Incident Cancer in a Cohort of 3,247 Cancer Diagnosis Free Ischemic Stroke Patients

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Key Words

Ischemic stroke · Stroke · Cancer · Death · Incidence · Carcinoma

Abstract

Background: Subclinical cancer can manifest as a thromboembolic event and may be detected at a later interval in ischemic stroke survivors. We determined the rate of incident cancer and effect on cardiovascular endpoints in a large cohort of ischemic stroke survivors. **Methods:** An analysis of 3,680 adults with nondisabling cerebral infarction who were followed for two years within the randomized, double-blind VISP trial was performed. The primary intervention was best medical/surgical management plus a daily supplementation of vitamin B6, vitamin B12, and folic acid. We calculated age-adjusted rates of incidence of cancer among ischemic stroke survivors and standardized incidence ratios (SIR) with 95% confidence intervals (CI) based on comparison with age-adjusted rates in the general population. The significant variables from univariate analysis were entered in a Cox Proportional Hazards analysis to identify the association between various baseline factors and incident cancer after adjusting age, gender, and race/ethnicity. A logistic regression analysis evaluated the association between incident cancer and various endpoints including stroke, coronary heart disease, myocardial infarction, and death after adjusting age, gender, and race/ethnicity. **Results:** A total of 3,247 patients (mean age $\pm$ SD of 66 ± 11 ; 2,013 were men) were cancer free at the time of enrollment. The incidence of

new cancer was 0.15, 0.80, 1.2, and 2.0 per 100 patients at 1 month, 6 months, 1 year, and 2 years, respectively. The age-adjusted annual rate of cancer in patients with ischemic stroke was higher than in persons in the general population at 1 year (581.8/100,000 persons vs. 486.5/100,000 persons, SIR 1.2, 95% CI 1.16–1.24) and 2 years (1,301.7/100,000 vs. 911.5/100,000, SIR 1.4, 95% CI 1.2–1.6) after recruitment. There was a higher risk for death (odds ratio (OR) 3.1, 95% CI 1.8–5.4), and composite endpoint of stroke, coronary heart disease, and/or death (OR 1.4, 95% CI 1.0–2.2) among participants who developed incident cancer compared with those who were cancer free after adjusting for potential confounders. **Conclusions:** The annual rate of age-adjusted cancer incidence was higher among ischemic stroke patients compared with those in the general population. The odds of mortality were three folds higher among stroke survivors who developed incident cancer.

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Introduction

Patients with stroke showed significantly higher mortality compared with the general population that was not entirely explained by stroke severity and cardiovascular deaths [1–3]. In the African American Antiplatelet Stroke Prevention Study (AAASPS) [4], vascular death comprised only half of all deaths observed in patients with non-cardioembolic ischemic stroke. The Oxfordshire Community Stroke Project [5] and Perth community

stroke study [6] found that non-cardiovascular death accounted for approximately a third of all deaths following ischemic stroke over a 5–10 year period. In the Warfarin Aspirin Symptomatic Intracranial Disease (WASID) trial [7], cancer was the most frequent cause of non-vascular death in a cohort of patients with symptomatic intracranial stenosis. The cohorts from the Oxfordshire Community Stroke Project, Lothian Stroke Register, and International Stroke Trial [8] were studied and included 7,710 patients. Of the 667 patients who died during follow-up, 251 (38%) died secondary to cancer. Other observational studies have reported a relatively high prevalence of cancer-related deaths among stroke survivors [9–11]. We performed this study to identify the risk of new cancer among stroke survivors in a well-defined cohort of ischemic stroke patients.

