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Long-Term Health Experience of Jet Engine Manufacturing Workers: IV. A Comparison of Central Nervous System Cancer Ascertainment Using Mortality and Incidence Data

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PURPOSE: To compare ascertainment of central nervous system (CNS) neoplasms with the use of mortality and incidence data as part of an occupational epidemiology study.
METHODS: Deaths were identified by matching the cohort of 223,894 jet engine manufacturing employees to the U.S. Social Security Administration death files and the National Death Index. Incident cancer cases were identified by matching the cohort to 19 state cancer registries.
RESULTS: We identified 718 cases overall: 59% by the use of both mortality and cancer incidence tracing; 24% by the use of only mortality tracing, and 17% by the use of only cancer incidence tracing. Compared with state cancer registries, death certificates missed 38% of the malignant, more than six times the benign and nearly 1.5 times the unspecified CNS cases. The positive predictive value of death certificates, with cancer registry as gold standard, was 6% for unspecified, 35% for benign, and 86% for malignant histologies.
CONCLUSIONS: Death certificates seriously underascertained benign and unspecified CNS tumors; analyses determined with mortality data would not accurately capture the true extent of disease among the cohort. Most state cancer registries have only collected nonmalignant CNS tumor information since 2004, which currently limits the usefulness of state cancer registries as a source of nonmalignant CNS tumor identification. Underascertainment of CNS deaths could seriously affect interpretation of results, more so if examining nonmalignant CNS.
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KEY WORDS: Brain Cancer, Cancer Incidence, Central Nervous System Neoplasms, Death Certificates, Methodology, Mortality.

INTRODUCTION

Typically, retrospective occupational cohort studies rely on mortality data for the identification of cancer cases or deaths. Because the United States has the National Death Index (NDI), a well-established and thorough repository for death information, vital status tracing and obtaining cause of death information is relatively straightforward. However, some researchers have expressed concern about the accuracy and completeness of cancer data available through death certificates (1–4). Aggregate cancer incidence and survival data are available from the Surveillance Epidemiology and End Results and central nervous system (CNS) cancer-specific aggregate incidence and mortality data are available from the Central Brain Tumor Registry of the United States (CBTRUS). These data warehouses are excellent resources for researchers but do not allow matching or identification of individual-level cancer information. To obtain individual-level cancer case information, researchers must request these data directly from state cancer registries. However, state cancer incidence tracing has limitations, including nonoverlapping time periods and extremely costly and time-consuming application and data-matching processes (5).

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Selected Abbreviations and Acronyms

NDI = National Death Index
CNS = central nervous system
CT = Connecticut
ICD = International Classification of Diseases
UCOD = underlying cause of death
CCOD = contributory cause of death
CBTRUS = Central Brain Tumor Registry of the United States
PPV = positive predictive value

In July 2002, in response to the perception of an unusual occurrence of glioblastoma at a jet engine manufacturing facility, the authors embarked on a multipart epidemiology study to determine whether mortality or incidence rates from CNS neoplasms were elevated at eight such facilities in Connecticut (CT). As part of this study, we identified CNS deaths through mortality tracing and incident CNS cases through state cancer registries. We report here a comparison of deaths caused by CNS neoplasms identified through either mortality or cancer incidence tracing. This comparison quantified the extent to which CNS neoplasms could be accurately identified through mortality tracing in a retrospective occupational cohort study. To our knowledge, this is the first such comparison.

METHODS

Details on the methods and results of our cohort enumeration, mortality tracing, cause of death ascertainment, and our statistical analysis methods are reported elsewhere (6–8). The following is a summary of these methods and results.

