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The crosstalk between Stroke and Cancer: a population-based study

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The Crosstalk between Stroke and Cancer: a population-based study

Dissertação de candidatura ao grau de Mestre em Medicina, submetida ao Instituto de Ciências Biomédicas Abel Salazar – Universidade do Porto

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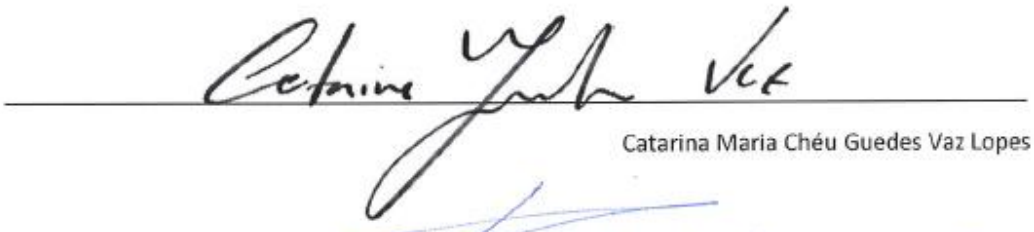

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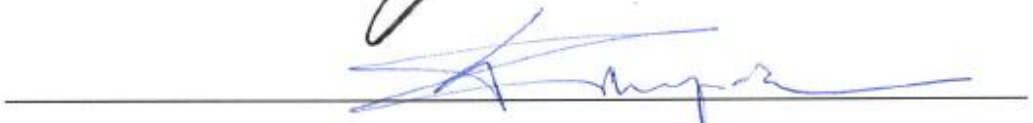

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Ao avô Tó, pelo modelo exemplar e estima incomensurável.

"E os passos que deres,

Nesse caminho duro

Do futuro

Dá-os em liberdade.

Enquanto não alcances

Não descanses.

De nenhum fruto queiras só metade."

Sísifo de Miguel Torga, in Diário XIII

RESUMO

Introdução e Objectivos: O cancro constitui um estado de hipercoagulabilidade. Até recentemente, não estava estabelecida uma associação com o tromboembolismo arterial. Novos estudos sugerem que o cancro pode desempenhar um papel na fisiopatologia de um acidente vascular cerebral (AVC) e os eventos cerebrovasculares decorrer de uma complicação subsequente ou configurar a primeira manifestação de um cancro oculto. Nós propusemo-nos a determinar a incidência de neoplasia maligna após um primeiro evento cerebrovascular (AVC ou Acidente Isquémico Transitório), compará-la com a incidência da população geral e analisar a relação entre etiologia do AVC e a ocorrência de cancro.

Métodos: Realizámos um estudo coorte retrospectivo tendo por base a amostra abrangida pelo ACIN2rpc, composta por doentes da região Norte de Portugal diagnosticados com um primeiro evento cerebrovascular entre 2009 e 2011. Recorrendo aos processos clínicos electrónicos, efectuámos uma pesquisa estruturada num período de 8 anos subsequentes ao evento índice e registámos as variáveis de interesse relacionadas com cancro e mortalidade. A incidência de neoplasia maligna foi posteriormente comparada com os dados do RORENO, um registo oncológico nacional.

Resultados: De um total de 1069 doentes com AVC ou AIT sem antecedentes de neoplasia, 90 (8.4%) foram diagnosticados com cancro após o evento cerebrovascular. O sexo masculino (HR 1.63, p=0.022), a idade avançada (HR 1.02, p=0.005), o tabagismo (HR 1.56, p=0.048) e a doença arterial periférica (HR 2.47, p=0.022) exibiram um maior risco de neoplasia. A mediana do intervalo entre a doença cerebrovascular e o diagnóstico de cancro foi de 3.2 anos (IQR 1.4-5.2). Os tumores do tracto respiratório inferior e colorretal (12.2%, respectivamente) apresentaram maior prevalência. A incidência anual de cancro após um AVC ou AIT foi de 1951 (95% CI, 1580-2404) por 100 000, 1477 (95% CI, 1052-2062) nas mulheres e 2481 (95%CI, 1887-3248) nos homens. As taxas ajustadas para a idade no total e por sexo foram superiores ao RORENO. Isto foi igualmente observado nas faixas etárias de 45-54 (1469, 95% CI 685-2992), 65-74 (2294, 95% CI 1534-3391) e 75-84 (2392, 95% CI 1678-3382).

Discussão e Conclusão: Constatou-se que a incidência de cancro numa coorte populacional de pacientes com AVC e AIT foi maior que a da população geral da mesma região geográfica. A ocorrência de cancro não foi associada a uma etiologia específica de AVC. Apesar de não ser possível inferir com certeza uma relação causal, o rastreio oportunístico de cancro nesta coorte poderá levar à detecção precoce de doenças oncológicas.

ABSTRACT

Background: Cancer is a known hypercoagulable state. Until recently, it was not clear if malignancy was also associated with an increased risk of arterial thromboembolism. New evidence suggests that cancer may play a role in stroke pathogenesis and cerebrovascular events may manifest as a subsequent complication or as a first sign of an occult malignancy. We aimed to determine the incidence of cancer after a first cerebrovascular event (Stroke or Transient Ischemic Attack), compare it to the incidence of the general population and analyse stroke aetiology and cancer occurrence.

Methods: We retrospectively studied ACIN2rpc population, composed by urban and rural patients from the northern region of Portugal with a first-ever cerebrovascular event diagnosed between 2009 and 2011. Using e-medical records, we conducted a structured search for a period of 8 years following the index event to register cancer related variables and case fatality. The incidence of cancer in Stroke and TIA patients was posteriorly compared to a northern region cancer registry (RORENO).

Results: From a total of 1069 stroke and TIA patients with no previous history of cancer, 90 (8.4%) were diagnosed with cancer after cerebrovascular event onset. Male sex (HR 1.63, p=0.022), older age (HR 1.02, p=0.005), tobacco use (HR 1.56, p=0.048) and peripheral artery disease (HR 2.47, p=0.022) were associated to higher risk of malignancy. The median time between cerebrovascular diseases and cancer diagnosis was 3.2 years (IQR 1.4-5.2). The most frequent types of tumours were lower respiratory tract and colorectal (12.2%, each). The overall annual incidence rate of a first cancer diagnosis after a stroke or TIA event was 1951 per 100 000 (95% CI, 1580-2404), 1477 (95% CI, 1052-2062) for women and 2481 (95% CI, 1887-3248) for men. Age-adjusted rates for European population in all incident cancer group and by sex were superior to the population of the same geographical origin. This was also observed in the age groups of 45-54 (1469, 95% CI 685-2992), 65-74 (2294, 95% CI 1534-3391) and 75-84 (2392, 95% CI 1678-3382).

Conclusion: The overall incidence of cancer in a population cohort of Stroke and Transient Ischemic Attack patients was higher than the general population from the same geographical region. Incident malignancy was not associated to a specific stroke aetiology. These findings support the implementation of adequate cancer screenings in Stroke patient survivors.

Keywords: Stroke; Transient Ischemic Attack; Cancer; Occult Malignancy.

ABBREVIATIONS

CNS: Central Nervous System

CRF: Case Report Form

CVD: Cerebrovascular diseases

CVE: Cerebrovascular event

HC: Health Centres

IC: Incident Cancer

IPO: Instituto Português de Oncologia

NBTE: Nonbacterial Thrombotic Endocarditis

NIC: Non-Incident Cancer

RORENO: Registo Oncológico Regional do Norte

TIA: Transient Ischemic Attack

TNA: Transient Neurological Attack

TOAST: Trial of Org 10172 in Acute Stroke Treatment

TABLE OF CONTENTS

LIST OF TABLES

LIST OF SUPPLEMENTAL TABLES

LIST OF FIGURES

LIST OF SUPPLEMENTAL FIGURES

INTRODUCTION

Cerebrovascular diseases (CVDs) and cancer occur frequently in the general population and constitute leading causes of morbimortality, particularly in developed countries.[1] In fact, approximately 15% of cancer patients have a concomitant CVD[2–4], picturing its second most common central nervous system (CNS) complication, following metastasis.[2,5] As the incidence of both conditions increases with age, it's expected that with the improvement of live expectancy of cancer patients and the ageing of the population, the number of stroke patients with malignancy will rise.[3,6–8]

A causal relation between cancer and venous thromboembolism has been established since the 19th century[6,9,10], when Armand Trousseau identified *thrombophlebitis migrans* as a signal of an occult malignancy as it may develop several months or years before the first clinical manifestation of a neoplastic disease.[3] This observation led to a well-recognized medical entity, Trousseau's syndrome, a hypercoagulable state associated with cancer[9,10].

Still, until recently, it was unclear if cancer also increased arterial thromboembolism risk.[3,11] New data from large-scale cohort studies provided some evidence that incident malignancy was associated with a significant increase of short-term risk of arterial thromboembolism, including ischemic stroke.[3,4,12] Importantly, it was associated with poorer prognosis, being responsible for fast clinical deterioration, recurrent cerebrovascular events and increased stroke-mortality.[4,9,12–14]

Nevertheless, most studies comprehended hospital-based cohorts, whereas only Selvik et al.[15] and Bengt et al.[16] have contributed to the population perspective of this relation.

