

Original Contributions

A CASE-CONTROL STUDY OF LEUKEMIA AT A NAVAL NUCLEAR SHIPYARD

FRANK B. STERN,¹ RICHARD A. WAXWEILER,⁴ JAMES J. BEAUMONT,⁵ SHIU T. LEE,¹
ROBERT A. RINSKY,¹ RALPH D. ZUMWALDE,² WILLIAM E. HALPERIN,¹
PHILIP J. BIERBAUM,¹ PHILIP J. LANDRIGAN,¹ AND WILLIAM E. MURRAY, JR.³

Stern, F. B. (NIOSH, Cincinnati, OH 45226), R. A. Waxweiler, J. J. Beaumont, S. T. Lee, R. A. Rinsky, R. D. Zumwalde, W. E. Halperin, P. J. Bierbaum, P. J. Landrigan, and W. E. Murray, Jr. A case-control study of leukemia at a naval nuclear shipyard. *Am J Epidemiol* 1986;123:980-92.

A matched case-control study was conducted of 53 leukemia deaths and of 212 controls within a previously studied cohort of 24,545 on-shore workers employed between January 1, 1952 and August 15, 1977 at the Portsmouth (New Hampshire) Naval Shipyard. The study sought to ascertain a priori whether there was an association between leukemia deaths and occupational exposure to either ionizing radiation or organic solvents. To obtain information on individual exposures, radiation dose histories and detailed work histories by job and shop were evaluated for each subject. No statistically significant associations were found either between ionizing radiation or presumed solvent exposure and myelogenous or lymphatic leukemia. However, when specific job categories and shops were examined without benefit of a priori hypotheses, two occupations, electrician and welder, were found to be associated with leukemia. For electricians, the Mantel-Haenszel odds ratio (OR_{MH}) was significantly elevated for all leukemias ($OR_{MH} = 3.00$, 95% confidence interval (CI) = 1.29-6.98), particularly for lymphatic leukemia ($OR_{MH} = 6.00$, 95% CI = 1.47-24.45). For welders, the odds ratio was not significantly elevated for all leukemias ($OR_{MH} = 2.25$, 95% CI = 0.92-5.53), but was significantly elevated for myeloid leukemia ($OR_{MH} = 3.83$, 95% CI = 1.28-11.46). These findings persisted when potential confounders were adjusted by means of a conditional logistic regression model.

leukemia; occupational diseases; radiation

In 1978, Najarian and Colton (1) reported that nuclear workers at the Portsmouth (New Hampshire) Naval Shipyard had experienced a fivefold increase in proportional mortality due to leukemia and a

twofold increase due to all cancers combined. Consequently, the Subcommittee on Health and the Environment of the United States House of Representatives requested that the Department of Health and Human

Received for publication April 10, 1985 and in final form November 6, 1985.

¹ Division of Surveillance, Hazard Evaluations and Field Studies, National Institute for Occupational Health and Safety (NIOSH), 4676 Columbia Parkway, Cincinnati, OH 45226. (Send reprint requests to Mr. Frank B. Stern.)

² Division of Standards Development and Technology Transfer, NIOSH, Cincinnati, OH.

³ Division of Biomedical and Behavioral Sciences, NIOSH, Cincinnati, OH.

⁴ Chronic Disease Division, Center for Environmental Health, CDC, Atlanta, GA.

⁵ Department of Internal Medicine, University of California at Davis, Davis, CA.

The authors thank the following persons at NIOSH: Edith Dodd, Pauline Bischak, Clorinda Battaglia, and their colleagues for clerical support; Dr. Leela Murthy for her helpful comments on the manuscript; and Ruth McGrath and Juanita Nelson for technical assistance with the manuscript.

Services conduct an epidemiologic investigation into increased mortality at the Portsmouth Naval Shipyard. The National Institute for Occupational Safety and Health was directed to undertake this research. A protocol was developed for a retrospective cohort mortality study of the entire shipyard population and, in particular, of workers exposed to ionizing radiation. In addition, the protocol indicated that follow-up case-control studies may have to be conducted on specific causes of death, in the event that any unusual patterns of mortality were uncovered during the cohort analysis.

The data from the cohort study conducted by the National Institute for Occupational Safety and Health (2, 3) did not support the previous findings (1) of increased mortality either due to leukemia or to all cancers combined. In addition, no excess mortality, from any cause, was observed in shipyard workers who had been occupationally exposed to radiation. The principal explanation for the discrepancies between the findings of the two studies appeared to have been misclassification of data on radiation exposure histories by the original researchers, due to faulty recall of work histories by the next of kin of deceased workers (4).

