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UC-41

Issued: June 1983

# Case-Control Study of Brain Tumors Among White Males Employed at the Rocky Flats Plant





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# CASE-CONTROL STUDY OF BRAIN TUMORS AMONG WHITE MALES EMPLOYED AT THE ROCKY FLATS PLANT

by

M. Reyes, G. Wilkinson, G. Tietjen, G. Voelz, J. Acquavella, and R. Bistline

#### **ABSTRACT**

We conducted a case-control study of 16 primary brain tumor deaths occurring among white males employed at the Rocky Flats Plant during 1952-1980 to investigate the relationship between these tumor cases and occupational radiation/nonradiation exposures. Three mutually exclusive control groups were selected from the white male employees: matched (individually matched on age and period of employment), deceased, and random. Each group consisted of a 4:1 control-case ratio. Analyses for exposure to internally deposited plutonium and external penetrating radiation were based on health physics dosimetry measurements. Potential exposure to nonradiation hazards was analyzed by job title and work area. Because evidence of exposure to beryllium and uranium existed in only one case, we did not analyze for these exposures. Our study showed no statistically significant association between exposure to internal radiation and brain tumor. We found no statistically significant differences in external radiation exposure between the tumor cases and the three control groups. In addition, no nonradiation occupational risk factors were identified.

# I. INTRODUCTION

Recently, two independent studies found an excess of brain tumors (BTs) among workers at the Rocky Flats (RF) Plant located in Jefferson County, Colorado. <sup>1-3</sup> In the RF cohort mortality study of white males, <sup>2,3</sup> a statistically significant excess of observed versus expected deaths occurred only in the benign and unspecified neoplasms category [8th Revision International Classification of Disease (ICD) codes 210-239]. Examination of the death certificates for individuals in this category revealed that these neoplasms were BTs. To investigate this finding, we conducted a case-control

study of the relationship between BTs and occupational radiation/nonradiation exposures, nested within the RF white male cohort.<sup>2,3</sup>

Since RF opened in 1952, employees at this plant have fabricated nuclear weapon components containing plutonium, beryllium, and uranium. The plant is geographically divided into four major work areas. Area A is primarily used for casting and machining depleted uranium. In 1958, beryllium and stainless steel casting and machining became an additional part of operations in the area. Other minor processes in Area A include incineration disposal of machining chips, stainless steel welding, mold coating, and graphite machining. In area

B, major activities include casting and machining depleted uranium, as well as rolling and pressing beryllium, depleted uranium, and until 1965 enriched uranium. In these two areas, workers may be exposed to radiation, degreasing agents, and solvents. Most plutonium-related work takes place in Area C and includes fabrication, casting, machining, inspection and assembly of plutonium weapon components, and recovery and processing of plutonium waste. Until the 1970s, the final assembly of all weapon components took place in Area D. In recent years, the activities in this area have included nondestructive testing research and the storage of plant materials. The enriched uranium work in Area B and the plutonium operations in Areas C and D are conducted in sealed glove boxes to prevent release of materials into the work environment. Exposures to radiation and the chemicals in these areas occur primarily as a result of accidents. Workers at RF may be exposed to external penetrating radiation in the form of gamma and beta rays and neutrons, or they may be exposed to internal radiation from plutonium particulates in various chemical forms that are inhaled, or from metallic <sup>239</sup>Pu that is introduced through puncture wounds. Because of the long, effective half-life of plutonium, internally deposited particulates irradiate adjacent tissues with alpha rays throughout an individual's life.

# II. BACKGROUND

Although neural tissue is relatively resistant to both external and internal radiation, BTs have been induced in primates following >400-rem doses of 55-MeV protons. Human studies have also demonstrated associations between BTs and external radiation exposure of >100 rads. There is some evidence that BTs are associated with lower levels of radiation. A case-control study of central nervous system cancer among children demonstrated statistically significant age-adjusted relative risk of 1.3 among those antenatally irradiated (dosages were estimated to be <5 rad). A study of 904 persons treated with nasopharyngeal radium implants found 3 malignant BTs in the exposed group (estimated exposure: 44-78 rads) and none in the 2021 controls.

Studies of persons employed in the nuclear industry have resulted in conflicting findings. Among white males employed at least 2 years at Hanford, no positive correlation of radiation exposure and the l6 deaths from malignant BT was demonstrated. Nuclear workers at Portsmouth who received <5 rem annually or 100 rem

cumulatively showed no increased mortality from malignant BTs. <sup>16</sup> Male employees at the Oak Ridge Y-12 Plant demonstrated a significantly elevated standardized mortality ratio (SMR) for brain cancer among those employed 5 to 10 years (SMR = 589, p-value < 0.05). Although detailed exposure analyses were lacking, exposures to uranium dust, the major radiation hazard at the plant, were reportedly low. <sup>17</sup> In a recent study of 3508 males employed at a nuclear fuels fabrication plant, the incidence of brain cancer was significantly more frequent than that expected [Standardized Incidence Ratio (SIR) = 2.67, 95% Confidence Interval (CI) = 1.15-5.26]. However, the excess could not be attributed to any specific radiation or other occupational exposure. <sup>18</sup>

Our primary objective in this case-control study was to investigate the following hypotheses: (1) an association exists between exposure to internally deposited plutonium and death caused by BTs among RF white males, and (2) BT cases have higher external penetrating radiation exposures than do controls. In addition, we compared the work histories of the cases and controls to investigate potential nonradiation occupational hazards.

