ORIGINAL ARTICLE

Cancer prevalence higher in stroke patients than in the general population: the Dutch String-of-Pearls Institute (PSI) Stroke study

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Background and purpose: The aim of this study was to assess the prevalence of cancer and its characteristics in patients with ischemic stroke and to compare this with cancer prevalence in the general population.

Methods: This was a multicenter cohort study with 2736 patients presenting with ischemic stroke or transient ischemic attack. The prevalence of cancer was assessed by interview and verified by reviewing all medical records. In stroke patients with a history of cancer, we studied the subtype of cancer and its treatment characteristics. We used the national database of The Netherlands Cancer Registry to calculate population-based age and sex cancer standardized prevalence ratios (SPRs) for patients with ischemic stroke.

Results: Cancer prevalence in ischemic stroke patients was 12%, corresponding to an SPR of 1.2 [95% confidence interval (CI), 1.0–1.3]. Increased SPRs were observed for cancer of the central nervous system (SPR, 18.2; 95% CI, 9.0–27.4), head and neck (SPR, 3.4; 95% CI, 2.3–4.6), lower respiratory tract (SPR, 2.4; 95% CI, 1.5–3.3) and urinary tract (SPR, 2.1; 95% CI, 1.4–2.9), but not for other cancer types. Cardiovascular risk factors, stroke etiology, treatment and outcome were not different between patients with or without a history of cancer.

Conclusions: In stroke patients, the prevalence of cancer, most prominently cancer of the central nervous system, head and neck, lower respiratory and urinary tract, was higher than in the general population. Medical treatment for the prevention of stroke in cancer survivors deserves further study.

Introduction

Cancer and cardiovascular diseases are the two leading causes of morbidity and mortality worldwide [1]. An autopsy study in patients with cancer showed that 15% had evidence of prevalent cerebrovascular disease [2]. This co-occurrence of cancer and cerebrovascular disease may be explained by the high prevalence of both diseases in the general elderly population and by the sharing of highly prevalent population risk factors, particularly smoking. Cancer may also have a causal relationship with cerebrovascular disease by inducing a hypercoagulable state, non-bacterial thrombotic endocarditis and tumor compression of blood vessels. Direct and late toxicity of anticancer treatment, either radiotherapy (RT)-related vasculopathy or chemotherapy-related hypercoagulability, could also be causative factors [2,3]. A large study of patients with cancer and matched controls showed a 3-month increased incidence of stroke in patients with lung, pancreatic and colorectal cancers [4]. Within a sample of 96 ischemic stroke patients with a known history of a cancer, the most frequent types of

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previous cancer were lung (30%), brain (9%) and prostate (9%) [5]. The population of long-term cancer survivors is growing, and several studies have reported on the long-term vascular complications in these patients [6–8]. Nevertheless, studies on the prevalence and characteristics of cancer in a large cohort of patients presenting with ischemic stroke are lacking.

The purpose of the current study was to investigate the long-term prevalence of previous cancer in patients diagnosed with stroke in comparison with that in the general population in The Netherlands.

Materials and methods

From May 2007 until March 2014, we recruited participants in a prospective multicenter cohort study, called the String of Pearls Institute, a collaboration of the eight university medical centers in The Netherlands. Details of this study protocol have been described previously [9]. In short, a national stroke database with a standardized central infrastructure allowed uniform data collection and storage of biomaterials in patients presenting with a recent cerebrovascular disease. For the current study, we included patients with ischemic stroke or transient ischemic attack as index event. All local Medical Ethical Committees of participating hospitals approved the study. The research was performed according to the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act and codes on 'good use' of clinical data and biological samples as developed by the Dutch Federation of Medical Scientific Societies (http://www.wma.net/en/10home/index.html). All patients provided written informed consent.

We collected data on age, sex, cardiovascular risk factors (smoking, hypertension, hypercholesterolemia, diabetes mellitus), presence or a history of atrial fibrillation, previous cardiovascular events (ischemic stroke, transient ischemic attack, acute myocardial infarction and peripheral arterial disease), stroke severity by means of the National Institutes of Health Stroke Scale score at admission and functional outcome at 3 months by the modified Rankin scale score [10]. Etiology of stroke was classified according to the modified Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria [11].

