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SHORT REPORT

Non-Traumatic Subdural Hematoma and Cancer: A Cohort Study

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Introduction: Cancer may increase the risk of bleeding. However, whether subdural hematoma is a marker of occult cancer remains unknown. We examined the association between non-traumatic subdural hematoma and cancer risk in a cohort study.

Materials and Methods: Using Danish nationwide health registries, we identified 2713 patients with non-traumatic subdural hematoma and no previous cancer diagnosis, who were hospitalized between April 1, 1996 and December 31, 2019. We computed age-, sex-, and calendar year-standardized incidence ratios (SIRs) as the ratio of the observed to expected number of patients with cancer by using national incidence rates as reference as a measure of relative risk.

Results: We identified 77 cancer cases within the first year of follow-up and 272 cancer cases thereafter. The one-year risk of cancer was 2.8% (95% confidence interval: 2.2–3.5), and the one-year SIR was 1.7 (95% confidence interval: 1.3–2.1). During the subsequent years, the SIR was 1.0 (95% confidence interval: 0.9–1.1). The relative risk was elevated for some hematological and liver cancers.

Conclusion: The risk of a new cancer diagnosis was clearly increased in patients with non-traumatic subdural hematoma compared with the general population during the first year of follow-up. However, the absolute risk was low, thus limiting the clinical relevance of pursuing early cancer detection in these patients.

Keywords: cancer, cohort study, epidemiology, non-traumatic subdural hematoma, population-based

Introduction

The association between cancer and coagulopathy is well established, because tumor cells may induce a hypercoagulable state that leads to clotting as well as vessel injury.[1] Thus, patients with cancer have an elevated risk of both thrombotic and hemorrhagic events.[2–4] Hence, bleeding and venous thromboembolism may be the first symptoms of an occult malignancy.[5–9] Trauma is the most common cause of subdural hematoma, while the etiologies of non-traumatic or spontaneous subdural hematoma include coagulopathy, vascular lesions, and arachnoid cysts[10,11] Due to coagulopathy and intratumoral hemorrhage, patients with cancer may present with non-traumatic subdural hematoma more frequently than the general population.[12,13]

Existing research on non-traumatic subdural hematoma as a presenting symptom of occult cancer is scarce, and it is unclear whether, and to what extent, non-traumatic subdural hematoma may be the precursor of some types of recessive cancer. We therefore conducted a nationwide cohort study to examine the risk of a cancer diagnosis in patients with non-traumatic subdural hematoma.

Methods

Denmark has a tax-supported health care system that grants free and equal access to hospitals for its approximately 5.8 million residents.[14] We used the Danish National Patient Registry (DNPR) and the Danish Cancer Registry to conduct this population-based cohort study in Denmark. Data for every individual are linked via the unique 10-digit civil

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registration number given to each Danish resident by the Central Registry System.[15] The civil registration number is issued at birth or upon immigration and is linked to each individual until death or emigration.[16]

The DNPR covers all Danish hospitals since 1977.[17] The Danish Cancer Registry has recorded any incident malignant neoplasms in the Danish population since 1943.[18]

We used diagnosis codes according to the 8th revision of the International Classification of Diseases (ICD) until 1993 and the 10th revision of ICD from 1994 onwards,[17] except for cancer codes, all of which were converted into the 10th revision of ICD. We then categorized the different types of cancer by using the classification according to the Danish Health Data Authority.[18]

Through the DNPR, we identified all patients with a first-time hospital-based diagnosis of non-traumatic subdural hematoma from April 1, 1996, to December 31, 2019. Patients who had a cancer diagnosis before the non-traumatic subdural hematoma were excluded from the analysis (n=537). We used the DNPR to acquire data on the date of diagnosis of non-traumatic subdural hematoma and comorbidity at the time of diagnosis.

Each patient was characterized by sex, age, year of non-traumatic subdural hematoma diagnosis, comorbidity, and whether they were treated in inpatient, outpatient hospital clinic, or emergency department settings.

We followed all patients with non-traumatic subdural hematoma from the diagnosis date until the first occurrence of any cancer, death, emigration, or the end of study on December 31, 2019. Because early detection might represent occult cancer, we divided the follow-up period into two subgroups: (1) The first year of follow-up after the non-traumatic subdural hematoma diagnosis and (2) the years thereafter. As a measure of absolute risk of cancer for patients with non-traumatic subdural hematoma, we calculated the cumulative incidence and 95% confidence interval (CI) for each subgroup of cancer, treating death as a competing risk. Based on the assumption that cancers diagnosed within the first year were present at the time of the non-traumatic subdural hematoma, by calculating the reciprocal excess risk, we computed the number of patients who would need to be examined for cancer at the time of diagnosis to identify one excess cancer case.