#### III. METHODS

The distinction between malignant and benign neoplasms of the brain is difficult to make in epidemiologic studies. Placement and size of the tumor mass often make benign tumors as life-threatening as malignant tumors, and this characteristic makes case identification difficult. The inoperability of such tumors and frequent lack of autopsies also hinder rigorous case identification. For this study, cases of primary BTs included all malignant and benign tumors of the brain, cranial nerves (intracranial portion), and cranial meninges, including tumors of the pituitary and pineal body. 19 Case ascertainment was based on the vital status follow-up of the RF white male cohort. Death certificates through 1980 were reviewed for any mention of BT or other central nervous system tumor or disease. For the 22 potential cases thus identified, we obtained medical, autopsy, and/or pathology reports and reviewed them to determine tumor classification and to exclude metastases from elsewhere in the body (Table I). This investigation resulted in 16 cases of primary BT including 14 gliomas (4 astrocytomas, 8 glioblastomas, 2 gliomas), 1 acoustic neuroma, and I pituitary tumor.

Three mutually exclusive control groups were selected from the white male cohort: matched, deceased, and random. Each group consisted of a 4:1 control-case ratio. The controls were selected as follows.

- (1) Potential matched controls were first selected for each case based on year of birth ( $\pm 5$  years). Minimum distance matching<sup>20</sup> was then used to match on hire and termination dates; the requirements were that the hire date for each control must precede that of the case ( $\le 2$  years) and that the termination date for each control must follow that of the case ( $\le 2.5$  years). The matching criterion for year of birth was expanded to  $\pm 10$  years for one case.
- (2) The random controls were selected at random from all white male employees.
- (3) The deceased controls were selected at random from the pool of deceased persons within the white male RF cohort after excluding all persons who died of cancer or of central nervous system diseases.

TABLE I. Detailed Information: Potential BT Cases

Study Number <sup>a</sup>	8th Revision ICD Code	Supplemental Information Diagnosis				
1	438.9	Astrocytoma				
2	191	Glioblastoma multiforme				
3	225.1	Acoustic neuroma				
4	238	Glioblastoma multiforme				
5	191	Glioblastoma multiforme				
6	191	Astrocytoma				
7	191	Glioblastoma multiforme				
8	192.9	Glioblastoma multiforme				
9	191	Glioma				
10	238.1	Glioblastoma multiforme				
11	192	Astrocytoma				
12	238	Astrocytoma				
13	191	Glioblastoma multiforme				
14	191	Glioblastoma				
15	238	Pontine glioma				
16	226.2	Pituitary tumor				
17	191	Metastatic, 1° lung				
18	238	1° kidney, 1° thalamus				
19	238	Metastatic, 1° unknown				
20	199	Metastatic, 1° lung				
21	199	Metastatic, 1° unknown				
22	162	Metastatic, 1° lung				

<sup>&</sup>lt;sup>a</sup>Study numbers 1-16 were used in the case-control study.

Demographic data, date and cause of death, and detailed work histories were obtained for cases and controls from employment records and death certificates. We divided job titles into nine categories (machinist, craftsman/maintenance, service worker, office worker, laborer, professional, technician, and manufacturing/production) according to a strict protocol developed after consultation with an RF industrial hygienist. Each worker's location within each of the four major work areas of the plant was abstracted also. We then calculated the amount of time spent in each job and area. Health physics records for all study subjects were referenced as the source of internal and external radiation exposure data. All information was computerized, and the accuracy of the data was verified.<sup>21</sup>

Because of the matching criteria used, the matched controls worked longer than the BT cases and therefore had more opportunity for exposure. To correct for this potential "bias towards the null," each control's duration of employment was truncated to equal that of the case. We then calculated exposure for each control from his date of hire through the time period equal to the duration of his case's employment.

The percentage of maximum permissible body burden (%MPBB) was used to measure internally deposited plutonium. The MPBB is a systemic deposition of plutonium that, when distributed and maintained in the body for 1 year, gives a dose equivalent to the allowable annual radiation dose from 40 nCi of plutonium. The Exposures of <5% of MPBB (2 nCi) are indistinguishable from background because samples from presumably unexposed persons can lead to calculated body burdens of as much as 3% of MPBB. The deposition values were computed from the Langham equation applied to urinalysis data collected periodically during an individual's employment at RF. 25

In this study, we used annual exposures to penetrating external radiation (x rays, gamma rays, and neutrons combined), recorded by the employee's film badge or thermoluminescent dosimetry (TLD) measurements. These measurements reflect only occupational exposure received at RF.

