Risk of Ischemic and Hemorrhagic Strokes in Occult and Manifest Cancers

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Background and Purpose—Manifest cancer is associated with increased risk of stroke. The risk of stroke in people with occult cancer in comparison to the risk in the background population without cancer has not been investigated. Smoking is a risk factor for both cancer and stroke, but the role of smoking for the risk of stroke in cancer has not been investigated.

Methods—We identified all incident cases of cancer in Denmark 2003 to 2012 (n=264.376) from the Danish Cancer Registry. Each person with cancer was matched by age, sex, and income with 10 randomly selected persons without cancer at index date (n=2.571.260). Linking data to the Danish Stroke Registry, we studied risk of ischemic/hemorrhagic stroke the year before (occult cancer) and after cancer diagnosis was established in the Danish Stroke Registry (manifest cancer) and stratified into the 15 most common cancer types related (lung, colon, bladder, rectum, pancreas, kidney, stomach, and head and neck cancer) and unrelated (non-Hodgkin lymphoma, breast, prostate, melanoma, central nervous system, ovary and endometrial) to smoking.

Results—Risk of ischemic/hemorrhagic stroke was increased for both occult (relative risk, 1.75/2.00) and manifest cancers (relative risk, 1.30/1.41). For occult cancer, risk of ischemic stroke was increased for all of the smoking-related cancers, but among cancers unrelated to smoking, only lymphoma, central nervous system, and endometrial cancer were associated with increased risk of stroke; breast, prostate, melanoma, and ovarian cancers were not. For occult cancer, risk of hemorrhagic stroke was generally increased for smoking-related cancers while not for cancers unrelated to smoking. For manifest cancer, risk of ischemic and hemorrhagic stroke was generally increased for cancers related to smoking while not for cancers unrelated to smoking.

Conclusions—Cancer, occult and manifest, is associated with increased risks for stroke. The increased risk is linked mainly to cancers related to smoking. **(*Stroke*. 2018;49:1585-1592. DOI: 10.1161/STROKEAHA.118.021373.)**

Key Words: cancer ■ hemorrhagic stroke ■ ischemic stroke ■ smoking

Manifest cancer is associated with an increased risk of stroke.[1,2] No studies have investigated the risk of stroke in persons with occult cancer in comparison to the risk of stroke in the background population without cancer. With the primary aim of studying the risk of stroke in occult cancer, we studied the risks for ischemic and hemorrhagic strokes in the year before (occult) and after (manifest) a diagnosis of cancer was established using information on incident cancer and stroke in Danish registries with national coverage during 2004 to 2012. Smoking is a risk factor for both cancer and stroke, but the role of smoking for the risk of stroke in cancer has not been investigated. Hence, we also stratified our analyses into cancers related and not related to smoking to elucidate whether smoking might be involved in the risk of patients with cancer for stroke.

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request. We studied the association between cancer and risk of stroke by merging data on incident cancer and stroke from Danish registries with nationwide coverage: the Danish Cancer Registry,[3,4] the Danish Stroke Registry,[5–7] the Danish National Patient Registry,[8] and Statistics Denmark.[9] All Danish residents are assigned a unique 10-digit registration number,[10] which allows unambiguous linkage among all Danish registries. We identified all incident cancers in Denmark between January 1, 2004 and July 1, 2012. For each cancer case, we randomly selected 10 population controls who had no diagnosis of cancer at the index date and were matched on sex, date of birth, income, and education. For all cases and controls, we then recorded whether and when they had a stroke, before the index date or during follow-up.