Methods

We analyzed the data that was collected as part of the Vitamin Intervention for Stroke Prevention (VISP) study [12, 13]. Briefly, the study was a double-masked, randomized, multicenter clinical trial that recruited patients at least 35 years old with a non-disabling ischemic stroke within 120 days, and screening plasma H(e) > the 25th percentile of benchmark population data [12, 13]. Patients with potential sources of emboli (atrial fibrillation within 30 days of stroke, prosthetic cardiac valve, intracardiac thrombus or neoplasm, or valvular vegetation) and those requiring endarterectomy, stent placement, or thrombectomy of carotid artery within 30 days prior to, or scheduled after, randomization were excluded. Patients were randomly assigned to receive once-daily doses of the high-dose formulation ($n = 1,827$), containing 25 mg of pyridoxine, 0.4 mg of cobalamin, and 2.5 mg of folic acid; or the low-dose formulation ($n = 1,853$), containing 200 μ g of pyridoxine, 6 μ g of cobalamin, and 20 μ g of folic acid. Risk factor control education and, usually, administration of aspirin, 325 mg/day, was concurrently performed. Each participant underwent baseline assessment including medical history, current medication and vitamin use, physical and neurological examination, dietary inventory, a stroke symptoms questionnaire, stroke severity determination (including the National Institutes of Health Stroke Scale (NIHSS), modified Rankin scale, and Barthel Index), the Mini-Mental State Examination, the Rose angina questionnaire, and serum plasma folate and B₁₂ levels, lipid profile, and creatinine. Cranial computed tomography (CT) or magnetic resonance imaging (MRI), and electrocardiogram (EKG) were also performed.

Participants were followed for up to 2 years after randomization by alternating between telephone contacts and in-clinic visits every 3 months. End-point determination at every contact was made by administration of the stroke symptoms questionnaire, inquiring about hospitalizations since the last contact, and occurrence of death. The 2-year visit (the exit visit) had an expanded clinical examination including CT or MRI. The local neurologist and 2 external review committee neurologists reviewed data from participants who had a follow-up assessment of likely stroke from

the stroke symptoms questionnaire; hospital discharge International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code of 433, 434, or 436; or a discharge diagnosis of stroke, cerebral infarction, or cerebrovascular accident. Coronary heart disease event end-point review occurred when the hospital discharge diagnosis included terms suggestive of MI, unstable angina, or coronary atherosclerosis or deaths with underlying cause of death related to CHD, including sudden death, or with ICD-9-CM codes 410, 411, 414.1, 429.2, 36.0, or 36.1 as the underlying cause of death on the death certificate. The site of cancer onset was not recorded in the primary database, and so we searched all relevant databases of adverse events to identify incident cancers as described previously [14].

Statistical Analysis

We did not perform sample size calculations for this secondary analysis and used all available data for this analysis. We calculated crude rates of incidence of cancer and then adjusted them for age and the standard US population based on the 2000 US census. The standard US population and age group distributions (for ages 30–89 years) were obtained from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program website. All incidence rates were expressed as the number of events per 100,000 persons. Using SEER's Cancer Query System: SEER Incidence Statistics (Accessed from: <http://seer.cancer.gov/canques/incidence.html>) interactive tool, we obtained age-adjusted incident cancer rates in the general population and calculated the standardized incidence ratios (SIR) with 95% confidence intervals (CI) for the comparison of cancer incidences between ischemic stroke patients and the general population. We performed univariate analyses using the IBM SPSS statistical software (IBM Corp., Armonk, N.Y., USA). Means and frequencies were compared using the one-way analysis of variance and the χ^2 method, respectively. The significant variables from univariate analysis were entered in a Cox Proportional Hazards analysis to identify the association between various baseline factors and incident cancer after adjusting for age, gender, and race/ethnicity. A second multivariate (logistic regression) analysis evaluated the association between incident cancer and various endpoints including stroke, coronary heart disease, and death after adjusting for age, gender, and race/ethnicity. We considered a p value <0.05 to be statistically significant.

Results

A total of 3,247 adults with non-disabling ischemic stroke were analyzed (mean age $\pm$ standard deviation (SD): 66 ± 11 years; 2,013 men). Incident cancer was detected in 133 of 3,247 participants over a 2-year period. The incidence of new cancer was 0.15, 0.80, 1.2, and 2.0 per 100 patients at 1 month, 6 months, 1 year, and 2 years, respectively. The locations of incident cancer were as follows: skin ($n = 47$) (unspecified ($n = 24$), basal cell carcinomas (15), malignant melanomas (7), squamous cell carcinoma (1)), prostate ($n = 24$), breast ($n = 8$), lungs ($n = 7$), colon ($n = 6$), bladder ($n = 5$), esophagus ($n = 4$),

Table 1. Baseline demographic and clinical characteristics and stroke-related data of ischemic stroke patients with and without incident cancer