For the deceased and random controls, the age standardized maximum likelihood estimate of the odds ratio (OR) was used as a measure of relative risk.<sup>26</sup> For the matched control group, matching was maintained and Miettinen's maximum likelihood procedure was

<sup>\*</sup>This information was supplied by J. Langsted, RF Plant, August 1981, and C. Lagerquist, RF, February 1981.

used.<sup>27</sup> The statistical significance of the resulting ORs was evaluated according to the associated lower 95% test-based confidence limit.

External exposure distributions for both cases and controls were extremely skewed toward the high-exposure values; therefore, analyses based on the normal distribution assumption were inappropriate. Because of the uncertainty inherent in film badge and TLD measurements, it was impossible to classify some of our subjects as exposed or unexposed, particularly those with recorded cumulative exposures between 1 and 100 mrem. As a consequence, we did not consider the usual question of whether the proportion of exposed persons in the two groups was equal; instead, we asked whether cases tended to have higher exposures than controls by using a nonparametric Mann-Whitney procedure.<sup>28</sup> For this analysis, the doses (rem) for BT cases and each control group were put into a single combined array, and ranks were assigned from I to 80. The test statistic was calculated as the sum of these ranks for the cases. Approximate p-values were calculated for each test statistic.

For matched controls, a similar procedure was developed. Each case was ranked with its associated controls. The sum of the case ranks, across the 16 cases, was calculated and called T. We obtained the distribution of T for the null case (no difference between cases and controls) by Monte Carlo simulation. We began by generating five uniform (0,1) variates, the first representing the case and the other four representing the controls. The case was then ranked among the controls, and the sum of the ranks  $T_1$  was calculated. Approximate p-values were calculated from 1000 values of  $T_1$ .

To evaluate job title and work area, we judged comparisons with matched controls to be the most appropriate because of the many changes in plant operations over time. For these analyses, we assumed that the greater the time spent in a particular category, the greater the potential for exposure. Each case and his controls were then ranked by time spent in each job and work area. Our matched version of the Mann-Whitney test was used to test whether the cases had spent more time in a particular category than did the controls.

Solid tumors may take years to develop after enough exposure to induce cancer.<sup>9,11</sup> To focus on relevant exposures, supplementary analyses excluded exposure received within the 10 years before death (or for living controls, the 10 years before the last date of follow-up).

#### IV. RESULTS

Characteristics of the BT cases and controls are presented in Table II; a more detailed description of the cases is given in Table III. Because the data were skewed, median values are reported. As expected because of the matching, the median years of birth for the cases and matched controls were very similar. Deceased controls were slightly older (6 years) than were cases, whereas random controls were considerably younger (15 years). The median age at death for the cases was 51 years compared with 58 years for deceased controls.

The median age at hire for the cases was 41 years. We selected matched controls that had been employed for approximately the same period and at the same age. The deceased controls began working 4 years earlier than the cases and at slightly older ages, whereas the random controls began employment later than the cases did but at much younger ages. The cases worked a median of 7.1 years, the deceased controls worked a median of 9.1 years, and the random controls worked a median of 5.5 years.

We noted no temporal clustering of employment period among the cases (Fig. 1). Among both the cases

TABLE II. Characteristics of BT Cases and Controls (Median Values)								
Variable	Cases	Matched Controls	Deceased Controls	Random Controls				
Year of birth	1921	1920	1915	1936				
Year of hire	1961	1961	1957	1963				
Age at hire (years)	41	40	45	28				
Year last employed	1970	1971	1968	1974				
Year of death	1972		1973					
Duration of employment (years)	7.1	8.4	9.1	5.5				

and deceased controls, 75% of the deaths occurred in 1970 or later. However, this finding would be expected based on the age structure of the cohort.<sup>3</sup>

For analytic purposes, we defined exposure to internal plutonium as any positive-value body burden. As shown in Table IV, no association between BTs and these exposures was found. ORs were <1 for all case-control comparisons. Of the 12 cases who had been tested for plutonium, only 4 had positive body burdens. When plutonium exposure was restricted to that received before the 10 years preceding death (or for living controls, the 10 years before the last date of follow-up), several individuals had to be dropped from the analysis for failing to meet this 10-year latency restriction. Here again, all case-control comparisons produced ORs <1 (Table V).

Uranium and beryllium exposures, as recorded for each employee in his plant medical record, were reviewed. Evidence of exposure to beryllium or uranium existed in only one case; therefore, we did not analyze for these exposures.

The distribution of cumulative external radiation for the BT cases and controls is illustrated in Fig. 2. Each distribution was extremely skewed toward the higher exposure values, and the range of exposures was quite varied. None of the cases had >16 rem of cumulative exposure; exposures for the matched controls ranged from 0 to 32 rem, for deceased controls 0 to 52 rem, and up to 60 rem for the random group. All exposures were less than the maximum permissible dose equivalent for radiation workers of 5 rem/year. The median exposure values in rem for the cases and the matched, deceased, and random control groups were 1.4, 0.4, 0.6, and 0.8, respectively.

Table VI shows the test statistics and their associated p-values for the nonparametric Mann-Whitney analyses of exposure to external penetrating radiation. Although the cases did appear to be more exposed to this form of radiation than were the controls, these differences were not statistically significant. When external exposures accumulated up to 10 years preceding death (or for living controls, 10 years before the last date of follow-up) were considered, no statistically significant difference in exposure levels existed between the cases and controls (Table VI).

