Brain Cancer and Nonoccupational Risk Factors: A Case-Control Study among Workers at Two Nuclear Facilities

ARVIND V. CARPENTER, DDS, DRPH, W. DANA FLANDERS, MD, DSC, EDWARD L. FROME, PHD, PHILIP COLE, MD, DRPH, AND SHIRLEY A. FRY, MD, MPH

Abstract: In a nested case-control study of nuclear workers, 82 brain cancer cases were compared with 328 matched controls to investigate the possible association with nonoccupational risk factors such as histories of epilepsy or head injury. We observed a moderately strong association between brain cancer occurrence and history of epilepsy (OR = 5.7, 95 per cent CI: 1.0, 32.1), but did not find a positive association with previous head injury (OR = 0.9, 95 per cent CI: 0.2, 4.2). (*Am J Public Health* 1987; 77:1180–1182.)

Introduction

Results of several epidemiologic studies have suggested that people with a history of epilepsy[1–4] or of head injury[3,5,6] have higher brain cancer rates than people without such histories, although results of two studies do not support this pattern.[7,8]

To investigate further the association between brain cancer and histories of epilepsy, head injury, or other nonoccupational factors, we analyzed medical histories for brain cancer cases and controls all of whom were selected from approximately 66,000 White workers employed any time between 1943 and 1977 at two nuclear facilities in Oak Ridge, Tennessee. Workers at the Y12 Plant (the Y12 cohort) under the management of the Tennessee Eastman Corporation from 1943 to 1947 were involved in the enrichment of uranium 235 in the form of uranium tetrachloride via an electromagnetic process and the subsequent conversion to uranium tetrafluoride.[9] After 1947, the Y12 Plant was operated until 1984 by the Union Carbide Corporation, and workers were primarily involved in fabrication and certification of components for nuclear weapons.[10] Workers at the Oak Ridge National Laboratory (the ORNL cohort) have been involved in research and the development of technology for production of energy.[11]

An advantage of this study compared with other types of case-control studies is that the possibility of "recall bias" is remote because data were recorded before diagnosis of brain cancer, and under similar conditions and for similar reasons for cases and controls.

Methods

Study Population

Cases were 67 White male and 15 White female workers who, according to death certificate information, died of primary malignant tumors of the brain (ICDA 8th revision code 191) between 1943 and 1979. For each of the 82 cases, four controls were selected who matched the case on race, sex, cohort (Y12 or ORNL), year of birth, and year of hire.

Address reprint requests to Arvind V. Carpenter, DDS, DrPH, Epidemiologist, Center for Epidemiologic Research, Oak Ridge Associated Universities, P.O. Box 117, Oak Ridge, TN 37831. Dr. Flanders, currently Medical Epidemiologist with CDC, Center for Environmental Health, Atlanta, was Assistant Professor, Department of Epidemiology, School of Public Health, University of Alabama at Birmingham at the time of the study. Dr. Frome is Statistician, Mathematics and Statistics Research, Oak Ridge National Laboratory; Dr. Cole is Professor and Chairman, Department of Epidemiology, UAB School of Public Health, Birmingham; Dr. Fry is Director, Center for Epidemiologic Research, Oak Ridge Associated Universities. This paper, submitted to the Journal September 12, 1986, was revised and accepted for publication April 21, 1987.

Data Collection

Information on demographic variables and other characteristics including race, sex, birth date, date and cause of death (if dead), socioeconomic status (using pay code as a surrogate), and job title had been abstracted previously, primarily from personnel files.[12] Each job title was assigned a "job classification" code (professional, skilled, or unskilled [PSU]), based on assumed educational requirements for the job. The PSU code was also used as a surrogate measure of socioeconomic status.

Medical records of cases and controls maintained at each facility provided information, for most study subjects, concerning histories of epilepsy and head injury. These medical data reflected information obtained from pre-employment medical histories and health status during employment. Information about epilepsy ("Have you suffered from epilepsy?" yes or no) and head injury ("Did you have a head injury?" yes or no) was self-reported on the history form. The date of diagnosis of epilepsy or date of and severity of head injury was not available from these medical records. The medical records also provided information about blood group (ABO and Rh), tobacco use (any use of tobacco—yes or no), and alcohol consumption (yes or no), although this information had been recorded for relatively few subjects. Medical records were abstracted without knowledge of the case-control status of the workers.