Danish Cancer Registry

We retrieved information on patients with incident cancer from the Danish Cancer Registry, which includes data on the topography, morphology, and date of diagnosis of virtually all cancers diagnosed in Danish residents. Cancer diagnoses are recorded according to the *International Classification of Diseases*, Tenth Revision.[3,4]

We used data for all cancers except nonmelanoma skin cancer and for the 15 commonest sites recorded in Denmark, that is, breast, lung, prostate, colon, melanoma, bladder, central nervous system (CNS), rectum, non-Hodgkin lymphoma, pancreas, kidney, ovary, stomach,

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endometrial, and head and neck.[4] Because cancer and stroke share smoking as an important risk factor, cancers were also grouped into those related to smoking (lung, colon, bladder rectum, pancreas, kidney, stomach, and head and neck) and those not related to smoking (non-Hodgkin lymphoma, breast, prostate, melanoma, CNS, ovary, and endometrial) according to the 2014 Surgeon General's report.[11] For group analyses, CNS cancer was not included because cancer and stroke may mimic each other, thus potentially leading to falsely overestimated risk estimates.

Danish Stroke Registry

We retrieved information on hospitalization for stroke from the Danish Stroke Registry,[5–7] which receives mandatory reports from all Danish hospitals on all patients hospitalized for acute stroke, including information on age, sex, stroke subtype, and cardiovascular profile. Stroke is defined according to the criteria of the World Health Organization.[12] Ischemic and hemorrhagic strokes are distinguished by computed tomography or magnetic resonance scanning. We included only incident hospital admissions for a first stroke (ischemic or hemorrhagic). Transient ischemic attacks, subarachnoid bleeding, and patients for whom scanning was not performed (1.1%) were not included.

The cardiovascular profile includes information on alcohol consumption (≤14/21 and >14/21 drinks per week for women and men, respectively, corresponding to under/over the limit set by the National Board of Health), smoking (never smoking versus current or ex-smoking), diabetes mellitus, atrial fibrillation (chronic or paroxysmal), arterial hypertension, previous myocardial infarction, previous stroke, and intermittent arterial claudication. In March 2012, the recommended limit for alcohol intake was lowered to 7/14 drinks per week for women/men. Diseases are diagnosed on current Danish standards.[5] The hospitalization rate for stroke according to the registry is 2.6 per 1000 per year, with high validity.[6,7] The registry now covers >89% of all admissions for stroke in Denmark.[7]

Danish National Patient Registry

The Danish National Patient Registry is a population-based administrative registry with complete nationwide coverage collecting data from all Danish hospital contacts since 1978.[8]

Statistics Denmark

Information on education and income was obtained from Statistics Denmark,[9] which is the central authority for Danish statistics. Education was grouped into basic/high school (7–12 years of primary, secondary, and grammar-school), vocational (10–12 years, including vocational training), and higher (≥13 years) education.[13] People for whom information on education was missing (14%) were included as a separate category. Disposable income was defined as income after taxation and interest per person and categorized into the 20th, 40th, 60th, and 80th percentiles of the age- and sex-specific income distribution.

Definition of Events and Time at Risk

We defined stroke before cancer diagnosis (occult cancer) as hospitalization for a first stroke within 1 year before cancer diagnosis was established in the Danish Cancer Registry for cases and within 1 year of the index date for matched controls. With this definition, all cohort members would have had 1 year at risk. In the analysis, cases and controls were compared according to the stratum of matching variables for the selection of controls, that is, age, sex, income, and education.

We defined stroke after cancer diagnosis (manifest cancer) as hospitalization for stroke within the first year after a cancer diagnosis for cases and 1 year after the index date for controls. With this definition, all cohort members contributed person–time as long as they were at risk, that is, up to 1 year. In the analysis, each case was compared with controls matched on the same cancer site, that is, with

Table 1. Descriptive Statistics of the Study Cohort, Number of Cases, and Distribution of Demographics

