adjust for all confounders is, however, impossible, especially in the field of NCDs and CVDs with their intricate and combined risk factors.
To illustrate this, we can once more use smoking as a starting factor in a fictive patient. It is well known that smoking can cause inflammation and atherosclerosis, and as such cardiovascular disease.[251] Moreover, smoking can also cause hypertension, an independent risk factor leading to stroke. Hypertension in a patient with atherosclerosis increases the risk of stroke further. Smoking may also cause lung cancer; another independent risk factor for stroke. If the fictive cancer patient is hypertensive or obese, the risk of stroke is yet again higher. Also, consumption of red meat has been linked to a higher risk of death from both stroke and cancer. There is a linear relationship between increased risk of dying from both stroke and cancer, and red meat consumption.[82] How do we control for meat eating in our patient with cancer-related stroke? The answer is that we cannot control for all confounders and risk factors, neither clinically, nor statistically.

Finally, there are socioeconomic factors and thus social determinants of health that come in to play in all levels of health – none necessarily controllable by the good will of the physician or researcher.

General strengths and limitations

The strengths of the present study are in large based on the high quality data of the NORSTROKE registry. Thanks to the prospective data registration, the data are reliable. None of the personnel in the Stroke Unit was privy to the present thesis' aims while obtaining patient information or in the following registration.
The registry uses a de facto community-based methodology, and includes patients from a well-defined area of about 250.000 inhabitants. This increases the strength and transferability of the population findings. Another strength of the study is the quality assurance of the cancer data, provided by linking NORSTROKE to the Cancer registry of Norway. This gives us the certainty that no known cancer diagnoses were missed for the patients included in the studies.

The value to conducting epidemiological research in a country like Norway is the grateful fact that every citizen has equal access to healthcare. In comparison, several of the larger studies from the US are based on ICD-codes. And when 20 % of the population does not have health insurance, the transferability of the results to a general population is not necessarily viable. In a private health care system there is also increased risk of selection bias since socioeconomic factors likely will decide who can afford to purchase health insurance.

There are limitations to the studies in the present thesis as well. Firstly, it would have been valuable to have data on cancer treatment and cancer stages. This is because hypercoagulability can be amplified with metastasis. Also, chemotherapy and radiation can increase risk of stroke. Moreover, other medications used, in addition to chemotherapy, would have been interesting to include since for instance statins can affect the cancer and stroke-related mortality. Another important limitation is the low number of cancer patients in studies II and III. This is hard to compensate for, but higher numbers would possibly have affected the statistical findings and the transferability to larger populations.

Cancer associated stroke- future perspectives

We expect that in the future there will be increased awareness of the risk of cancer-associated stroke. This will likely lead to detection of more cancer in the Stroke Unit, and that at an earlier stage. We recommend considering cancer as a possible etiology in young patients with a history of smoking and signs of hypercoagulation.
We suggest a less restrictive use of IV tPA in cancer patients. Given the hypercoagulability in cancer patients, one could speculate whether they have increased efficacy of IV tPA because they have fibrin rich clots.

I believe we will see new developments in the new fields of CVD and NCDs.
It has been shown that monoclonal antibodies in patients with known CVD and increased CRP reduced the rate of recurrent CVD events significantly, and that patients who suffered from cancer while receiving the monoclonal antibody had a significantly lower mortality, especially in those with lung cancer.[252]
Given the shared risk factors for CVD and cancer, uncovering the biological overlap of the pathogeneses of these two disease entities can not only give us new medical treatments, but furthermore serve as potential for more efficient preventative strategies.[67]
It is not unlikely that we will also see traditional medical therapies, like statins and aspirin, used more frequently to modify inflammation as a key component in CVD *and* cancer development simultaneously.[10]

Conclusions

I: We showed that the prevalence of prior cancer is increased in the stroke population compared to the general population of Western Norway, especially for those below the age of 70. The outcome of stroke patients with prior cancer was poorer than in stroke patients with no history of cancer, and for an ischemic stroke patient with prior cancer, the risk of death was doubled.

II: We showed that the most common cancer types diagnosed post stroke are lung cancer, prostate cancer, breast cancer and colorectal cancer. The cancer types with the shortest median time from stroke ictus to cancer diagnosis were colorectal cancer, followed by lung cancer. These could have been underlying at stroke ictus. Routine investigation for occult cancer in all ischemic stroke patients seems unwarranted. However, in younger patients with increased CRP and D-dimer and a history of smoking, underlying cancer should be considered.

III: We showed that the prevalence of active cancer in our stroke population was 5 %. In order to predict active cancer in ischemic stroke patients, a score comprising increased D-dimer (> 3 mg/L), lower Hb (< 12.0 g/dL) and a history of current or previous smoking was constructed to select patients for screening of cancer. This score was feasible for patients below the age of 75.

Appendix

1. **Trial of Org in 10172 in Acute Stroke Treatment (TOAST)**
2. **National Institutes of Health Stroke Scale (NIHSS)**
3. **The modified Rankin Scale (mRS)**

TOAST klassifikasjon

☐ **Aterosklerose (sannsynlig)**
- Ingen / eller medium risiko kardial embolikilde (sykehistorie eller undersøkelser)
- Angiografi forenlig med diagnosen, eller Duplex halskar forenlig med diagnosen

☐ **Aterosklerose (mulig)**
- Ingen høy risiko kardial embolikilde (sykehistorie eller undersøkelser)
- Angiografi eller Duplex halskar ikke utført eller Duplex halskar forenlig med diagnosen, men angiografi inkonsistent

☐ **Kardial emboli (sannsynlig)**
- Høy eller medium risiko kardial embolikilde (sykehistorie eller undersøkelser)
- Medium risiko pasienter: Ingen annen årsak
- Angiografi forenlig med diagnosen, eller Duplex halskar forenlig med diagnosen

☐ **Kardial emboli (mulig)**
- Høy eller medium risiko for kardial embolikilde (sykehistorie eller undersøkelser)
- Medium risiko pasienter: Ingen annen årsak
- Angiografi ikke utført, eller Duplex halskar forenlig med diagnosen, men angiografi inkonsistent

☐ **Småkarsykdom (sannsynlig)**
- Ingen høy/medium risiko for kardial embolikilde Ingen andre årsaker funnet
- Angiografi forenlig med diagnosen, eller Duplex halskar forenlig med diagnosen

☐ **Småkarsykdom (mulig)**
- Ingen høy risiko for kardial embolikilde
- Ingen andre årsaker funnet.
- Angiografi og Duplex halskar ikke utført eller Duplex halskar forenlig med diagnosen, men angiografi inkonsistent

☐ **Annen årsak (sannsynlig)**
- Fullstendig utredning forenlig med årsaken
- Aterosklerose eller kardial emboli utelukket

☐ **Annen årsak (mulig)**
- Undersøkelser (ikke fullstendige) forenlige med annen årsak