Moreover, stroke in cancerous diseases follows widely the general population and its most frequent causes rest on traditional cerebrovascular risk factors as Arterial Hypertension, Dyslipidaemia, Diabetes Mellitus, Atrial Fibrillation and tobacco use[3,4,6,17,18]. Though, other causes have been considered. In cancer patients, a cancer-specific mechanism can be proposed as the main cause of cerebrovascular events, particularly if patients do not present the most frequent stroke aetiologies (Atherosclerosis, Cardioembolism or Small vessel disease).[3,16,17] Several lines of evidence support that underlying malignancy can determine stroke either directly or by aberrant coagulation, inducing a hypercoagulable state or through infections and anti-neoplastic treatments.[2–4,15,19] Direct tumour effects like tumour invasion or compression of the cerebrovascular arterial system, tumour embolization and intratumoral haemorrhage, rarely constitute the stroke aetiology.[3,4,20] In the case of haematological malignancies, CNS leukostasis and hyperviscosity syndrome have been associated with stroke.[3,4,8,21]

Contrastingly, coagulation disorders account for the most important cause of CVD in cancerous diseases without conventional mechanisms.[3,4,9,12,19] Different mechanisms have been proposed for

such hypercoagulable state: 1) malignant cells can overexpress procoagulant factors as factor X, tissue factor and indirectly factor VII[3,4,6,12] and proinflammatory cytokines[3,4,9]; 2) adenocarcinomas, in particular, are thought to promote thrombosis by producing mucin.[3,4] 3) Cancer can also cause neutrophils to secrete decondensed chromatin, resulting in the formation of neutrophil extracellular traps (NETs)[3,4,12,22]. Consistently, the rate of cryptogenic stroke has been reported as high as 20 to 50%[4,9,12,17,23] among cancer patients in whom it is conceivable a neoplastic-specific mechanism.[12,24,25] Several of them are thought to be the result of cardioembolic manifestations of cancer-mediated hypercoagulability, respectively, nonbacterial thrombotic endocarditis (NBTE)[3,4,7,12,18], a negative blood culture endocarditis involving sterile, platelet-fibrin vegetations.[3,12]
Other causes for stroke in cancer patients have been proposed: 1) infections may impair the vascular endothelium inducing cerebrovascular events in cancer patients[3,4]; 2) antineoplastic treatments as platinum chemotherapy regimen[3,4,8,12,26], L-asparaginase[3,12] and angiogenesis inhibitors[8,26] increase thromboembolism via direct endothelial toxicity and coagulopathies[4,12]; 3) radiotherapy vasculopathy, precipitating accelerated atherosclerosis, is an important CVD risk factor[4,12], particularly among solid head and neck cancers or lymphoma.[3,27]
Considering the association between thrombotic events and cancer, it is conceivable that stroke could be the first sign of an undiagnosed[3,15,23] or recently diagnosed cancer[5,6,9,14].
Thus, we hypothesize that the incidence of cancer in stroke or TIA (Transient Ischemic Attack) patients is higher than the general population and that some patients may have an underlying malignancy at the cerebrovascular event onset. If proven, this could implicate a different approach of stroke inpatient cancer screening or active malignancy surveillance.

OBJECTIVES

In the present study, we aimed to: (i) determine the incidence of cancer in patients suffering the first stroke or TIA; (ii) compare the incidence of cancer in stroke patients with the cancer incidence from the general population; and (iii) characterize cancer incidence according to stroke type and aetiology.

METHODS

ACIN Study Population and Design

We used the ACIN2rpc study to identify patients with a first-ever-in-a-lifetime cerebrovascular event (CVE) diagnosed between October 2009 and September 2011[28,29]. ACIN2 is a prospective population-based registry that identified all stroke and Transient Neurological Attacks (TNA), including Transient Ischemic Attacks, between 2009 and 2011, in the northern region of Portugal. Study population included patients from 3 Health Centres (HC) in the city of Porto that were under the reference area of Hospital Geral de Santo António-Centro Hospitalar Universitário do Porto and 2 HCs from rural areas of Mirandela and Vila Pouca de Aguiar. The diagnosis of stroke and TIA was made independently by at least one neurologist working in the corresponding stroke unit. Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria[30] were used to determine the aetiology of acute ischemic stroke, in five categories: Large-artery Atherosclerosis, Cardioembolism, Small-vessel occlusion, stroke of Other determined aetiology and stroke of Undetermined aetiology, which includes Two or more causes identified, a Negative evaluation and an Incomplete evaluation. The TIA's aetiology was established based on the initial routine evaluation at the emergency department and in the outpatient clinic follow-up consultations.

Demographic characterization of the study population and prior vascular risk factors for stroke were obtained from the ACIN2 study registry, which included Arterial Hypertension, Diabetes Mellitus, Dyslipidemia, Tobacco use, Peripheral Artery Disease, Coronary Disease, history of thrombotic events and Atrial Fibrillation. Vascular risk factors were deemed present if diagnosed by a physician previously to the cerebrovascular event and defined by the following criteria[28]: previous diagnosis of high blood pressure or antihypertensive treatment; use of oral anti-diabetic agents/insulin or history of known diabetes (fasting blood glucose ≥ 126 mg/dL; 2 hr post prandial glycemia ≥ 200 mg/dL; random blood glucose ≥ 200 mg/dL with symptoms of hyperglycaemia; HbA1c ≥ 6,5%[31]); previous diagnosis/treatment of dyslipidaemia; current smokers if history of tobacco use in the past 12 months; atrial fibrillation documented in patients' records; prior superficial and deep venous

thrombosis or pulmonary thromboembolism. All patients of the ACIN2 study gave informed consent and were subjected to a one-year follow up after the first cerebrovascular episode.

Stroke and Cancer Study Design

To determine the incidence of cancer in the eight years following the cerebrovascular event of all ACIN patients presenting stroke or TIAs, we did a retrospective study. For that reason, we excluded non-ischemic TNA, subdural and epidural hematomas.

We used e-medical records and a structured CRF to register cancer related variables for a period of 8 years (2922 days) following the index event. The variables included, prior history of cancer diagnosis, definite diagnosis by a physician, date of diagnosis, primary location of cancer and its staging and evidence of metastatic disease. The primary location of cancer was subsequently divided into organ systems: Respiratory System (Larynx; Trachea, Bronchi, Lung), Hematopoietic System (Hodgkin Lymphoma; Non-Hodgkin's Lymphoma; Lymphoid Leukaemia; Myeloid Leukaemia; Myelodysplastic Syndrome; Chronic Myeloproliferative Neoplasms; Multiple Myeloma), Gastrointestinal System (Oral Cavity and Pharynx; Oesophagus; Stomach; Small Intestine; Colon and Rectum; Liver; Gallbladder and Biliary Tract; Pancreas), Genitourinary System (Cervix; Uterus Body; Ovary; Prostate; Testicle; Kidney; Ureter and Bladder), Breast, Skin Melanoma and Others (Central Nervous System; Carcinoma of Unknown Primary Origin; Bones and Joints; Thyroid Gland; Salivary Gland; Adrenal Gland). Non-Melanoma Skin Cancer (Basal cell and Squamous cell Carcinoma) were not contemplated in this analysis.

Additionally, data pertaining to the vital status of the patient as date, cause, and place of death, along with succeeding recurrent cerebrovascular events was also registered.

Subsequently, we used Registo Oncológico Regional do Norte (RORENO), a comprehensive cancer registry, from the northern population, under the supervision of Instituto Português de Oncologia (IPO) of Porto and we compared the incidence of cancer in stroke and TIA patients with the cancer incidence from the general population.

The present study was approved by the Centro Hospitalar Universitário do Porto/Instituto de Ciências Biomédicas Abel Salazar and IPO-Porto Ethics Committee.

Statistical Methods

The index cerebrovascular event patients were dichotomized as CVE patients diagnosed with cancer after the cerebrovascular event onset, Incident Cancer group, and the CVE patients who had no history of cancer after the cerebrovascular event, Non-Incident Cancer group. On account of an increased theorical risk of cancer posterior to a previous diagnosis of cancerous diseases and

interference of malignancy treatment in stroke pathogenesis, patients with previous history of cancer were not contemplated in the main statistical analysis.

Continuous variables are reported as median and interquartile range or as mean and standard deviation (SD) and categorical variables are reported as count or percentage. Student's t test and χ^2 analysis were conducted for the univariate analysis. Survival curves were constructed using Kaplan-Meier method and compared using log-rank test. Cox regression was used to estimate the risk of cancer for specific factors and covariates.