Although no overall excess mortality due to cancer of any site was observed in the cohort study, a decision was made to conduct a case-control analysis of deaths due to leukemia to examine a variety of potential occupational risk factors. This decision followed the observation that leukemia deaths occurred more often than expected for persons who had accumulated a lifetime radiation dosage of at least 1.0 rem while employed at the Portsmouth Naval Shipyard. In this subgroup of workers, four deaths were observed versus 2.5 expected (standardized mortality ratio = 1.60, 95 per cent confidence interval = 0.51-3.86).

Ideally, an assessment of relationships between occupational exposures and leukemia deaths at the Portsmouth Naval Shipyard would have been accomplished by

stratification of work histories in the cohort analysis. However, this approach would have required coding of complete work histories for the entire shipyard work force (24,545 workers). Such an effort would have been prohibitively difficult. Thus, a case-control study was undertaken which required that work history information be coded only for leukemia cases and for their matched controls. Odds ratios for leukemia could then be derived by comparing exposures and/or jobs and shops of the leukemia cases with those of the controls.

In addition to radiation exposure, workers at the Portsmouth Naval Shipyard were potentially exposed to a variety of organic solvents including benzene, a known human leukemogen. The association of benzene with leukemia, particularly with acute myelogenous leukemia, has been reported in numerous case studies and established in several epidemiologic analyses (5-10). These results have been reviewed and confirmed by the International Agency for Research on Cancer (11) and by the National Institute for Occupational Safety and Health (12). In addition, the shipyard workers may have been exposed to other organic solvents such as xylene, toluene, acetone, methylene chloride, methyl ethyl ketone, carbon tetrachloride and tetrachloroethane. An excess risk of leukemia has been suggested (7, 13, 14), but not established, among workers exposed to organic solvents other than benzene.

This report presents the results of the case-control study of leukemia deaths at the Portsmouth Naval Shipyard conducted by the National Institute for Occupational Safety and Health. Risk factors of a priori interest in the study included exposures to ionizing radiation and solvents. However, all other job categories and shops at the shipyard were also evaluated for possible associations with leukemia.

MATERIALS AND METHODS

Case and control selection

The study population in which this case-control analysis was carried out included

all white males who had worked at the Portsmouth Naval Shipyard at any time between January 1, 1952 and August 15, 1977 ($n = 24,545$). Within this population, cases were defined for the present study as all deceased persons as of the end of 1980 (end of follow-up period) for whom leukemia had been coded as an underlying or contributory cause of death. This procedure differed from the cohort study (2, 3), which only included those deaths that occurred through August 15, 1977 for which leukemia was coded as the underlying cause of death. Medical records were sought for all individuals for whom the underlying or contributory cause of death was listed on the death certificate as leukemia, but not for any potential controls. If the coding of leukemia from the death certificate could not be confirmed by the available medical records, the case was excluded from further analysis. The leukemia cases were then characterized by specific cell types as noted in the medical records.

Matched controls for each leukemia case were selected from the 24,545 member study population after excluding persons who had died from hematopoietic or lymphatic malignancies. Controls were further required to have lived as long as the case, so that they had the same chance of developing disease. Each case was then compared to every potential remaining control based on three criteria: absolute difference in years between birth dates, dates first employed, and duration of employment at the Portsmouth Naval Shipyard. These differences were summed to constitute a score. For each case, the four noncases with the lowest scores were selected as controls. Each case had an equal opportunity of being matched with its four best controls since the controls were "moved" from one case to another until the most appropriate matches resulted. This was done to ensure utmost distributional comparability between the cases and their matching controls. The 4:1 matching ratio yielded an 80 per cent power of detecting a true relative risk of dying from leukemia of 2.2 ($\alpha =$

0.05) among those workers exposed to ionizing radiation.

Radiation exposure and occupational history

The Portsmouth Naval Shipyard is a large industrial complex which employs on-shore workers in various trades of designing, manufacturing, overhauling, and refueling of conventional and nuclear naval vessels. Any employee who worked on a nuclear-powered submarine had a potential for radiation exposure (15). The major source of both internal and external radiation exposure at the Portsmouth Naval Shipyard is cobalt-60, which is an activation product found in the nuclear reactor cooling system. A few employees at the Portsmouth Naval Shipyard also have been exposed to neutron radiation over the years, but only one worker (a control) in this study had received neutron exposure (0.122 rem). All radiation workers (i.e., employees who entered controlled radiation areas or who handled radioactive material) were monitored for radiation exposure.