As a measure of relative risk, age-, sex-, and calendar year-standardized incidence ratios (SIRs) with 95% CI were computed comparing number of cancer cases among patients with non-traumatic subdural hematoma with the expected number of cases, according to national cancer incidence rates.[18] As with the cumulative incidences, we calculated the SIRs for the first year of follow-up and the subsequent years separately. In addition, we calculated SIRs for the first three months and the subsequent months in a sensitivity analysis to investigate the impact of the one-year cut-off on our results. We stratified our analyses by sex, age, and year of non-traumatic subdural hematoma diagnosis, cancer type, and the hospital department to which the patients were admitted.

Results

We identified 2713 patients with an inpatient (84.3%), outpatient hospital clinic, or emergency department diagnosis of non-traumatic subdural hematoma. In total, 1260 (46.4%) of patients underwent surgical treatment within 30 days after the diagnosis of non-traumatic subdural hematoma. The majority were men (60.7%), and the median age was 71.2 years (interquartile range: 58.9–80.7 years) at the time of diagnosis. The median follow-up time was 3.6 years (interquartile range: 0.2–8.6 years).

Seventy-seven patients with non-traumatic subdural hematoma were diagnosed with cancer within the first year of follow-up, corresponding to an absolute risk of any cancer within the first year of 2.8% (95% CI 2.2–3.5) (Table 1). Thirty-one excess cancer cases were detected during the first year, thus indicating that 63 patients with non-traumatic subdural hematoma would need to be examined to detect one excess cancer case. The SIR within the first year was 1.7 (95% CI 1.3–2.1). The relative risk for male patients (SIR = 1.6 [95% CI 1.2–2.1]) was slightly lower than that for female patients (SIR = 1.9 [95% CI 1.2–2.8]). Patients with hematoma before the age of 60 had a higher relative risk than patients in older age groups. We found strong associations with lung cancer (SIR = 1.6 [95% CI 0.6–3.2]), meningeal cancer (SIR = 25.8 [95% CI 10.4–53.2]), non-Hodgkin lymphoma (SIR = 4.7 [95% CI 1.9–9.8]), and myeloid leukemia (SIR = 16.3 [95% CI 5.3–37.9]) among patients with non-traumatic subdural hematoma during the first year of follow-up. The SIR within the first three months was 3.3 (95% CI 2.3–4.4).

Table 1 Absolute Risks and Standardized Incidence Ratios of Site-Specific Cancers During the First Year of Follow-Up Among Patients with Non-Traumatic Subdural Hematoma, Denmark, 1996–2019. Only Sites with Five or More Recorded Cancer Cases are Presented

	Observed (n)	Expected (n)	Risk % (95% CI)	SIR (95% CI)
Overall	77	45.3	2.8 (2.2–3.5)	1.7 (1.3–2.1)
Lungs, bronchi, and trachea	7	4.5	0.3 (0.1–0.5)	1.6 (0.6–3.2)
Prostate	5	6.2	0.2 (0.1–0.4)	0.8 (0.3–1.9)
Membranes of the brain and spinal meninx	7	0.3	0.3 (0.1–0.5)	25.8 (10.4–53.2)
Non-Hodgkin malignant lymphoma	7	1.5	0.3 (0.1–0.5)	4.7 (1.9–9.8)
Myeloid leukemia	5	0.3	0.2 (0.1–0.4)	16.3 (5.3–37.9)
Basal cell skin carcinoma	11	9.7	0.4 (0.2–0.7)	1.1 (0.6–2.0)
Other skin cancers (excluding basal cell skin carcinoma)	5	2.6	0.2 (0.1–0.4)	1.9 (0.6–4.4)
All other cancers	30	20.3	1.1 (0.8–1.6)	1.5 (1.0–2.1)

Abbreviations: CI, confidence interval; SIR, standardized incidence ratio.

In the subsequent years of follow-up, 272 patients with hematoma were diagnosed with cancer, corresponding to an absolute risk of 27.8% (95% CI 19.1–37.2) (Table 2). The SIR for cancer in the following years was 1.0 (95% CI 0.9–1.1). The relative risk was similar for males (SIR = 0.9 [95% CI 0.8–1.1]) and females (SIR = 1.1 [95% CI 0.9–1.3]). We

Table 2 Absolute Risks and Standardized Incidence Ratios of Site-Specific Cancers During Subsequent Years of Follow-Up Among Patients with Non-Traumatic Subdural Hematoma, Denmark, 1996–2019. Only Sites with Five or More Recorded Cancer Cases are Presented. The Median Follow-Up Time Was 3.6 Years (Interquartile Range: 0.2–8.6 Years)