Incidence is reported as crude rates and age-standardized rates for the European population 2013. Person-years were calculated from the time at which subjects were included in the study until first diagnosis of cancerous disease, death, latest contact with public health services or the end of the study period. The 95% confidence intervals for incidence were calculated applying the Wilson score interval.[32,33]

For storage and data analysis, the IBM SPSS Statistics 26 was used. A p-value < 0.05 was considered statistically significant.

RESULTS

ACIN2 patients

We identified 1185 eligible patients, included in the ACIN2 study, who had a first-ever cerebrovascular event, between October 2009 and September 2011 and met the study criteria (Figure 1). Among these, ninety-eight (8.3%) had a diagnosis of cancer following the index cerebrovascular event, through the 8 years of follow-up. 8 (8.2%) patients from the Incident Cancer (IC) group and 108 (9.9%) from the Non-Incident Cancer (NIC) group had an history of cancerous diseases previous to the CVE. The median follow-up time of all subjects was 4.8 years (interquartile range (IQR) 1.1-8.0), 10.8% (n=128) of which were considered lost to follow-up.

Incident Cancer patients had a mean age of 71.5 years (standard deviation (SD), 10.4 years) and 40% were women, compared to 55% of the Non-Incident Cancer patients ($p<0.01$) (Table I). Cumulative 8-year cancer-free survival, by sex, in all Stroke and TIA patients, decreased significantly over time with a proportion of 89.6% in Female sex and 82.9% in Male sex ($p<0.05$), by the end of the study (Figure 2).

Arterial hypertension and dyslipidaemia were the most frequent traditional vascular risk factors for stroke in both groups (Table I). There were no differences between IC and NCI groups concerning vascular risk factors and recurrent cerebrovascular events, except for tobacco use ($p=0.002$) and peripheral artery disease ($p=0.019$). Male sex [HR 1.63 (95% CI 1.07-2.49), $p=0.022$], older age [HR 1.02 (95% CI 1.01-1.04), $p=0.005$], tobacco use [HR 1.56 (95% CI 1.00-2.43), $p=0.048$] and peripheral artery disease [HR 2.47 (95% CI 1.14-5.34), $p=0.022$] were associated with higher risk of malignancy (Table II). Although, in the multivariable Cox regression model, only age showed an independent association ($p<0.001$).

Stroke and tumour types

The most frequent primary incident tumour location was Gastrointestinal (n=32, 35.6%), specifically Colorectal (n= 11, 12.2%); followed by Genitourinary (n=21, 23.3%), particularly Prostate and Bladder (equally n=6, 6.7%); Trachea, Bronchi, Lung (n= 11, 12.2%) and Breast (n=8, 8.8%) Cancer. The different types of tumours corresponding to all Stroke and TIAs and Ischemic events are listed in Table III. Metastatic disease was objectified in 34 (37.8%) cancer patients. Trachea, Bronchi, Lung (n=9, 81.8%), Colorectal (n=6, 54.5%) and Pancreas (n=3, 60%) tumours were associated with higher systemic malignancy ($p=0.035$) compared to other tumour types. The mean age of cancer diagnosis was 75.4 years (SD 10.5). The median time interval between cerebrovascular event onset and the diagnosis of cancer was 3.2 years (IQR 1.4-5.2), eighteen (20%) were diagnosed within 1 year, 14 (15.2%) of which within 6 months after index CVE. Trachea, Bronchi, Lung tumours had the shortest

median time from CVE onset, namely 1.1 years (IQR 0.3-4.2), followed by Genitourinary, 2.6 years (IQR 1.5-5.1) and Gastrointestinal Cancer, the longest, 3.8 years (IQR 1.75-5.5) (Figure 4).

Cancer incidence in ACIN2 patients

The crude overall annual incidence of a first cancer diagnosis after a cerebrovascular event (all Stroke and TIAs) per 100 000 was 1951 (95% CI, 1580-2404) and 1782 (95% CI, 1701-1866) adjusted for the European standard population (Table IV). The crude annual incidence was 1477 (95% CI, 1052-2062) for women and 2481 (95%CI, 1887-3248) for men in all Stroke and TIA patients. Comparing it to RORENO data (Supplemental Table I and Figure 3), the overall incidence rate was higher in the age groups of 45-54 (1469, 95% CI 685-2992), 65-74 (2294, 95% CI 1534-3391) and 75-84 (2392, 95% CI 1678-3382) in Incident Cancer patients than in the general population. This increased tendency was also observed in age-adjusted rates for European population in all IC group and by sex. For Male sex, age groups of 45-54 (1619, 95% CI 598-3955) and 65-74 (3512, 95% CI 2187-5531) showed a significant elevated rate comparable to the Male northern population. This was not observed in Female patients and in Ischemic Events patients.

Regarding the type of tumours (Table V), age-adjusted rates for Trachea, Bronchi, Lung and Genitourinary Tract Tumours were overall higher than the general population and for both Female and Male sex. Age-adjusted rates for Gastrointestinal Tract Tumours in all and male Incident Cancer patients were superior to the northern population. Contrastingly, Gastrointestinal Tract Tumours in all Stroke and TIAs patients and Trachea, Bronchi and Lung Cancer in Ischemic Events in female patients were not significantly different from RORENO data. Given the low incident number, comparison between other tumours was not done.

The same comparative analysis was made including patients with previous cancer in Ischemic Events and in all Strokes and TIAs. In general, there were not significantly differences comparing to Incident Cancer group without history of previous Cancer (Supplemental Table II – III and Supplemental Figure 3).

Stroke Aetiology and Cancer in ACIN2 patients

Common stroke aetiologies, according to TOAST classification, were more frequent in the Incident Cancer group (64.4%), particularly, the small-vessel occlusion (28.8%). Stroke of undetermined aetiology accounted for 32.2% of cancer patients with Ischemic Stroke (Table I). However, cerebrovascular event aetiology was not significantly different among IC and NCI groups (p=0.419; p=0.604) and was not related with increased risk of neoplastic disease (Table II). Consistently, we did not observe a significant difference within CVE aetiology after Kaplan-Meier analysis (p=0.455), with the lowest cumulative cancer-free survival proportion of 84.7 % assigned to stroke of

determined aetiology (Large-artery Atherosclerosis, Cardioembolism, Small-vessel occlusion) (Figure 5).

Patient outcome in ACIN2 patients

By the end of follow-up, 510 (47.7%) patients had died. The most frequent causes of death were Cerebrovascular Diseases (n=120, 37.3%), 70.8% of which in the 28 days following the index Cerebrovascular event, Infection (n=106, 20.8%) and Cancer (n=22, 6.8%). Mortality was higher in the Incident Cancer group ($p<0.001$) with a total of 66.7% of deaths, being cancerous diseases responsible for the majority of those deaths (Figure 6).

DISCUSSION

The present study demonstrated that the overall incidence of cancer in a population-based cohort of cerebrovascular events is higher than the general population from the same geographical region. To the best of our knowledge, this study is the first to compare age- and sex-specific incidence rates of cancerous diseases in Stroke and TIA patients to national cancer registries, providing a populational perspective on this problem.

We found that the incidence was 1.76-fold higher in Stroke and TIA patients whole cohort compared to the general population. In particular, male patients of 45-54 and 65-74 age groups had higher incidence rates placing them at higher risk of cancer after the first stroke. Yet, it is not surprisingly noted as male sex has been described a risk factor for most types of cancer[34] and it is concordant to RORENO superior rates in male population. Tobacco use was also associated with higher malignancy risk.

The aforementioned findings support our initial hypothesis, emphasizing the relation between arterial cerebrovascular diseases and cancer. Our results are in line with previous findings documented in cohort studies[8,15,16,35] and therefore open a broader discussion on whether a thorough cancer screening in stroke patients could impact cancerous diseases prognosis, leading to early malignancy detection.