	Patients who developed new cancer	Patients who did not develop new cancer	p value
Overall number (%)	133 (4.1)	3,114 (95.9)	
Age, years, mean $\pm$ SD	69 $\pm$ 8.9	66 $\pm$ 10.9	<0.001
Gender			
Women	37 (27.8)	1,197 (38.4)	
Men	96 (72.2)	1,917 (61.6)	0.01
Race/ethnicity			
White	117 (88)	2,435 (78.2)	
African Americans	12 (9.0)	487 (15.6)	
Others	4 (3.0)	192 (6.2)	0.03
History of			
Hypertension	101 (75.9)	2,288 (74.3)	0.5
Diabetes mellitus	35 (26.3)	915 (29.4)	0.4
Myocardial infarction	26 (19.5)	494 (15.9)	0.3
Congestive heart failure	8 (6.0)	156 (5.0)	0.01
Chronic lung disease	14 (10.5)	258 (8.3)	0.4
Current cigarette smoker	22 (16.5)	541 (17.4)	0.9
Alcohol consumption	83 (62.4)	1,801 (57.8)	0.5
Coronary angioplasty	9 (6.8)	203 (6.5)	0.9
Coronary artery bypass surgery	15 (11.3)	291 (9.3)	0.5
Carotid endarterectomy	12 (9.0)	191 (6.1)	0.2
Mini-mental state examination score, mean $\pm$ SD	26.8 $\pm$ 3.3	26.9 $\pm$ 3.4	0.8
Body mass index, kg/m ² , mean $\pm$ SD	28.0 $\pm$ 5.1	28.4 $\pm$ 5.8	0.5
Blood pressure, mm Hg, mean $\pm$ SD			
Systolic	141 $\pm$ 20	142 $\pm$ 20	0.8
Diastolic	78 $\pm$ 11	78 $\pm$ 11	0.8
Serum cholesterol level, mg/dl, mean $\pm$ SD			
Total	196.2 $\pm$ 39.3	202.8 $\pm$ 47.6	0.1
High-density lipoprotein	43.1 $\pm$ 12.8	45.4 $\pm$ 15.2	0.09
Low-density lipoprotein	124.6 $\pm$ 33.7	122.8 $\pm$ 40.9	0.4
Triglyceride level, mg/dl, mean (95% CI)	162.0 (144.9–179.1)	175.5 (169.9–181.4)	0.6
National Institutes of Health Stroke Scale Score, median (minimum, maximum)	1 (0, 18)	1 (0, 10)	0.9
Barthel index score, mean $\pm$ SD	19.4 $\pm$ 1.6	19.5 $\pm$ 1.4	0.6
Modified Rankin scale score			
0	30 (22.6)	637 (20.5)	
1	56 (42.1)	1,351 (43.4)	
2	31 (23.3)	753 (24.2)	
3	16 (12.0)	373 (12.0)	0.9
Homocysteine levels, μ mol/l, mean $\pm$ SD	13.6 $\pm$ 5.1	13.4 $\pm$ 5.0	0.6
Treatment assignment			
High dose vitamins	66 (49.7)	1,544 (49.6)	
Low dose vitamins	67 (50.3)	1,570 (50.4)	0.99
Stroke pathology			
Superficial but not deep infarct	13 (9.8)	451 (14.5)	
Deep but not superficial infarct	52 (39.1)	1,315 (42.2)	
Both superficial and deep infarct	26 (19.5)	402 (12.9)	
Abnormality other than above	1 (0.8)	25 (0.8)	
Pathology not reported	13 (9.8)	195 (6.3)	0.1

SD = Standard deviation; CI = confidence interval.

Table 2. Odds of cardiovascular endpoints and death in ischemic stroke patients with and without incident cancer

End points (follow-up 2 years)	Patients who developed new cancer	Patients who did not develop new cancer	p value	Adjusted odds ratio 95% CI	p value
Fatal/disabling stroke or death	23 (17.3)	244 (7.8)	<0.001	2.3 (1.4–3.7)	0.001
Stroke, coronary heart disease, and/or death	29 (21.8)	501 (16.1)	0.08	1.4 (1.0–2.2)	0.04
Stroke or coronary heart disease	15 (11.3)	429 (13.8)	0.4	0.8 (0.5–1.5)	0.6
Death	19 (14.3)	147 (4.7)	<0.001	3.1 (1.8–5.4)	<0.001

CI = Confidence interval.

