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The risk of amyotrophic lateral sclerosis after cancer in U.S. elderly adults: a population-based prospective study

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Abstract

Although epidemiologic studies have examined the risk of amyotrophic lateral sclerosis (ALS) in relation to cancer, none have been large population-based studies using incident ALS and adjusting for medical surveillance. Addressing those limitations, we used all first primary cancer cases from the Surveillance, Epidemiology and End Results (SEER) Program (1992–2005), linked to Medicare claims data. Cases were followed from cancer diagnosis until the earliest date of ALS diagnosis, a break in Medicare claims data, death, age 85 or December 31, 2005. We selected a comparison group from a 5% random Medicare sample in the SEER areas who were cancer-free and censored as above, or until a cancer diagnosis. ALS outcomes were derived from medical claims. We used proportional hazards models to estimate ALS hazard ratios (HRs), using age as the time scale, adjusting for sex, race, and physician visits, and stratifying the baseline hazard on birth year and SEER registry. A total of 303 ALS cases were ascertained in cancer patients (2,154,062 person-years) compared to 246 ALS cases (2,467,634 person-years) in the reference population. There was no overall relationship between cancer and ALS (HR = 0.99; 95% CI = 0.81–1.22), nor by gender or race. Except for an elevated ALS risk in the first year after a leukemia diagnosis, the relationship between site-specific cancers and ALS was null after correcting for multiple comparisons. Having a cancer diagnosis was not associated with an overall risk of incident ALS. The short-term ALS risk after leukemia may reflect screening or reporting errors.

Keywords

cancer; amyotrophic lateral sclerosis; Medicare; SEER Program

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Introduction

Several studies suggest an inverse relationship between cancer incidence and the two most common neurodegenerative diseases, Parkinson's disease[1–3] and Alzheimer's disease.[4–5] The relationship between cancer and neurodegenerative diseases could potentially provide insight into underlying pathophysiologic mechanisms for the two sets of diseases because of related, but seemingly inverse, disease processes: at a simple level, cancer involves resistance to cell death whereas neurodegenerative diseases relate to premature cell (neuron) death.[6–8]

A number of epidemiologic studies have also examined cancer in relation to another neurodegenerative disease, amyotrophic lateral sclerosis (ALS). Although these studies generally observed no association between cancer and ALS, most were limited by small size,[9–10] non-population-based controls,[11] or reliance on mortality data as a surrogate for incident ALS.[12] None, to our knowledge, has taken into account the intensity of medical surveillance preceding ALS diagnosis.[9–13] To explore whether there is a link between cancer and ALS, we examined the risk of incident ALS among a large group of Medicare patients residing within the Surveillance, Epidemiology and End-Results (SEER) Program registry areas using a database that allowed controlling for the frequency of physician visits, a surrogate for medical surveillance.

Materials and Methods

We used all first primary cancer cases from the SEER Program (1992–2005) from 16 registries, linked to Medicare health insurance claims data. The SEER program includes population-based state and metropolitan cancer registries, which cover about one-quarter of the U.S. population.[14] Medicare is a federal health insurance program that covers 97% of the U.S. population who are 65 or older. All Medicare beneficiaries are entitled to Part A for hospital care and 96% of beneficiaries subscribe to Part B for physician and outpatient care.[14] In addition, Medicare data were also available for a 5% random sample of Medicare beneficiaries from the SEER areas.[14] Information on medical conditions and procedures were derived from claims filed by medical providers for Medicare reimbursement. Medicare beneficiaries enrolled in health maintenance organizations (HMO), which provide capitated care, were excluded from the current study because HMO providers are not required to submit individual claims to Medicare. Therefore data were not available on medical conditions or procedures for the HMO patients.[15]

Primary cancer cases diagnosed at age 66 or older were included if they had 13 months of continuous Medicare coverage prior to cancer diagnosis (with full claim information, i.e., Parts A and B, non-HMO) and did not have a prior diagnosis of ALS (recorded by Medicare). Cases were followed from age at cancer diagnosis until the earliest age of ALS diagnosis, discontinuation of Part B Medicare coverage (physician's visits), transfer to an HMO (and thus unavailable claims data), death, attaining age 85 or December 31, 2005. We did not include health outcomes beyond age 85 because of potential under-ascertainment of medical conditions in the oldest elderly.[16] We selected a comparison group from a 5% random sample of the Medicare population in the SEER areas (1992–2005) who were

initially cancer-free, and met the other eligibility criteria for cases. Individuals in the cancer-free group were followed from their earliest eligibility age and censored as above, or until a cancer diagnosis. ALS outcomes were ascertained based on at least one hospital claim or at least two physician/ outpatient claims 30 days apart using the International Classification of Diseases, ninth revision (ICD-9) diagnostic code 335.2. Although this code category corresponds to motor neuron disease (MND), previous large population-based studies have used it to identify ALS because it is the dominate subtype and accounts for about 90% of MND deaths.[17] For ALS cases the date of ALS diagnosis was defined as the earliest of the claims dates.