To check on the results of the Mann-Whitney analyses, we also calculated ORs with exposure dichotomized at different levels (that is, the case median and values >1 rem) for both 0 and 10 years latency. None of the accompanying 95% CIs were statistically significant.

Table VII presents the Mann-Whitney scores and the associated p-values for each job category. The cases did not appear to have spent significantly more time in any particular job than did the controls. In analyses restricting exposure to that received 10 years before the death of the case, the cases and controls demonstrated no differences. Analysis by work area showed similar results (Table VIII).

These factors were further examined in an OR analysis based on usual job title and usual work area for both 0 and 10 years latency. No significant association between the cases and controls was noted for any category. To evaluate possible dose-response relationships for work area and job title, standardized rate ratios (standardized to the lowest exposure level) were examined using the Mantel extension procedure;<sup>29</sup> duration of employment was broken into three mutually exclusive categories (never employed, employed up to 2 years, and employed 2 or more years). In analyses for both 0 and 10 years latency, no statistically significant dose-response trends were observed for any job title or work area.

Because different histological types of BTs have demonstrated different epidemiologic patterns, <sup>19,30</sup> we eliminated the acoustic neuroma and the pituitary tumor and repeated the analyses for the more homogeneous set of glial-type tumors. Our findings, however, were not altered.

# V. DISCUSSION

Our primary purpose in this study was to investigate the relationship between BTs and occupational radiation exposure. We found no significant association between exposure to internally deposited plutonium and BTs among the RF cohort members. The health physics experience at RF suggested that only estimated depositions of >5.0% MPBB be considered evidence of positive exposure.\* Because none of the cases demonstrated body burdens of >2.5% MPBB, it is questionable if they were exposed at all. Although the cases were exposed to higher levels of penetrating radiation than were controls, these differences were not statistically significant.

Another objective of this investigation was to identify potential nonradiation occupational hazards. No

<sup>\*</sup>This information was supplied by J. Langsted, RF Plant, August 1981.

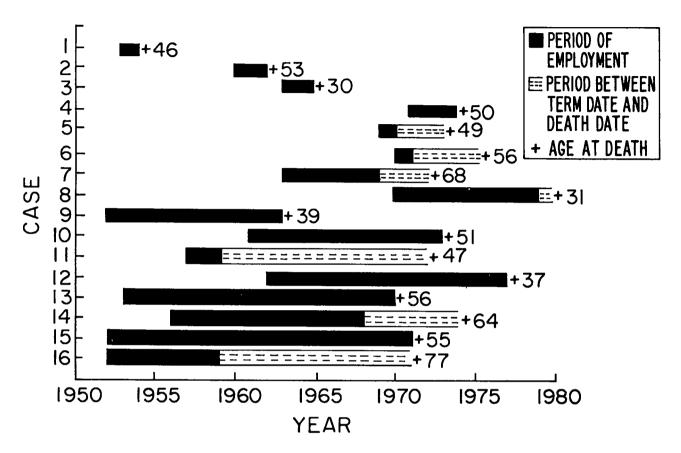


Fig. 1. Age at death and work histories for BT cases.

TABLE	III. C	haracteri	istics o	f BT Cases					
Study	Year of	Prehire Work	Year of	Years Employed	Year of	Prehire Information	18	RF Information	
Number	Birth	Years*	Hire	at RF	Death	Employment	Years	Employment	Years
1	1908	25.0	1953	1.5	1954	Postman Transfer freight Filling station Parts mover	4 13 4 1	Patrolman	1.5
2	1909	31.1	1960	1.3	1962	Unknown		Inspector	1.3
3	1935	8.0	1963	2.0	1965	Air-filter serviceman	2	Laborer Clerk	0.5 1.5
4	1924	27.2	1971	3.2	1974	Sheetmetal foreman Production foreman	5 7	Sheetmetal worker	3.2
5	1924	24.4	1969	1.0	1973	Stationary engineer Steam plant operator Military	2 9 3	Stationary operator engineer	1
6	1919	30.9	1970	0.4	1975	Technician Mechanic	8	Stationary operator engineer	0.4
7	1904	38.6	1963	6.4	1972	Electrical construction	25	Electrician	6
8	1949	1.3	1970	8.3	1980	Stereo installer	1	Janitor Chemical process operator Metallurgy operator	1 6 1
9	1924	8.0	1952	11.3	1963	Accountant Military	5 3	Accountant	11.3
10	1922	19.1	1961	11.7	1973	Tool grinder Machinist Military	6 10 3	Machinist	11.7
11	1925	11.3	1957	2.0	1972	Developmental engineer Radio repairman Linesman Military	4 2 1 4	Physicist	2
12	1940	2.0	1962	14.7	1977	Grocery clerk	1.5	Quality control chemist Laboratory supervisor Standards engineer	6 6 3
13	1914	19.2	1953	16.7	1970	Maintenance Machinist Foreman Military	4 4 8 4	Machinist Machine foreman Supervisor	4 5 7
14	1910	25.7	1956	12.1	1974	Foundry foreman Grocery clerk Shop analyst Production foreman	2 2 2 7	Production foreman	12.1
15	1916	15.7	1952	19.4	1971	Military Laborer	3 0.5	Inspector	19.4
16	1894	38.0	1952	7.0	1971	Motorman	16	Janitor	7
*Assumes v	vork beg	an at age	20 years	<b>5.</b>					

