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Diagnostic Sensitivity Bias — An Epidemiologic Explanation for an Apparent Brain Tumor Excess

Peter Greenwald, M.D.; Barry R. Friedlander, M.D.; Charles E. Lawrence, Ph.D.; Terry Hearne, M.S.; and Kenneth Earle, M.D.

Preliminary data showing over-representation of the Eastman Kodak Company (Rochester) on death certificates of brain tumor patients, and higher risk for older workers when compared to the general population, led to a case-control epidemiologic study. Chemical exposure histories of 56 workers with brain tumors were compared with those of other Kodak employees. No differences were found in exposure to a variety of chemicals. In addition, employees with brain tumors were compared to other upstate New York brain tumor patients; there was no difference in histology. However, the Kodak employees had diagnoses more frequently confirmed by histologic examination and more thorough diagnostic studies. Thus, the apparent initial excess of diagnosed tumors may have resulted from a "diagnostic sensitivity bias" arising from more complete medical evaluation of Kodak employees.

Hypothesis-generating studies, done coincidentally by the New York State Department of Health and Eastman Kodak Company in 1976, raised the question of whether there was a brain tumor excess among Kodak employees. In order to investigate these preliminary findings, a cooperative study was undertaken by the Department of Health and the company.

The Health Department conducted a case-control study of 20-to-64-year-old men dying in 1968 through 1973 with brain tumors (International Classification of Disease, Eighth Revision Code — ICDA-8:191, 238.1) in New York State, exclusive of New York City. Two controls for each decedent with a brain tumor were randomly selected from men dying from all other causes matched by five-year age group at death and the same multi-county area of the state. The study, exploratory in nature, focused on occupation. Death certificates in New York State note "usual lifetime occupation" and "kind of business." The name of the employer is commonly entered under kind of business for 12 major New York State companies because of their large size and ease of identity. A relative risk of four (Fishers p = 0.04) for employment at Eastman Kodak was found both by the initial analysis of 1968 through 1969 data (six cases) and by a confirmatory analysis for 1970 through 1973 (six additional cases).

The possibility that this finding may have been due to an excess of brain tumors in the region of the Kodak plant prompted further study. A second case-control study identical to the first but limited to Monroe County (including the city of Rochester) and covering the interval 1958 through 1976 was conducted. A highly significant although less-marked relative risk of 1.62 (p = 0.004) emerged.

Concurrently, Eastman Kodak investigators had been reviewing sickness-absence data. Noticeable absences due to brain malignancy prompted the estimation of risk (for both mortality and incidence) for persons working during the period 1964 through 1975 for which population denominators were available. The expected number of deaths from brain tumors (ICDA-8, 191) was computed by applying age-sex-specific mortality rates for the U.S. white population, 1950-1969,[1] to the Kodak Rochester age-sex-specific person-years-at-risk. Incident cases were estimated from age-sex-race-specific data from the U.S. cancer survey data 1969-1971.[2] Only person-years contributed by active (or disabled) employees were included for incidence analysis since completeness of information was uncertain for persons diagnosed after leaving the company. Neither the overall standardized mortality ratio for brain malignancy (SMR 128, lower 95% confidence limit [CL] of 91.8) nor the standardized incidence ratio (SIR 132, lower 95% CL of 92.4) was significantly increased. However, two groups did show elevated risk.

1. The SIR for women was 217 (based on 10 cases; 95% CL = 104 - 399).
2. The incidence ratio for the 55-to-59-year age group (both sexes) was 281 (based on 14 cases; 95% CL = 153 - 472).

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A relative risk declining with time explains the difference in significance levels found in the two studies. Thus, the two studies clearly indicated the need for further study and suggested special emphasis on women and on the 55-to-59-year age group for both sexes

In view of the consistency in these preliminary results, an intensive joint investigation was carried out, the results of which are reported.

Methods

The general design is that of a retrospective, case-control, epidemiologic study. Cases are all Eastman Kodak Rochester employees identified as having died with primary intracranial neoplasms* between January 1, 1956, and December 31, 1975 Two control groups of Eastman Kodak employees were selected — one from employees who had died from causes not including brain tumors; the second from a historical file of full-time employees. Chemical and other occupational exposures were the key study variables.