We used Cox proportional hazards models, with age as the time metric, to estimate the hazard ratio (HR) of developing ALS by cancer status. Models were adjusted for sex, race, and frequency of physician visits and the baseline hazard was stratified on birth year and cancer registry (to account for potential secular trends and geographic differences in recording practices/ underlying rates respectively). We assessed the relationship stratified by race, sex, and age category, as well as after diagnosis with site-specific cancers. ALS risks were analyzed over several time intervals following cancer diagnosis:<1 year; 1–<5 years; 5–<10 years; and 0–<10 years, to examine separately the initial post-diagnosis period when cancer patients would be under especially close medical surveillance compared to non-cancer patients. Because cancer patients often receive ongoing medical surveillance and care for many years after the initial cancer diagnosis, which could increase the likelihood of ALS diagnosis, we adjusted for the number of physician visits as a surrogate for medical surveillance. Physician “visits,” a maximum of one per day, were counted during six-month intervals between the cancer/selection date and ALS/censor date, but excluding the six month intervals encompassing the start date and the interval in which ALS was diagnosed. Six month intervals began in January and July of each year; thus medical visits were not adjusted for during a part of the interval in which the cancer and ALS diagnoses occurred, which was no greater than six months. Claims by physicians considered to have limited responsibility for direct patient care (e.g., radiologists, anesthesiologists, pathologists) were not included. In models physician visits were categorized as 0, 1–5, 6–10, >10 visits per six month interval.

Only cancer sites for which there were 10 or more ALS cases diagnosed were presented, with the exception of melanoma, which was included because it had been reported as positively associated with ALS mortality.[12, 18]

We also evaluated the relationship between cancer and subsequent injuries due to an auto accident (ICD-9 E810–819), which we expected to be null. Injuries due to auto accidents were based on either one hospital visit or one outpatient visit (rather than two) because of the acute nature of the injury. This association was intended to serve as a “control” to help evaluate whether the study design operated as we would have predicted when no relationship with cancer was expected.

We applied the Bonferroni correction method to account for the multiple comparisons made in the study.

Results

A total of 303 ALS cases were ascertained in 758,898 cancer patients over 2.15 million person-years compared to 246 ALS cases in 422,686 persons (2.47 million person-years) in the comparison population.

There was no risk for ALS after all cancers combined in the 10-year follow-up period (HR= 0.99; 95% confidence interval (CI) = 0.81–1.22)(table 1). In the first year after diagnosis of all cancers, ALS risk was elevated (HR = 1.98; 95% CI 1.10–3.57), but in subsequent years the risk of ALS after cancer was reduced (table 1). We present risks unadjusted for doctors' visits in supplementary table 1, which shows that adjusting for the frequency of medical visits reduced the magnitude of the HRs observed.

Overall, there was no relationship between cancer and ALS in any subcategory: men, women, whites, or non-whites (table 1). Although the risk of ALS after cancer was also null in strata defined by age at cancer diagnosis, the magnitude of the (non-significant) 10-year risks declined with advancing age from 1.19 (95% CI = 0.84–1.67) for those aged 66–70 years at cancer diagnosis to 0.82 (95% CI = 0.49–1.38) for those aged ≥80 years

ALS risk was not generally associated with the individual cancer sites examined, including breast cancer, colon cancer, prostate cancer and melanoma (table 2). The exception was ALS after a diagnosis for leukemia. Because of the 10-fold increased risk in the first year after leukemia, over the full 10-year follow-up period there was a two-fold increased risk of ALS, despite the risk being substantially reduced after the first year. The 10-year risk of ALS after leukemia was not statistically significant after correction for multiple testing, while the risk of ALS in the first year after leukemia remained statistically significantly elevated.

We also examined the association between ALS and all cancers excluding leukemia. Excluding leukemia reduced the overall HR somewhat in the first year to HR = 1.54 (95% CI 0.82–2.86). Overall the HR remained null, HR=0.93 (95% CI=0.76–1.15) when ALS cases after all cancers other than leukemia were analyzed (data not shown).

When we examined the relationship between auto accident injuries following cancer diagnosis, we found no association, as expected for this comparison condition. For the 10-year follow-up period, the HR was 1.03 (0.95% CI = 0.98–1.07).

Discussion

In this large, population-based study of incident ALS risk after cancer in elderly Medicare patients, we found an elevated ALS risk in the first year after diagnosis of all cancers combined, but no association overall. There was no association between combined cancer and ALS for all years across race, sex or age groups. Associations between ALS and specific cancer sites were also null over the extended (10-year period), after correcting for multiple comparisons. The only association that remained statistically significant was in the first year following leukemia diagnosis. That we found no association between cancer diagnosis and

subsequent injuries due to auto accidents supports the validity of the study design to examine the risk of medical conditions such as ALS following cancer.