☐ **Ukjent årsak**
- Ingen mulig årsak
- To eller flere årsaker hvor ingen peker seg ut som mer sannsynlig

Klinikk
- Klinikk må være forenlig med subtype
- TIA i samme gebet taler for aterosklerose
- TIA i annet gebet taler for kardial emboli
- Angina pectoris eller perifer karsykdom taler for aterosklerose
- Systemiske embolier taler for kardial emboli
- Hypertensjon/diabetes støtter småkarsykdom

Høy risiko kardial embolikilde
- Mekanisk ventil
- Atrieflimmer
- Sick Sinus Syndrom
- Akutt hjerteinfarkt < 4 uker
- Venstre ventrikkeltrombe
- Dilatert kardiomyopati
- akinetisk venstre ventrikkelsegment
- Venstre atriumtrombe
- Atriemyxom
- Endokarditt

Medium risiko kardial embolikilde
- Hjerteinfarkt > 4 uker, men <6 måneder
- Hjertesvikt
- Hypokinetisk venstre ventrikkelsegment
- Atrieflutter
- Biologisk ventil
- Mitralklaffprolaps
- Atrieseptumdefekt (ASD)
- Patent foramen ovale (PFO)
- Interatrialt septumaneurysme

Cerebral CT / MR (kan være negativ)
- skal ved småkarsykdom vise et lakunært infarkt < 1,5 cm sentralt i hemisfæren eller i hjernestammen
- skal ved aterosklerose eller kardial emboli vise infarkt kortikalt og/eller subkortikalt i hemisfæren eller infarkt tilsvarende en sirkumferensarterie i hjernestammen eller cerebellum
- Ved andre subtype: lingen spesifikke krav

Angiografi og Duplex ultralyd
- skal ved aterosklerose vise en stenose ≥ 50% eller ulcerasjon ≥ 2 mm i relevant arterie

Annen sannsynlig årsak (tillegg til TOAST - velg én)

Disseksjon	☐	Atrieflimmer	☐	Hjerteinfarkt	☐
Protrombotisk tilstand	☐	Endokarditt	☐	Klaffefeil	☐
Graviditet	☐	PFO	☐		

Annen patologi (beskriv) _____

☐ ☐ Status ved innleggelse ukjent

		Akutt-mottak	Slag-enhet	NIHSS score dag 0-1						
	Dato									
	Kl									
1a	**Bevissthetsnivå** 0 = Våken 1 = Døsig, reagerer adekvat ved lett stimulering 2 = Døsig, reagerer ved kraftigere stimulering 3 = Reagerer ikke, eller ikke-målrettet									
1b	**Orientering** (spør om måned + alder) 0 = Rett svar på 2 spørsmål 1 = Rett svar på 1 spørsmål (og ved alvorlig dysartri) 2 = Svarer ikke rett på noe spørsmål									
1c	**Respons på kommando** (lukke øyne + knyte hånd) 0 = Utfører begge kommandoer korrekt 1 = Utfører en kommando korrekt 2 = Utfører ingen korrekt									
2	**Blikkbevegelse** (horisontal bevegelse til begge sider) 0 = Normal 1 = Delvis blikkparese (eller v/øyenmuskelparese) 2 = Fiksert blikkdreining til siden, total blikkparese									
3	**Synsfelt** (bevegelse i laterale synsfelt) 0 = Normalt 1 = Delvis hemianopsi 2 = Total hemianopsi 3 = Bilateral hemianopsi / blind									
4	**Ansikt** (vise tenner, lukke øynene, løfte øyenbryn) 0 = Normal 1 = Utvisket nasolabialfure, asymmetri ved smil 2 = Betydelig lammelse i nedre ansiktshavdel 3 = Total lammelse i halve ansiktet (eller ved coma)									
5	**Kraft i armen** (holde arm utstrakt 45° i 10 sek.) 0 = Normal (også ved "ikke testbar") **hø** 1 = Drifter til lavere posisjon 2 = Drifter til sengen 3 = Faller til sengen **ve** 4 = Ingen bevegelse									
6	**Kraft i benet** (holde benet utstrakt 30° i 5 sek.) 0 = Normal (også ved "ikke testbar") **hø** 1 = Drifter til lavere posisjon 2 = Drifter til sengen 3 = Faller til sengen **ve** 4 = Ingen bevegelse									
7	**Koordinasjon / ataxi** (finger-nese- / hæl-kne-prøve) 0 = Normal (og ved "ikke testbar" eller ved coma) 1 = Ataksi i arm eller ben 2 = Ataksi i arm og ben									
8	**Hudfølelse** (sensibilitet for stikk) 0 = Normal 1 = Lettere sensibilitetsnedsettelse 2 = Markert sensibilitetstap (også ved coma)									
9	**Språk /afasi** (spontan tale, taleforståelse) 0 = Normal 1 = Moderat afasi, samtale mulig 2 = Markert afasi, samtale vanskelig eller umulig 3 = Ikke språk (også ved coma)									
10	**Tale / dysartri** (spontan tale) 0 = Normal 1 = Mild - moderat dysartri 2 = Nær uforståelig tale eller anartri (og ved coma)									
11	**"Neglect"** (bilateral simultan stimulering syn / hud) 0 = Normal (+ ved hemianopsi m/normal hudfølelse) 1 = Neglect i en sansemodalitet 2 = Neglect i begge sansemodaliteter									
	Total NIHSS-Score									
	Undersøkerens signatur									

Rankin Scale (mRS) Dag 7 (eller tidligere hvis avreise <7 døgn)

Ja ☐ Nei ☐ Dato ☐☐.☐☐.☐☐ Score: ☐

Score	
0	**Ingen symptomer og ingen begrensninger i dagliglivet**
1	**Lette symptomer, men i stand til å utføre alle vanlige aktiviteter** *"Er det problemer med å lese/skrive, snakke eller finne riktige ord, problemer med balanse, synsproblemer, nummenhet, svakhet, vanskeligheter med å svelge, eller andre symptomer som følge av slaget?"*
2	**Begrensninger i sosiale aktiviteter, men uavhengig i ADL** *"Er det blitt en endring i arbeidsevne eller evne til å ta seg av andre?"* *"Er det blitt en endring i evne til å delta i tidligere sosiale aktiviteter eller fritidsaktiviteter?"* *"Har han/hun problemer i samvær eller er blitt isolert?"*
3	**Har behov for noe hjelp (instrumental ADL), men kan gå uten hjelp** *"Er det nødvendig med hjelp til å lage et enkelt måltid, gjøre husarbeid, passe på penger, gjøre innkjøp eller reise med buss, bil nær hjemmet?"*
4	**Kan ikke gå uten hjelp, trenger hjelp i daglige aktiviteter (basic ADL), men trenger ikke kontinuerlig oppfølging og hjelp** *"Er det nødvendig med hjelp til spising, daglig hygiene, bruk av toalettet, eller å gå?"*
5	**Sengeliggende, inkontinent, avhengig av kontinuerlig hjelp** *"Trenger pasienten kontinuerlig pleie og omsorg?"*
6	**Død**