Records maintained by the Portsmouth Naval Shipyard on each employee's radiation dose since the early 1950s were used to evaluate individual risk of exposure to ionizing radiation. During the early 1950s, film badges were required to be worn by only a small group of industrial radiographers who were involved in the x-ray examination of the integrity of welds. When nuclear propulsion work began at the Portsmouth Naval Shipyard in 1958, the radiologic control program was expanded so that any employee at the Portsmouth Naval Shipyard who had a possibility of being exposed to radiation, regardless of job classification, was required to wear a film badge. The badges were processed at least monthly. In October 1974, the film badges were replaced by calcium fluoride thermoluminescent dosimeters. These badges were processed daily. Individual doses were recorded at least monthly in the employee's radiation exposure record (DD 1141) and medical record. Internal deposition of ra-

radioactive material was monitored by bioassay and whole body counting techniques.

The radiologic control program at the Portsmouth Naval Shipyard consisted of approximately 140 professional, technical, and support personnel. These individuals had the responsibility of assuring that adequate radiologic control procedures were employed and that personnel were being monitored continuously for radiation doses. The program was constantly being evaluated by on-site representatives of the US Department of Energy and audited by the Naval Sea Systems Command Headquarters staff.

Detailed job history information was coded for each case and control. A classification system was developed which grouped the numerous shops and jobs by commonality of processes, materials handled, and occupational exposures utilizing information from the Portsmouth Naval Shipyard staff, personnel records, and an industrial hygiene survey conducted in 1980 by staff of the National Institute for Occupational Safety and Health. This classification system was supplemented by the limited historical industrial hygiene data provided by the Portsmouth Naval Shipyard. As an example, an "electrical" shop was a specific area where electricians and other skilled and unskilled workers performed their tasks at the Portsmouth Naval Shipyard facility. The title "electrician," to illustrate a job title, included both electricians who were assigned to the electrical shop as well as electricians who worked in and were assigned to other shops at the Portsmouth Naval Shipyard. Personnel records indicated any changes for workers in shop or job assignment and the date of each new assignment. Every job held by the cases and controls was assigned a shop and a job code. This classification system allowed examination of potential health risk by shop, job, or combination of both shop and job. However, no individual exposure monitoring program for potentially hazardous agents, other than radiation, was maintained by the Portsmouth Naval Shipyard.

Therefore, the intensity or extent of potentially hazardous exposures associated with each shop and job could not be directly quantified.

The job categories with the greatest potential for exposures to organic solvents included cleaner (tool, equipment, or industrial), carpenter, painter, fuel worker, and rubber and/or plastic worker. Because of the diversity of job types and potential exposures within any one shop, it was recognized that the extent of solvent exposure varied considerably among the workers within each shop.

Analysis

Matched odds ratios were calculated using a computer program developed at the University of North Carolina (16) for analyzing case-control studies. For each exposure group tested, a Mantel-Haenszel odds ratio (17) and a 95 per cent confidence interval were obtained. Analyses were performed for all leukemias as well as for specific cell types. Radiation exposures were compared between cases and controls with the cumulative radiation dose categories defined as follows: 1) never in the radiation program, 2) in the radiation program, but having no measurable radiation dose (0.0 rem), 3) 0.001-0.999 rem, and 4) 1.0 rem or greater. For calculation of the odds ratios, nonexposure was defined as never having been in the radiation program, and exposure was defined as having been in any of the three other dose categories. A comparison was also made between those workers in the most highly irradiated group (≥ 1.0 rem) and those persons who had been in the radiation program but with no measurable radiation dose (0.0 rem). This comparison was intended to reduce any selection bias which might have resulted from radiation workers being pre-selected from the Portsmouth Naval Shipyard population after a mandatory physical examination and, therefore, being "healthier" than other shipyard workers. A comparison between cases and controls of potential exposures to organic solvents was undertaken for

three job categories: ever exposed; exposed less than 10 years; and exposed 10 or more years. Potential associations with leukemia were also sought in all other jobs and shops at the Portsmouth Naval Shipyard in which at least three cases had worked; however, no a priori hypotheses existed with regard to these other jobs and shops.

The Mantel-Haenszel method (17) is best suited for examination of one exposure variable at a time when using matched controls. To control for possible confounding exposures other than the one being examined, and to evaluate interactions on a multiplicative scale, a conditional logistic regression model was employed. This model allowed assessment of each exposure variable while controlling for the possible effects of other exposure variables and for interactions between them (18-20). Two separate analyses were applied within the conditional logistic regression model: one in which cumulative radiation dose and the number of years employed in jobs and shops were considered as categoric variables; and the other in which these variables were considered as continuous. The categoric analysis was conducted because its exposure classifications were comparable with those in the univariate analysis. The continuous variable analysis was conducted to make use of the more precise exposure information (cumulative radiation dose and length of employment in various jobs) that was actually available for each study member. The average exposures of the exposed controls were assumed to be representative of the average exposures in the entire shipyard work force. These values were used to calculate odds ratios in the continuous variable analyses. For radiation exposure, the values were the average accumulated radiation dose (in rem); for jobs and shops, the values were the average number of years employed in that job or shop. (Odds ratios for other values of the exposure variables, X , can be calculated as $\exp(\beta X)$ and their 95 per cent confidence interval as $\exp(\beta X \pm ZXS)$, where β is the regression coefficient,