In the subset of patients with a history of cancer ($n = 321$), we retrospectively collected information by reviewing the clinical records and contacting the general practitioner or treating oncological physician about the type and stage of the cancer and treatment (type of chemotherapy, use of angiogenesis inhibitor, RT dosage and location). In those cases where the patient had died, we also collected oncological information by reviewing medical records and contacting the general practitioner or treating physician. The interval between cancer and stroke was calculated in years.

For comparison of our data, we used information from the database of The Netherlands Cancer Registry, which registers the most important statistics on cancer in The Netherlands and is managed by the Netherlands Comprehensive Cancer Organisation (Integraal Kanker Centrum Nederland (IKNL)). Data collected included incidence, prevalence, survival, mortality and risk of different cancer types, as well as localization and morphological classification of tumors. Combining localization and morphology enables precise classification of diagnosis. The definitions used for cancer in stroke were in accordance with the classification of tumors used by The Netherlands Cancer Registry based on the 10th edition of the International Classification for Diseases (ICD-10). The ICD-10 codes used were: C81–C96, C38, C40–C41, C46–C49, C50, C70–C72, C73–C75, C00–C14, C30–C32, C69, C43–C44, C60–C63, C33–C34, C45, C15–C26, C51–C58, C37, C39, C76 and C80.

Basal cell carcinoma and adenoma of the pituitary are not registered by The Netherlands Cancer Registry.

Data analysis

Stroke characteristics (cardiovascular risk factors, stroke etiology, treatment and outcome) in the patients with and without a history of cancer were compared after stratification for age. All cancer characteristics were separately analyzed for patients who had active cancer (defined as not disease free), had been cancer free ≤5 years [short-term cancer-free patients (CFPs)] and had been cancer free >5 years (long-term CFPs).

We used Fisher's test and chi-squared test to assess unadjusted differences in proportions and a t-test to assess differences in mean values. In order to determine if any cancer type was more common amongst stroke patients, we compared the 20-year prevalence of cancer diagnosis with the 20-year prevalence of diagnosis in the Dutch population for specific cancer localizations. We used data from The Netherlands Cancer Registry to calculate the expected number of cases in our cohort, based on its age and sex distribution. We calculated standardized prevalence ratios (SPRs) by dividing the observed cancer number by the expected cancer number.

Results

We included 2736 patients with a mean (±SD) age of 65 (±14) years of whom 59% were men. Of these patients, 321 (12%) had a history of cancer. The total

number of cancers was 360. Patients with a history of cancer were significantly older (mean age 72 ± 12 years) than patients without a history of cancer (mean age 64 ± 14 years) (Table 1). There were no significant differences in stroke characteristics between the patients with and without a history of cancer. The majority of strokes were caused by large artery disease in both groups (39%).

Cancer characteristics

Among the 321 stroke patients with a history of cancer, 13 different types of cancer were identified. The most common primary malignancy locations were male genital tract (16%), breast (16%), digestive tract (13%), urinary tract (10%) and head and neck (9%) (Table 2). A total of 53% of the patients with cancer were long-term CFPs at the time of stroke. Of the short-term CFPs, 42 (26%) were treated with chemotherapy versus 15% of the long-term CFPs ($P < 0.02$). Most frequently used chemotherapy included platinum-based (45%) or alkylating (33%) agents in the short-term CFPs and alkylating (65%) or antibiotic (55%) agents in the long-term CFPs. A total of 66 (41%) of the short-term CFPs versus 82 (47%) of the long-term CFPs had received RT, most frequently for head and neck cancer (Table 3).

In the current cohort of stroke patients, increased SPRs were observed for cancer of the central nervous system (CNS) [SPR, 18.2; 95% confidence interval (CI), 9.0–27.4], head and neck (SPR, 3.4; 95% CI, 2.3–4.6), lower respiratory tract (SPR, 2.4; 95% CI, 1.5–3.3) and urinary tract (SPR, 2.1; 95% CI, 1.4–2.9) (Table 4). Patients with CNS cancer showed a mean cancer–stroke interval of 9.2 years and 40% had an undetermined etiology of stroke. A total of 57% of patients with CNS cancer had received RT with a mean (±SD) dose of 55 (±8) Gy. The subgroup of 23 patients with CNS cancer consisted mostly of glial tumors ($n = 8$) and meningioma ($n = 8$) (Appendix S2). Patients with head and neck cancer had a mean cancer–stroke interval of 7.2 years, TOAST classification showed mostly large artery disease (71%) and 44% were current smokers. Patients with lower respiratory tract cancer had a mean cancer–stroke interval of 6 years and 77% were current or former smokers. Patients with urinary tract cancer had a mean cancer–stroke interval of 7.4 years and 62% were current or former smokers.