	Cancer Population			Background Population			
Time of Stroke	No Stroke	Stroke Before Index (Occult Cancer)	Stroke After Index (Manifest Cancer)	No Stroke	Stroke Before Index	Stroke After Index	*P* Value
n	258721	1605	1078	2496184	8691	9659	
Age							
Mean (SD)	66.60 (13.55)	72.47 (10.96)	72.95 (10.82)	66.49 (13.43)	75.28 (9.66)	75.55 (9.76)	<0.001
Sex							
Female	129829 (50.2)	678 (42.2)	472 (43.8)	1260993 (50.5)	3469 (39.9)	4008 (41.5)	<0.001
Disposable income*							
<20	50542 (18.6)	348 (21.2)	198 (17.8)	465072 (18.6)	1665 (19.2)	1922 (19.9)	
20–40	52178 (20.4)	321 (20.1)	256 (23.9)	507490 (20.3)	1940 (22.3)	2114 (21.9)	
40–60	51703 (20.2)	371 (23.3)	233 (21.8)	504531 (20.2)	1802 (20.7)	2043 (21.2)	
60–80	51809 (20.3)	304 (19.1)	184 (17.2)	506743 (20.3)	1746 (20.1)	1908 (19.8)	
>80	52460 (20.5)	261 (16.4)	207 (19.3)	512348 (20.5)	1538 (17.7)	1672 (17.3)	
Education							<0.001
Basic/voc	193453 (75.7)	1279 (80.1)	844 (78.8)	1914778 (76.7)	6785 (80.0)	7524 (77.9)	
Higher	46388 (18.1)	190 (11.9)	130 (12.1)	449761 (18.0)	948 (10.9)	995 (10.3)	
Unknown	18880 (6.2)	136 (8.0)	104 (9.1)	131645 (5.3)	958 (11.0)	1140 (11.8)	
Stroke type							<0.001
Hemorrhage	…	112 (7.0)	94 (8.7)	…	524 (6.0)	842 (8.7)	
Infarct	…	1493 (93.0)	984 (91.3)	…	8167 (94.0)	8817 (91.3)	

*Income groups corresponds to <20: <20th income percentile, 20–40: between 20th and 40th income percentile, 40–60: between 40th and 60th income percentile, 60–80: between 60th and 80th income percentile, >80: above 80th income percentile. All percentiles are age and sex specific.

Table 2. Distribution Risk Factors in Patients With Stroke Stratified by Cancers Related and Not Related to Smoking

Variable	Level	Cancer Related to Smoking		Cancer Not Related to Smoking		*P* Value
		n	%	n	%	
Sex	Female	482	39.8	396	41.9	0.344
	Male	728	60.2	548	58.1	0.344
Income*	<20	341	28.1	271	28.6	<0.001
	20–40	425	35.2	248	26.3	<0.001
	40–60	187	15.5	146	15.5	<0.001
	60–80	139	11.5	128	13.6	<0.001
	>80	116	9.6	151	16.0	<0.001
Education	Basic/voc	984	81.6	720	76.4	0.012
	Higher	133	11.0	138	14.7	0.012
	Unknown	91	7.4	84	8.9	0.012
Alcohol	Under	932	77.0	766	81.1	0.017
	Over	104	8.6	53	5.6	0.017
	Unknown	174	14.4	125	13.3	0.017
Smoking†	Never	242	20.0	315	33.4	<0.001
	Smoker/ex	783	64.7	466	49.3	<0.001
	Unknown	185	15.3	163	17.3	<0.001
Diabetes mellitus	Yes	161	13.3	111	11.8	0.562
	No	1012	83.6	804	85.2	0.562
	Unknown	37	3.1	29	3.0	0.562
Atrial fibrillation	Yes	206	17.0	150	15.9	0.503
	No	965	79.8	756	80.1	0.503
	Unknown	39	3.2	38	4.0	0.503
Previous myocardial infarct	Yes	96	7.9	83	8.8	0.017
	No	1043	86.2	830	87.9	0.017
	Unknown	71	5.9	31	3.3	0.017
Hypertension	Yes	537	44.4	442	46.8	0.440
	No	607	50.2	458	48.5	0.440
	Unknown	66	5.5	44	4.7	0.440
Intermittent arterial claudication	Yes	37	3.1	17	1.8	0.161
	No	870	71.9	696	73.7	0.161
	Unknown	303	25.0	231	24.5	0.161
Stroke type	Hemorrhage	78	6.4	92	9.7	0.006
	Ischemic	1132	93.6	852	90.3	0.006
		Mean	Range	Mean	Range	
Age		72.9	35–96	72.7	27–97	0.70

*Income groups corresponds to <20: <20th income percentile, 20–40: between 20th and 40th income percentile, 40–60: between 40th and 60th income percentile, 60–80: between 60th and 80th income percentile, >80: above 80th income percentile. All percentiles are age and sex specific.