In order to identify the case group, New York State death certificate files were abstracted for all residents of Monroe and adjacent counties whose stated cause of death was a brain tumor during the study period. These were matched against the Eastman Kodak mortality data file (January 1, 1956, to December 31, 1975) and population data file (January 1, 1964, to December 31, 1975). Rochester area Eastman Kodak employees who died outside of Monroe and adjacent counties were identified from the same file.

Deceased controls were selected from the company's mortality data file (January 1, 1956, to December 31, 1975), matched to cases on sex and five-year age group, and picked at random from within these groups in a 2:1 control to case ratio. Another control group, including both living and dead persons who were also matched to cases on sex and five-year age group with a 2:1 ratio, was chosen from the company's population data file (January 1, 1964, to December 31, 1975). This latter control group was derived from a computerized employee record system begun on January 1, 1964, and was used only for comparisons to cases who had worked after that time. The rationale for the second control group was that it might be more representative of the employed population than controls selected from the mortality file.

Cases and controls were combined so that investigators searching for exposure data did not know whether an individual was a case or a control. Job histories for cases and controls were obtained from mortality and population files, supplemented by abstracting divisional personnel records. The combined case and control groups were then separated into divisions. Review of job titles and organizational units within the company demonstrated that these were not sufficient for identifying industrial exposures of the study subjects. Thus, it was necessary to have the occupational physicians responsible for each division determine potential exposures, including time and duration, for each study subject who had worked in their division. These occupational physicians knew neither what disease was under study nor the case-control status of the study subjects A structured exposure evaluation form containing the complete job history was provided for each study subject. Physicians and the investigators worked with plant chemists, industrial hygienists, department supervisors, long-time employees, department personnel officers, safety coordinators and others who might be able to assist them to identify exposures Based on a review of the major processes of the company and relevant carcinogenesis literature, the 18 categories of exposure shown in Table 1 were used. Heat was considered a control variable, since no case-control difference was expected Physicians were queried about any gaps or inconsistencies in the data they collected

In general, it was not possible to distinguish between potential for exposure and actual exposure. There was no method of determining who actually had absorbed or ingested chemicals into his body Thus, throughout this report, "exposure" means "potential for exposure" Relative risks and significance levels were calculated by the method of Miettinen.[3]

Histopathology observed in cases was compared to that noted in other brain tumor decedents in order to see whether the pattern of cell types of brain tumors among Eastman Kodak employees differed significantly from those of others in upstate New York. Two tumor comparison groups were used. These were obtained by matching cases to New York State's death certificate files for other persons of the same sex, five-year age group, and year of death who died with brain tumors. One tumor comparison group consisted of residents of the nine-county Rochester Health Department region, excluding Kodak employees; the other comprised residents of New York State, exclusive of New York City and the Rochester area.

Case and tumor comparison slides were obtained from hospital pathologists and reviewed by the neuropathologist (Dr. Earle), who was blinded as to case or tumor comparison status. The World Health Organization classification was used, supplemented by coding of anatomic site within the brain. If pathology slides could not be obtained, or were found not to show a primary brain tumor, an alternate comparison tumor was drawn using the same matching criteria.

Hospital records and death certificates were abstracted, in order to compare demographic, medical and family data on cases with those of the tumor comparison group. Information about procedures used in making the diagnoses was recorded in the hospital records abstract form.

Results

Case selection procedures provided a case group of 56 employees who had died with primary brain tumors during the study period. Based on matching criteria, 112 deceased controls were selected from the company's mortality data file; a subgroup of 31 cases working after January 1, 1964, was matched to the company's population file, providing a second control group of 62 alive or dead persons.

The exposures of the cases and controls were analyzed for each set of controls. Results are shown in Table 1. No significant increases were found. With 18 hypotheses it would not be at all surprising to find one difference signif-

*ICD-8, 191, 192.1, 192.9, 225.0, 225.2, 225.9, 236.1, 238.3, 238.6,

Table 1. — Exposure of Cases Dying with Tumors of the Central Nervous System (1956-1975) and Matched Controls. The Number Exposed Refers to Those Ever Having the Potential for Exposure While Employed.