The elevated ALS risk in the first year after leukemia diagnosis may reflect ascertainment bias due to increased medical review. Blood work-ups associated with early non-specific symptoms of ALS, such as fatigue, could result in early cancer diagnoses, particularly of leukemia, and subsequent ALS diagnosis as ALS signs and symptoms progress to satisfy diagnostic criteria. Also, as noted, we did not adjust for medical visits during the initial six month period in which the leukemia diagnosis occurred. It is also possible that transcription errors contributed to the elevated risks observed. A majority of the ALS cases following leukemia occurred subsequent to a specific histologic-type, AML, and recording errors transcribing “AML” from “ALS” have been seen on death certificates.[19] Our review of death certificate data for the subjects with both leukemia and subsequent claims for ALS showed that only one of the death certificates with available data listed ALS as a cause of death. This is not evidence of error inasmuch as leukemia is also potentially highly fatal, but it is consistent with possible errors on some claims for ALS.

By linking Medicare data to SEER, we were able to use incident ALS rather than mortality outcomes, which helped illuminate the temporal relationship between cancer and ALS. Both U.S.[12] and Australian[18] population-based studies using ALS deaths as outcomes found elevated risks of ALS mortality after melanoma, but these studies could not define the interval or temporal relationship between melanoma and ALS diagnoses, and thus could not confidently evaluate the sequence of diseases or the likelihood that screening for one disease led to detection of the other. In the present study using ALS incident outcomes, we found no relationship between melanoma and ALS. This may simply be a chance finding given the small number of cases with both melanoma and ALS diagnoses. It could, however, reflect a true null relationship if an elevated relationship between melanoma and ALS, such as previously seen,[12] exists only when melanoma is found in the course of an ALS work-up and thus ALS actually precedes the melanoma. Under these circumstances, we would not expect to see a heightened ALS risk because we examined the initial diagnosis of ALS *after* melanoma. The recent Swedish registry study by Fang et al.[13] found an elevated ALS risk confined to the first year after melanoma diagnosis. However, because Fang et al. relied mainly on hospital discharge data to identify ALS, not the earliest physician diagnosis, it is not possible to know whether the ALS diagnoses preceded the melanoma or *vice versa*. Thus, the results of the present study are not necessarily inconsistent with Fang et al., but they do not support an elevated risk of ALS after melanoma.

In an earlier study of cancer and ALS mortality in the U.S., the only significant inverse relationship that was observed was between prostate cancer and subsequent ALS death.[12] In the present report ALS incidence was not related to prostate cancer; thus, the current findings do not argue for a special relationship between prostate cancer and ALS.

As noted, risks were null in all age groups (over the 10-year follow-up) but lowest, although non-significantly, in the oldest age group. The declining risk relationship may reflect decreased efforts to detect some diseases in the aged, particularly those that share some hallmarks of frailty, such as ALS.

Strengths of this study include its large size (nearly 5 million person-years), the availability of incident ALS cases identified by physician visits as well as hospital stays, the inclusion of a population with multiple races, and access to data on the frequency of physician visits, so as to control for the intensity of medical surveillance. A key limitation is the difficulty of assessing risk for individual cancer sites and sub-populations given the rarity of ALS. Other limitations include the restricted age range of the Medicare population and the fact that the likelihood of medical work-ups for ALS may vary depending on age and the fatality of the cancer. Medicare also lacks information on potential covariates, but there are few known risk factors for ALS. In addition, the generalizability of the study may be limited slightly by the fact that Medicare beneficiaries who participate in HMOs were excluded, although we note that during a major part of the study period (1996–2005) the average percentage of participants in HMOs was relatively low (<14%) and differences between the HMO and non-HMO populations that were observed (on race and age) were small.[20]

In sum, in this large prospective study of the relationship between ALS following cancer we found that having a cancer diagnosis was not associated with a lower risk of incident ALS. Except for the elevated risk of ALS in the first year after a leukemia diagnosis, which may reflect heightened screening or reporting errors, the relationship between site-specific cancers and ALS was null after correcting for multiple comparisons.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ALS	amyotrophic lateral sclerosis
SEER	Surveillance, Epidemiology and End Results
HR	hazards ratio
CI	confidence interval
HMO	health maintenance organizations

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Table 1

Hazards Ratio (HR) for amyotrophic lateral sclerosis (ALS) after first primary cancer diagnosis, 1992–2005[1]