Cohort Enumeration

The mortality study cohort includes all persons ever employed at one or more of the eight CT study plants from 1952 through 2001, where 1952 is the start-up date of the North Haven plant where the "index" cases arose. The mortality study cohort includes 223,894 subjects who contributed 7,713,434 person-years of observation during the 1952 to 2004 study period. For purposes of the incidence study, we limited the cohort to those workers who were at risk of becoming a case during the January 1, 1976, to December 31, 2004, study period. This truncated time period, which excludes subjects who died or were lost to follow-up before 1976, accounts for major advancements in diagnostic specificity and sensitivity for brain cancer that began in the mid-1970s, as well as the release of the first International Classification of Diseases (ICD) for specialized oncologic coding (ICD-O) in 1976. The incidence study cohort includes 212,513 subjects who contributed 5,037,369 person-years of observation during the truncated 1976–2004 study period.

Vital Status Tracing

We used our standard two-stage vital status tracing protocol to identify deaths among cohort members (9) with unconfirmed vital status (not known from company-held records to be alive as of the study end date, December 31, 2004). We sent the names of all cohort members not known to be alive to the U.S. Social Security Administration; subjects' identified as having died before 1979 were sent to the health department of the state of death to obtain a death certificate. Subjects identified as unknown or deceased after 1978 were sent to the National Death Index-Plus to obtain the coded cause of death. Death certificates were coded to the underlying cause of death (UCOD) by a National Center for Health Statistics nosologist using the ICD rules in effect at time of death. We also reviewed the contributory causes of death (CCOD) for mention of CNS neoplasm.

Cancer Incidence Tracing

We identified states through which we needed to trace the cohort for cancer incidence on the basis of the states in which 95% of the deaths in the total cohort occurred. Twenty-four states comprised 95% of the deaths in our cohort and were included in our tracing protocol. We applied for permission to match our cohort to the state cancer registries and requested all CNS neoplasm matches with their diagnostic data, including date of diagnosis, histology, behavior, topography, residence at diagnosis, and last known vital status from January 1, 1976, or the registry start date through 2004. The coding scheme used in these analyses is advocated by the CBTRUS (10). We focused our comparison of CNS deaths on the period of 1976 to 2004 to enhance the comparability with our cancer incidence tracing.

We compared the cause of death from the death certificate and histologic code from the state cancer registry for deceased cases. We calculated the sensitivity and positive predictive value (PPV) of the death certificate in identifying an incident cancer case as identified by a state cancer registry. We also calculated the rate of case underascertainment by using death certificates as performed by Freedman (11). The research proposal was approved by the institutional review boards of the University of Pittsburgh and the Connecticut Department of Public Health.

RESULTS

We limited the CNS deaths used in our comparison to those occurring between 1976 and 2004 to correspond with our cancer incidence tracing. We identified 597 CNS neoplasm deaths with underlying or contributory CNS causes from mortality tracing (6) and 722 incident CNS neoplasm cases

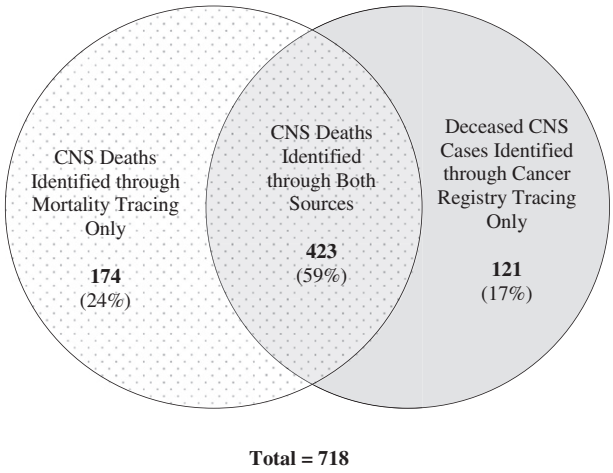

FIGURE 1. Source of CNS Case information.

through cancer incidence tracing (8) between 1976 and 2004. One hundred seventy-eight of the incident CNS cases were alive as of December 31, 2004, and were not included in these comparisons, leaving 544 incident CNS neoplasm deaths. Figure 1 depicts the identification source for the CNS cases and deaths. As shown, of the 718 total deceased cases identified by either source, 423 (59%) were identified in both the mortality and cancer incidence tracing. One hundred seventy-four (24%) were identified only through mortality tracing, and 121 (17%) were identified only through cancer incidence tracing.