†Smoker/ex: ever smoker.

the same matching variables for the selection of controls. People who died or emigrated during the first year were censored. Strokes registered on the same day as cancer were considered as strokes in occult cancer.

The study protocol was approved by the board of the Danish Stroke Registry and the Danish Data Protection Agency (journal number 2012-41-0719).

Statistical Methods

Descriptive statistics were reported as means and proportions stratified by cancer status. All risk estimates were presented on a relative scale in comparison to the cancer-free background population, matched on age, sex, disposable income, and education, and furthermore adjusted for calendar year. We investigated the association between occult cancer

and risk of stroke by conditional logistic regression, with strata defined according to each unique combination of the matching variables. Analyses were run for all cancers and for each of the 15 major cancer sites separately. The risk of stroke after a cancer diagnosis was studied prospectively in survival analysis models in terms of Cox proportional hazard models. We censored for the competing event of death, as well as administrative censoring because of end of follow-up or emigration. We present hazard ratios within the 1 year after cancer to compare stroke risk between cancer sites. Departure from proportional hazards after cancer diagnosis was evaluated graphically. All estimates were obtained with control for age at cancer diagnosis (or index date for controls) and birth year. Odds ratio for occult cancer and average hazard ratios for manifest cancer were used as relative risks (RR) for the association between cancer and stroke. The risk estimates are presented with 95% confidence intervals, the reference being people of the same age, sex, and socioeconomic status without a previous cancer diagnosis. In a sensitivity analysis of stroke after cancer, we furthermore adjusted for comorbidities extracted from the Danish Registry of Patients,[8] for both cancer patients and controls. These included myocardial infarction, congestive heart disease, peripheral vascular disease, renal disease, chronic pulmonary disease, diabetes mellitus, hypertension, and atrial fibrillation calculated by date of cancer diagnosis. Standard model control was applied to verify the fit of the applied models. We examined the linearity of continuous variables (age at diagnosis and calendar year) by comparing nested models with continuous terms included as higher-order orthogonal polynomials. Analyses were conducted at a server at Statistics Denmark, with id-based encryption. We used the statistical software R with packages for statistical analysis.[14]

Results

During the inclusion period, 261 404 patients were registered with incident cancer; of these, 2683 (1.02%) were also registered as having been hospitalized for a first stroke. The control group, matched 1:10 by age, sex, income, and education and who were free of cancer on the index date, comprised 2 514 534 people, of whom 18 350 (0.71%) had a first stroke during the study period. Descriptive statistics on the demographics of the cancer patients and controls are shown in Table 1.

Table 2 shows characteristics of stroke in patients with smoking-related cancers and cancers unrelated to smoking. Stroke patients with smoking-related cancers were more often smokers (ex- or current) and consumers of alcohol over the recommended limit, and they had more often low income and short length of education.

Stroke Rate

The Figure shows rate of stroke (all stroke, hemorrhagic, and ischemic strokes collapsed) in patients with cancer in the years before and after diagnosis with the rate of control persons in the background population for comparison. Rate of stroke was increased compared with controls in the first year before (occult cancer) and after (manifest cancer) diagnosis peaking around the date of cancer diagnosis where rate of stroke had tripled in cancer patients compared with controls.