Source of data

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Papers I-III

I

Prior Cancer in Patients with Ischemic Stroke: The Bergen NORSTROKE Study

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Background: To compare the prevalence of prior or on-going cancer in patients with ischemic stroke and in the general population. We hypothesized that cardioembolic stroke is the most common stroke etiology in patients with prior cancer and that the outcome for ischemic stroke patients (ISP) with prior cancer is poor. *Methods:* All ISP registered in the Norwegian Stroke Research Registry (NORSTROKE) as part of the ongoing Bergen NORSTROKE Study were included. Stroke etiology was determined by the Trial of Org 10172 in Acute Stroke Treatment criteria, and the severity of the stroke was defined from the National Institutes of Health Stroke Scale score. Information about prior or ongoing cancer disease and type was retrospectively obtained from the medical patient record and The Cancer Registry of Norway. The prevalence of cancer among stroke patients was compared with the prevalence of cancer in the general population. *Results:* Among 1456 ISP, 229 (15.7%) patients had 1 or more cancer diagnoses before the stroke. The prevalence of cancer was higher among stroke patients compared with the general population ($P = .001$). The most common cancer types were colorectal cancer (20.2%), prostate cancer (15.6%), breast cancer (12.7 %), cancer of the urinary tract system (10.3%), gynecological cancer (6.2%), and lung cancer (4.5%). Logistic regression analysis showed that patients with prior cancer had cardioembolic strokes at a higher rate ($P = .03$). *Conclusions:* The prevalence of prior cancer is higher in ISP than in the general population. ISPs with prior cancer are more prone to cardioembolism. **Key Words:** Stroke—ischemic stroke—embolic—cancer—prothrombotic—etiology—stroke risk factors—outcome.

Introduction

A connection between cancer and thromboembolic episodes was first recognized by Armand Trousseau in 1865 and has been debated ever since.[1] Some studies suggest that stroke occurs more frequently in cancer patients than in the average population and that stroke is the second most common finding overall at autopsy in patients with cancer, after metastasis of the primary tumor.[2] According to autopsy studies, up to 15% of cancer patients may experience a thromboembolic event during their clinical course,[3] although more recent clinical studies have shown a lower occurrence of cancer-associated stroke.[4,5] Cancer can lead to stroke through various biologic mechanisms. Solid tumors and hematologic cancer affect the vascular system by direct tumor effect or through coagulation disorders.[2,6] Cancer and its treatment may lead to a hypercoagulable state, causing stroke.[3,7] Cancer and stroke may also share similar risk factors. Stroke can also occur because of cancer-associated infections.[2] For patients with stroke and cancer, outcome may be poor.[8]

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Further understanding of factors causing stroke in cancer patients is important for stroke prevention and treatment in this population. The aim of this community-based study was to assess the prevalence of prior cancer in patients with ischemic stroke, their prognosis, the most common cancer and stroke subtypes, risk factors, and the cancer's possible involvement in stroke pathogenesis. We hypothesized that cardioembolic stroke is common in patients with prior cancer and that outcome is poor. Hypercoagulable states cause ischemic stroke more frequently by cardioembolic mechanisms than other pathophysiologic mechanisms such as atherosclerosis.[4]

Methods

All consecutive patients with acute ischemic stroke (the index stroke) admitted to the stroke unit, Department of Neurology, Haukeland University Hospital, between February 2006 and August 2011 were prospectively registered in a database (The Bergen NORSTROKE Registry). We obtained written informed consent from all patients. The stroke unit at Haukeland University Hospital serves a well-defined region of ≈250,000 people. Ischemic stroke was defined in accordance to the Baltimore–Washington Cooperative Young Study Criteria as neurologic deficit lasting more than 24 hours or transient ischemic attacks where computed tomography or magnetic resonance imaging showed infarctions related to the clinical findings.[9]

The stroke severity was assessed by the National Institutes of Health Stroke Scale (NIHSS) on admission. The minimum score is 0, whereas the maximum score of a stroke with high severity is 42. Short-term functional outcome was determined by the modified Rankin Scale (mRS) score 7 days poststroke onset (or on discharge if earlier than 7 days). On admission, blood pressure, C-reactive protein, D-dimer, fibrinogen, gamma-GT, hemoglobin, blood glucose, and ALAT were registered. Electrocardiogram and duplex of the carotid arteries were obtained. Holter monitoring was performed in selected patients. The Trial of Org 10172 in Acute Stroke Treatment criteria were used to determine the cause of stroke by the admitting physician.[10] These criteria are used to classify 5 causes of stroke (large-vessel diseases, cardiac embolism, small-vessel disease, other etiology, and unknown etiology). This physician was blinded to the study hypothesis. The patients' medical history and radiological images were also obtained.

Registered stroke risk factors included hypertension, atrial fibrillation (AF), diabetes mellitus (DM), angina pectoris (AP), acute myocardial infarction (AMI), peripheral artery disease, and tobacco use. Hypertension, AP, AMI, and peripheral artery disease were considered present if diagnosed by a physician any time before onset of the stroke. DM was defined as treatment with glucose-lowering medications or diet before admission. AF was defined as chronic or paroxystic AF confirmed by electrocardiogram before the stroke.

The medical records were searched for prior diagnoses of cancer. Thereafter, the Cancer Registry of Norway was searched for prior diagnoses for assuring data quality. The Cancer Registry of Norway was established in 1951, and registration of all cancer cases in Norway is mandatory; therefore, it is a reliable source of cancer data. The patient's social security number was used to identify the cancer diagnoses; thus, all the patients remained unique and were not counted more than once. The date of diagnosis, cancer type, and histology were noted. The prevalence rates of cancer in the general population in the community served by Haukeland University Hospital by December 31, 2009, were obtained from the Cancer Registry of Norway. Patients with cancer diagnosed after admission were excluded from this study. Twenty-nine patients with a history of nonmelanoma skin cancer before stroke were also excluded.

The study was approved by the Norwegian Regional Ethics Committee.

Statistics

The ischemic stroke patients (ISP) were dichotomized as ISP who had prior diagnosis of cancer (cancer-ISP) and the ISP who had no diagnosis of cancer (noncancer-ISP). Student *t* test and chi-square analyses were used for the univariate analyses of differences between the 2 groups and between the group of noncancer-ISP and the 6 subgroups of the most common types of cancer. Logistic regression analysis with cancer-ISP versus noncancer-ISP as the dependent factor was used to determine independent variables associated with cancer. Cox regression analysis was used to investigate survival. Statistical software Stata 12.0 was used for the statistical analyses.

Results

Among 1456 patients with ischemic stroke, 229 (15.7%) patients had 1 or more cancer diagnoses before the stroke.