Regarding stroke aetiology, previous studies observed a higher rate of cryptogenic strokes in cancer patients, whenever a neoplastic-specific mechanism was suspected.[9,12,17,23] We have not found an association between a specific stroke aetiology and cancer occurrence. Conventional stroke causes accounted for the majority of cerebrovascular events in the Incident Cancer group, that did not differ from the Non-Incident Cancer group. Classic vascular factors frequency, with the exception of tobacco use and peripheral artery disease were similar in patients with or without incident cancer. This is consistent with cancer-related stroke literature[3,4,15,18,25], highlighting the fact that both pathologies share similar risk factors. However, a higher incidence of cancerous diseases in stroke and TIA patients, prompt the hypothesis that malignancy-specific mechanisms may co-exist and eventually contribute to cerebrovascular disease anticipation.[4,16,36] In fact, this may be more prominent among younger patients, as we found that the incidence rate of cancer in age group of 45-54 years is higher than the age- and geographical region-matched population. It has been demonstrated that in younger patients, specially under 49 years, traditional stroke aetiologies play a minor role in cerebrovascular events and a prothrombotic state is frequently stated[37–39], adding to the relevant clinical question whether a first-ever stroke in a malignancy naïve patient can be the initial presentation of a systemic cancer and be consider an immune-mediated paraneoplastic syndrome.[11]

The tumour type has been shown of relevance to explain stroke pathophysiology in cancer patients.[3–5,15,19] In our study, Trachea, Bronchi, Lung and Colorectal tumours were the most frequent cancer types, as well as Breast and overall Gastrointestinal and Genitourinary tumours, which is consistent with previous studies.[5,7,13,15,23,40,41] This can be partially explained by the higher prevalence of tobacco use in Incident Cancer group as smoking-related cancers (i.e., Lung, Bladder, Pancreas, Colorectal tumours) are overrepresented in our study and show increased incidence comparing to RORENO data. Nevertheless, several tumour types not associated with tobacco, as Breast Cancer and Non-Hodgkin Lymphoma, observed in our cohort, also exhibit heightened risks of arterial thromboembolism[3,16,36]. Interestingly, Prostate Cancer, the most common male cancer type, have not presented the highest prevalence among our male population, as would be expected, what could be concordant with Prostate tumours being rarely associated with prothrombotic states.[15,23,26,42]

It has been shown that stroke risk may be correlated to tumour's aggressiveness since Lung, Pancreatic and Colorectal tumours, related to higher arterial thromboembolism risk, usually manifest at advanced stages.[3,4,6,12] This is consistent to our study findings as we observed a significantly higher frequency of metastatic disease in Trachea, Bronchi, Lung; Colorectal and Pancreatic cancer. In addition, our tumour type observed distribution could reflect the link between Adenocarcinomas, especially of Pancreas, Colorectal, Lung, Biliary System and Ovary, and direct mucin secretion, a high weight molecule prone to potentiate platelet rich microthrombi and a subsequent hypercoagulable state.[3,4,12] Tissue-factor-bearing microvesicles were also associated with Colorectal tumours.[6] Unfortunately, this was not possible to corroborate in the present study, as its retrospective nature and impaired quality of hospital records precluded data collection regarding tumour histology and detailed metastatic status.

The median time observed from cerebrovascular event to cancer diagnosis was 3.2 years, contrastingly to 1.2 years perceived in The Bergen NORSTROKE[15], a Norwegian population-based study. This may have been due to a shorter follow-up time in NORSTROKE compared to our study [5.5-year (vs. 8 years)]. In fact, in the first 6 months after stroke, the cancer frequency in the NORSTROKE ischemic stroke (1.0%)[15] was similar to ours (1.3%). It is tempting to strictly consider that this particular group of patients had an underlying cancerous disease at the time of cerebrovascular event onset. Still, given the different time intervals between the onset of a specific tumour and its diagnosis should warn us not to neglect longer surveillance of these patients. In fact, we observed a lower median time amongst Lung tumours (1.1 years; IQR 0.3-4.2), in opposition to Gastrointestinal Cancer (3.8 years; IQR 1.75-5.5). This may suggest that either the tumour was not present at the time of stroke or that it was present and remained undiagnosed for a longer period,

which may be justified by the different cancer cell behaviour regarding tumour cell proliferation and tumour systemic impact.[34,43,44]

Our study strengths, compared to previous ones, stand on a community-based approach and exclusion of patients with a prior diagnosis of cancerous diseases, excluding the theoretical higher risk of a subsequent cancer diagnosis and considerable role of antineoplastic treatments in stroke pathophysiology[3,4,27]. However, the present study holds limitations. First, it was a retrospective study and data collection was obtained through medical patient records, conditioned by its quality and detail, that could have underestimated a potential higher incidence of cancer in Stroke and TIA patients. Secondly, due to an increased case fatality linked to cerebrovascular events and the aged population, by the end of the study, half of the patients had died. This may have led occult malignancies to never been reported. Further, owing to their CVE, our study population may have been under closed medical surveillance, raising the possibility of early cancer detection. A relative low number of study subjects have limited part of the statistical analysis, specially of tumour types, and comparison with robust national records.

Despite unequivocal higher incidence of cancer in Stroke and TIA patients, it is unclear to what extent it contributes to cerebrovascular events pathogenesis and its subsequent initial clinical manifestation. Further research is necessary to fully understand this causal relation as previous studies have focused specifically on cryptogenic strokes, not acknowledging the potential synergistic role of cancer in conventional stroke mechanisms.

Such heightened risk should not be overlooked as cancer-related stroke is frequently associated with worst outcomes[3,6,8,18], as we observed higher case fatality in Incident Cancer group, and ageing of the population may enhance this problem.

As there is no consensus on screening cancer in cerebrovascular diseases patients and current biomarkers, like high levels of D-Dimers, fibrinogen and C-Reactive Protein[9,15,17,35], exhibit low specificity, the discovery of more specific biomarkers would constitute a major advance in patient care and early cancer detection.

CONCLUSION

The incidence of cancer in our population cohort of Stroke and TIA patients is higher than the general population from the same geographical region. This was particularly notorious in age groups of 45 to 85 years and for gastrointestinal, genitourinary, and lower respiratory tract tumours. A specific stroke aetiology was not associated with malignancy occurrence.

Our study supports the relation between cancer and cerebrovascular events, prompting a higher risk of neoplastic disease in Stroke and TIA patients. However, our results prevent us from infer a causal association, as sharing vascular risk factors, increased tobacco use in incident cancer group or an occult malignancy at cerebrovascular event onset may be in its origin. Further studies are necessary to clarify this contribution to stroke pathogenesis.

Yet, clinicians should be aware of this heightened risk and consider an incisive approach that could comprise a selection of a subgroup of patients who would benefit from active malignancy surveillance, particularly male sex and tobacco use, after a cerebrovascular event. Such approach could contribute to early identification of potentially treatable cancers.

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TABLES

Table I - Demographics, Vascular Risk Factors and Cerebrovascular characteristics in ACIN2 Stroke and TIA patients according to incident Cancer.

	All	Non-Incident Cancer Group (n=979)	Incident Cancer Group (n=90)	p
Female, n (%)	574 (53.7)	538 (55.0)	36 (40.0)	**0.006**
Age, mean ± SD	70.9 ± 14.3	70.8 ± 14.6	71.5 ± 10.4	0.552
Vascular Risk Factors, n (%)				
Arterial Hypertension	749 (70.1)	682 (69.7)	67 (74.4)	0.343
Diabetes Mellitus	251 (23.5)	229 (23.4)	22 (24.4)	0.822
Dyslipidaemia	391 (36.6)	360 (36.8)	31 (34.4)	0.661
Tobacco use	210 (19.6)	181 (18.5)	29 (32.2)	**0.002**
Peripheral Artery Disease	37 (3.5)	30 (3.1)	7 (7.8)	**0.019**
Coronary disease	114 (10.7)	100 (10.2)	14 (15.6)	0.116
Previous Thrombotic events	30 (2.8)	26 (2.7)	4 (4.4)	0.325
Previous AF	134 (12.5)	126 (12.9)	8 (8.9)	0.275
Cerebrovascular Event, n (%)				0.505
Ischemic Stroke	727 (68.0)	668 (68.2)	59 (65.6)	0.419
Large - artery Atherosclerosis	85 (11.7)	76 (11.4)	9 (15.3)	
Cardioembolism	168 (23.1)	156 (23.4)	12 (20.3)	
Small-vessel occlusion	170 (23.4)	153 (22.9)	17 (28.8)	
Stroke of other determined aetiology	30 (4.1)	28 (4.2)	2 (3.4)	
Stroke of undetermined aetiology	274 (37.6)	255 (38.2)	19 (32.2)	
Two or more causes identified	33 (4.5)	28 (4.2)	5 (8.5)	
Negative evaluation	89 (12.2)	85 (12.7)	4 (6.8)	
Incomplete evaluation	152 (20.9)	142 (21.3)	10 (16.9)	
Haemorrhagic Stroke	128 (12.0)	119 (12.2)	9 (10.0)	
Transient Ischemic Accident	214 (20.0)	192 (19.6)	22 (10.3)	0.604
Large - artery Atherosclerosis	12 (5.6)	10 (5.2)	2 (9.1)	
Cardioembolism	13 (6.1)	10 (5.2)	3 (13.6)	
Small-vessel occlusion	12 (5.6)	11 (5.7)	1 (4.5)	
Stroke of other determined aetiology	1 (0.5)	1 (0.5)	0	
Stroke of undetermined aetiology	176 (82.2)	160 (83.3)	16 (72.7)	
Two or more causes identified	2 (0.9)	2 (1.0)	0	
Negative evaluation	41 (19.2)	39 (20.3)	2 (9.1)	
Incomplete evaluation	133 (62.1)	119 (62.0)	14 (63.6)	
Recurrent Cerebrovascular Event	126 (11.8)	116 (11.8)	10 (11.1)	0.835

Table II – Univariable and multivariable Cox regression analysis associated with incident cancer in all Stroke and TIA patients.

