SHORT REPORT

Epilepsy as a risk factor for cancer

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Aim: Epilepsy and long term use of antiepileptic drugs have been suggested to be associated with an increased risk of cancer. The authors therefore set out to analyse previous diagnosis of epilepsy as a risk factor for certain cancer forms in a case control study.

Methods: Incident cases of leukaemia, lymphoma, myeloma, and pancreatic cancer were identified from the Swedish Cancer Registry 1987–99, a total of 52 861 cases. Controls (n = 137 485) were randomly selected from the Swedish Population Registry stratified on age, sex, and year of cancer diagnosis. Cases and controls were linked to the Swedish Hospital Discharge Registry for 1969–99 to identify individuals with first time hospital discharge for epilepsy.

Results: While an epilepsy diagnosis the same year as a cancer diagnosis carried an increased risk of non-Hodgkin's lymphoma (OR = 2.89, 95% CI 1.89 to 4.41), Hodgkin's disease (OR = 4.77, 95% CI 1.77 to 13.30), leukaemia (OR = 2.55, 95% CI 1.50 to 4.32), acute myeloid leukaemia (OR = 3.65, 95% CI 1.68 to 7.93), and pancreatic cancer (OR = 2.05, 95% CI 1.22 to 3.45), the authors found no support for an association between discharge with a diagnosis of epilepsy two years or more before the diagnosis of cancer and an increased risk of any of the types of cancer included in this analysis. The lack of association was also evident for individuals with an epilepsy diagnosis preceding malignancy/reference year by >10 years.

Conclusions: Clinical examinations prompted by seizure onset probably mainly explain the observed association between epilepsy diagnoses the year before a cancer diagnosis. However, these results lend no support to the suggestion that epilepsy, and presumably long term exposure to antiepileptic drugs, is associated with an increased risk of the types of cancer included in the present study.

As epilepsy is the most common chronic neurological disease, the population treated by antiepileptic drugs (AEDs) represents a sizeable proportion of the general population in western countries.¹ Potential long term adverse effects of AEDs are thus a major concern in particular since treatment in general is maintained for years, and sometimes for life. One important example is the possibility that use of AEDs might be associated with an increased risk of different forms of cancer. The question was raised early, based on observations of increased mortality in non-central nervous system (CNS) cancer among institutionalised people with epilepsy,² and later partly confirmed in other hospital based large epilepsy cohorts.³ Lymphoma, myeloma, and cancers of the lung, liver, pancreas, and gastrointestinal tract have been the types of malignancies most frequently discussed in relation to use of AEDs^{4–7} and the classic enzyme inducing AEDs phenobarbital and phenytoin, most often considered implicated. An increased risk of CNS tumours has also been seen as late as 20 years after epilepsy diagnosis.⁸

Despite its potential importance, this issue has received little attention as highlighted in a recent review by Singh *et al*⁹ and, as the authors conclude, the results of the relatively few clinical studies available are partly conflicting. The question of whether AEDs may be carcinogenic in humans or indeed if epilepsy is associated with an increased risk of non-CNS malignancy is thus unresolved and further studies are needed.

We therefore conducted a case control study of epilepsy as a risk factor for some non-CNS malignancies using the Swedish Cancer Registry to identify cases with different forms of cancer and the Swedish Hospital Discharge Registry for identification of cases and controls with a previous diagnosis of epilepsy.

PATIENTS AND METHODS

We analysed previous diagnosis of epilepsy as a risk factor for certain cancer forms in a case control study where we identified all cases of leukaemia, lymphoma, myeloma, and pancreatic cancer among individuals at least 15 years old, reported to the Swedish Cancer Registry from 1987 to 1999—a total of 52 861 cases.

The Swedish cancer registry classifies tumours according to the International Classification of Disease (ICD), where we used version 8 (ICD-8) classification codes for leukaemia (codes 204–207) and version 7 (ICD-7) for lymphoma (codes 200–202), myeloma (code 203), and pancreatic cancer (code 157).

Controls (n = 137 485) were randomly selected from the continuously updated Swedish Population Registry stratified on age, sex, and year of cancer diagnosis. Reference year was defined as the year of diagnosis of malignancy for cases and year of identification for controls. The number of controls selected depended on the age of the cases at the time of diagnosis. For each cancer case older than 19 years at diagnosis, two controls were selected. For cases diagnosed at ages 15–19 years, five controls were selected. The material used in this study was compiled to address several issues unrelated to the present analysis, including questions regarding children and adolescents where these forms of cancer are rare. To increase the statistical power for studies of these age groups, a larger number of controls was selected. This has no impact on the results in this specific study, as the results are age adjusted.