gastric (n = 3), leukemia (n = 3), metastatic (n = 3), lymphoma (n = 2), pancreas (n = 2), liver (n = 2), bone (n = 2), glioblastoma (n = 1), meningioma (n = 1), vagina (n = 1), cervical (n = 1), gallbladder (n = 1), kidney (n = 1), ovarian/endometrial (n = 1), appendix (n = 1), and unspecified (n = 7). The age-adjusted annual rate of cancer in patients with ischemic stroke over 1 year after recruitment was 581.8/100,000 persons, which was higher than the age-adjusted cancer rate of 486.5/100,000 persons in the general population (SIR 1.2, 95% CI 1.16–1.24). The age-adjusted annual rate of cancer in patients aged less than 50 years with ischemic stroke was 462/100,000 persons, which was higher than the age-adjusted cancer rate of 382.1/100,000 persons in persons aged less than 50 years in the general population (SIR 1.2, 95% CI 1.16–1.24). The age-adjusted annual rate of cancer in patients with ischemic stroke over 2 years after recruitment was higher for all ischemic stroke patients (1,301.7/100,000 vs. 911.5/100,000, SIR 1.4, 95% CI 1.2–1.6) and those under the age of 50 years (582.3/100,000 vs. 405.4/100,000, SIR 1.4, 95% CI 1.2–1.6).

At baseline evaluation, the mean age $\pm$ SD of the participants who developed incident cancer was higher than those who did not within 2 years (68 ± 9 vs. 66 ± 11 years, $p < 0.001$, see table 1). The proportions of participants with a history of congestive heart failure (6.0 vs. 5.0%, $p = 0.01$) was higher but those with previous MI (19.5 vs. 15.9%, $p = 0.5$), or coronary artery bypass grafting (11.3 vs. 9.3%, $p = 0.5$) was similar among those who developed incident cancer. The proportion of participants who were active cigarette smokers or those who were regular alcohol consumers was not different between those who did or did not develop incident cancer. The mean $\pm$ SD body mass index at baseline was similar among participants who developed incident cancer (28.0 ± 5.1 vs. 28.4 ± 3.4 years, $p = 0.5$). There was a trend toward lower mean concentration $\pm$ SD of high density lipoproteins (43.1 ± 12.8 vs.

45.4 ± 15.2 , $p = 0.09$) among participants who developed incident cancer. There was no difference in the mean $\pm$ SD systolic or diastolic blood pressure between participants who did or did not develop incident cancer. In the multivariate analysis, a history of congestive heart failure was associated with risk of incident cancer (relative risk (RR) 1.2, 95% confidence interval (CI) 1.1–1.2; $p = 0.007$) after adjusting for age, gender, and race/ethnicity.

During the follow-up, 166 (5.1%) of 3,247 participants had died. The unadjusted 2-year survival was significantly lower in patients with incident cancer than in those without incident cancer (85 vs. 95.3%, $p < 0.001$). The cause of death among participants was cancer (n = 35), cerebrovascular (including carotid) (n = 23), cardiovascular (n = 58), gastrointestinal (n = 3), respiratory (n = 11), endocrine/metabolic (n = 2), vascular (n = 6), renal disease (n = 3), accident/trauma (n = 4), and others not specified (n = 21). A total of 429 (13.2%) patients had suffered a recurrent ischemic stroke. There was a higher risk for death (odds ratio (OR) 3.1, 95% CI 1.8–5.4), fatal/disabling stroke or death (OR 2.3, 95% CI 1.4–3.7), and composite endpoint of stroke, coronary heart disease, and/or death (OR 1.4, 95% CI 1.0–2.2) among participants who developed incident cancer compared with those who were cancer free after adjusting for potential confounders (see table 2). There was no difference in risk for stroke and/or coronary heart disease (OR 0.8, 95% CI 0.5–1.5), among participants who developed incident cancer compared with those who were cancer free after adjusting for potential confounders.