Discussion

The current study is the first and largest multicenter study among stroke patients that combines patient,

Table 1 Demographics and characteristics of patients with ($n = 321$) and without ($n = 2415$) a history of cancer at the time of diagnosis of ischemic stroke

	Stroke patients with cancer history ($n = 321$) (12%)	Stroke patients without cancer history ($n = 2415$) (88%)	P value[a]
Demographics			
Men	186 (58)	1435 (59)	0.77
Age (years)	72 ± 12	64 ± 14	<0.001
Risk factors			
Smoking			
Never	113 (38)	847 (37)	0.18
Stopped > 6 months	123 (41)	761 (33)	
Stopped < 6 months	8 (3)	48 (2)	
Current	57 (19)	637 (28)	
Hypertension	190 (59)	1271 (53)	0.85
Hypercholesterolemia	116 (37)	831 (35)	0.49
Diabetes	60 (19)	376 (16)	0.86
Atrial fibrillation	53 (17)	286 (12)	0.72
Alcohol use	158 (56)	1317 (61)	0.31
Past arterial events			
IS/TIA	98 (32)	655 (29)	0.97
AMI	43 (14)	259 (11)	0.82
PAD	28 (9)	180 (8)	0.92
Stroke characteristics			
Duration < 24 h	58 (19)	419 (18)	0.57
TOAST			
LAD	84 (39)	645 (39)	0.05
CE	42 (19)	222 (14)	
SVD	30 (14)	291 (18)	
Other	62 (28)	480 (29)	
NIHSS score	4 ± 5	4 ± 5	0.94
Treatment			
IV thrombolysis	44 (16)	386 (19)	0.29
Outcome at 3 months (MRS score)			
0	64 (28)	589 (31)	0.20
1	64 (28)	500 (28)	
2	39 (17)	400 (22)	
3	27 (12)	183 (10)	
4	19 (8)	81 (5)	
5	2 (1)	24 (1)	
6	13 (6)	56 (3)	

Data are given as n (%, complete case analysis) and mean ± SD. AMI, acute myocardial infarct; CE, cardioembolism; IS, ischemic stroke; IV, intravenous; LAD, large artery disease; MRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; PAD, peripheral arterial disease; SVD, small vessel disease; TIA, transient ischemic attack; TOAST, Trial of Org 10172 in Acute Stroke Treatment. [a]P value for difference adjusted for age.

stroke and cancer characteristics, and compares these with those in the general population. As cancer survival improves, it is increasingly relevant to have knowledge of and to pay attention to vascular complications in patients with cancer. It is important to define types of cancer associated with stroke risk and their specific risk factors. These findings are useful in the development of prevention

Table 2 Absolute and relative frequencies of prevalent cancer subtypes at the time of ischemic stroke diagnosis

Type of cancer	Total ($n = 360$)	Cancer free ≤ 5 years ($n = 171$)	Cancer free > 5 years ($n = 189$)
Male genital tract	59 (16)	36 (21)	23 (12)
Breast	57 (16)	16 (9)	41 (22)
Digestive tract	48 (13)	23 (14)	25 (13)
Urinary tract	35 (10)	19 (11)	16 (9)
Head and neck	33 (9)	14 (8)	19 (10)
Blood, lymph and bone marrow	28 (8)	14 (8)	14 (7)
Lower respiratory tract	27 (8)	15 (9)	12 (6)
Skin	26 (7)	10 (6)	16 (9)
Central nervous system	20 (6)	16 (9)	4 (2)
Female genital tract	15 (4)	4 (2)	11 (6)
Endocrine	7 (2)	3 (2)	4 (2)
Bone and soft tissue	4 (1)	1 (1)	3 (2)
Eye and orbit	1 (0)	0 (0)	1 (1)

Data are expressed as absolute n (%).

guidelines for patients who survive cancer. The prevalence of cancer was higher in ischemic stroke patients than in the general population. In particular, CNS, head and neck, lower respiratory tract and urinary tract cancers were more prevalent in ischemic stroke patients than in the age- and sex-matched general population. Stroke etiology and outcome did not differ between ischemic stroke patients with and without a cancer history.