	Observed (n)	Expected (n)	Risk % (95% CI)	SIR (95% CI)
Overall	272	283.9	27.8 (19.1–37.2)	1.0 (0.9–1.1)
Colorectal	29	30.1	2.3 (1.4–3.5)	1.0 (0.6–1.4)
Liver	6	2.6	0.5 (0.2–1.0)	2.3 (0.9–5.0)
Pancreas	7	5.9	0.5 (0.2–1.0)	1.2 (0.5–2.4)
Lungs, bronchi, and trachea	29	26.6	6.3 (1.1–18.5)	1.1 (0.7–1.6)
Malignant melanoma	8	7.6	0.6 (0.3–1.1)	1.0 (0.5–2.1)
Other skin cancers (excluding basal cell skin carcinoma)	16	18.3	1.8 (0.7–3.6)	0.9 (0.5–1.4)
Basal cell skin carcinoma	57	64.9	4.6 (2.9–6.8)	0.9 (0.7–1.1)
Breast	13	16.0	1.4 (0.6–2.6)	0.8 (0.4–1.4)
Prostate	32	36.9	2.4 (1.6–3.4)	0.9 (0.6–1.2)
Urinary bladder	11	15.3	0.8 (0.4–1.4)	0.7 (0.4–1.3)
Brain	7	3.6	0.5 (0.2–1.0)	1.9 (0.8–4.0)
Non-Hodgkin malignant lymphoma	12	9.6	1.1 (0.5–2.0)	1.3 (0.7–2.2)
Lymphoid leukemia	6	3.3	0.4 (0.2–0.8)	1.8 (0.7–4.0)
Metastases and non-specified cancer in lymph nodes	10	4.5	1.9 (0.5–5.1)	2.2 (1.1–4.1)
All other cancers	29	38.7	3.0 (1.8–4.6)	0.7 (0.5–1.1)

Abbreviations: CI, confidence interval; SIR, standardized incidence ratio.

found an elevated relative risk of liver cancer (SIR = 2.3 [95% CI 0.9–5.0]), brain cancer (SIR = 1.9 [95% CI 0.8–4.0]), non-Hodgkin malignant lymphoma (SIR = 1.3 [95% CI 0.7–2.2]), lymphoid leukemia (SIR = 1.8 [95% CI 0.7–4.0]), and non-specified cancer in lymph nodes (SIR = 2.2 [95% CI 1.1–4.1]) in the subsequent years of follow-up.

Discussion

In this Danish cohort study, we found a dichotomous pattern of risk with time. The absolute risk of any cancer was 2.8% within the first year of follow-up after a non-traumatic subdural hematoma. This percentage corresponds to a 1.7-fold increased relative risk of any cancer during the same period, compared with that in the general population. We observed no overall association between non-traumatic subdural hematoma and cancer risk in the following years of follow-up, but we did observe an elevated risk of certain cancers, notably liver cancer.

Non-traumatic subdural hematoma might be associated with cancer diagnoses for several reasons. Heightened diagnostic efforts and the physiological effects of occult cancer probably explain the association during the first three months and one year of follow-up. The early periods of increased cancer diagnosis were not followed by a potential compensatory deficit pattern in cancer risk; consequently, a diagnostic bias is not likely. The elevated long-term risk of liver cancer after the first year of follow-up suggests that non-traumatic subdural hematoma and cancer might share risk factors such as alcohol use. The site-specific relative risks indicated associations among non-traumatic subdural hematoma, hematological cancers, and brain cancer, probably because coagulation disturbances and potential tumor growth in the bloodstream may occur with cancers in the brain and meninges.

Although a strength of our study is that the cohort was population-based and had virtually no losses to long-term follow-up, our data lack clinical details, particularly regarding shared risk factors for non-traumatic subdural hematoma and cancer, except for age, sex, and comorbidities. Moreover, our risk estimates are somewhat imprecise. Cancer diagnoses in the Danish Cancer Registry are of high quality.[18] The recorded non-traumatic subdural hematoma diagnoses might, in some cases, have been misclassified. If non-differential, such misclassification would tend to underestimate the strength of the associations.

In conclusion, our data indicated an increased risk of cancer within the first year after a diagnosis of non-traumatic subdural hematoma. However, the absolute risk during the first year of follow-up was low, which refrained us from recommending cancer detection guidelines for the clinical care of patients with non-traumatic subdural hematoma.

Ethics Approval and Informed Consent

This study was conducted in accordance with the Declaration of Helsinki. The study was approved by the National Board of Health and by the Danish Data Protection Agency. According to Danish law, approval from the Danish Committee on Health Research Ethics was not necessary. Since this is a register-based study, written consent was not required.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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