TABLE IV. Comparison of Plutonium Body Burdens Between BT Cases and Controls

Pu Measurements	Cases (N = 16)	Matched Controls (N = 64)	Deceased Controls (N = 64)	Random Controls (N = 64)
Number with positive Pu measurements at date of termination	4	28	17	28
OR (lower 95% confidence limit)		0.29ª (0.09)	0.80 <sup>b</sup> (0.26)	0.60 <sup>b</sup> (0.19)

<sup>&</sup>lt;sup>a</sup>Miettinen's maximum likelihood estimate of the OR for matched case-control analysis.

TABLE V. Comparison of Plutonium Body Burdens Between BT Cases and Controls: Exposure
Restricted to 10 Years Before Death

Pu Measurements	Cases (N = 8)	Matched Controls (N = 32)	Deceased Controls (N = 47)	Random Controls (N = 50)
Number with positive Pu measurements 10 years before death	2	14	12	21
OR		0.86ª	0.82 <sup>b</sup>	0.73 <sup>b</sup>
(lower 95% confidence limit)		(0.14)	(0.17)	(0.15)

<sup>&</sup>lt;sup>a</sup>Miettinen's maximum likelihood estimate of the OR for matched case-control analysis.

statistically significant differences in exposure by job title or work area were demonstrated among the cases and the matched controls.

Power calculations for this study were based on the threefold excess of BTs reported in the cohort study.<sup>2,3</sup> The power to detect three times as much external exposure among the cases was 70%, whereas the power to detect a threefold difference in length of employment for job title or work area was approximately 40%. The same conclusions were obtained in the supplementary analyses based on the slightly more powerful parametric statistical tests.

Each control group demonstrated certain strengths and weaknesses. Unlike the cases, many of the random controls were recently hired employees whose duration of employment was truncated at the end-of-study date. They appeared to have begun work at younger ages than did the cases and to have worked for shorter periods of

time. Therefore, crude comparisons with this group would have been biased. However, age standardization minimized these differences.

The deceased controls were older and tended to have begun work at older ages than did the cases. However, in both the crude and age standardized assessments of employment duration, the deceased controls worked longer than the cases did, thus providing no evidence that length of employment was a BT risk factor. It is possible that death was an exposure correlate, thereby decreasing the likelihood of detecting any real difference that might exist between the cases and these controls.

The matched controls (matched on age and period of employment) were selected to minimize the potential confounding effects resulting from changes in plant operations, industrial processes, industrial hygiene regulations, and health physics standards. However, we may have overmatched on period of employment, thus

<sup>&</sup>lt;sup>h</sup>Gart's maximum likelihood estimate of the pooled OR.

bGart's maximum likelihood estimate of the pooled OR.

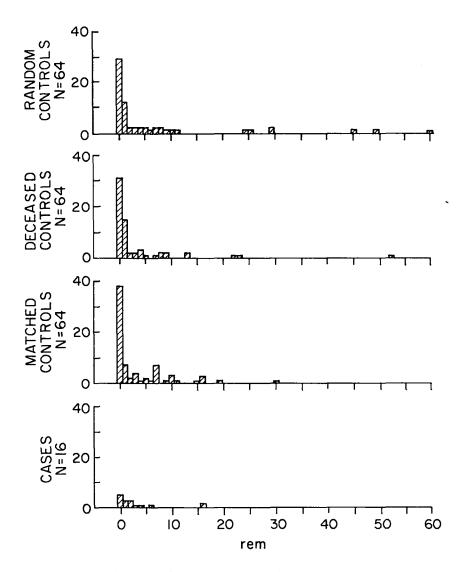


Fig. 2. Distribution of cumulative external radiation for BT cases and controls.

hindering our ability to recognize differences in the occupational exposures of interest.

The potential for overmatching was examined briefly in additional case comparisons with control pools matched on the following criteria: (1) date of birth only ( $\pm 2$  years); (2) birth date ( $\pm 2$  years) and hire date ( $\pm 2$  years); and (3) the original matching on birth date ( $\pm 5$  years), hire date ( $\pm 2$  years), and term date ( $\pm 2.5$  years). Each pool contained all potential controls. For a given control pool, the cumulative external radiation exposure for each case was ranked among his controls. Ranks were converted to percentiles, and the sum of the case percentiles was calculated. The respective scores for the

three pools were 8.6, 8.9, and 8.5. None of the scores were statistically different than the expected value of 8.0. On the basis of this examination, we have no reason to believe that overmatching was a major problem in our study design.