The strongly increased SPR of CNS cancer in stroke patients has never been described before. The underlying pathology might partly be explained by a long-term RT-induced intracranial vasculopathy. There are no previous reports of increased stroke risk in patients with meningioma. The association of glioblastoma multiforme and ischemic strokes might be explained by post-operative complications, late complications of RT, a hypercoagulable state induced by the tumor or vessel occlusion that is caused by an adjacent tumor [12,13]. In head and neck cancer, post-radiation vasculopathy of the carotid artery is the most likely and best-known link with an increased risk of stroke [7,14]. The relatively high percentage of RT in this type of cancer and the relatively long mean latency period (9 years) between cancer and stroke support this association. Furthermore, head and neck, lower respiratory and urinary tract cancer, and stroke have similar risk factors, in particular smoking. Most patients treated with chemotherapy had received platinum-based or alkylating therapy, which are associated with a known increased risk of stroke [15]. The most frequent cancer types in previous smaller retrospective studies in stroke patients included urogenital, breast, gastrointestinal, hematological and lung [16]. A high frequency of stomach cancer was observed in a retrospective case-control study in stroke patients in Korea [17].

We did not find an increased prevalence of stomach cancer; however, cancer type distributions differ around the world. The purpose of the current study was to investigate the long-term prevalence of previous cancer in stroke patients in comparison with the general population. We found increased prevalence ratios of cancer types more associated with long-term survival. Underlying mechanisms for increased risk of stroke in these long-term survivors are long-term RT-induced vasculopathy or shared risk factors like smoking. In contrast, other studies evaluated the more short-term risk of stroke in patients with active cancer [4,18–21]. Increased risk of stroke was reported mostly in lung, pancreatic and colorectal cancers. In these patients, cancer may also have a causal relationship with stroke by inducing a hypercoagulable state, non-bacterial thrombotic endocarditis and compression of blood vessels by the tumor. The discrepancy in cancer types associated with stroke in long-term survivors versus patients with active cancer can be explained by different underlying associated mechanisms. The study of Selvik *et al.* of cancer prevalence in stroke patients in Norway [22] was similar to our study setting. In a cohort of 1456 ischemic stroke patients, 15.7% of the patients had one or more cancer diagnosis before stroke. This prevalence of cancer in stroke patients was higher than the prevalence of cancer in the general population. These results are similar to the results of the current study. The added value of the current study is the larger stroke cohort and, more importantly, the reporting of SPRs of different cancer types compared with the general population instead of the reporting of only prevalence of cancer types, which makes comparison of the prevalence of different cancer types with the general population more difficult.

Furthermore, we found that stroke characteristics were not different between patients with or without a

Table 3 Characteristics of cancer treatment in an ischemic stroke population

Treatment characteristic	Total ($n = 360$)	Cancer free ≤ 5 years ($n = 171$)	Cancer free >5 years ($n = 189$)	P value
Chemotherapy	68 (20)	42 (26)	26 (15)	0.02
Alkylating	26 (44)	13 (33)	13 (65)	0.04
Platinum-based	21 (36)	17 (45)	4 (20)	0.12
Antibiotic	17 (29)	6 (15)	11 (55)	0.004
Topoisomerase inhibitor	12 (21)	9 (24)	3 (16)	0.73
Antimetabolite	9 (16)	7 (18)	2 (11)	0.70
Antimitotic	9 (16)	3 (8)	6 (30)	0.07
Methotrexate	6 (11)	3 (8)	3 (16)	0.65
Local	7 (13)	4 (11)	3 (16)	0.68
Other	20 (34)	14 (36)	6 (30)	0.87
Other systemic treatments				
Rituximab	7 (12)	6 (16)	1 (5)	0.48
Tyrosine kinase inhibitor	3 (5)	3 (8)	0 (0)	0.53
Angiogenesis inhibitor	7 (2)	5 (3)	2 (1)	0.39
RT	148 (44)	66 (41)	82 (47)	0.29
Location of RT				
Head or neck	54 (37)	25 (39)	29 (35)	0.06
Chest	41 (28)	12 (19)	29 (35)	
Other	52 (35)	28 (43)	24 (29)	
Dose (Gy)				
Head or neck	52 ± 15	53 ± 16	50 ± 15	0.51
Chest	51 ± 11	52 ± 14	50 ± 9	0.69
Other	50 ± 30	40 ± 24	62 ± 33	0.08

Data are expressed as n (%) (complete case analysis) and mean ± SD. Valid percentages do not add up to 100% due to overlap and multiple treatments. P value for difference between cancer free ≤ 5 years and cancer free > 5 years by chi-squared test and for differences in radiotherapy (RT) dose by independent sample t-test.