	All Cases (N = 56) vs. Dead Controls (N = 112)				Cases with Last Employment 1964 or Later (N = 31) vs. Population Controls (N = 62)			
Exposure Category	No. of Cases Exposed	No. of Dead Controls Exposed	Relative Risk	(95% CL)	No. of Cases Exposed	No. of Pop. Controls Exposed	Relative Risk	(95% CL)
Chlorinated solvents	16	36	0 82	(0 44-1 55)	7	13	1 10	(0 45-2 71)
Other solvents	32	56	1 40	(0 77-2 55)	18	32	1 40	(0 61-3 26)
Plasticizers	8	18	0 86	(0 39-1 89)	5	7	1 55	(0 53-4 54)
Amines	7	13	1 09	(0 47-2 53)	3	5	1.23	(0 34-4 49)
Oil Mist	7	21	0 65	(0 31-1 36)	4	7	1 16	(0.39-3 43)
Other and mixed chemicals	13	25	1 06	(0 54-2 09)	8	19	0.78	(0.34-1 79)
Silver	10	21	0 93	(0 44-1 97)	5	7	1.48	(0 54-4 08)
Other heavy metals	9	24	0 69	(0 33-1 43)	5	17	0 48	(0 19-1 25)
Radiation	0	8	—	(0.00-0 95)	0	5	—	(0.00-1 25)
Heat	9	21	0 79	(0 36-1 77)	6	10	1.23	(0 49-3 08)
Animal tissue	13	22	1 32	(0.63-2.80)	6	11	1.09	(0 47-2.51)
Color forming agents (dyes and couplers)	6	12	1.00	(0 39-2.54)	2	4	1.00	(0.24-4 16)
Black and white developers	7	11	1 31	(0.56-3 07)	5	6	2.26	(0 63-8 15)
Color developers	6	6	2.16	(0.78-5 93)	4	6	1 50	(0 43-5 27)
Hardeners	7	18	0.73	(0.33-1 65)	4	7	1.23	(0.34-4 49)
Wetting and spreading agents	5	13	0.75	(0.30-1.86)	2	4	1 00	(0.24-4.16)
Photographic sensitized product	5	13	0.72	(0.27-1.88)	1	4	0.50	(0.08-3 15)
Film and photographic paper dusts	4	8	1.00	(0.37-2 74)	2	4	1.00	(0.21-4.76)

icant at the 0.05 level. Thus the significant decrease in risk observed for radiation exposure (which included work in rooms with only very low-level radiation source, e.g., tritium buttons) is well within the realm of chance. Comparison of time of exposure, duration of exposure and exposure-to-diagnosis intervals among exposed cases versus exposed controls also showed no differences.

The case group included 18 women. Twelve of the 18, including four of six in the 55- to 59-year age group, had had no exposures. The "other solvents" category, with four cases, was the only category containing more than one woman. The relative risk estimates for this category were less than one. The 55- to 59-year age group of men included eight cases. Again there were no clusters in any exposure category, and the extent of exposure for controls was about the same as for cases. Few of these workers had been located in any one setting. A review of age and employment data showed no evidence of a cohort effect.

Findings on the histological type of tumor are shown in Table 2. Here, cases are compared to two groups of other upstate New York residents diagnosed as having brain tumors. It can be seen that the diagnosis was pathologically confirmed and reconfirmed by the review patholo-

Table 2. — Histologic Types of Eastman Kodak Cases and Tumor Comparison Groups for Whom Slides Were Available for Reexamination. Numbers in Each Category Are Shown.