Prevalence of Cancer in Ischemic Stroke Patients and the General Population

Figure 1, A-C shows the distribution of cancer prevalence among the 10-year age groups and 1 group of the younger patients aged 15-49 years in cancer-ISP and in the general population. Comparing all cases of prior cancer, the prevalence of cancer was higher in cancer-ISP than in the general population ($P = .001$). This was significant in the age groups of 15-49, 50-59, and 60-69 years. However, in the patients with cancer diagnosed 5 years or less before ictus, prevalence was higher only in cancer-ISP in the age groups of 15-49 and 50-59 years ($P < .001$). For patients with cancer diagnosed 1 year or less before ictus, cancer prevalence was significantly

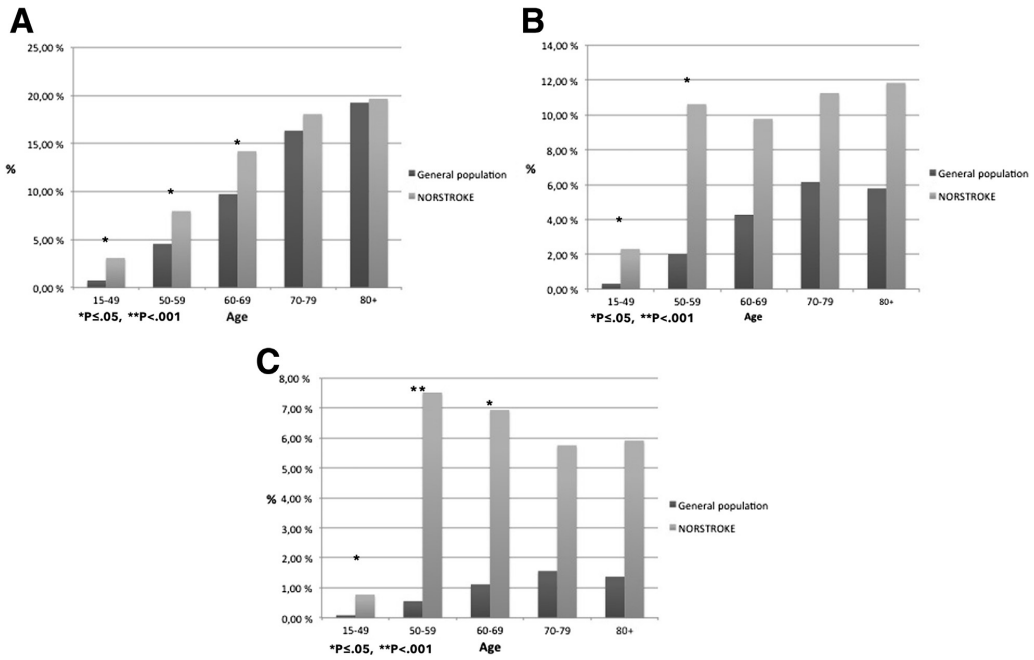

Figure 1. *(A) Comparison of cancer prevalence in ischemic stroke patients and the general population of Western Norway in separate age groups. (B) Comparison of cancer prevalence in ischemic stroke patients and the general population of Western Norway in separate age groups within the last 5 years. (C) Comparison of cancer prevalence in ischemic stroke patients and the general population of Western Norway in separate age groups within the last year.*

higher in the same age groups as when comparing all cases of prior cancer (both $P \leq .001$).

Patient Characteristics

The most common cancer types were colorectal cancer (22.5%), prostate cancer (16.7%), breast cancer (13.7%), cancer of the urinary tract system (11.0%), gynecological cancer (6.6%), and lung cancer (4.9%). Twenty (8.7%) patients had 2 cancer diagnoses and 2 (.9%) patients had 3 cancer diagnoses. Table 1 shows characteristics of cancer-ISP and noncancer-ISP before ictus. The mean age was higher in cancer-ISP than for noncancer-ISP ($P < .001$). The median NIHSS score on admission was higher in cancer-ISP than in noncancer-ISP ($P = .001$) (Table 2). Cancer-ISP had a higher frequency of chronic AF ($P < .001$), heart disease ($P = .01$), and ex- or current smoking ($P = .008$). The mean blood levels of fibrinogen were higher in cancer-ISP than noncancer-ISP (mean 4.0 [SD 1.1] versus mean 3.7 [SD .9], $P < .001$). Mean blood levels of D-dimer were similar in the 2 groups (mean 1.8 [SD 2.7] versus mean 1.4 [SD 2.4], $P = .06$).

The frequency of prior ischemic stroke was similar in the 2 groups, yet during the hospital stay, more of cancer-ISP had a recurrent ischemic stroke (n = 3 [1.3%] versus n = 4 [.3%] in noncancer-ISP, $P = .05$). These 3 cancer-ISP had breast, prostate, and lung cancer, respectively. The cancer-ISP had 21 types of cancer: colorectal cancer (n = 55, 22.4%), prostate cancer (n = 42, 17.1%), breast cancer (n = 31, 12.7%), cancer of the urinary tract system (n = 28, 11.4%), malignant melanoma (n = 17, 6.9%), gynecological cancer (n = 16, 6.5%), lung cancer (n = 12, 4.9%), metastasized cancer of unknown primary site (n = 8, 3.3%), stomach cancer (n = 6, 2.4%), non-Hodgkin lymphoma (n = 5, 2.0%), cerebral cancer (n = 5, 2.0%), carcinoma in situ (n = 4, 1.6%), pancreatic cancer (n = 4, 1.6%), testicular cancer (n = 3, 1.2%), gallbladder cancer (n = 2, .8%), lymphoma (n = 2, .8%), larynx cancer (n = 2, .8%), thyroid cancer (n = 1, .4%), liver cancer (n = 1, .4%), and myelomatosis (n = 1, .4%). Thirty-seven cancer diagnoses not in NORSTROKE or the patient records were discovered in the Cancer Registry of Norway.

Stroke Etiology

Table 2 shows stroke etiology according to the Trial of Org 10172 in Acute Stroke Treatment criteria. Cardioembolic strokes were more common in cancer-ISP compared with noncancer-ISP ($P = .016$). On logistic regression, cancer before stroke was independently associated with higher age ($P < .001$), cardioembolic stroke ($P = .03$), and having smoked ($P < .001$). Adding blood fibrinogen levels to the logistic regression analysis showed that prior

Table 1. *Patient characteristics in ischemic stroke patients with and without prior cancer before stroke*

	Cancer diagnosis before index stroke, N = 229	Stroke patients with no history of cancer, N = 1227	*P*
Male, n (%)	124 (54.1)	694 (56.6)	.5
Female	105 (45.9)	533 (43.4)	
Age, mean (SD)	76.1 (11.1)	69.5 (15.1)	<.001
Prior ischemic stroke, n (%)	36 (15.7)	169 (13.8)	.4
Stroke during hospital stay	3 (1.3)	4 (.3)	.05
Hypertension	127 (55.5)	619 (50.5)	.2
Atrial fibrillation, chronic	33 (14.4)	88 (7.2)	<.001
Atrial fibrillation, paroxysmal	24 (10.5)	107 (8.7)	.4
Diabetes mellitus	30 (13.1)	170 (13.9)	.8
Acute myocardial infarction	39 (17.0)	163 (13.3)	.1
Heart disease	37 (16.2)	124 (10.1)	.01
Ex- and current smoking	141 (61.6)	664 (54.1)	.008

cancer was associated with elevated fibrinogen level ($P = .013$), whereas cardioembolic origin was no longer associated with prior cancer ($P = .096$).