For monitored workers, film badge readings were summed over each calendar year to calculate the annual external radiation dose. For each member of a matched set, annual doses were summed to calculate a cumulative dose up to the year of death of the case.[12] Nonmonitored workers were considered unexposed.

Analysis

Matched conditional logistic regression analyses for categorical exposure variables were conducted using a SAS program (PHGLM),[13] and interpreted as described by Breslow and Day.[14] The logistic regression model was used to control for potential confounding by socioeconomic status. Confidence intervals are approximate because the number of discordant matched sets generally is small. Matched sets were included in the analyses only if information was available for the case and at least one of the corresponding controls. Because brain cancer can cause epilepsy, in some analyses we allowed for five-year, 10-year, and 15-year latency periods by excluding the positive history of epilepsy five, 10, or 15 years prior to the death of case, respectively, for cases and their matched controls.[15]

Results

The proportion of skilled workers was higher among the cases (81 per cent) than among the controls (72 per cent) (Table 1). Fifty-six (68 per cent) cases were known to have had malignant tumors of glial origin, of which 21 (38 per cent) were glioblastomas and 20 (36 per cent) were astrocytomas.

The odds ratio, comparing brain cancer occurrence among those with history of epilepsy with that among subjects without such a history, was 5.7 (95 per cent CI: 1.0, 32.1, cases = 4) (Table 2), which remained unchanged when analysis was repeated to adjust for the effect of external radiation or socioeconomic status. After allowing for a five-year latency period, the odds ratio was 3.1 (95 per cent CI: 0.4, 22.4, cases = 2), and the odds ratio after allowing for 10-year and 15-year latency periods was 1.8 (95 per cent CI: 0.2, 20.1, cases = 1). After controlling for head injury, the odds ratio was 6.5 (95 per cent CI: 1.1, 38.6, cases = 4). When restricted to brain cancer cases of glial origin, the matched odds ratio was infinite because four cases but none of the matched controls reported history of epilepsy in this group ($p = 0.002$).

The odds ratio comparing brain cancer occurrence among workers with a history of head injury with that among those without was 0.9 (95 per cent CI: 0.2, 4.2, cases = 2) (Table 2). When restricted to brain cancer of glial origin, the odds ratio was 1.4 (95 per cent CI: 0.3, 7.2, cases = 2).

The odds ratio comparing workers paid hourly with salaried workers was 1.5 (95 per cent CI: 0.7, 3.3, cases = 70). Similarly, the risk of brain cancer was increased for the skilled workers (OR = 1.6, 95 per cent CI: 0.7, 3.7, cases = 66) when compared to the professional workers (Table 2). Odds ratios for other factors, except for Rh blood factor, were near unity (Table 2).

Odds ratios for all these factors remained unchanged when controlled for the socioeconomic status.

TABLE 1—Distribution of Cases and Controls

Variable	Level	Cases No.	Cases (%)	Controls No.	Controls (%)
Total		82	(100.0)	328	(100.0)
Sex*	Male	67	(82.0)	268	(82.0)
	Female	15	(18.0)	60	(18.0)
Cohort*	Y12	66	(81.0)	264	(81.0)
	ORNL	10	(12.0)	40	(12.0)
	Multi†	6	(7.0)	24	(7.0)
Age at Hire*	Mean	33.6 years		33.6 years	
	Median	33.0 years		33.0 years	
Age at Death for Cases	Mean	52.5 years		———	
	Median	52.3 years		———	
SES (Pay Code)	Hourly	70	(85.0)	268	(82.0)
	Monthly	12	(15.0)	60	(18.0)
SES (PSU)	Professional	10	(12.0)	50	(15.0)
	Skilled	66	(81.0)	236	(72.0)
	Unskilled	6	(7.0)	42	(13.0)