Cell Type (World Health Organization Classification)	Eastman Kodak	Rochester Area Tumor Comparison Group	Statewide Tumor Comparison Group
Glioblastoma	32	30	26
Giant Cell Glioblastoma	3	2	2
Glioblastoma with sarcomatous component	4	2	3
Primitive polar spongioblastoma			1
Anaplastic astrocytoma	4	4	5
Astrocytoma, protoplasmic	3	1	1
Astrocytoma, gemistocytic		2	1
Mixed oligo-astrocytoma			2
Oligodendroglioma	1		
Anaplastic oligodendroglioma		1	
Medulloblastoma	1		
Chromophobe adenoma	1		
Neurilemmoma			1
Craniopharyngioma			1
Meningotheliomatous meningioma			1
Fibrous meningioma	1	2	2
Transitional meningioma		2	
Total	51	46	44

Table 3. — Frequency of Pathology Confirmation and Diagnostic Procedures on Cases and Tumor Comparison Groups.

	Eastman Kodak Cases			Rochester Area Tumor Comparison Groups				Statewide Tumor Comparison Groups			
	Total	No.*	%	Total	No.*	%	p	Total	No.*	%	p
Coded as Brain Tumor on Death Certificate											
No hospital records available	64	3†	4 7	84	15	17.9	0 036	100	13	13 0	0 166
Not cancer or metastatic cancer	64	7	10 9	84	10	11 9	0 623	100	17	17 0	0 170
Clinical diagnosis (no pathology)	64	3	4 7	84	7	8 3	0 381	100	10	10 0	0 219
Pathologically confirmed‡	64	51	79 7	84	52	61 9	0 019	100	60	60 0	0 008
Pathological or Clinical Diagnosis of Brain Tumor											
Craniotomy brain surgery or biopsy	54	48	88 9	59	49	83.1	0 373	70	53	75 7	0 061
Brain scan	54	33	61 1	59	25	42 4	0 046	70	21	30 0	0 0005
Angiogram	54	41	75 9	59	40	67 8	0.338	70	45	64 3	0 163
EEG	54	20	37 0	59	20	33 9	0.727	70	23	32 9	0 627
Pneumoencephalogram	54	19	35.2	59	9	15.3	0.014	70	12	17 1	0 021
Autopsy	54	28	51.9	59	28	47.5	0.782	70	24	34 3	0 049
Skull x-ray	54	50	92.6	59	50	84.7	0 191	70	67	95 7	0 455

*Number that hospital records indicated procedure was performed

†Two of these are included with the 54 pathologically or clinically diagnosed cases for the study of exposures, giving the 56 cases shown in Table 1 (see text for details)

‡Of the pathologically confirmed cases, slides could be obtained for review on 51 cases, 46 Rochester area matched controls, and 44 Statewide matched controls as shown in Table 2

p = Significance levels for differences in proportions having procedures between Kodak cases and comparison groups

gist for 51 of the 56 cases listed in Table 1. Three cases were based on a clinical diagnosis: The diagnosis for one patient was supported by a ventriculogram and a craniotomy showed necrotic tissue unsatisfactory for histological examination; for the second by a brain scan; and for the third by clinical signs of a brain mass and an autopsy that excluded a non-brain primary but permission was denied to examine the brain. Two additional cases were included on the basis of death certificate reports, when no hospital records could be located. One certificate stated "glioblastoma multiforme of left cerebellum" and the other, "right temporal brain tumor." Another death certificate report noting "brain tumor" was excluded; this report had come from a nursing home and no other information could be found.

The distribution of central nervous system tumors by cell type showed no differences between cases and either tumor comparison group. Glioblastoma and its variants accounted for about 70% of diagnoses for the case and each tumor comparison group. There were no case-comparison group differences in anatomic location of the brain tumors.

A significant contrast is seen in the extent of pathological confirmation for Eastman Kodak cases when they are compared with those in the Rochester area or statewide tumor groups (Table 3). This finding of a higher percentage of histologically confirmed brain tumors among Eastman Kodak employees suggests that diagnosis may be more thorough for these workers than for either tumor comparison group. The top section of Table 3 refers to those coded on death certificates as having brain tumors, rather than the final study groups. Table 3 also shows the frequency of diagnostic procedures for the cases and for decedents in the tumor comparison groups for whom complete hospital records were available and obtained. It can be seen that the cases had a significantly higher frequency of brain scans and pneumoencephalograms than did either tumor comparison group. It is noteworthy that all eight procedures were more commonly performed in cases than in Rochester-area controls and that seven of eight procedures were more commonly performed in cases than in statewide controls. It should be noted that the study covered a period before the availability of computed tomography.