Short-term Outcome

As defined by mRS on day 7, cancer-ISP had a poorer outcome than noncancer-ISP ($P = .003$) (Table 2).

Cancer Types

Table 3 shows a comparison between noncancer-ISP and the 6 subgroups of the most common cancer types. Among the 6 subgroups, lung cancer patients had the highest median NIHSS score ($P < .001$). Patients with colorectal cancer also had a higher median NIHSS score on admission compared with noncancer-ISP ($P \leq .05$). Both lung and colorectal cancer patients had a higher median mRS on day 7 (both $P = .05$). Time from cancer diagnosis to stroke ictus varied among the 6 most common cancer types. Lung cancer patients had the shortest time from diagnosis with a median time of .78 years. The other time intervals were 3.6 years in prostate cancer patients, 6.7 years in colorectal cancer patients, 7.8 years for both patients with cancer of the urinary tract system and breast cancer, and 17.7 years for gynecological cancer patients.

Median follow-up time for all patients after ischemic stroke ictus was 3.8 years (interquartile range 2.6-4.8 years). On Cox regression analysis, age, sex, prior cancer, DM, AMI, prior smoking, and high NIHSS score on admission were associated with long-term mortality (Table 4). Prior cancer was associated with a doubled risk of death ($P < .001$).

Discussion

In the present study 15.7% of our ISP had prior cancer. This is similar to what was found in an autopsy study (15%) in 1985.[3] However, in a clinical study of cancer patients, only 3.5% of their cancer patients experienced stroke after their cancer was diagnosed.[11] The difference between this study and the present study may be because of different study design or that we were able to disclose more patients with prior cancer because of obligatory reporting to the Cancer Registry of Norway. Yet, another more recent study of cancer patients that

Table 2. *Patient characteristics in ischemic stroke patients with and without prior cancer poststroke*

	Cancer diagnosis before index stroke, N = 229	Stroke patients with no history of cancer, N = 1227	*P*
NIHSS, median (IR)	5 (2-12)	3 (1-8)	.001
mRS, day 7	2 (1-4)	2 (1-4)	<.001
TOAST, n (%)			.02
Atherosclerosis	26 (11.4)	150 (12.2)	
Cardioembolic	89 (38.9)	349 (28.4)	
Small-vessel disease	23 (10.0)	175 (14.3)	
Other	3 (1.3)	35 (2.9)	
Unknown	87 (38.0)	516 (42.1)	

Abbreviations: mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; IR, interquartile range; TOAST, Trial of Org 10172 in Acute Stroke Treatment.

Table 3. *Characteristics of the noncancer ischemic stroke patient group versus cancer ischemic stroke patient subgroups*

Cancer types	Noncancer, n = 1227	Colorectal, n = 55	Prostate, n = 42	Breast, n = 31	Urinary system, n = 28	Gynecological, n = 16	Lung, n = 12
Age, mean (SD)*	69.5 (15.1)	78.6 (10.3)†	76.2 (9.1)‡	75.5 (12.5)‡	75.5 (10.4)‡	76.1 (10.1)	67.2 (11.8)
Male, n (%)	694 (56.6)	32 (13.4)	42 (18.3)	—	25 (10.9)†	—	5 (2.2)
NIHSS, median (IR)	3 (1-8)	5 (1-14)‡	4 (2-7)	4 (3-12)	3 (1-7)	5 (3-10)	14 (4-19.5)†
mRS, day 7	2 (1-4)	3 (1-4)‡	2 (1-3)	3 (2-4)	2 (1-4)	3 (1.5-4)	4 (2-4.5)‡
Time from cancer to index stroke, y*	—	6.7	3.6	7.8	7.8	17.7	.78
Etiology, n (%)							
Cardioembolic	349 (28.4)	25 (45.5)‡	16 (38.1)	10 (32.3)	8 (28.6)	4 (25.0)	3 (25.0)
Atherosclerosis	150 (12.2)	5 (9.1)	5 (11.9)	2 (6.5)	5 (17.9)	2 (12.5)	1 (8.3)
Small-vessel disease	175 (14.3)	9 (16.4)	6 (14.3)	5 (16.1)	—	1 (6.3)	—
Other	35 (2.9)	—	—	—	—	—	1 (8.3)
Unknown	516 (42.1)	16 (29.1)	15 (35.7)	14 (45.1)	15 (53.6)	8 (50.0)	7 (58.3)

Abbreviations: mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; IR, interquartile range.
*Stroke patient's first cancer diagnosis.
†$P \leq .001$.
‡$P \leq .05$.

had ischemic strokes found that 26% of the strokes were defined as "cancer-associated ischemic strokes."[12] In that study, strokes were defined as cancer-associated strokes in all cancer patients whom were undergoing treatment while presenting with elevated fibrinogen and D-dimer levels.

In the present study, the prevalence of prior cancer in stroke patients was higher than in the general population for all age groups, especially among patients younger than 70 years. This suggests that cancer may be an independent cause of stroke or that cancer and stroke have common risk factors. Also, there may be unknown risk factors that predispose patients to both stroke and cancer.

Median time from cancer diagnosis to stroke ictus among our patients was 6.8 years. We have found now comparable data in the literature. However, in a clinical study of stroke patients with stroke as an initial presentation of cancer, 83.3% had a second stroke within 4 months of their index stroke.[5] This indicates that time to stroke is short with an on-going cancer disease, whereas the long time interval from cancer diagnosis to stroke in our patients is likely because of high frequency of cured cancer.

Table 4. *Cox regression analysis in ischemic stroke patients with and without prior cancer with Hazard ratios for long-term mortality*

	Hazard ratio (CI)	*P*
Prior cancer	2.0 (1.7-2.5)	<.001
Age	1.1 (1.07-1.1)	<.001
Sex	.98 (.8-1.3)	.9
Diabetes mellitus	1.4 (1.0-1.97)	.02
Myocardial infarction	1.7 (1.3-2.2)	<.001
Smoking	1.7 (1.2-2.3)	.002
NIHSS	1.1 (1.09-1.12)	<.001

Abbreviations: CI, confidence interval; NIHSS, National Institutes of Health Stroke Scale.