Table 4 Standardized 20-year prevalence ratio of cancer subtypes in ischemic stroke patients

Type of cancer	Observed number	Expected number	SPR	95% CI
Male genital tract[a]	56	54	1.0	0.8–1.3
Breast[a]	43	42	1.0	0.7–1.3
Digestive tract	38	46	0.8	0.6–1.1
Urinary tract	31	15	2.1	1.4–2.9
Head and neck	29	9	3.4	2.3–4.6
Blood, lymph and bone marrow	23	18	1.3	0.8–1.8
Lower respiratory tract	26	11	2.4	1.5–3.3
Skin	21	38	0.6	0.3–0.8
Central nervous system	15	1	18.2	9.0–27.4
Female genital tract[a]	5	12	0.4	NA
Bone and soft tissue	2	2	1.1	NA
Endocrine	4	1	2.7	NA
Any cancer	273	238	1.2	1.0–1.3

Expected number calculated from the age-specific 20-year prevalence in the Dutch population (source: Dutch Cancer Registration, www.cijfe rsoverkanker.nl). Cancer diagnosis > 20 years before 2011 was excluded in these analyses. CI, confidence interval; NA, not applicable; SPR, standardized prevalence ratio. [a]SPR for male genital tract, female genital tract and breast cancer was calculated for men only and women only, respectively. 95% CI for cancer types with low prevalence (i.e. <5 cases) could not be calculated.

cancer history, which is in line with previous smaller retrospective analyses [16,17,23].

Our study is the first and largest multicenter study in stroke patients in The Netherlands that combined patient, stroke and cancer characteristics. Furthermore, this study compared these characteristics with those in the general population. As cancer type distributions are different over the world and depend on age and sex, it was important that we were able to compare the prevalence of the different cancer types in our stroke cohort with that from the same source population, stratified by age and sex.

Our study has some limitations. Patients with a history of cancer potentially have a higher likelihood of

being diagnosed with stroke due to long-term surveillance with lower threshold to perform more extensive evaluations. However, we did not observe differences in stroke subtypes or severity between patients with and without a cancer history. If this bias had occurred one would expect more relatively mild strokes in those with a cancer history. Furthermore, patients with a history of cancer could have been more often referred to university medical centers because of their cancer history. This is not very likely because in The Netherlands almost all hospitals provide acute stroke care and patients are referred to the nearest hospital. Furthermore, we did not observe differences between participating hospitals with large specialized oncology departments and those without. The retrospective identification and verification of cancer cases may have resulted in some misclassification. However, it is unlikely that cancer is under-reported by the patients themselves because of the impact of this disease. Furthermore, the systematic registration of cancer diagnosis and treatment makes it unlikely that false-positive cases are included. Comparison of cancer frequencies in a stroke cohort with those in the general population does not take into account that stroke was not excluded among the latter. This would result in an underestimation of risk ratios if compared with a stroke-free population. Due to our study design, we were not able to calculate absolute stroke risks for the different types of cancer and cancer treatments.

As the group of cancer survivors increases, it is clinically relevant to define types of cancer associated with an increased stroke risk and its associated specific risk factors. This could be helpful in finding potentially modifiable risk factors to develop prevention guidelines and to optimally inform patients.

Conclusions

In conclusion, we showed an overall increased prevalence of cancer and particularly in specific types of cancer in stroke patients as compared with the general population. Cancer types that showed an increased prevalence were CNS, head and neck, lower respiratory and urinary tract. Stroke characteristics were not different between patients with and without cancer. These findings may have clinical relevance given that at least a part of this association is driven by factors potentially amenable to treatment. Further studies should address whether treatment of cardiovascular risk factors in survivors of CNS, head and neck, lower respiratory and urinary tract cancers prevents stroke.

Disclosure of conflicts of interest

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Study group.
Appendix S2. Characteristics of patients with central nervous system cancer.

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