Stroke Risk

Occult Cancer

Ischemic Stroke

The overall risk of ischemic stroke in the year before cancer was diagnosed was increased by RR 1.75 (confidence interval [CI], 1.65–1.85; Table 3). The overall risk of people with the 8 most common smoking-related cancers (lung, colon, bladder, rectum, pancreas, kidney, stomach, and head and neck) for ischemic stroke was increased by RR 1.68 (CI, 1.55–1.83) and that of people with 6 cancers not related to smoking (non-Hodgkin lymphoma, breast, prostate, melanoma, ovary, and endometrial) was increased by RR 1.18 (CI, 1.05–1.32). Of these, the risks were increased only for those with occult non-Hodgkin lymphoma or endometrial cancer; patients with occult cancer of the breast, prostate, or ovary or with melanoma were not at increased risk of ischemic stroke (Table 3). Risk of ischemic stroke in occult CNS cancer turned out to be RR 10.62 (CI, 8.43–13.39).

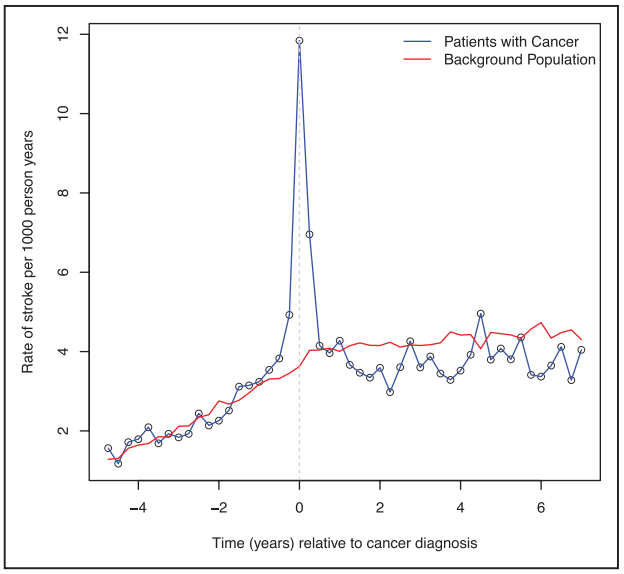

Figure. Risk of stroke in patients with cancer before and after cancer diagnosis was established in comparison to that of the background population without cancer.

Hemorrhagic Stroke

The overall risk of hemorrhagic stroke is presented in Table 4. In the year before cancer was diagnosed, the risk of hemorrhagic stroke was increased by RR 2.00 (CI, 1.63–2.45). The overall risk of people with 1 of the 8 most common smoking-related cancers was increased by RR 1.42 (CI, 1.00–2.03) while that of patients with 1 of 6 cancers unrelated to smoking was not increased 1.27 (CI, 0.82–1.97). The risk of hemorrhagic stroke in occult CNS cancer turned out to be RR 21.1 (CI, 11.2–39.9). For the 8 smoking-related occult cancers and the occult cancers not related to smoking, risk of stroke was increased only for kidney cancer RR 6.86 (CI, 2.17–21.64).

Smoking status for stroke in occult cancer (hemorrhagic and ischemic strokes collapsed) is shown in Table 5. For occult cancer related to smoking, the relationship between strokes associated and not associated with smoking (ex or current) was 3.3:1. For occult cancer not related to smoking, the relationship was 1.4:1. Dividing smokers into current smokers and ex-smokers, there was no significant difference in the distribution of stroke associated with current smoking and ex-smoking.

Manifest Cancer

Ischemic Stroke

The overall risk of ischemic stroke in the year after cancer was diagnosed was increased by RR 1.30 (CI, 1.23–1.38; Table 3) and by RR 1.67 (CI, 1.51–1.83) for the 8 commonest

Table 3. Risk of Ischemic Stroke in Occult and Manifest Cancers Compared With the Background Population