Colorectal cancer, prostate cancer, breast cancer, cancer of the urinary tract system, gynecological cancer, and lung cancer were the most common cancer types in our study. Other studies of stroke patients with history of cancer showed that lung and breast cancer were the most common types of cancer,[4,5] where lung cancer was the most frequent of the 2.[4] In our study, breast and lung cancer were, respectively, the third and fifth most common cancer types. The discrepancy with previous studies may be because of the short time from cancer diagnosis to stroke ictus (median 284.5 days or .78 years) among our patients with lung cancer. Different study design and poor prognosis of lung cancer may explain this discrepancy. The community-based approach in the present study suggests that our results are more realistic.

Lung cancer patients had a worse outcome despite their mean age being lower than the other cancer groups and stroke patients without cancer. A significantly higher number of the lung cancer patients were deceased 7 days postictus, compared with the other groups of cancer.

We confirmed the hypothesis of cardioembolic strokes being the most common stroke etiology in the ISP with prior cancer. This has also been shown in previous studies.[4,13] Comparing stroke etiology between the most common types of cancer and the noncancer-ISP, only the colorectal cancer stroke patients had a significantly higher number of strokes because of cardiac embolism. It is possible that some strokes were caused by a cancer-induced hypercoagulable state. Hypercoagulable states cause

ischemic stroke more frequently by cardioembolic mechanisms than other pathophysiologic mechanisms such as embolism in atherosclerosis.[4] However, this is still a subject for discussion in need of further research.[2]

Cardioembolic mechanisms are associated with severe stroke. Compatible to this, the cancer-ISP had more severe neurologic deficits on admission and poorer short-term functional outcome than patients without prior cancer. This pertained specially to patients with prior lung cancer and colorectal cancer. Others have also reported more severe strokes in patients with cancer.[5]

An association between cancer and thromboembolic events has been well established by numerous studies.[14] The cancer and the cancer treatment can be complicated by such events. Both venous and arterial complications, such as stroke, are seen as cancer patients can develop a hypercoagulable state.[15] The cancer cells can affect the coagulation cascade causing thrombin generation and thrombosis and causing a thrombogenic surface of the vascular lining. As cancer therapies become increasingly aggressive, the risks of thromboembolic events increase.[7,16] Some chemotherapies have been shown to increase the risk of stroke, particularly chemotherapies used for lung and breast cancer.[2,17] Small-cell lung cancer is often treated with Cisplatin and Gemcitabine, which yield high risk for cerebrovascular events.[2,18] The various types of chemotherapies may present different risks, which may explain why the lung cancer patients have poorer outcome, despite a significantly lower age. However, the risk may also vary between various cancer types. In patients with ovarian cancer, the treatment as such may not necessarily cause the greatest risk for ischemic stroke but rather the reduced ovarian activity.[19] In accordance to the varying risk depending on cancer type, all patients with nonmelanoma skin cancer were excluded. The likelihood of a cancer of that type causing a hypercoagulable state is low.

We found elevated fibrinogen and a trend toward elevated D-dimer in cancer-ISP compared with noncancer-ISP. It has previously been shown that in patients with suspected thromboembolic disorders, fibrinogen degradation products were consistently elevated in hemostatic disorders.[20] This may suggest that a hypercoagulable state was more frequent in the cancer-ISP group. This possibility is also supported by the fact that ISP with prior cancer experienced a higher number of recurrent stroke during the hospital stay compared with the noncancer-ISP even though the recurrence frequencies were low.

The strength of this community-based study is the high number of unselected stroke patients included. Another strength is that the NORSTROKE research registry was linked to the Cancer Registry of Norway; thus, all stroke patients with a history of cancer were registered. A weakness of our study is that we had no data neither on cancer treatment before the index stroke nor on withdrawal of care.

Conclusions

Prior cancer has a higher prevalence in ISP than in the general population, especially among patients younger than 70 years. Our study indicates that ISP with prior cancer are more prone to strokes with a cardioembolic origin etiology and that outcome is poorer compared with noncancer-ISP.

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Cancer-Associated Stroke: The Bergen NORSTROKE Study

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Key Words
Ischemic stroke · Cancer · Prothrombotic · Hypercoagulability · Stroke etiology

Abstract
Background: Underlying malignancy can cause ischemic stroke in some patients. Mechanisms include the affection of the coagulation cascade, tumor mucin secretion, infections and nonbacterial endocarditis. The release of necrotizing factor and interleukins may cause inflammation of the endothelial lining, creating a prothrombotic surface that triggers thromboembolic events, including stroke. The aims of this study were to assess the occurrence of cancer in patients who had recently suffered an ischemic stroke and to detect possible associations between stroke and cancer subtypes. ***Methods:*** All ischemic stroke patients registered in the Norwegian Stroke Research Registry (NORSTROKE) as part of the ongoing Bergen NORSTROKE study were included. Blood samples were obtained on admission. Stroke etiology was determined by the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria, and the severity of stroke was defined according to the National Institute of Health Stroke Scale score. Information about cancer disease after stroke was obtained from patient medical records and The Cancer Registry of Norway. ***Results:*** From a total of 1,282 ischemic stroke patients with no history of cancer, 55 (4.3%) patients were diagnosed with cancer after stroke. The median time from stroke onset to cancer diagnosis was 14.0 months (interquartile range 6.2–24.5). Twenty-three (41.8%) patients were diagnosed with cancer within 1 year and 13 (23.6%) within 6 months. The most common cancer type was lung cancer (19.0%). By Cox regression analysis, cancer after stroke was associated with elevated D-dimer levels on admittance (p <

The study has used data from the Cancer Registry of Norway.

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0.001), age (p = 0.01) and smoking (p = 0.04). ***Conclusions:*** Cancer-associated stroke is rare, and routine investigation for cancer seems unwarranted in acute ischemic stroke. However, in stroke patients with elevated levels of blood coagulation factors, C-reactive protein, higher age and a history of smoking, underlying malignancy should be considered. Our study suggests that an unknown stroke etiology does not predict malignancy.

Introduction

A link between cancer and stroke has long been recognized [1]. Some studies suggest that stroke, in some cases, is caused by underlying malignancy [2, 3]. Mechanisms include the affection of the coagulation cascade, tumor mucin secretion, infections and nonbacterial endocarditis [4]. The release of necrotizing factor and interleukins may cause inflammation of the endothelial lining, creating a prothrombotic surface that triggers thromboembolic events, including stroke [5, 6]. Elevated D-dimer and fibrinogen levels can indicate a cancer-induced prothrombotic state [7, 8]. Elevated C-reactive protein (CRP) may represent cancer-mediated inflammation [9]. Cancer patients are at an increased risk of stroke, especially within 1 year of cancer proliferation [10]. Though rarely, ischemic stroke has been seen as the first sign of underlying malignancy [7, 10].

The aims of this community-based study were to assess the occurrence of cancer in patients who had recently suffered an ischemic stroke. We hypothesized that some of the patients had an underlying malignancy at stroke onset, which contributed to a cancer-associated stroke. We also aimed to detect possible associations between stroke and cancer subtypes.