	Univariable			Multivariable		
	HR	95% CI	p	HR	95% CI	p
Sex	1.63	1.07– 2.49	**0.022**	1.52	0.95–2.44	0.079
Age	1.02	1.01–1.04	**0.005**	1.04	1.02–1.06	**<0.001**
Arterial Hypertension	1.23	0.77–1.98	0.388	1.07	0.65–1.75	0.794
Diabetes Mellitus	1.17	0.73–1.90	0.514	1.24	0.75–2.04	0.403
Dyslipidaemia	0.78	0.50–1.20	0.253	0.70	0.45–1.10	0.118
Tobacco use	1.56	1.00–2.43	**0.048**	1.64	0.99–2.70	0.055
Peripheral Artery Disease	2.47	1.14–5.34	**0.022**	1.95	0.86–4.40	0.109
Coronary disease	1.76	1.00–3.12	0.051	1.48	0.81– 2.71	0.206
Previous Thrombotic events	1.42	0.52–3.88	0.489	1.69	0.61–4.66	0.314
Previous AF	0.99	0.48–2.04	0.975	0.72	0.34–1.53	0.387
Recurrent Cerebrovascular Event	0.82	0.42–1.58	0.549	0.79	0.41– .53	0.485
Cerebrovascular Event Aetiology	-	-	0.293	-	-	0.393

Table III - Distribution of type of tumours posterior to the CVE in all Stroke and TIA patients and Ischemic Events.

	All Strokes and TIAs	Ischemic Events (Stroke and TIA)
Respiratory System	**11 (12.2)**	**10 (12.3)**
Larynx	0	0
Trachea, Bronchi, Lung	11 (12.2)	10 (12.3)
Hematopoietic System	**11 (12.2)**	**11 (15.6)**
Hodgkin Lymphoma	0	0
Non-Hodgkin's Lymphoma	4 (3.8)	4 (4.9)
Lymphoid Leukaemia	0	0
Myeloid Leukaemia	2 (1.9)	2 (2.5)
Myelodysplastic Syndrome	1 (1.0)	1 (1.2)
Chronic Myeloproliferative Neoplasms	3 (2.9)	3 (3.7)
Multiple Myeloma	1 (1.0)	1 (1.2)
Gastrointestinal System	**32 (35.6)**	**27 (33.3)**
Oral Cavity and Pharynx	3 (3.3)	3 (3.7)
Oesophagus	2 (2.2)	2 (2.5)
Stomach	5 (5.6)	4 (4.9)
Small Intestine	1 (1.1)	1 (1.2)
Colorectal	11 (12.2)	8 (9.9)
Liver	3 (3.3)	2 (2.5)
Gallbladder and Biliary Tract	2 (2.2)	2 (2.5)
Pancreas	5 (5.6)	5 (6.2)
Genitourinary System	**21 (23.3)**	**21 (25.9)**
Cervix	2 (2.2)	2 (2.5)
Uterus Body	2 (2.2)	2 (2.5)
Ovary	2 (2.2)	2 (2.5)
Prostate	6 (6.7)	6 (7.4)
Testicle	0	0
Kidney	3 (3.3)	3 (3.7)
Ureter	0	0
Bladder	6 (6.7)	6 (7.4)
Breast	**8 (8.9)**	**7 (8.6)**
Melanoma	**0**	**0**
Others	**7 (7.8)**	**5 (6.2)**
Central Nervous System	3 (3.3)	2 (2.5)
Carcinoma of Unknown Primary Origin	2 (2.2)	1 (1.2)
Bones and Joints	1 (1.1)	1 (1.2)
Soft tissue	0	0
Thyroid Gland	0	0
Salivary Gland	1 (1.1)	1 (1.2)
Adrenal Gland	0	0
Total	**90**	**81**

Table IV - Age- and Sex-Specific Annual Incidence per 100 000 for Cancer in Ischemic Events and all Stroke and TIA patients.

	All				Female				Male			
	n	Person-Years	Rate	95% CI	n	Person-Years	Rate	95% CI	n	Person-Years	Rate	95% CI
Ischemic Events (Stroke and TIA)												
45-54	5	493	1015	374-2494	2	222	902	156-3570	3	270	1111	287–3482
55-64	16	1040	**1538**	**912-2543**	5	407	1227	453-3009	11	633	1739	917–3186
65-74	22	1033	2430	1372-3262	6	545	1102	449-2506	16	488	3278	1949- 5383
75-84	31	1269	**2442**	**1693-3491**	16	793	2019	1198-3332	15	477	3145	1836–5252
+ 85	7	309	2265	996-4813	5	304	1647	608-4022	2	87	2312	402–8887
Total	81	4225	1917	1535-2390	34	2270	1498	1056-2111	47	1954	2405	1791– 3212
ASR	-	-	**1656**	**1579-1738**	-	-	**1234**	**1167-1305**	-	-	**2129**	**2041-2221**
RORENO ASR	-	-	1014	1005-1023	-	-	782	771-793	-	-	1329	1313-1345
All Strokes and TIAs												
45-54	8	545	**1469**	**685-2992**	3	236	1272	329-3979	5	309	**1619**	**598-3955**
55-64	16	1135	1409	836-2331	5	435	1150	424-2821	11	701	1570	828-2880
65-74	26	1134	**2294**	**1534-3391**	7	593	1181	519-2530	19	541	**3512**	**2187-5531**
75-84	33	1380	**2392**	**1678-3382**	16	855	1871	1110-3089	17	525	3240	1959-5242
+ 85	7	420	1666	732-3555	5	319	1570	579-3836	2	102	1965	341-7605
Total	90	4614	1951	1580-2404	36	2437	1477	1052-2062	54	2177	2481	1887-3248
ASR	-	-	**1782**	**1701-1866**	-	-	**1319**	**1250-1392**	-	-	**2286**	**2194-2381**
RORENO ASR	-	-	1014	1005-1023	-	-	782	771-793	-	-	1329	1313-1345

*ASR: Age-Adjusted Rate for European population

Table V - Sex-Specific Annual Incidence per 100 000 for Cancer, stratified by type of tumours, in Ischemic Events and all Stroke and TIA patients.

	All			Female			Male		
	n	Rate	95% CI	n	Rate	95% CI	n	Rate	95% CI
Ischemic Events (Stroke and TIA)									
Lower Respiratory	10	237	120-451	2	88	15-355	8	409	191-840
Age-Adjusted Rate		**231**	**202-263**		36	25-50		**431**	**392-474**
RORENO ASR	-	94	88-92	-	38	36-41	-	165	159-170
Gastrointestinal	27	639	430-942	10	441	224-838	17	870	524-1420
Age-Adjusted Rate		**502**	**459-548**		**275**	**244-310**		**730**	**678-785**
RORENO ASR	-	354	349-360	-	236	230-242	-	508	498-517
Genitourinary	21	497	316-773	9	397	134-781	12	614	333-1103
Age-Adjusted Rate		**438**	**398-481**		**331**	**297-369**		**580**	**535-630**
RORENO ASR	-	241	236-245	-	100	97-104	-	428	419-438
Other Tumours	23	544	354-830	13	573	319-1005	10	512	260-972
Age-Adjusted Rate		486	444-532		592	546-642		388	351-429
All Strokes and TIAs									
Lower Respiratory	11	238	125-440	3	123	32-392	8	368	171-754
Age-Adjusted Rate		**231**	**202-263**		**72**	**57-91**		**383**	**346-424**
RORENO ASR	-	94	88-92	-	38	36-41	-	165	159-170
Gastrointestinal	32	694	483-990	10	410	209-780	22	1011	650-1553
Age-Adjusted Rate		**575**	**530-625**		256	226-290		**893**	**836-954**
RORENO ASR	-	354	349-360	-	236	230-242	-	508	498-517
Genitourinary	21	455	289-708	9	369	180-727	12	551	299-990
Age-Adjusted Rate		**400**	**363-442**		**310**	**277-347**		**518**	**475-565**
RORENO ASR	-	241	236-245	-	100	97-104	-	428	419-438
Other Tumours	26	564	376-837	14	575	327-988	12	551	299-990
Age-Adjusted Rate		576	530-625		682	632-735		491	450-537