Table 1 indicates that 88% of the malignant incident CNS cases were identified as CNS neoplasm deaths when we used the UCOD or CCOD from NDI or death certificates, although 68 (17%) were categorized as unspecified neoplasms, and 3 (0.8%) were categorized as benign. Sixty-three of benign incident CNS cases (80%) were listed as dying from a non-CNS cancer UCOD; only 11 (14%) of the total 79 benign incident CNS cases were identified as such when we used the UCOD. Two-thirds (n = 10) of the 15 uncertain incident CNS cases were identified as CNS deaths.

Table 2 shows the detailed listing for the 121 incident CNS cases coded as a non-CNS death using UCOD. Forty percent (n = 50) of the primary incident CNS cases were coded as dying from another form of cancer based on their UCOD. Lymphohematopoietic tissue cancers were the most commonly recorded UCOD for malignant CNS cases (n = 10) whereas digestive and respiratory cancers were most common for benign (n = 6) and uncertain (n = 1) CNS cases. Heart disease accounted for one quarter of UCODs for benign cases but was much less common for malignant cases (9%). An additional 71 malignant CNS cases had benign (n = 3) or unspecified histologies (n = 68). Lack of histologic information on the death certificate accounted for misclassification of malignant CNS cases identified through cancer registries as unspecified.

Figure 1 and Table 1 also show that 174 CNS deaths were identified through the mortality tracing but not as incident CNS cases from the state cancer registries. Ninety-eight (56%) of these were malignant CNS, and 53 (30%) were unspecified CNS deaths. Figure 2 indicates that these 174 deaths were identified in 33 different states; 27 cases came from 17 states not included in our tracing protocol. The remaining deaths were from 16 states where we did conduct tracing, although 45 of those deaths were from the period before the registry began. However, 102 deaths occurred in 16 states where we traced during the time the registry existed.

Table 3 shows select demographic and occupational factors for 102 deaths not identified by cancer registry tracing as compared with the 423 deaths identified as matches by the state cancer registries. A greater percentage of the deaths that matched to the cancer registries were malignancies (73%), according to the death certificate, compared with deaths that did not match to a cancer registry (46%). In addition, compared with registry matches, those who were not matched to a registry were more likely born before 1920 (33% vs. 21%), to have died during 1976–1979 (15% vs. 6%), and died at older ages (age at death 70+: 42% vs. 29%). They were also more likely to have been short-term

TABLE 1. Comparison of cause of death and histology for deceased CNS cases identified through mortality and incidence tracing

CNS deaths identified by UCOD or CCOD, 1976–2004	Deceased CNS incident cases identified through registry tracing, 1976–2004								CNS deaths not identified through registry tracing	Total
	Malignant		Benign		Uncertain		Total			
	Number	Percent	Number	Percent	Number	Percent	Number	Percent		
CNS neoplasm deaths	397	88.2	16	20.3	10	66.7	423	77.8	174	597
Malignant	(326)	(82.1)	(3)	(18.8)	(2)	(20.0)	(331)	(78.3)	(98)	429
Benign	(3)	(0.8)	(11)	(68.8)	(1)	(10.0)	(15)	(3.5)	(23)	38
Unspecified	(68)	(17.1)	(2)	(12.5)	(7)	(70.0)	(77)	(18.2)	(53)	130
Other causes of death	53	11.8	63	79.7	5	33.3	121	22.2	0	121
Total	450	100.0	79	100.0	15	100.0	544	100.0	174	718

CCOD = contributory cause of death; CNS = central nervous system; UCOD = underlying cause of death.