Methods

Study Design

All patients admitted to the Department of Neurology, Haukeland University Hospital, Bergen, Norway, with confirmed ischemic stroke were prospectively included in the Norwegian Stroke Research Registry (NORSTROKE) as part of the Bergen NORSTROKE study.

Ischemic stroke was defined in accordance to the Baltimore-Washington Cooperative Young Study Criteria as neurologic deficit lasting >24 h or transient ischemic attacks where CT or MRI showed infarctions related to the clinical findings [11]. The severity of the stroke was assessed by the National Institute of Health Stroke Scale (NIHSS) on admittance. Short-term outcome was determined by the modified Rankin Scale (mRS) score 7 days after stroke onset (or on discharge if the patient was discharged earlier than after 7 days). On admission, vital parameters and blood analyses were obtained. Clinical characteristics were registered by a neurologist <1 day after admission. Investigations included electrocardiogram, Duplex and transthoracic echocardiography or transesophageal echocardiography. The Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria were used to determine the cause of stroke [12].

Stroke risk factors including hypertension, atrial fibrillation (AF), persistent foramen ovale, diabetes mellitus, angina pectoris, coronary artery disease and tobacco use were registered. Hypertension, angina pectoris, acute myocardial infarction, peripheral artery disease and chronic or paroxystic AF were considered present if diagnosed by a physician any time before stroke onset or during admission for stroke.

Table 1. Patient characteristics in ISP with and without later cancer

	Cancer diagnosis after index stroke (n = 55)	ISP with no history of cancer (n = 1,227)	p
Male, n	34	694	0.4
Female, n	21	533	
Mean age ± SD, years	72.7±11.5	69.5±15.1	0.1
Median NIHSS (IQR)	4 (2–9)	3 (1–8)	0.9
Median mRS (IQR)	2 (1–4)	2 (1–4)	0.4
Mean temperature on admission ± SD, °C	36.6±0.8	36.6±2.8	0.9
Prior ischemic stroke	13 (23.6)	169 (13.8)	0.04
Hypertension	26 (47.3)	619 (50.4)	0.7
Chronic AF	6 (10.9)	88 (7.2)	0.3
Paroxysmal AF	6 (10.9)	107 (8.7)	0.5
Diabetes mellitus	10 (18.2)	170 (13.9)	0.3
Previous myocardial infarction	6 (10.9)	163 (13.3)	0.6
Heart disease	5 (0.9)	124 (10.1)	0.8
Smoking	36 (65.5)	664 (54.1)	0.3
Blood values			
Mean D-dimer ± SD, mg/l	2.7±4.6	1.4±2.4	0.003
Mean fibrinogen ± SD, mmol/l	4.7±5.3	3.7±0.9	<0.001
Mean hemoglobin ± SD, g/dl	14.0±1.9	14.3±1.5	0.2
Mean glucose ± SD, mmol/l	7.2±2.9	6.7±2.5	0.1
Mean CRP ± SD, mg/l	18.8±41.2	10.0±26.4	0.02
Mean cholesterol ± SD, mmol/l	5.1±1.3	5.4±1.3	0.1

Values are expressed as n (%), unless otherwise specified.

The study period started in February 2006 and ended on September 15, 2011. Study end points were September 15, 2011, or the date of death. Cancer data was obtained from the ischemic stroke patients (ISP) medical records and the Cancer Registry of Norway.

The study was approved by the Norwegian Regional Ethics Committee.

Statistics

The patients formed two groups; the ISP who were diagnosed with a new diagnosis of cancer after stroke onset (cancer-ISP) and the ISP who had no history of cancer (non-cancer-ISP) before or after stroke. Student's t test and χ^2 analyses were used for the univariate analyses when appropriate. The Cox regression model was applied for multivariate analyses, and the statistical software Stata 13.0 was used for the statistical analyses.

Results

From a total of 1,282 patients with confirmed ischemic stroke, 55 (4.3%) patients had one or two cancer diagnoses after their stroke. The mean age in the cancer-ISP group was 72.7 years [standard deviation (SD) 11.5], and for the non-cancer-ISP group it was 69.5 years (SD 15.1). The median follow-up time of the entire study population was 26.9 months [interquartile range (IQR) 13.7–42.5], while for non-cancer-ISP alone (n = 1,227), the median follow-up time was 27.7 months (IQR 14.2–43.1). Table 1 shows the baseline characteristics of all ISP.

Table 2. Subtypes of cancer versus non-cancer ISP

	No cancer (n = 1,227)	Lung (n = 12)	Prostate (n = 10)	Colorectal (n = 7)	Breast (n = 7)	Gyn. cancer (n = 5)	CUP (n = 4)	Lymphoma (n = 4)
Age	69.5±15.1	68.4±11.2	75.2±12.4	74.6±14.6	76.5±8.9	71.7±13.7	62.4±5.4	71.6±12.6
Male, n (%)	694 (56.6)	6 (50.0)	10 (100.0)	5 (71.4)	1 (14.3)	–	4 (100.0)	3 (75.0)
Median NIHSS (IQR)	3 (1–8)	5 (1–8)	4 (3–9)	3 (0–9)	2 (2–3)	5 (4–7)	3 (2–7.5)	7 (4.5–10)
Median mRS (IQR)	2 (1–4)	2 (1–4)	1.5 (1–3)	2 (2–4)	2 (2–3)	1 (1–1)	2 (81.5–2)	2.5 (1.5–3)
Median time from stroke to cancer (IQR), months	–	8.7 (5.5–27.3)	14.0 (6.0–20.3)	4.0 (1.3–22.0)	12.2 (8.1–25.8)	14.3 (2.2–18.1)	16.8 (7.1–23.8)	15.9 (12.4–20.1)
Smoking, n (%)	664 (54.1)	10 (83.3)*	7 (70.0)	5 (71.4)	3 (42.9)	3 (60.0)	4 (100)**	2 (50.0)
Blood values								
Fibrinogen, mmol/l	3.7±1.1	4.0±1.5	4.3±1.6	9.2±13.6**	4.5±2.1	3.7±0.4	3.6±0.4	3.5±0.8
Hemoglobin, g/dl	14.3±1.5	13.9±2.2	14.0±1.9	13.5±2.8	13.2±2.0	13.9±1.8	14.8±1.3	14.1±0.9
Cholesterol, mmol/l	5.3±1.3	5.2±1.4	5.0±1.0	4.9±1.5	5.0±1.7	5.0±1.3	5.5±0.4	5.2±1.4
D-dimer, mg/l	1.4±2.5	3.7±6.3*	1.7±1.4	1.0±1.1	1.8±2.7	3.5±4.8	–	3.0±1.8
CRP, mg/l	10.0±26.4	29.7±68.4*	14.3±33.7	12.3±21.3	25.6±34.8	31.6±59.5	3.5±2.5	3.0±1.8
Glucose, mmol/l	6.7±2.5	8.2±4.6*	6.2±1.3	6.7±1.5	6.7±2.8	6.5±1.8	8.1±2.0	6.2±1.8

Values are expressed as mean ± SD, unless otherwise specified. * $p \leq 0.05$; ** $p \leq 0.01$.