Comparing death certificates with the supplemental autopsy, hospital, and/or pathology data allowed us to evaluate misclassification resulting from inaccurate cause-of-death statements. Among the 16 BT cases, we found a 36% discrepancy between the cause-of-death statement and additional information. This discrepancy rate was similar to that reported in the literature, which documents discrepancies ranging from 39 to 57%. 31,32

TABLE VI. Comparison of Cumulative External Radiation Exposure Between BT Cases and Controls

		No Latency (N = 16)		Exposure 10 Years Before D $(N = 8)$		
	Matched Controls (N = 64)	Deceased Controls (N = 64)	Random Controls (N = 64)	Matched Controls (N = 32)	Deceased Controls (N = 47)	Random Controls (N = 50)
Mann-Whitney Score						
Observed	54	579	513	23.5ª	227.5	178.0
Expected	48	512	512	24	188.0	200.0
Approximate						
one-sided p-value	0.15	0.21	0.50	0.55	0.17	0.69

<sup>&</sup>lt;sup>a</sup>Because the Mann-Whitney procedure is not appropriate for matched controls, a similar test was devised using Monte Carlo simulation.

Comparing ICD codes with the cause-of-death statements identified another source of error: one case appeared as a false negative. These exercises demonstrated the importance of careful review of all death certificate data used for case definition in case-control studies.

Because of the paucity of data on BT etiology, we can only speculate about other factors that may have been responsible for the excess of BTs among the RF cohort members. On the basis of animal studies, numerous chemicals and viral agents have been recognized as brain carcinogens.33,34 Population-based epidemiologic studies of humans have been less definitive. The possibility that environmental factors are involved in brain tumorigenesis has been suggested based on geographic variations in disease rates.30 Genetic factors have also been implicated as BT risk factors. 19,30 Within the past decade, excess deaths from BTs have been reported among a variety of occupational groups including rubber workers, aluminum workers, chemists, veterinarians, oil refinery workers, electricians, pattern makers, machinists, and asbestos insulators.35,36 However, we found no association at RF with specific job titles or occupational exposures.

Another possible explanation for our observed excess of BT deaths is a "diagnostic sensitivity bias." This bias is purported to result from comparing the general population to an employed population that may have better medical care and diagnosis.

Investigation of these suspected risk factors was beyond the scope of our study. Also, we could not evaluate radiation and other potential carcinogenic exposures received before employment at the plant or received nonoccupationally. In reviewing the pre-RF occupational histories of the cases (Table III), note that the median for pre-RF employment was 21.8 years. Eleven cases had been previously employed in industrial occupations; nine of these were employed for more than 10 years. However, no common occupation was identified.

# VI. CONCLUSIONS

Although limited by a small number of cases, we found no statistically significant differences in exposure between BT cases and the three control groups for plutonium or external penetrating radiation. In addition, no potential nonradiation occupational hazards were identified. These same conclusions held in our supplementary analyses by latency and for glial-type tumors alone.

# **ACKNOWLEDGMENTS**

We acknowledge the valuable assistance of everyone involved in the collection and organization of the data files used in this study. We especially thank Laurie Wiggs, Jeannene Masterson, and Joan Essington; Roy Tally of RF for providing the radiation dosimetry data; Eva Woods for computer support; and Stan Ferguson of

TABLE VII.	Comparison of Jo	b Titles Between BT	Cases and Matched Contr	ols
	COMPANISON OF 10	U I ILICS DCI WCCII DI	Cases and Materica Cond	· VII

		Ever Exposed (N = 16)				Ever Exposed 10 Years Before Death $(N = 8)$		
Occupation	Number of Exposed Cases	Mann-Whi Observed	tney Score Expected	Approximate One-Sided p-Value	Number of Exposed Cases	Mann-Whi Observed	tney Score Expected	Approximate One-Sided p-Value
Professional	4	49.0	48.0	0.43	3	27.5	24.0	0.20
Technician	1	43.5	48.0	0.77	0			
Craftsmen/ Maintenance	2	37.5	48.0	0.97	0			
Machinist	3	48.5	48.0	0.50	3	28.0	24.0	0.17
Manufacturing & Production	6	53.0	48.0	0.20	3	27.0	24.0	0.23
Service Personnel	4	48.0	48.0	0.50	0			
Office Workers	3	46.5	48.0	0.59	2	25.0	24.0	0.40
Laborers	3	46.0	48.0	0.62	1	26.5	24.0	0.27

TABLE VIII. Comparison of Work Area Between BT Cases and Matched Controls Ever Exposed 10 Years Before Death Ever Exposed (N = 16)(N = 8)Approximate Number of **Approximate** Number of One-Sided Mann-Whitney Score One-Sided Exposed Mann-Whitney Score Exposed Observed Work Area Cases Observed Expected p-Value Cases Expected p-Value 49.0 0.43 23.5 24.0 0.55 8 48.0 3 Α 22.0 24.0 0.69 51.5 48.0 0.26 2 В 9 C 12 53.5 48.0 0.19 3 23.5 24.0 0.55 D 6 44.0 48.0 0.74 2 20.0 24.0 0.84

the Colorado State Health Department. Our thanks go to all reviewers and the Epidemiology Advisory Committee for their valuable suggestions and advice, with special appreciation to Strother Walker, Roy Shore, and Richard Waxweiler.