TABLE 2. Specific cause of death for deceased incident cases with non-CNS causes of death

CNS incident cases without UCOD or CCOD of CNS neoplasm, 1976–2004	Deceased CNS incident cases identified through registry tracing, 1976–2004						
	Malignant		Benign		Uncertain		
	Number	Percent	Number	Percent	Number	Percent	Total
Non-CNS cause of death							
Other cancer	26	49.1	22	34.9	2	40.0	50
Digestive	3	11.5	6	27.3	1	50.0	10
Respiratory	2	7.7	6	27.3	1	50.0	9
Breast	0	0.0	1	4.5	0	0.0	1
Prostate	1	3.8	3	13.6	0	0.0	4
Kidney	0	0.0	2	9.0	0	0.0	2
Bladder	1	3.8	1	4.5	0	0.0	2
Melanoma	2	7.7	0	0.0	0	0.0	2
LHT	10	38.5	3	13.6	0	0.0	13
All other cancer	7	26.9	0	0.0	0	0.0	7
Benign neoplasms	1	1.9	0	0.0	0	0.0	1
AIDS	6	11.3	0	0.0	0	0.0	6
Cerebrovascular disease	3	5.7	2	3.2	0	0.0	5
Heart disease	5	9.4	16	25.4	0	0.0	21
NMRD	1	1.9	5	7.9	2	40.0	8
Other nonmalignancy	7	13.2	13	20.6	1	20.0	21
Accident	1	1.9	2	3.2	0	0.0	3
Suicide	1	1.9	2	3.2	0	0.0	3
Unknown	2	3.8	1	1.6	0	0.0	3
Total	53	100.0	63	100.0	5	100.0	121

CCOD = contributory cause of death; CNS = central nervous system; LHT = lymphohematopoietic tissue; NMRD = nonmalignant respiratory disease; UCOD = underlying cause of death.

employees (67% employed less than 5 years compared with 56% of the matches). No differences by sex or plant group were found.

Table 4 demonstrates the sensitivity and PPV of the death certificate to ascertain CNS case status. For CNS deaths identified through mortality tracing, only 102 of 174 deaths not identified by state cancer registries where tracing occurred were included in the total counts (Figure 2 and Table 3). Malignant CNS deaths had the highest sensitivity (72%) and PPV (86%). Sensitivity was lowest for benign CNS deaths (14%) and PPV was lowest for unspecified CNS deaths (6%). The high number of false-positive results among unspecified CNS deaths was caused by malignant CNS cases whose death certificates simply read "brain

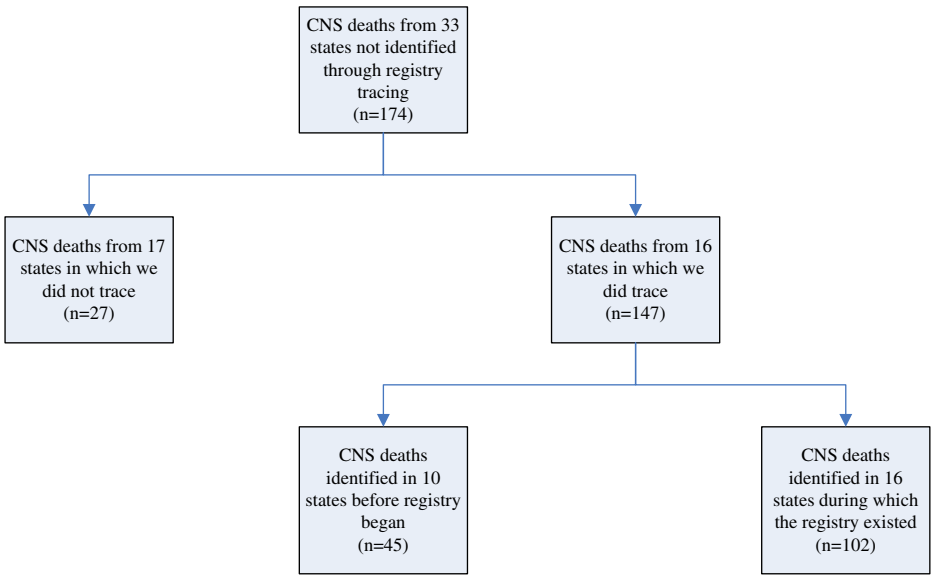

FIGURE 2. State cancer registry status for CNS deaths not identified through registry tracing.