*ASR: Age-Adjusted Rate for European population

FIGURES

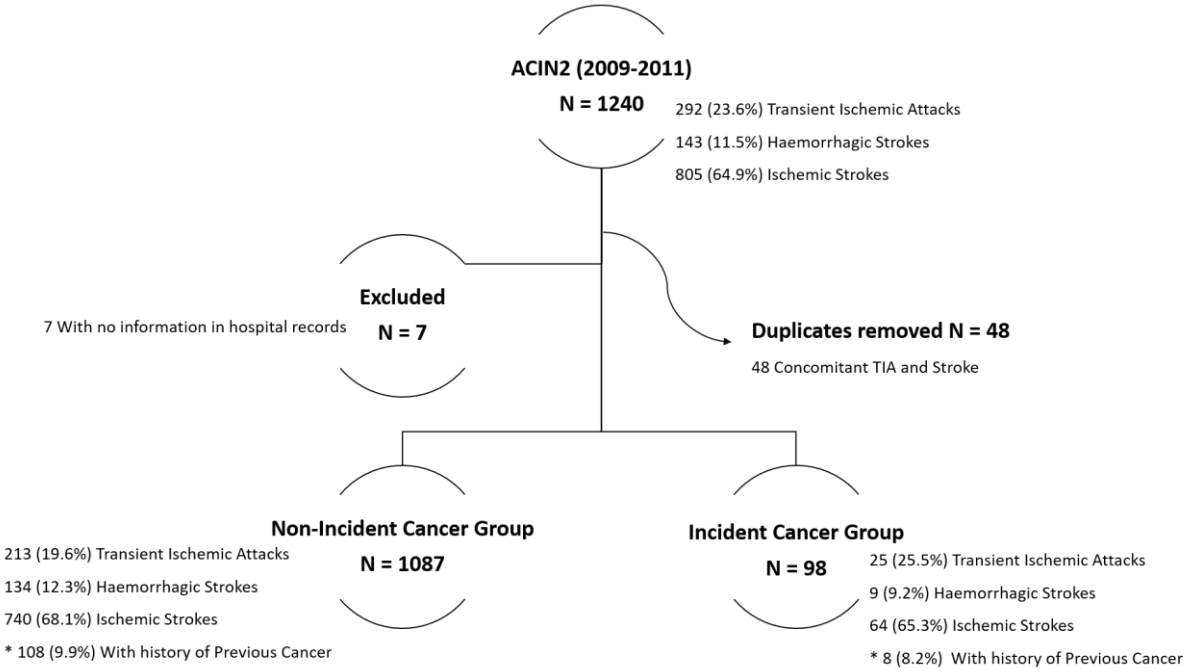


Figure 1 - Flowchart describing study design and patient selection.

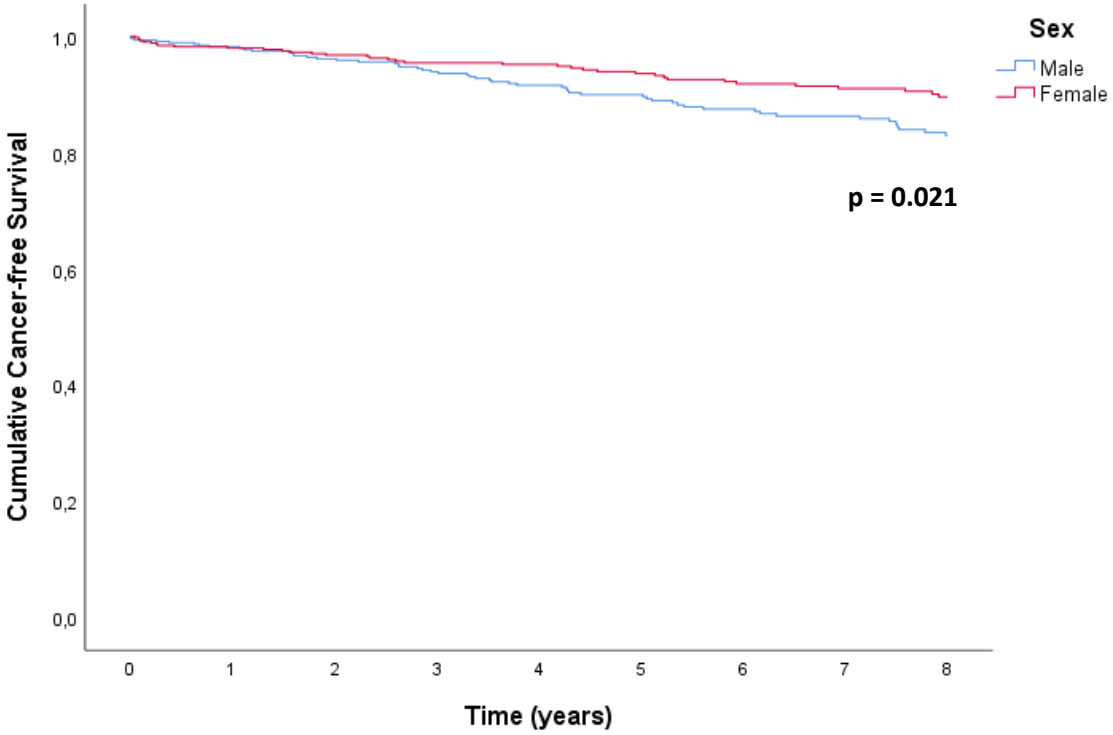


Figure 2 - Cumulative Cancer-free Survival over 8 years of follow-up, by Sex, in all Stroke and TIA patients.

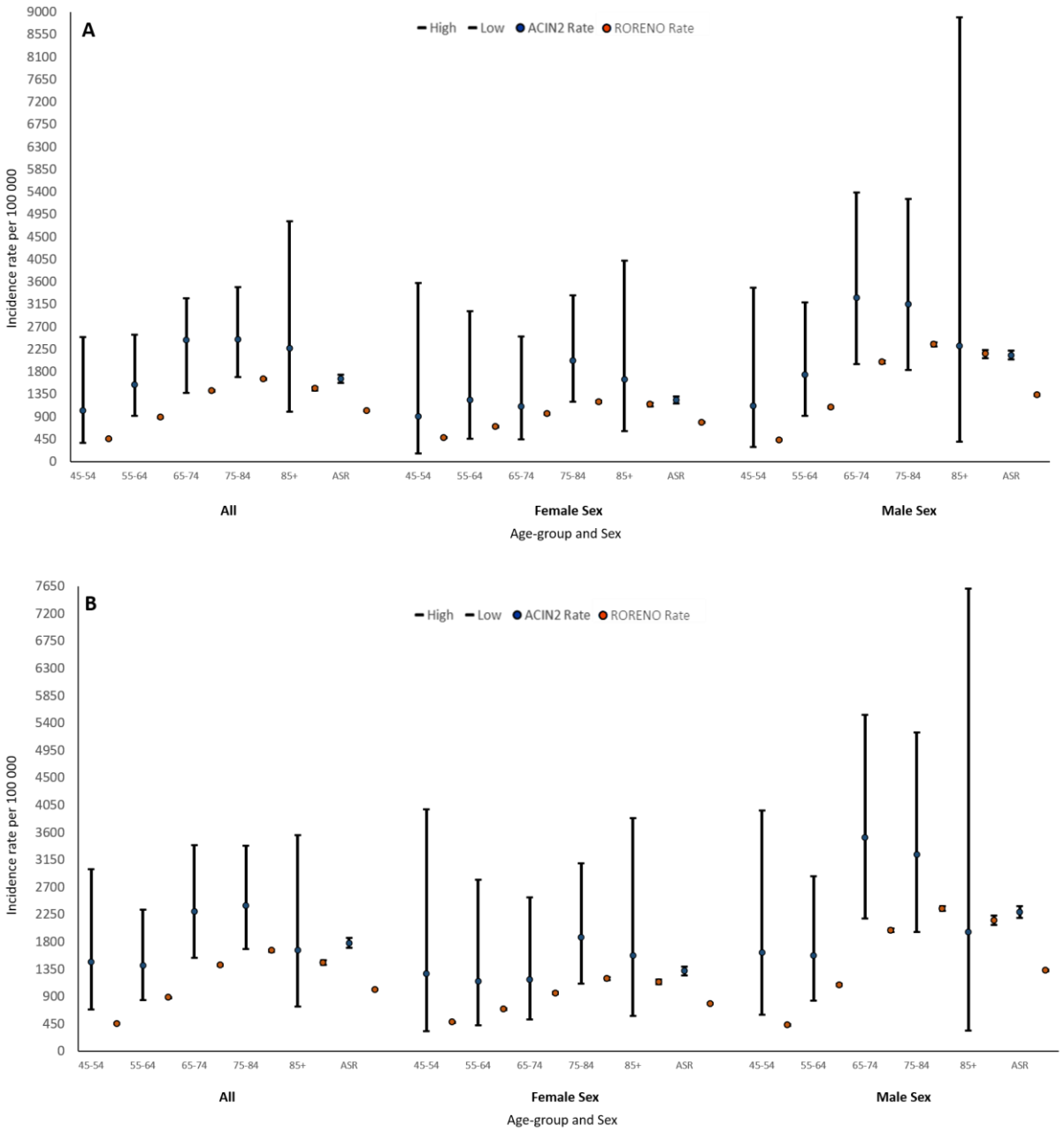


Figure 3 – Age and Sex-specific annual incidence rates for Cancer in ACIN2 patients and RORENO population.