	Relative Risk of Stroke 1 y Before Cancer Diagnosis Compared With Background Population*			Relative Risk of Stroke 1 y After Cancer Diagnosis Compared With Background Population†		
Cancer Site	RR	Low 95%	Upper 95%	RR	Low 95%	Upper 95%
Bladder	1.39	1.1	1.76	1.4	1.14	1.72
Colon	1.52	1.27	1.83	1.31	1.09	1.56
Head and neck	1.87	1.29	2.7	0.82	0.51	1.32
Kidney	2.42	1.67	3.51	1.43	0.95	2.15
Lung	1.94	1.68	2.23	1.95	1.67	2.28
Pancreas	1.78	1.3	2.42	2.99	2.13	4.19
Rectum	1.36	1.02	1.8	1.29	1.01	1.65
Stomach	1.58	1.06	2.36	1.25	0.76	2.04
Smoking‡	1.68	1.55	1.83	1.67	1.51	1.83
Breast	1.12	0.9	1.4	1.15	0.96	1.37
Endometrial	1.73	1.14	2.63	0.93	0.58	1.47
Melanoma	0.99	0.67	1.46	1.02	0.73	1.41
Non-Hodgkin	1.99	1.45	2.72	0.77	0.51	1.17
Ovarian	1.53	0.87	2.7	0.87	0.46	1.66
Prostate	1.09	0.92	1.28	1.14	0.99	1.30
Nonsmoking§	1.18	1.05	1.32	1.10	0.98	1.24
CNS	10.62	8.43	13.39	1.4	0.85	2.3
All cancer‖	1.75	1.65	1.85	1.3	1.23	1.38

CNS indicates central nervous system; and RR, relative risk.

*Relative risk presented by means of odds ratio obtained from conditional logistic regression matched to the background population on age, sex, disposable income, and education.

†Relative risk presented by means of hazard ratio obtained from Cox proportional regression adjusted for age, sex, disposable income, and education. Sex-specific cancers are not adjusted for sex.

‡Estimate includes all smoking-related cancers listed above: bladder, colon, head and neck, kidney, lung, pancreas, rectum, and stomach.

§Estimate includes all nonsmoking-related cancers (except CNS) listed above: breast, endometrial, melanoma, non-Hodgkin, ovarian, and prostate.

‖Estimate includes all cancers recorded in the Danish Cancer Registry, excluding nonmelanoma skin cancer.

smoking-related cancers. The overall risk of ischemic stroke of patients with one of cancers unrelated to smoking was not increased (RR, 1.10; CI, 0.98–1.24), and the risk of ischemic stroke was increased for patients with only 5 of the 15 cancers, all of which were associated with smoking (lung, colon, bladder, rectum, and pancreas).

Hemorrhagic Stroke

The overall risk of hemorrhagic stroke in the year after cancer was diagnosed was increased by RR 1.41 (CI, 1.14–1.75; Table 4). Risk was increased only for patients with smoking-related cancers RR 1.50 (CI, 1.08–2.07) and significantly only for lung cancer. The risk of patients with cancers unrelated to smoking was not increased RR 1.23 (CI, 0.87–1.76).

Smoking status for stroke in manifest cancer (hemorrhagic and ischemic strokes collapsed) is shown in Table 5. For manifest cancer related to smoking, the relationship between strokes associated and not associated with smoking (ex or current) was 3:1. For manifest cancer not related to smoking, the relationship was 1.6:1. Dividing smokers into current smokers and ex-smokers, there was no significant difference in the distribution of stroke associated with current smoking and ex-smoking.

Discussion

Both occult and manifest cancers were associated with increased risks for stroke. The increased risk was linked mainly to smoking-related cancers.

In the year before cancer was diagnosed, people with occult cancer had almost twice the risk of ischemic and hemorrhagic strokes than the background population, and the increased risk was associated with any of the 8 commonest smoking-related cancers (lung, colon, bladder, rectum, pancreas, kidney, stomach, and head and neck). Among persons with 1 of 6 cancers unrelated to smoking (non-Hodgkin lymphoma, breast, prostate, melanoma, ovary, and endometrial), those with the 3 commonest cancers (breast, prostate, and melanoma) were not at increased risk of stroke. Patients with manifest cancer also had increased risks for ischemic and hemorrhagic strokes, and again the increased risk was linked mainly to smoking-related cancers.