Discussion

We observed an annual rate of age-adjusted cancer incidence, which appeared to be higher among ischemic stroke patients compared with those in the general popu-

lation. The risk of mortality was three folds greater among stroke survivors who developed incident cancer. The magnitude of increased risk of cancer was similar to the slightly higher risk of incident cancer among patients with deep venous thrombosis or pulmonary embolism [15–17]. The increased rate of incident cancer among patients with deep venous thrombosis and pulmonary embolism can be as high as 50% (relative risk) within the first year of thrombotic event [17]. The highest risk of cancer is seen in patients aged less than 60 years and those with recurrent episodes of deep venous thrombosis or pulmonary embolism [15]. We did not observe a disproportionately higher risk in ischemic stroke patients aged less than 50 years. The explanation underlying the increased risk of cancer in stroke survivors in all age groups is not fully known. A relatively high prevalence of preexisting or incident cardiovascular disease and risk factors has been recognized in patients with cancer [18–21]. There may not be a cause-and-effect relationship between the two disease processes. Since ischemic stroke and cancer share some of the same risk factors, the occurrence of both these conditions in the same individual may be secondary to dual predisposition by shared risk factors such as cigarette smoking and alcohol consumption [22, 23]. Occult cancer at the time of ischemic stroke occurrence leading to a prothrombotic state is another possibility [24]. The high rate of skin cancer in stroke survivors may be related to increasing rates of melanoma seen in Asians and Hispanics, people in lower socioeconomic groups, and elderly White men, all of whom are at higher risk for ischemic stroke [25]. Several disease processes that effect anticoagulation and fibrinolytic pathways, platelet function, serum viscosity, and endothelial integrity have both dermatological and cerebrovascular manifestations [26]. There was a higher risk for death and composite endpoint of stroke, coronary heart disease, and/or death among participants who developed incident cancer compared with those who were cancer free. The death in cancer patients is attributed to cancer-specific mortality and mortality due to other causes (competing mortality) [27, 28]. Previous studies [27–29] have found almost equal proportion of cancer-specific and competing mortalities among patients with cancer with higher rates of competing mortality in persons with increasing age and men.

Most medical organizations recommend routine screening for breast, cervical, and colorectal cancers [30, 31] to reduce the number of new cancer cases, as well as the illness, disability, and death caused by cancer as specified in the Healthy People 2020 initiative [32]. Current recommendations [33] state that all men and women

aged 50 years or older undergo screening for colorectal cancer [33]. A more intense surveillance is recommended for individuals at higher risk due to family history or previous adenomatous polyps, inflammatory bowel disease, or hereditary syndromes [34]. The U.S. Preventive Services Task Force guidelines recommend mammography screening by age and biennial screening mammography for all women aged 50–74 years [35]. Mammography screening is associated with a 19% overall reduction of breast cancer mortality (approximately 15% for women in their 40s and 32% for women in their 60s) [36]. Cervical cancer screening should begin no later than 21 years of age [34, 37]. The American Cancer Society also recommends that for men and women aged ≥ 20 years, periodic health examination should include examination for cancers of the thyroid, testicles, ovaries, lymph nodes, oral cavity, and skin, and counseling about tobacco, sun exposure, diet and nutrition [34]. It remains unclear whether the stroke physician should ensure compliance with the aforementioned guidelines or initiate a more focused cancer-screening effort in stroke survivors. The benefit of a more focused and intensive cancer-screening effort in a patient with venous thromboembolism has been controversial [38] and is not cost effective [39]. Current evidence only supports the use of simple methods of screening in patients with signs and symptoms of cancer [40, 41]. Screening for skin cancer may have particular relevance to stroke survivors. Both self-assessment of risk factors or clinician examination can classify a small proportion of patients as at highest risk for melanoma [42]. However, the accuracy of routine screening by primary care providers for early detection of melanoma or non-melanoma skin cancer is not high [43].

We used the expected rate of cancer in general population to identify any incremental risk among stroke survivors, a method that has been used in previous studies [44, 45]. It should be remembered that apparent increases or decreases in cancer incidence between populations may reflect differences in diagnostic methods or case reporting rather than true changes in cancer incidence. The standardized rates are averaged across strata and may obscure unique attributes of certain strata in population. The stroke survivors were recruited in the VISP trial within 6 months of the index event, which may have excluded certain patients who developed cancer early after onset of ischemic stroke. Due to small numbers, the SIR for specific cancers could not be estimated. There may be unmeasured imbalances in population characteristics between stroke survivors and the general population that could lead to biased results in the comparisons.

Conclusions

We observed an annual rate of age-adjusted cancer incidence, which appeared to be higher among ischemic stroke patients compared with the general population. In-

cident cancer increased the risk of mortality by three folds in stroke survivors. Further research would be needed to define the subset of patients who could benefit from cancer screening and to define whether such screening can reduce the long-term mortality among stroke survivors.

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