*Matching factors
†Worked in both the Y12 and ORNL cohorts

TABLE 2—Matched Univariate Analyses for Nonoccupational Risk Factors

Variable	Level	Odds Ratio	95% Confidence Interval	No. of Cases	No. of Controls
Epilepsy	No	1.0	—	65	249
	Yes	5.7	1.0–32.1	4	2
Head Injury	No	1.0	—	80	319
	Yes	0.9	0.2–4.2	2	9
Tuberculosis	No	1.0	—	72	276
	Yes	1.1	0.2–5.6	2	7
ABO blood group	O	1.0	—	15	52
	A	1.0	0.4–2.4	10	38
	B	0.6	0.1–3.3	2	10
	AB	0.6	0.1–5.5	1	6
RH factor	Neg	1.0	—	2	19
	Pos	2.9	0.6–13.0	25	81
Tobacco Use	No	1.0	—	16	47
	Yes	1.1	0.5–2.7	25	57
Alcohol Use	No	1.0	—	30	66
	Yes	0.6	0.2–2.4	7	26
SES (Pay code)	Monthly	1.0	—	12	60
	Hourly	1.5	0.7–3.3	70	268
SES (PSU)	Professional	1.0	—	10	50
	Skilled	1.6	0.7–3.7	66	236
	Unskilled	0.8	0.2–2.5	6	42

Discussion

We observed a moderately strong association between brain cancer and history of epilepsy, although confidence intervals were wide, reflecting the low prevalence of epilepsy and the modest number of subjects studied. These results are consistent with those of at least three other studies,[1-3] although Choi, *et al*,[7] failed to find such an association.

A possible explanation for the association of brain cancer with a history of epilepsy may be that epilepsy is causally related to the development of brain cancer, perhaps by increasing the permeability of the blood brain barrier to blood-borne carcinogens at the focus of the seizure.[1] Other possibilities may be that a common etiologic factor causes both epilepsy and brain cancer, or that a slow-growing brain cancer such as astrocytoma causes seizures for some time before its diagnosis.[3] The unavailability of date of diagnosis of epilepsy made it difficult to estimate the odds ratio for brain cancer after allowing for various latency periods. Even though odds ratios remained elevated when allowance was made for five-, 10-, or 15-year latency periods, these estimates are based on only one or two cases and are, therefore, unstable statistically.

A weakness of this study, as with most epidemiologic studies,[16] is the potential for misclassification of subject's exposure and/or disease status. Histories of epilepsy and of head injury were abstracted from the same historical records, created prior to death of the case, for cases and controls so that misclassification of epilepsy or of head injury is likely to have been nondifferential. Bias resulting from such nondifferential misclassification would be toward the null implying that our results for epilepsy might well have been stronger, if history of epilepsy were not subject to misclassification. In fact, our use of historical records to determine history of epilepsy is more objective and probably less subject to differential misclassification than the methods used in some previous studies.[3,8]

Results of this study do not support the hypothesis that head injury increases the risk of brain cancer, consistent with results of Choi, *et al*,[7] and of Ahlbom, *et al*.[8] However, Hochberg, *et al*,[3] found an association between head trauma and development of glioblastoma, and Preston-Martin and colleagues[5,6] demonstrated an association between head injury and development of meningiomas.

Several reasons may explain our failure to find an association between head injury and brain cancer. First, no causal relationship may exist between head injury and brain cancer, or the association may be weak and therefore difficult to detect in a study of modest size such as this. Second, history of head injury, noted on a medical history form completed by the study subject, may have been incompletely or inaccurately reported. Also a mild head injury that had occurred in the immediate past may have been remembered by a study subject, while a similar injury that had occurred a few years back may have been missed by other subjects. Furthermore, diagnosis of brain cancer based primarily on death certificates could be inaccurate. Each of these latter possibilities would result in misclassification and if nondifferential, would bias the odds ratios towards unity.

The matched study design and matched analyses precluded confounding by several demographic factors including age, sex, cohort, and socioeconomic status, although the possibility remains that unidentified factors could have confounded the results. Selection bias, a potentially important source of bias particularly in case-control studies, is probably of less importance in this study than in many other case-control studies because of the nested study design and because of the relatively complete follow-up of the cohorts from which subjects were selected.