TABLE 3. Selected characteristics of CNS neoplasm deaths not identified compared to those identified through incidence tracing

	Deaths not matched to registry (n = 102)		Deaths matched to registry (n = 423)	
Factor	Number	Percent	Number	Percent
Histology (per DC)				
Malignant	47	46.1%	331	78.3%
Benign	16	15.7%	15	3.5%
Unspecified	39	38.2%	77	18.2%
Sex				
Male	84	82.4%	366	86.5%
Female	18	17.6%	57	13.5%
Year of birth				
<1920	34	33.3%	91	21.5%
1920–1929	28	27.5%	122	28.8%
1930–1939	21	20.6%	117	27.7%
1940+	19	18.6%	93	22.0%
Year of death				
1976–1979	15	14.7%	25	5.9%
1980–1989	22	21.6%	127	30.0%
1990–1999	44	43.1%	181	42.8%
2000–2004	21	20.6%	90	21.3%
Age at death				
<60	33	32.4%	157	37.1%
60–69	26	25.5%	147	34.8%
70–79	25	24.5%	95	22.5%
80+	18	17.6%	27	6.4%
Year of termination				
<1960	38	37.3%	122	28.8%
1960–1969	26	25.5%	131	31.0%
1970–1979	25	24.5%	66	15.6%
1980+	13	12.7%	104	24.6%
Duration of employment				
<5years	68	66.7%	237	56.0%
5–19 years	17	16.7%	87	20.6%
20+ years	17	16.7%	99	23.4%
Plant group				
Only NH	14	13.7%	56	13.2%
Partial NH	9	8.8%	15	3.5%
Never NH	66	64.7%	293	69.3%
Unknown	13	12.7%	59	13.9%

tumor" without regard to tumor behavior. Death certificates underascertained 38% of the malignant CNS cases and over 600% and 100% of the benign and unspecified CNS cases, respectively.

DISCUSSION

This analysis represents the first attempt to quantify the extent to which death certificate cause of death information can accurately identify CNS neoplasms in individuals. Only 59% of total cases were identified through both mortality and cancer incidence tracing. However, almost 90% of the malignant CNS cases were identified as CNS deaths. Nearly one-half of malignant CNS cases with non-CNS causes of death were reported to have died from other forms of cancer. This may have been caused in part by our use of the CBTRUS coding scheme for CNS neoplasms, which includes lymphatic cancers occurring in the brain and spinal cord (10); state nosologists may have recorded these lymphatic cancers without regard to the CNS site. A lack of histologic information on the death certificate accounted for the misclassification of malignant CNS cases identified through cancer registries as unspecified.

Most cases identified by cancer registries but not death certificates were benign. Benign CNS tumors are less often fatal than malignant CNS tumors and were not included on the death certificate, even as an underlying or contributory cause of death; accurate identification of these cases has to occur through cancer incidence tracing. A slightly greater proportion of missed deaths compared with matches died during 1976 to 1979. Many of these deaths may have been prevalence cases diagnosed before 1976 who died during our period of eligibility; these deaths could also indicate potential underascertainment. They may also have been incorrectly coded to CNS causes of death on the death certificate and may not reflect an incident CNS neoplasm. When these deaths were included in a sensitivity analysis with the malignant CNS cases, their inclusion did not change the magnitude or direction of any of our findings (8).

Our results are similar to those found in other studies of death certificate accuracy. Engel et al. (3) found that 12 of 83 cancer deaths (14%) were not attributed as such on the death certificate. Percy et al. (4) found that the cancer site recorded on the death certificate matched the information found on the Surveillance Epidemiology and End Results record 86% of the time. The effects can be particularly strong for types of cancers that are not rapidly fatal. Demers et al. (12) compared cancers ascertained by mortality tracing with those ascertained by incidence tracing and identified 22 additional cases of bladder cancer through the incidence rather than mortality tracing. In a study examining the misclassification of urinary tract cancer cases on death certificates, Chow and Devesa (13) found that between 28% of deaths (renal pelvis cancer) and 48% of deaths (kidney cancer) were ascribed to noncancer causes.