Cases and controls were linked to the Swedish Hospital Discharge Registry from 1969 to 1999 to identify first time hospital discharge for epilepsy. The epilepsy diagnosis was defined with the ICD version 8 and 9, code 345.

Ethical approval was granted by the Ethics Review Board at the Karolinska Institute, Stockholm.

Abbreviations: AED, antiepileptic drug; AML, acute myeloid leukaemia; CLL, chronic lymphatic leukaemia; CNS, central nervous system; HD, Hodgkin's disease; NHL, non-Hodgkin's lymphoma.

Table 1 Age, sex, and reference year adjusted odds ratios (OR) and 95% confidence intervals (CI) between first time discharged from hospital with epilepsy (1969–99) and risk of subsequent malignancy by years prior to malignancy diagnosis or reference year

Type of malignancy	Time between first epilepsy discharge diagnosis and malignancy					Reference year OR (95% CI)
	≥11 years OR (95% CI)	10–8 years OR (95% CI)	7–6 years OR (95% CI)	5–4 years OR (95% CI)	3–2 years OR (95% CI)	
Non-Hodgkin's lymphoma	0.72 (0.52–0.99)	1.03 (0.65–1.64)	0.92 (0.55–1.52)	0.88 (0.55–1.41)	0.98 (0.63–1.51)	2.89 (1.89–4.41)
Epilepsy with malignancy (n)	41	21	17	20	23	30
Hodgkin's disease	0.86 (0.38–1.94)	1.07 (0.26–4.36)	1.37 (0.43–4.37)	2.07 (0.75–5.70)	1.71 (0.62–4.69)	4.77 (1.71–13.30)
Epilepsy with malignancy (n)	6	2	3	4	4	4
Chronic lymphatic leukaemia	0.70 (0.38–1.27)	1.14 (0.53–2.45)	0.57 (0.18–1.79)	0.72 (0.30–1.76)	0.89 (0.39–2.01)	1.56 (0.63–3.88)
Epilepsy with malignancy (n)	11	7	3	5	6	5
Acute myeloid leukaemia	0.78 (0.39–1.56)	1.62 (0.71–3.66)	0.60 (0.15–2.42)	1.73 (0.81–3.70)	0.46 (0.11–1.85)	3.65 (1.68–7.93)
Epilepsy with malignancy (n)	8	6	2	7	2	7
Leukaemia	0.68 (0.45–1.02)	1.14 (0.67–1.94)	0.77 (0.39–1.50)	1.30 (0.81–2.10)	0.53 (0.26–1.08)	2.55 (1.50–4.32)
Epilepsy with malignancy (n)	25	15	9	19	8	17
Myeloma	0.89 (0.56–1.39)	1.14 (0.60–2.17)	0.79 (0.35–1.79)	0.61 (0.27–1.39)	1.08 (0.59–2.00)	1.52 (0.70–3.30)
Epilepsy with malignancy (n)	20	10	6	6	11	7
Pancreatic cancer	1.20 (0.89–1.62)	0.89 (0.52–1.52)	1.27 (0.77–2.09)	0.93 (0.56–1.53)	0.83 (0.49–1.38)	2.05 (1.22–3.45)
Epilepsy with malignancy (n)	49	15	18	17	16	18
Controls	424	147	136	159	172	75

RESULTS

A diagnosis of epilepsy the same year as a cancer diagnosis carried an increased risk for leukaemia, pancreatic cancer, non-Hodgkin's lymphoma (NHL), acute myeloid leukaemia (AML), and Hodgkin's disease (HD) but not for chronic lymphatic leukaemia (CLL) or myeloma (table 1). No significant increase was noted for any of the cancer forms included in the analysis with an epilepsy diagnosis two years or more before a diagnosis of NHL (odds ratio (OR) 0.86, 95% confidence interval (CI) 0.71 to 1.04), HD (OR = 1.24, 95% CI 0.78 to 1.97), leukaemia (OR = 0.83, 95% CI 0.66 to 1.05), CLL (OR = 0.78, 95% CI 0.55 to 1.11), AML (OR = 0.97, 95% CI 0.65 to 1.45), myeloma (OR = 0.90, 95% CI 0.68 to 1.19), and pancreatic cancer (OR = 1.05, 95% CI 0.87 to 1.28). This lack of association was evident also for individuals with an epilepsy diagnosis preceding malignancy/reference year by >10 years. A detailed analysis by different time intervals between year of discharge and year of cancer diagnosis/reference year is presented in table 1.