A - Ischemic Events (Stroke and TIA)

B - All Strokes and TIAs

* Age-Adjusted Rate for European population

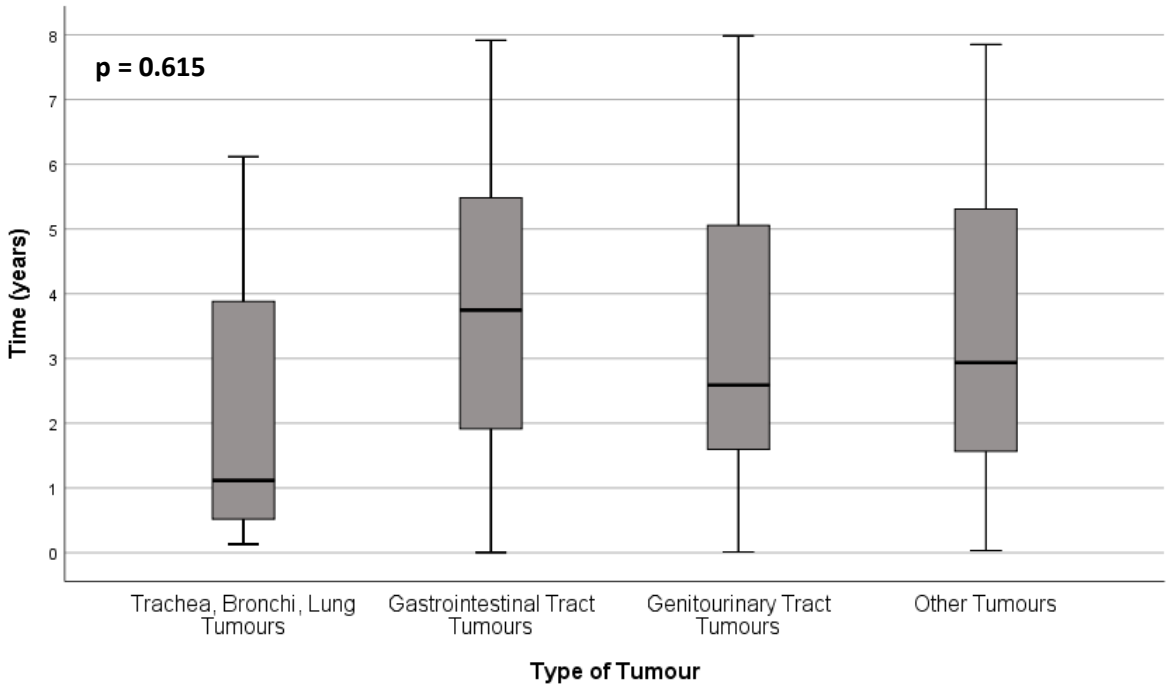


Figure 4 - Median time interval between Cerebrovascular Event onset and the diagnosis of cancer, by type of tumour.

*Other Tumours: Hematopoietic System, Breast, Melanoma, Others (CNS, Carcinoma of Unknown Primary Origin, Bones and Joints, Salivary Gland) Tumours.

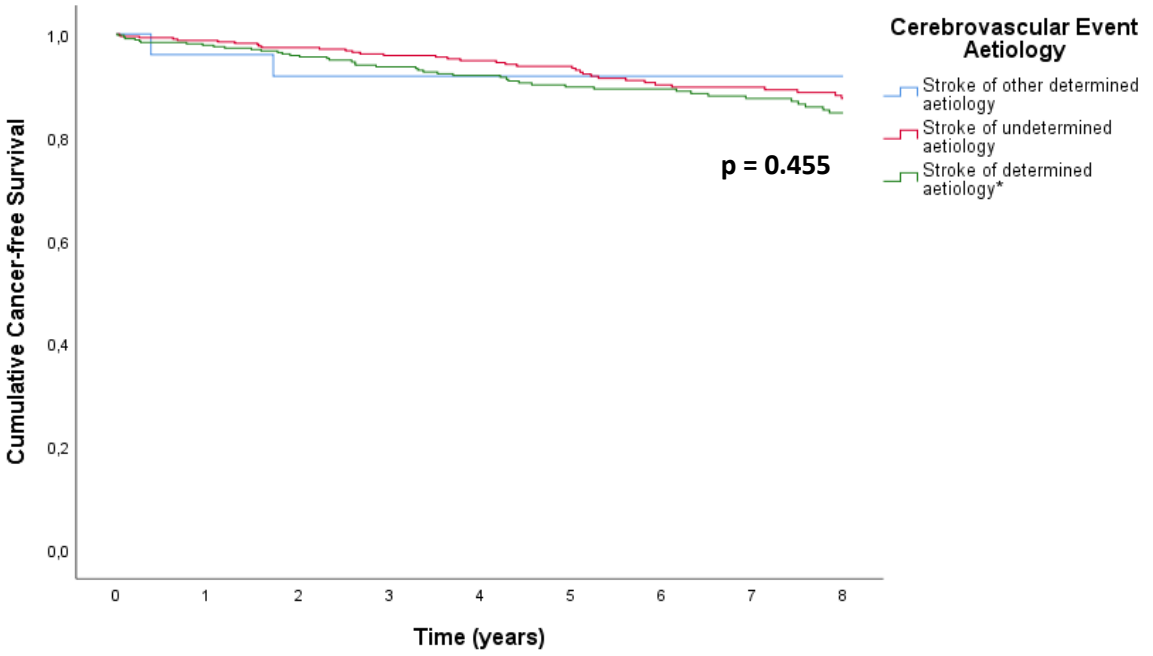


Figure 5 - Cumulative Cancer-free Survival over 8 years of follow-up, according to aetiology, in all Stroke and TIA patients.

*Large-artery Atherosclerosis, Cardioembolism, Small-vessel occlusion

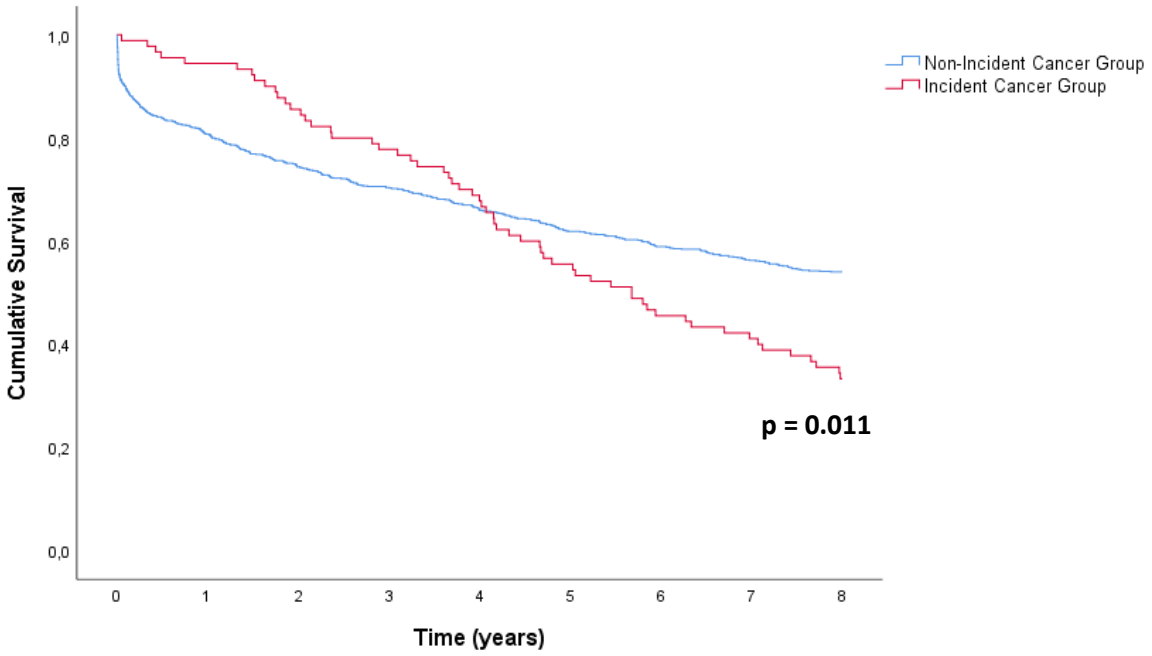


Figure 6 - Overall Survival over 8 years of follow-up, by Incident Cancer, in all Stroke and TIA patients.

APPENDIX

Supplemental Table I - Age- and Sex-Specific Annual Incidence per 100 000 for Cancer and stratified by type of tumours, in Northern Portugal (2009-2014), RORENO data.

	All		Female		Male	
	Rate	95% CI	Rate	95% CI	Rate	95% CI
Age Group						
45-54	454	447-461	476	466-487	431	420-441
55-64	882	871-893	695	681-709	1090	1072-1108
65-74	1415	1398-1432	954	936-972	1987	1958-2017
75-84	1652	1630-1673	1193	1170-1217	2345	2304-2386
+ 85	1458	1421-1494	1139	1100-1178	2152	2073-2232
Total	968	970-982	778	770-785	1215	1205-1226
Age-Adjusted Rate	1014	1005-1023	782	771-793	1329	1313-1345
Type of Tumours						
Trachea, Bronchi, Lung Tumours	90	88-92	38	36-40	153	150-157
Age-Adjusted Rate	94	91-96	38	36-41	165	159-170
Gastrointestinal Tract Tumours	339	335-343	235	231-239	465	459-471
Age-Adjusted Rate	354	349-360	236	230-242	508	498-517
Genitourinary Tract Tumours	229	226-232	99	97-102	385	379-391
Age-Adjusted Rate	241	236-245	100	97-104	428	419-438

Supplemental Table II - Age- and Sex-Specific Annual Incidence per 100 000 for Cancer in Ischemic Events and all Stroke and TIA patients, including history of previous Cancer.