The lack of detailed histology on death certificates was one of the primary reasons for the 38% underascertainment found for malignant CNS deaths. However, this is similar to the 35% underascertainment rate for all malignancies identified by Freedman et al. (11) when they compared cancer incidence with death certificate diagnosis in their cohort of U.S. radiologists. Similar to the benign results seen here, they found greater rates of underascertainment for more survivable cancers, like endometrial, which was underascertained in their cohort by 80%.

The sensitivity (72%) and PPV (86%) of the malignant CNS deaths identified in our study are slightly higher than

TABLE 4. Sensitivity and positive predictive value of the death certificate for coding death from CNS neoplasm

Death certificate diagnosis	True positive A	False positive B	False Negative C	Sensitivity[a] (%) and 95% CI	Positive predictive value[b] (%) and 95% CI	Underascertainment[c] (%) and 95% CI
Malignant CNS	326	52	124	72 (68–76)	86 (82–89)	38 (33–43)
Benign CNS	11	20	68	14 (7–24)	35 (20–55)	618
Unspecified CNS	7	109	8	47 (22–73)	6 (3–12)	114

CI = confidence interval; CNS = central nervous system.
[a]Sensitivity = A/(A+C)
[b]Positive Predictive Value = A/(A+B)
[c]Underascertainment = C/A (calculated as per Freedman et al. [11]).

those found by Sington and Cottrell for all malignancies (14). They compared 440 necropsy results with cause of death recorded on the death certificate and found for all malignancies a sensitivity of 65% and a PPV of 67%; however, the sample size for each cause of death examined in their study was very small. Lloyd-Jones et al. (15) found that, compared with cause of death as determined by a panel of physicians, death certificates for all malignancies had a sensitivity of 90% and a PPV of 95%. The sensitivity of death certificates was almost 90% in a study of lung cancer compared with 72% for malignant and 14% for benign CNS in this study (16). The very low sensitivity and PPV found here for the benign CNS deaths reflects the inability of the death certificate to accurately and completely capture information on causes of death that are more survivable. Cheng et al. found that death certificate sensitivity was only 35% for diabetes (17).

Although the state cancer registries identified six times more deceased benign cases than were accurately identified from death certificates, benign CNS incident case identification is still problematic (5). State cancer registries began collecting data as early as 1935 (Connecticut) and as late as 2005 (South Dakota); the reporting to state cancer registries of benign CNS cases was only mandated in 2004 (5, 15). This limitation can lead to inflated expected values and artificially reduced standardized incidence ratios because of erroneously counting person-years in pre-registry time periods (18). We estimate that, even with the use of state cancer registries for the identification of benign CNS cases, we have underascertained these cases by approximately one-third.

This comparison of CNS tumors identified through incidence and mortality tracing found a 59% overlap between the two sources. Cancer incidence tracing identified 17% more cases than would have been found using mortality tracing alone. Equally as important was the identification of CNS deaths not found during cancer incidence tracing. These deaths may reflect not only the time period limitations of some state cancer registries but also inaccurate or incomplete recording of CNS causes of death on death certificates. Compared to cancer registry identification of CNS neoplasms, the positive predictive value of death certificates for predicting case status was 6% for unspecified, 35% for benign and 86% for malignant histologies.

The results for malignant CNS tumors are similar to other detailed investigations of death certificate accuracy (3, 14). The main concern with the use of death certificates for malignant CNS case reporting is the lack of specificity regarding the type of tumor; this limitation precludes detailed analyses by histology using only mortality data. More problematic for researchers are analyses of nonmalignant CNS tumors. Death certificates seriously underascertained both benign and unspecified CNS tumors; analyses based on mortality data would not accurately capture the true extent of disease among the cohort. However, most state cancer registries have only collected nonmalignant CNS tumor information since 2004, which currently limits the usefulness of state cancer registries as a source of nonmalignant CNS tumor information. The underascertainment of CNS deaths could seriously affect any interpretation of results, more so if examining nonmalignant CNS-related causes.

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