With one exception, no family history or demographic differences were observed between the cases and the tumor comparison groups. The hospital records indicated that three study cases had family histories of epilepsy, while the less complete hospital records of those in the tumor comparison groups showed no such family history.

Discussion

Employees in this study had a more thorough medical diagnostic examination than did either of the tumor comparison groups. That is, workers in this large company who died with brain tumors had pathologically confirmed diagnoses and sophisticated diagnostic procedures more frequently than did other brain tumor patients living in the same region or scattered throughout upstate New York. Such differences in diagnostic effort may account for the initial observations that led to the study. This study showed an absence of exposure differences between employees with and without brain tumors.

Age-specific incidence rates for brain tumors appear to peak in the 55-to-64-year age group and then decline in most population based reports,[4] but the incidence continues to rise with age in Rochester, Minnesota (location of the Mayo Clinic).[5] Schoenberg et al[4] offer as a possible

explanation that more complete case ascertainment and higher autopsy rates in the Mayo Clinic area account for this difference. Higher rates are seen for all age groups of adults, although the difference is most marked in the elderly. It appears that many brain tumors in the general population are undiagnosed or misdiagnosed. Retrospective industrial or other studies that determine expected rates on the basis of general population data thus may show artificially high rates because of underdiagnosis in the general population. It remains to be seen whether computed tomography will change this in the future.

The improved diagnosis and case ascertainment of workers under certain circumstances of employment such as observed here might be called the "diagnostic sensitivity bias." Sensitivity is the probability that persons with the disease are correctly classified, and the bias comes from a difference in sensitivity between the study population and the non-exposed comparison population. This bias would appear to pertain especially to conditions that are difficult to diagnose, such as brain tumors, and to industries where workers have such benefits as health insurance and high-quality employee medical services with referral and follow-up. Of course, the opposite could occur in an industry with substandard medical services or in a community where the disease is overdiagnosed. The bias would also apply to nonindustrial studies having this type of difference in diagnosis.

A method for detecting this potential bias may be an essential part of many industrial and other studies. Ideally, one would detect this bias through the identification of persons with the disease under study who were misdiagnosed as having other diseases. In reality this ideal approach may rarely be feasible. Thus, surrogate measures will often be required. In this study, the diagnostic sensitivity bias was revealed through the use of tumor comparison groups to examine histopathological and diagnostic procedures. Such diseased comparison groups rarely have been used in epidemiologic research. In this study they only provided partial information about the extent of bias, as any brain tumors that may have been misdiagnosed were still undetected.

The medical literature contains several reports of apparent industrial excesses of brain tumors that might be influenced by medical diagnosis and ascertainment differences, but study designs do not allow for assessment of this possibility.[6,7,8] Studies showing no general excess could be influenced in a reverse manner if industrial detection is poor. Rubber industry worker studies[9-13] have shown conflicting results suggesting that tumor comparison groups might be vital if we are to distinguish the possibilities of artifact of diagnosis from true exposure effect. A study[14] in another large company with an extensive medical program also reported rates that were somewhat higher for brain tumors than for other cancers. Higher brain tumor rates have been reported for upper socioeconomic levels, particularly professional and managerial[15]; this increase may be attributable to better diagnosis.

The diagnostic sensitivity bias adds to the list of problems associated with occupational studies. For example, McMichael et al[16,17] described the selection of healthy workers by industry, making comparisons to population statistics difficult. This is called the "healthy worker effect." In order to evaluate the possibility of a "diagnostic sensitivity bias" in occupational studies, we suggest the use of diseased comparison groups and detailed attention to the level of diagnostic medical procedures used.

Furthermore, this bias may have an importance outside of the occupational setting. It could, for example, distort the perception of the influence of socioeconomic variables or geographic patterns. On the other hand, this bias may be important only in a few specific studies, such as this one. The extent and importance of the diagnostic sensitivity bias will be resolved only through further study.

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