DISCUSSION

We found no significant association between a hospital discharge diagnosis of epilepsy and risk of NHL, HD, leukaemia, myeloma, or pancreatic cancer two years or more after the epilepsy diagnosis. The confidence intervals for NHD, CLL, leukaemia, myeloma, and pancreatic cancer were tight whereas we could not exclude an up to twofold increase in the risk of HD. The increased risk seen for most of the cancer forms the same year as the diagnosis of epilepsy was most probably due to clinical examinations prompted by the seizure onset. However it is possible that in some cases the diagnosed cancer could have contributed to the development of epilepsy.

Hence, in this nationwide study we were unable to confirm previous observations suggesting an association between epilepsy and the risk of some types of cancer.^{3–8} The main advantage of our study is the large numbers and the fact that

it is based on a nationwide cancer registry. There are, however, important limitations with our study design. Firstly, we rely on the hospital discharge registry for the epilepsy diagnosis. We have previously found that the diagnosis of epilepsy in this registry may be erroneous in approximately 20% of the cases³ due to inclusion of some patients with single seizures, acute symptomatic seizures, and non-epileptic attacks. Although an external reviewer of the medical records thus questioned the epilepsy diagnosis in a proportion of patients, many of those cases were nevertheless probably prescribed AEDs since they were considered by their physicians to have epilepsy. Furthermore, a cohort based on the hospital discharge registry is likely to be selected towards more severe epilepsy. However, if anything, such selection bias would most probably strengthen rather than weaken an association with cancer, should there be one. The minority of epilepsy patients who have not been hospitalised and thus evade identification with our methodology may erroneously be included among the epilepsy controls. Their contribution will however be minimal. Also, not all regions of Sweden were served by the Hospital Discharge Registry in 1969. By 1980, 80% of the Swedish regions were covered by the Registry and after 1987 the Registry served the entire country. There are no known differences in incidence rates of the malignancies in this study by region in Sweden. Failure to register hospital stays would thus not be expected to differ between cases and controls and would therefore result in non-differential misclassification of discharge diagnoses.

Secondly, although we included in the present analysis for each individual only the *first* discharge from hospital for epilepsy, this may not represent the time of onset of seizures. Finally, although the vast majority of patients with epilepsy are prescribed AEDs, we have no individual data on drug treatment of the epilepsy patients. However, we know from national sales statistics that phenytoin, carbamazepine, and phenobarbital were the most frequently prescribed AEDs in Sweden during the time period assessed in the present study.

These are also the AEDs that have mainly been discussed in relation to possible carcinogenicity.

Therefore, although we have studied the association between a prior diagnosis of epilepsy and the risk of cancer, our negative findings also suggest that there is no major increase in risk with long term use of these AEDs regarding the types of cancer studied. Lamminpää *et al*⁶ used a national drug reimbursement registry to identify individuals prescribed AEDs in Finland. They were thus also able to identify a large cohort of AED users that was followed for subsequent cancers through the Finnish Cancer Registry. In addition to an excess of cancers of the brain, they reported an increased risk for cancers of the larynx, liver, pancreas, colon, stomach, and lung. This is an attractive and more direct method to assess the potential association between AEDs and cancer. However, it is not clear if this registry could distinguish between AED prescriptions for epilepsy from those for other indications. This is a potentially important confounding factor because some AEDs are frequently prescribed for non-epilepsy conditions such as pain, which may be related to cancer.

We restricted our study to include only lymphoma, leukaemia, myeloma, and cancer of the pancreas of all possible cancer forms. With the present methodology, cancer of the liver and lung would be burdened by the confounding factors of smoking and alcohol consumption, which is important since this may be present at higher frequency among people with epilepsy.¹⁰ With the exception of cancer of pancreas, where Lamminpää *et al*⁶ found an increased risk, our negative results are in line with the observations from the Finnish study indicating that a diagnosis of epilepsy, and a presumed long term use of AEDs, is not associated with a significantly increased risk of the types of cancer included in the present analysis.

In conclusion, our data lend no support for an association between epilepsy and the cancer forms studied, although further independent confirmatory studies are needed to exclude such association with greater strength.

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