#### REFERENCES

- C. J. Johnson, "A Preliminary Evaluation of Brain Cancer, Melanoma and Respiratory Cancer of Employees of the Rocky Flats Nuclear Weapons Plant in Jefferson County, Colorado," American Public Health Association Meeting, Detroit, Michigan, October 22, 1980.
- G. L. Voelz, G. S. Wilkinson, J. F. Acquavella, G. L. Tietjen, R. Brackbill, M. Reyes, and L. Wiggs, "An Update of Epidemiologic Studies of Plutonium Workers," Proceedings of the International Conference on the Radiobiology of Radium and the Actinides in Man, Lake Geneva, Wisconsin, October 11-16, 1981 (to be published in Health Phys.).
- G. S. Wilkinson, G. L. Voelz, J. F. Acquavella, G. L. Tietjen, M. Reyes, R. Brackbill, and L. Wiggs, "Mortality Among Plutonium and Other Workers at a Nuclear Facility," 16th Midyear Topical Meeting, Health Physics Society, Epidemiology Applied to Health Physics, Albuquerque, New Mexico, January 9-13, 1983.
- Committee on the Biological Effects of Ionizing Radiations, The Effects on Populations of Exposure to Low Levels of Ionizing Radiation: 1980 (National Academy Press, Washington, DC, 1980).
- W. Haymaker, L. Rubinstein, and J. Miquel, "Brain Tumors in Irradiated Monkeys," Acta Neuropathol. (Berlin) 20, 267-277 (1972).
- G. Splitter, J. Kirk, and H. Casey, "Radiation-Related and Spontaneous Tumors in Primates," in Radionuclide Carcinogenesis, C. Sanders et al., Eds. (US Atomic Energy Commission, Washington, DC, 1973) pp. 55-89.
- J. Traynor and H. Casey, "Five-Year Followup of Primates Exposed to 55-MeV Protons," Radiat. Res. 47, 143-148 (1971).

- 8. B. Modan, D. Baidatz, H. Mart, R. Steinitz, and S. Levin, "Radiation-Induced Head and Neck Tumors," Lancet I, 277-279 (1974).
- 9. R. E. Shore, R. E. Albert, and B. S. Pasternack, "Follow-up Study of Patients Treated by X-Ray Epilation for Tinea Capitis," Arch. Environ. Health 31, 17-24 (1976).
- M. Colman, M. Kirsch, and M. Creditor, "Tumors Associated with Medical X-Ray Therapy Exposure in Childhood," in *Late Biological Effects of Ionizing Radiation*, Vol. I (International Atomic Energy Agency, Vienna, 1978).
- S. Seyama, T. Ishimaru, S. Iijima, and M. Kazuo, "Primary Intracranial Tumors Among Atomic Bomb Survivors and Controls, Hiroshima and Nagasaki, 1961-1975," Radiation Effects Research Foundation report RERFTR 15-79.
- G. Matanoski, R. Seltser, P. Sartwell, E. Diamond, and E. Elliott, "The Current Mortality Rates of Radiologists and Other Physician Specialists: Specific Causes of Death," Am. J. Epidemiol. 101, 199-210 (1975).
- J. F. Bithell and A. Stewart, "Prenatal Irradiation and Childhood Malignancy: A Review of British Data from the Oxford Survey," Br. J. Cancer 31, 271 (1975).
- D. P. Sandler, G. W. Comstock, and G. M. Matanoski, "Neoplasms Following Childhood Radium Irradiation of the Nasopharynx," J. Nat. Cancer Inst. 68, 3-8 (1982).
- E. Gilbert and S. Marks, "Analysis of Workers in a Nuclear Facility," Radiat. Res. 79, 122-148 (1979).
- 16. R. A. Rinsky, R. D. Zumwalde, R. J. Waxweiler, W. E. Murray, Jr., P. J. Bierbaum, P. J. Landrigan, M. Terpilac, and C. Cox, "Cancer Mortality at a Nuclear Naval Shipyard," US Department of Health and Human Services, Centers for Disease Control, National Institute for Occupational Safety and Health, Cincinnati, Ohio (1980).
- 17. C. C. Lushbaugh, "The Development and Present State of the DOE Health and Mortality Studies,"