	<1 year follow-up				1–<5 year follow-up				5–<10 year follow-up				0–<10 year follow-up			
	control[2] (n)	case[2] (n)	HR	95% CI	control (n)	case (n)	HR	95% CI	control (n)	case (n)	HR	95% CI	control (n)	case (n)	HR	95% CI
Overall	37	94	1.98	1.10–3.57	96	162	0.74	0.51–1.07	113	47	0.56	0.35–0.90	246	303	0.99	0.81–1.22
Sex																
Men	17	64	2.81	1.33–5.96	49	114	0.80	0.50–1.30	60	32	0.74	0.42–1.32	126	210	1.10	0.84–1.43
Women	20	30	1.16	0.44–3.09	47	48	0.65	0.35–1.19	53	15	0.31	0.13–0.75	120	93	0.83	0.59–1.15
Race																
White	32	77	2.03	1.05–3.91	83	140	0.69	0.46–1.04	100	41	0.54	0.33–0.90	215	258	0.92	0.74–1.15
Non-white	*	*	1.74	0.44–6.86	13	22	0.88	0.33–2.35	*	*	0.76	0.17–3.31	31	45	1.58	0.90–2.79
Age at cancer diagnosis, (years)																
66–<70	22	24	2.32	1.04–5.18	46	36	0.84	0.47–1.49	58	12	0.52	0.24–1.14	126	72	1.19	0.84–1.67
70–<80	25	55	1.92	0.89–4.12	86	116	0.84	0.56–1.26	97	35	0.58	0.35–0.98	208	206	0.93	0.74–1.17
≥ 80	21	*	1.32	0.49–3.56	43	*	0.59	0.28–1.25	.	.	.	.	64	25	0.82	0.49–1.38

[1]Models have been adjusted for race, sex and number of doctors' visits, stratified on birth year and cancer registry area, except that sex was not adjusted for in the subpopulation based on sex, nor race, in the subpopulation defined by race. There were a total of 758,898 cancer patients and 422,686 persons in the comparison population. Data source is SEER-Medicare.

*Cell sizes with numbers less than 11 or that allow derivation of numbers less than 11 are suppressed due to SEER-Medicare Data Use Policy.

Table 2

Hazards ratios (HR) for amyotrophic lateral sclerosis (ALS) after first primary site-specific cancer diagnosis (1992–2005)[1]

	<1 year follow-up				1–<5 year follow-up				5–<10 year follow-up				0–<10 year follow-up			
	control[2] (n)	case[2] (n)	HR	95% CI	control (n)	case (n)	HR	95% CI	control (n)	case (n)	HR	95% CI	control (n)	case (n)	HR	95% CI
Cancer site:																
Oral cavity[3]	37	*	-	-	96	*	0.78	0.15–3.93	113	*	-	-	246	*	0.50	0.12–2.06
Colon	37	*	0.48	0.10–2.23	96	*	0.36	0.14–0.91	113	*	0.74	0.25–2.21	246	20	0.63	0.38–1.05
Rectum[4]	37	*	2.07	0.55–7.84	96	*	1.07	0.43–2.69	113	*	0.94	0.21–4.21	246	17	1.47	0.85–2.53
Lung/ bronchus	37	*	0.36	0.10–1.22	96	*	0.37	0.12–1.18	113	0	.	.	246	12	0.55	0.30–1.00
Breast	20	*	0.68	0.17–2.63	47	20	0.69	0.31–1.54	53	*	0.40	0.14–1.18	120	37	0.83	0.54–1.29
Prostate	17	22	1.53	0.51–4.54	49	69	0.92	0.54–1.56	60	23	0.76	0.40–1.44	126	114	1.00	0.74–1.36
Bladder	37	*	0.82	0.24–2.88	96	*	0.81	0.34–1.95	113	*	0.39	0.09–1.77	246	18	0.81	0.48–1.39
Melanoma[5]	32	*	1.21	0.18–8.15	83	*	0.86	0.27–2.73	100	*	0.29	0.03–2.37	215	*	0.75	0.34–1.65
Leukemia[6]	37	*	10.40	3.54–30.44	96	*	0.44	0.09–2.09	113	0	.	.	246	12	2.06	1.11–3.81

[1] Models have been adjusted for race, sex and number of doctors' visits, stratified on birth year and cancer registry area. There were a total of 758,898 cancer patients compared to 422,686 persons in the comparison population. Data source is SEER Medicare.

[2] n = Number of ALS cases.

[3] Includes tongue, floor of mouth, gum and mouth, tonsil, oropharynx, hypopharynx.

[4] Includes rectum and rectosigmoid junction.

[5] Limited to whites.

[6] The HR for leukemia in the period <1 year of follow-up is the only value that remained statistically signficant after applying the multiple comparisons correction.

* Cell sizes with numbers less than 11 or that allow derivation of numbers less than 11 are suppressed due to SEER-Medicare Data Use Policy.