The odds ratio of 1.0 comparing risk of brain cancer among people with blood group A with that among people with blood group O is consistent with results of two published studies,[7,17] although other researchers estimated a higher risk among people with blood group A.[18,19] Although we found increased risk associated with Rh positivity, the width of our confidence limits make our results consistent with those of Choi, *et al*,[7] who reported no association. For the remaining risk factors reported here, little association was found with brain cancer mortality.

Identification of cases was based on information contained on death certificates, information which could be confirmed for only a small percentage of cases. Since this information may be inaccurate, disease status may have been misclassified. Again, if misclassification of disease were nondifferential, then associated bias would be toward the null implying that our results for epilepsy would likely have been stronger with perfectly accurate information. On the other hand, if decedents with a history of epilepsy were more likely than other decedents to have death attributed to brain cancer, then a positive bias could have been introduced.

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REFERENCES

1. Gold E, Gordis L, Tanascia J, Szklo M: Risk factors for brain tumors in children. Am J Epidemiol 1979; 109:309–319.
2. White SJ, McLean AEM, Howland C: Anticonvulsant drugs and cancer: A cohort study in patients with severe epilepsy. Lancet 1979; 2:458–461.
3. Hochberg F, Toniolo P, Cole P: Head trauma and seizures as risk factors of glioblastoma. Neurology 1984; 34:1511–1514.
4. Shirts SB, Annegers JF, Hauser WA, Kurland LT: Cancer incidence in a cohort of patients with seizure disorders. JNCI 1986; 77:83–87.
5. Preston-Martin S, Paganini-Hill A, Henderson BE, Pike MC, Wood C: Case-control study of intracranial meningiomas in women in Los Angeles County, California. JNCI 1980; 65:67–73.
6. Preston-Martin S, Yu MC, Henderson BE, Roberts C: Risk factors for meningiomas in men in Los Angeles County. JNCI 1983; 70:663–666.
7. Choi NW, Schuman LM, Gullen WH: Epidemiology of primary central nervous system neoplasms. II. Case-control study. Am J Epidemiol 1970; 91:467–485.
8. Ahlbom A, Navier IL, Norell S, Olin R, Spannare B: Nonoccupational risk indicators for astrocytomas in adults. Am J Epidemiol 1986; 124:334–337.
9. Polednak AP, Frome EL: Mortality among men employed between 1943 and 1947 at a uranium processing plant. JOM 1981; 23:169–178.
10. Polednak AP: Long-range studies of uranium workers and the Oak Ridge radiation worker population. *In*: Hubner KF, Fry SA (eds): The Medical Basis for Radiation Accident Preparedness. New York: Elsevier/North-Holland, 1980; 401–409.
11. Checkoway H, Mathew RM, Shy CM, Watson JE, Tankersley WG, Wolf SH, Smith JC, Fry SA: Radiation, work experience and cause-specific mortality among workers at an energy research laboratory. Br J Ind Med 1985; 42:525–533.
12. Carpenter AV: An epidemiologic investigation of central nervous system cancers among workers at diverse nuclear facilities. Doctoral Dissertation, University of Alabama at Birmingham. Ann Arbor, MI: University Microfilms International, 1986.
13. Harrell FE: The PHGLM Procedure. *In*: SAS Institute, Inc: SUGI Supplemental Library User's Guide. Cary, NC: SAS Institute, 1983; 267–294.
14. Breslow NE, Day NE: Statistical Methods in Cancer Research. Vol. I. The analysis of case-control studies. Lyon, France: International Agency for Research on Cancer, 1980.
15. Rothman KJ: Induction and latent periods. Am J Epidemiol 1981; 114:253–259.
16. Rothman KJ: Modern Epidemiology. Boston: Little, Brown and Company, 1986.
17. Garcia JH, Okazaki H, Aronson SM: Blood-group frequencies and astrocytomata. J Neurol 1963; 20:397–399.
18. Buckwalter JA, Turner JH, Gamber HH, Raterman L, Soper RT, Knowler LA: Psychoses, intracranial neoplasms and genetics. Arch Neurol Psychiatry 1959; 81:480–485.
19. Selverstone B, Cooper DR: Astrocytomas and ABO blood groups. J Neurosurg 1961; 18:602–604.