Time from Index Stroke to Cancer Diagnosis

The median time from stroke onset to cancer diagnosis was 14.0 months (IQR 6.2–24.5). Twenty-three (41.8%) patients were diagnosed within 1 year, 13 (23.6%) within 6 months and 9 (16.4%) within 3 months after stroke onset, including 4 (7.3%) diagnosed within 1 month. Three were diagnosed within 1 week after stroke onset with the following cancer diagnoses: lung cancer, prostate cancer and lymphoma. Of the patients diagnosed with cancer within 1 month, 2 had been diagnosed with lung cancer. Colorectal cancer (n = 4) had the shortest median time from stroke onset to cancer diagnosis, namely 4.0 months (IQR 1.3–22.0), followed by lung cancer (n = 12) with a median time from stroke onset to cancer diagnosis of 8.7 months (IQR 5.5–27.3).

Cancer Diagnoses

In total, the 55 patients had 64 cancer diagnoses, distributed among 13 different cancer types. The 7 most common cancer types were lung cancer (n = 12, 19.0%), prostate cancer (n = 10, 15.9%), colorectal cancer (n = 7, 11.1%), breast cancer (n = 7, 11.1%), gynecological cancer (n = 5, 7.9%), lymphoma (n = 4, 6.3%) and metastatic cancer of unknown primary site (CUP; n = 4, 6.3%). Table 2 describes the characteristics of the cancer subtypes. The 6 other types of cancer included 4 bladder, 4 gastric and 3 pancreatic cancers, 2 carcinomas in situ, 1 malignant melanoma and 1 sarcoma.

Smoking

There was no difference in smoking habits between the cancer-ISP group and the non-cancer-ISP control group. However, by cancer subtypes, lung cancer ($p = 0.03$) and lymphoma ($p = 0.003$) had a higher rate of smoking compared to non-cancer-ISP.

Blood Samples

CRP was elevated in the cancer-ISP on admittance ($p = 0.02$). Among cancer subtypes, only lung cancer had increased mean CRP levels of 29.7 (SD 68.4, $p \leq 0.05$). The D-dimer level was elevated in the cancer-ISP on admittance ($p = 0.003$). Among the cancer subtypes, lung cancer patients had increased D-dimer levels compared to ISP with a mean D-dimer of 3.7 (SD 6.3, $p \leq 0.05$).

Table 3. Cox regression analysis in ISP with and without cancer after stroke

	Hazard ratio	95% confidence interval	p
Sex	0.68	0.3–1.4	0.3
Age	1.04	1.0–1.0	0.01
Smoking	1.59	1.0–2.5	0.04
D-dimer	1.13	1.1–1.2	<0.001

Stroke Etiology and Outcome

Of the 55 cancer-ISP, 21 (38.2%) had an unknown stroke etiology compared to 516 (42.1%) of the non-cancer-ISP (p = 0.09). Cardioembolic etiology was found in 32.7% of the cancer-ISP and 28.5% of the non-cancer-ISP. Among cancer subtypes, lymphoma had a higher frequency of cardioembolic etiology ($p \leq 0.05$). The mRS score did not differ between non-cancer-ISP and cancer subtypes.

By Cox regression analysis, cancer after stroke was associated with increased D-dimer levels on admittance ($p < 0.001$), age (p = 0.01) and smoking (p = 0.04; table 3).

Discussion

We found that malignancy was detected in few patients (0.3%) within the first month after acute ischemic stroke. However, several previous studies have shown that ischemic stroke can be the first manifestation of cancer [2, 7, 13, 14]. One study found an underlying malignancy in 0.4% of their ischemic stroke patients [7]. We found that of all ischemic stroke patients with no prior cancer, 1.8% were diagnosed with cancer within 1 year. It has previously been reported that mainly advanced cancers create a massive risk [3]. For the ischemic stroke patients diagnosed with cancer within 6 months (1.0%), it is likely that they had an underlying malignancy at the time of stroke onset.

Knowing that specific tumor types may affect the vascular system in different ways, and that some cancers have similar risk factors as for stroke, analyses of subtypes of cancer are important [15]. Lung cancer, prostate cancer, colorectal cancer, breast cancer, gynecological cancer, CUP and lymphoma were the most common cancer types in our study. Prothrombotic states have previously been documented in cancer of the lung and colon as well as lymphomas. Lung cancer was overrepresented in our study, which also has been reported by similar studies of cancer-associated stroke [16]. Gynecological tumors are also reported to have a potential for being included in ischemic stroke pathogenesis [13]. Of the prostate cancer patients, 50% had an unknown stroke etiology. However, as prostate cancer is rarely mentioned in relation to prothrombotic state, our findings may be due to prostate cancer being the most common male cancer type in general and thus incidental to the stroke [17]. Both lung and colon cancer have been linked to smoking [18]. Smoking is also a risk of ischemic stroke and may be a confounding factor in some cancer-associated strokes.

Of the classic risk factors for ischemic stroke, smoking was the only one associated with cancer. Higher D-dimer and CRP levels were associated with cancer, especially with lung cancer. In concordance, previous studies have also shown a higher risk for stroke in lung cancer patients [19]. Increased D-dimer and CRP levels may be caused by cancer development [8, 9].

The ISP with cancer were older than those in the control group. However, looking at the subtypes of cancer, the patients diagnosed with lung cancer and CUP were slightly younger than the control group. It has been shown that younger patients, below 49 years of age, often

have different stroke etiologies than older stroke patients; prothrombotic state is more common and classic risk factors such as atherosclerosis are less common [20].

Stroke severity was similar between the two groups. A previous study defined stroke as being cancer related if stroke etiology was unknown and cancer was diagnosed within 6 months of stroke [10]. In contrast, we found no difference in etiology between our two groups. Thus, etiology may not be a predictor of cancer-associated stroke.

A limitation to our study was that the follow-up time differed among the study subjects. This may have caused a possible underestimation of cancer occurrence. On the other hand, patients diagnosed with cancer within 6 months after stroke onset may have been under careful medical surveillance due to their strokes, increasing the possibility of early cancer detection [16]. Because of the likelihood of stroke involvement in various cancers, it was necessary to study the subtypes of cancer separately. In doing so, each group consisted of a low number of study subjects. An advantage of the present study, as compared to previous studies, is the exclusion of patients with prior cancer [19]. This eliminates the question of whether the cancer treatment or the malignancy itself was the potentially involved factor in stroke pathogenesis.

Conclusion

Cancer-associated stroke is rare, and routine investigation for cancer seems unwarranted in acute ischemic stroke. However, in stroke patients with elevated levels of blood coagulation factors, CRP, higher age and a history of smoking, underlying malignancy should be considered. Our study suggests that an unknown stroke etiology does not predict malignancy.

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