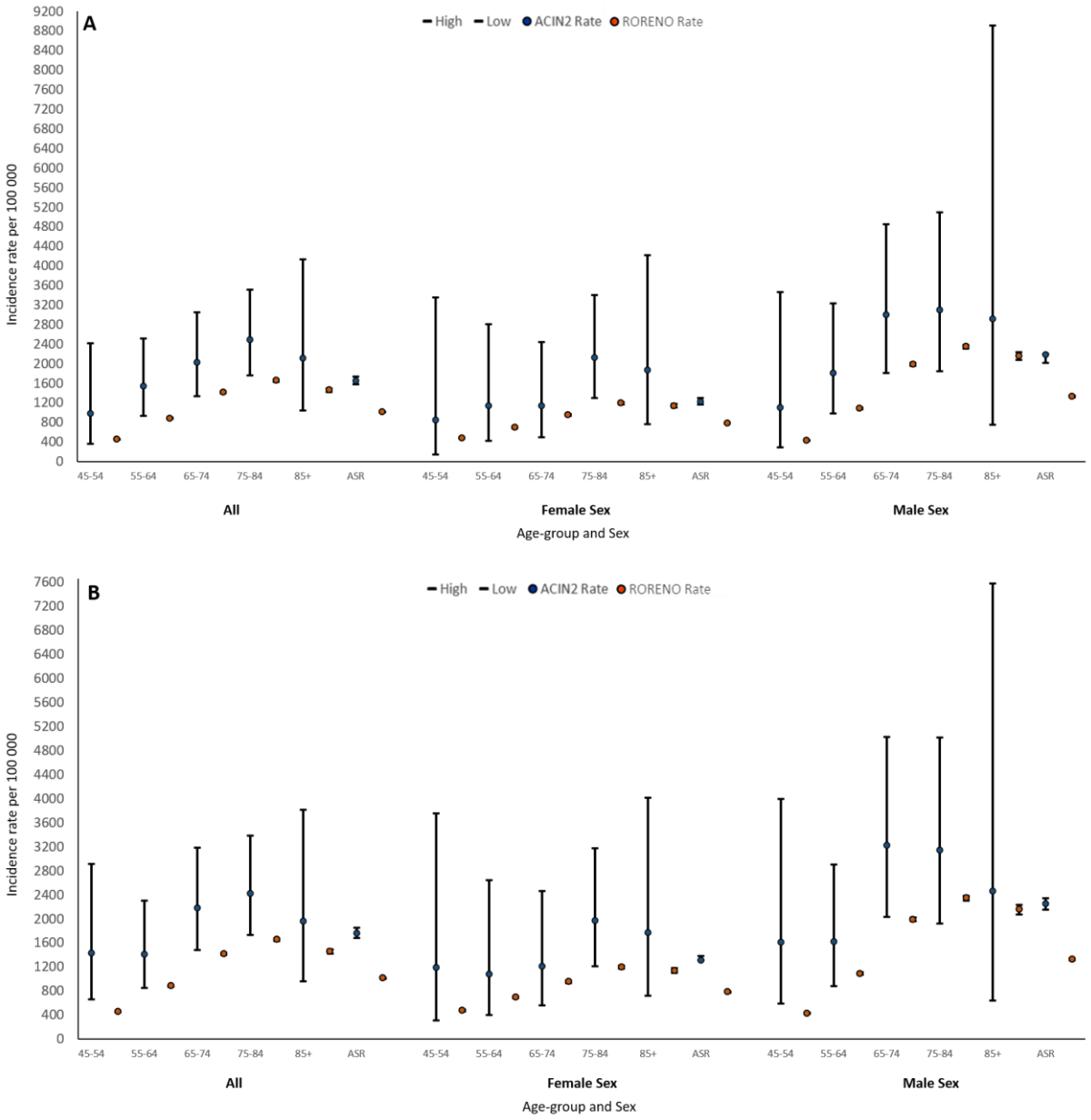
	All				Female				Male			
	n	Person-Years	Rate	95% CI	n	Person-Years	Rate	95% CI	n	Person-Years	Rate	95% CI
Ischemic Events (Stroke and TIA)												
45-54	5	508	984	363-2417	2	237	845	147-3348	3	218	1104	286-3462
55-64	17	1099	**1547**	**933-2519**	5	437	1145	422-2809	12	662	1812	985-3236
65-74	24	1182	2031	1334-3054	7	615	1139	500-2441	17	567	2997	1812-4854
75-84	34	1363	**2494**	**1760-3508**	18	846	**2127**	**1304-3408**	16	517	3097	1841-5088
+ 85	9	425	2119	1038-4129	6	322	1864	760-4214	3	103	2918	757-8913
Total	89	4277	1945	1573-2399	38	2456	1547	1112-2140	51	2121	2405	1814-3175
ASR	-	-	**1651**	**1573-1732**	-	-	**1230**	**1163-1301**	-	-	**2190**	**2021-2200**
RORENO ASR	-	-	1014	1005-1023	-	-	782	771-793	-	-	1329	1313-1345
All Strokes and TIAs												
45-54	8	560	**1428**	**665-2908**	3	251	1196	309-3755	5	310	**1615**	**596-3995**
55-64	17	1202	1414	853-2304	5	464	1077	397-2644	12	738	1626	883-2906
65-74	28	1283	**2182**	**1482-3182**	8	663	1207	562-2462	20	620	**3225**	**2034-5026**
75-84	36	1485	**2424**	**1728-3377**	18	911	1975	1210-3167	18	574	3138	1926-5011
+ 85	9	460	1957	958-3816	6	338	1774	723-4014	3	122	2463	638-7572
Total	98	4991	1964	1604-2398	40	2628	1522	1104-2088	58	2363	2454	1890-3183
ASR	-	-	**1766**	**1686-1850**	-	-	**1308**	**1239-1381**	-	-	**2247**	**2156-2341**
RORENO ASR	-	-	1014	1005-1023	-	-	782	771-793	-	-	1329	1313-1345

*ASR: Age-Adjusted Rate for European population

Supplemental Table III - Sex-Specific Annual Incidence per 100 000 for Cancer, stratified by type of tumours, in Ischemic Events and all Stroke and TIA patients, including history of previous Cancer.

	All			Female			Male		
	n	Rate	95% CI	n	Rate	95% CI	n	Rate	95% CI
Ischemic Events (Stroke and TIA)									
Lower Respiratory	12	262	142-472	3	122	32-389	9	424	207-385
Age-Adjusted Rate		**251**	**222-285**		51	38-67		**436**	**397-479**
RORENO ASR	-	94	88-92	-	38	36-41	-	165	159-170
Gastrointestinal	31	677	469-973	11	448	236-826	20	943	593-1481
Age-Adjusted Rate		**514**	**471-561**		270	240-305		**789**	**735-846**
RORENO ASR	-	354	349-360	-	236	230-242	-	508	498-517
Genitourinary	22	481	309-740	10	407	207-774	12	566	307-1016
Age-Adjusted Rate		**416**	**377-458**		**324**	**291-362**		**531**	**487-579**
RORENO ASR	-	241	236-245	-	100	97-104	-	428	419-438
Other Tumours	24	524	344-792	14	570	325-980	10	472	240-896
Age-Adjusted Rate		522	479-569		697	647-751		353	318-393
All Strokes and TIAs									
Lower Respiratory	13	261	145-458	4	152	49-418	9	381	171-754
Age-Adjusted Rate		**248**	**218-281**		**82**	**66-102**		**389**	**346-424**
RORENO ASR	-	94	88-92	-	38	36-41	-	165	159-170
Gastrointestinal	36	721	513-1009	11	419	220-772	25	1058	650-1553
Age-Adjusted Rate		**580**	**534-630**		252	222-286		**929**	**836-954**
RORENO ASR	-	354	349-360	-	236	230-242	-	508	498-517
Genitourinary	22	441	283-679	10	381	194-724	12	508	275-912
Age-Adjusted Rate		**381**	**344-422**		**304**	**271-341**		475	433-520
RORENO ASR	-	241	236-245	-	100	97-104	-	428	419-438
Other Tumours	27	541	364-798	15	571	332-963	12	508	275-912
Age-Adjusted Rate		557	512-606		669	620-722		455	414-499

*ASR: Age-Adjusted Rate for European population



Supplemental Figure 1 - Age and Sex-specific annual incidence rates for Cancer in ACIN2 patients and RORENO population, considering history of previous Cancer.

A - Ischemic Events (Stroke and TIA)

B - All Strokes and TIAs

* Age-Adjusted Rate for European population