Table 4. Risk of Hemorrhagic Stroke in Occult and Manifest Cancer Compared With the Background Population

	Relative Risk of Stroke 1 y Before Cancer Diagnosis Compared With Background Population*			Relative Risk of Stroke 1 y After Cancer Diagnosis Compared With Background Population†		
Cancer Site	RR	Low 95%	Upper 95%	RR	Low 95%	Upper 95%
Bladder	0.89	0.27	2.90	1.22	0.48	3.08
Colon	1.33	0.63	2.79	1.47	0.81	2.68
Head and neck	1.49	0.33	6.62	1.88	0.42	8.44
Kidney	6.86	2.17	21.64	2.81	0.94	8.37
Lung	1.31	0.72	2.41	1.99	1.09	3.63
Pancreas	1.22	0.28	5.33	2.45	0.73	8.20
Rectum	1.63	0.48	5.56	1.23	0.44	3.47
Stomach	2.34	0.26	21.03	…	…	…
Smoking‡	1.42	1.00	2.03	1.50	1.08	2.07
Breast	1.64	0.73	3.65	0.91	0.41	1.96
Endometrial	0.66	0.08	5.00	…	…	…
Melanoma	1.27	0.38	4.23	1.45	0.61	3.43
Non-Hodgkin	1.29	0.29	5.67	1.01	0.23	4.30
Ovarian	…	…	…	…	…	…
Prostate	1.24	0.66	2.34	1.47	0.92	2.36
Nonsmoking§	1.27	0.82	1.97	1.23	0.87	1.76
CNS	21.1	11.2	39.9	2.48	0.54	11.28
All cancer‖	2.00	1.63	2.45	1.41	1.14	1.75

CNS indicates central nervous system; and RR, relative risk.

*Relative risk presented by means of odds ratio obtained from conditional logistic regression matched to the background population on age, sex, disposable income, and education.

†Relative risk presented by means of hazard ratio obtained from Cox proportional regression adjusted for age, sex, disposable income, and education. Sex-specific cancers are not adjusted for sex.

‡Estimate includes all smoking-related cancers listed above: bladder, colon, head and neck, kidney, lung, pancreas, rectum, and stomach.

§Estimate includes all nonsmoking-related cancers (except CNS) listed above: breast, endometrial, melanoma, non-Hodgkin, ovarian, and prostate.

‖Estimate includes all cancers recorded in the Danish Cancer Registry, excluding nonmelanoma skin cancer.

Among occult cancers, CNS cancer held a unique place as the risk of ischemic stroke was increased 11× and that for hemorrhagic stroke 21×. This finding is hardly a true expression of a highly increased risk of stroke in occult CNS cancer. It is rather a likely expression of CNS cancer and stroke mimicking each other, hence leading to misdiagnosis and consequently overestimation of stroke risk. In support of this explanation, there was no increased risk when CNS cancer had become manifest. Hence, we excluded CNS cancer from group analyses in this study.

Higher risks for stroke have been reported in patients with a variety of manifest cancers.[1,2,15–19] In a recent study of patients with breast, colorectal, lung, or prostate cancer in the United States, the 1-year cumulative incidence of ischemic/hemorrhagic stroke was increased by 1.3/1.6 in those with colorectal cancer and 1.8/3.4 in those with lung cancer but not in those with breast or prostate cancer,[2] as in our study. In a study of patients with cancers at 34 sites in the Swedish Registry of Cancers, the risks for ischemic/hemorrhagic stroke within 6 months of cancer diagnosis were increased by 1.6/2.2 for 18/20 cancer sites.[1] In contrast to our study, the Swedish study found an increased risk of stroke also among people with cancers unrelated to smoking, including breast, prostate, and melanoma (RR, 1.2–1.5). Another Swedish study on manifest breast cancer, with 5.7 years of follow-up, found a slightly increased risk of ischemic stroke (RR, 1.12) but not for hemorrhagic stroke.[17]