- Proceedings of the DOE Radiation Contractors Workshop, Rockville, Maryland, April 13-14, 1982 (United States Department of Energy) pp. 1-36.
- O. C. Hadjimichael, A. M. Ostfeld, D. A. D'Atri, and R. E. Brubaker, "Mortality and Cancer Incidence Experience of Employees in a Nuclear Fuels Fabrication Plant," J. Occup. Med. 25, 48-61 (1983).
- B. S. Schoenberg, B. W. Christine, and J. P. Whisnant, "The Descriptive Epidemiology of Primary Intracranial Neoplasms: The Connecticut Experience," Am. J. Epidemiol. 104, 499-510 (1976).
- A. H. Smith, J. C. Kark, J. C. Cassell, and G. Spears, "Analysis of Prospective Epidemiologic Studies by Minimum Distance Case-Control Matching," Am. J. Epidemiol. 105, 567-573 (1977).
- M. Reyes, G. S. Wilkinson, and J. F. Acquavella, "Quality Control Activities of Coding Consistent for Data Collected at Rocky Flats," LA-9462-MS (to be published).
- 22. "Maximum Permissible Body Burdens and Maximum Permissible Concentrations of Radionuclides in Air and in Water for Occupational Exposure (includes Addendum 1 to NBS Handbook 69 issued in August 1963)," National Council on Radiation Protection and Measurements report 22, Washington, DC (1959).
- International Commission on Radiological Protection, "Report of ICRP Committee II on Permissible Dose for Internal Radiation (1959)," Health Phys. 3, 1-380 (June 1960).
- John W. Healy, "Los Alamos Handbook of Radiation Monitoring," Los Alamos Scientific Laboratory report LA-4400 (March 1970).
- J. N. P. Lawrence, "A History of PUQFUA (Plutonium Body Burden Q) from Urine Assays)," Los Alamos Scientific Laboratory report LA-7403-H (October 1978).
- J. J. Gart, "Point Internal Estimation of the Common Odds Ratio in the Combination of 2 x 2 Tables with Fixed Margins," Biometrics 57, 471-475 (1970).

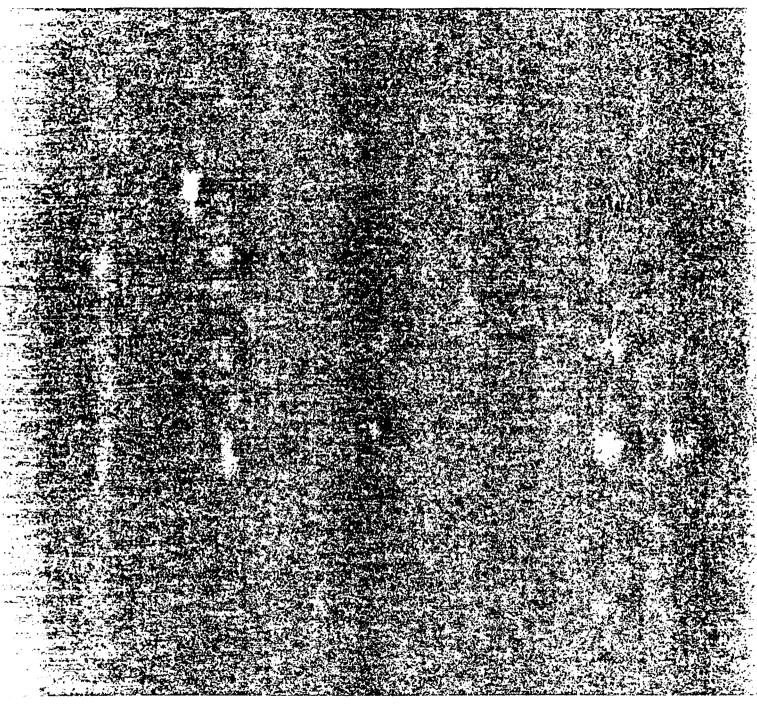
- 27. O. S. Miettinen, "Estimation of Relative Risk from Individually Matched Series," Biometrics 26, 75-86 (1970).
- 28. J. Conover, *Practical Nonparametric Statistics* (John Wiley & Sons, Inc., New York, 1971).
- N. Mantel, "Chi-Square Tests with One Degree of Freedom: Extension of the Mantel-Haenszel Procedure," J. Am. Stat. Assoc. 59, 690-700 (1963).
- E. Gold, "Epidemiology of Brain Tumors," in Reviews in Cancer Epidemiology, A. Lilienfeld, Ed. (Elsevier-North Holland Publishing Company, New York, 1980), Vol. I.
- A. Gittlesohn and J. Senning, "Studies on the Reliability of Vital Health Records: I. Comparison of Cause of Death and Hospital Record Diagnoses," Am. J. Public Health 69, 680-688 (1979).
- G. J. James, P. E. Patton, and A. S. Heslin, "Accuracy of Cause-of-Death Statements on Death Certificates," US Public Health report 70, 39-51 (1955).
- 33. J. Swenberg, "Chemical and Virus-Induced Brain Tumors," J. Nat. Cancer Inst. Monograph 46, 3-10 (1977).
- D. D. Bigner and C. N. Pegram, "Virus-Induced Experimental Brain Tumors and Putative Associations of Viruses with Human Brain Tumors: A Review," Adv. Neurol. 15, 57-83 (1976).
- V. Alexander, S. Leffingwell, W. Lloyd, R. J. Waxweiler, and R. L. Miller, "Brain Cancer in Petrochemical Workers: A Case Series Report," Am. J. Ind. Med. 1, 115-123 (1980).
- 36. R. Waxweiler, "A Review of Occupational Risk Factors of Brain Cancer," Nikko Brain Cancer Therapy Conference, Nikko, Japan, October 14, 1981.
- P. Greenwald, B. R. Friedlander, C. E. Lawrence, T. Hearne, and K. Earle, "Diagnostic Sensitivity Bias—An Epidemiologic Explanation for an Apparent Brain Tumor Excess," J. Occup. Med. 23, 690-694 (1980).

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