Focus has been on the interaction between cancer and the clotting cascade in the search for an explanation for cancer patient's increased risk of stroke; the literature contains ample evidence of this interaction.[20,21] Our study was not designed to investigate causes of stroke in cancer, but our findings nevertheless point in the direction of possible causal relationships. For occult cancer, the risk of stroke increased as the time of diagnosis approached; for manifest cancer, it declined over time after diagnosis as was also the case with other studies on manifest cancer.[1,2] This might reflect an effect of tumor load on the risk of stroke. However, our study may also give rise to suspect that smoking may contribute to the increased risk of stroke of cancer patients. Overall, the risk of stroke was

Table 5. Stroke in Occult and Manifest Cancers Stratified According Smoking Status

Occult Cancer	Stroke (All Stroke)			
	Associated With Smoking	Not Associated With Smoking	Smoking Status Unknown	
Cancer related to smoking	437 (67.2%)	134 (20.6%)	79 (12.2%)	*P*<0.01
Cancer not related to smoking	169 (50.1%)	123 (36.5%)	45 (13.4%)	*P*<0.01
Manifest cancer				
Cancer related to smoking	313 (60.0%)	104 (20.0%)	104 (20.0%)	*P*<0.01
Cancer not related to smoking	177 (48.9%)	109 (30.1%)	76 (21.0%)	*P*<0.01

P value is for comparison of smoking distribution in patients with stroke by cancer related and not related to smoking.

significantly greater for smoking-related cancers than for cancers unrelated to smoking. Although the increased risk was present for all smoking-related cancers, no increased risk was associated with the 3 most frequently occurring nonsmoking-related cancers, that is, breast and prostate cancers and melanoma. In addition, for smoking-related cancer, stroke associated with smoking occurred 3× more often than stroke not associated with smoking, far more often than in nonsmoking-related cancer. It is not possible to quantify extent to which smoking may contribute to cancer patients' increased risk of stroke, but it might be of significance, and our findings call for further investigation.

A major strength of this study was the large data set and the population-based design, with information on incident cancer and stroke from high-quality Danish registries with almost complete nationwide coverage. Moreover, the cohort of controls represented the Danish background population. The weaknesses include the fact that the cancer and control groups were matched only for age, sex, income, and education and not for other stroke risk factors. For the statistical analysis of risk of stroke in manifest cancer, we were nevertheless able to account for diseases extracted from the Danish Registry of Patients, for both cancer patients and controls.[8] These included important risk factors, such as myocardial infarction, congestive heart disease, peripheral vascular disease, renal disease, chronic pulmonary disease, diabetes mellitus, hypertension, and atrial fibrillation.[8] The results of analyses with and without inclusion of these comorbidities did not differ significantly (data not shown). Smoking and alcohol were not included among the risk factors; however, separate analyses for cancers related and not related to smoking indicated a contribution of smoking to the increased risk of cancer patients for stroke. Light-to-moderate alcohol consumption is associated with a reduced risk of stroke, whereas heavier alcohol consumption increases the risk.[22] We adjusted for income and educational status, which to some degree are proxies for lifestyle factors, such as smoking and alcohol consumption.[13,23] Data on smoking habits of patients with stroke were obtained from the Danish Stroke Registry. These data are based solely on information from patients/relatives. They are not subject to further formal control for validity and should be interpreted cautiously in this light. We had no information on cancer treatment that might have influenced the subsequent risk of stroke; however, the marked reduction in the risk of stroke observed in some cancer types when cancer became manifest indicates an effect of treatment on stroke risk. As cancer patients who die cannot have a subsequent stroke, our estimates of the risk of stroke may be somewhat underestimated.

Conclusions

Occult and manifest cancers are both associated with increased risks for ischemic and hemorrhagic strokes. In addition to tumor-related effects on the risk of stroke, our study points to smoking as a contributing factor for the excess risk of stroke in cancer.

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Disclosures

None.

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