S is the standard error of β , and Z is the normal value at the desired significance level.) Because the latent period for leukemia induced by radiation is suspected to be as short as a few years (21), a separate analysis was conducted employing the conditional logistic regression model in which radiation exposures received by cases and their respective controls five years or fewer prior to the date of death of the case were eliminated. In all analyses, a 5 per cent α level was used to determine statistical significance.

RESULTS

Fifty-seven cases of leukemia were identified, in comparison with the 39 leukemia deaths considered in the previous cohort mortality study (3). The additional 18 cases resulted from 12 cases with leukemia coded as a contributory cause of death, and six cases who died of leukemia subsequent to the closing date of the cohort study in 1977. Four deaths in which leukemia was listed on the death certificate were subsequently eliminated from case selection because medical records indicated that two were plasma cell dyscrasias (multiple myeloma), one was an aleukemic leukemia, and one was a cytopenic leukemia. According to the above criteria, we established 53 cases of leukemias, which included 29 myeloid, 21 lymphatic, one monocytic, and two of unknown cell type. No attempt was made to classify these cases with regard to whether the leukemia was acute or chronic. Very close agreement was obtained between the 53 cases and their respective controls on all matching variables (figures 1-3). The average number of jobs held by cases (1.96) and controls (2.08) at the Portsmouth Naval Shipyard was also very similar.

Univariate analysis

Radiation. Eleven of 53 cases (21 per cent) had a history of having been monitored for radiation exposure; of these, six had accumulated a radiation dose of at least 1 rem. In comparison, 55 of the 212 controls

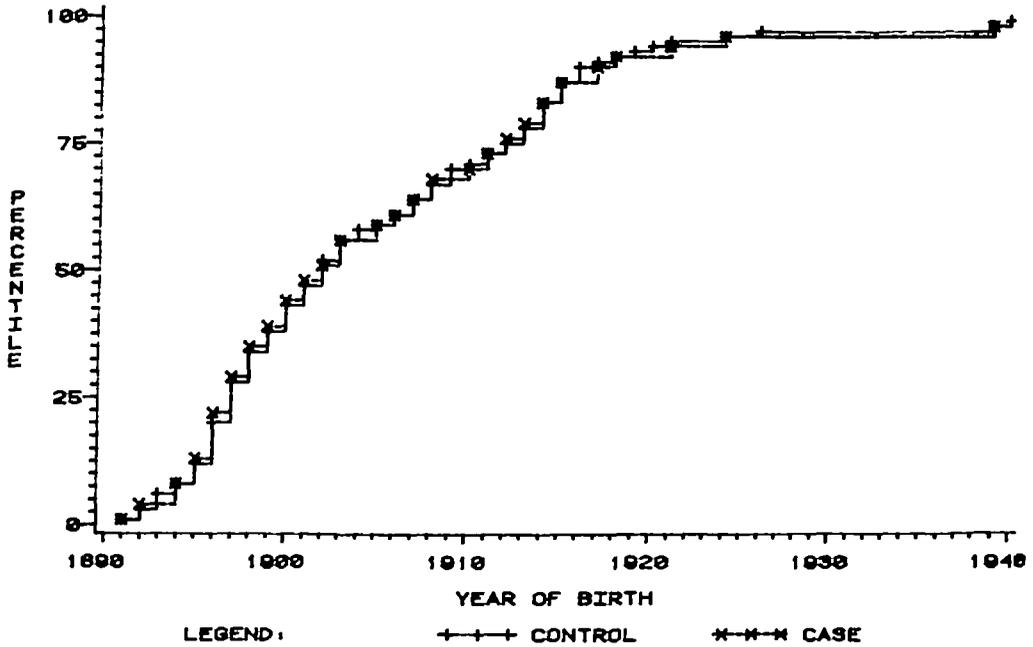


FIGURE 1. Agreement on percentile of birth year between 53 leukemia cases and their matched controls at a naval nuclear shipyard: Portsmouth Naval Shipyard, New Hampshire, January 1, 1952-August 15, 1977. Cases: mean = 1904; range = 1892-1939. Controls: mean = 1904; range = 1892-1940.

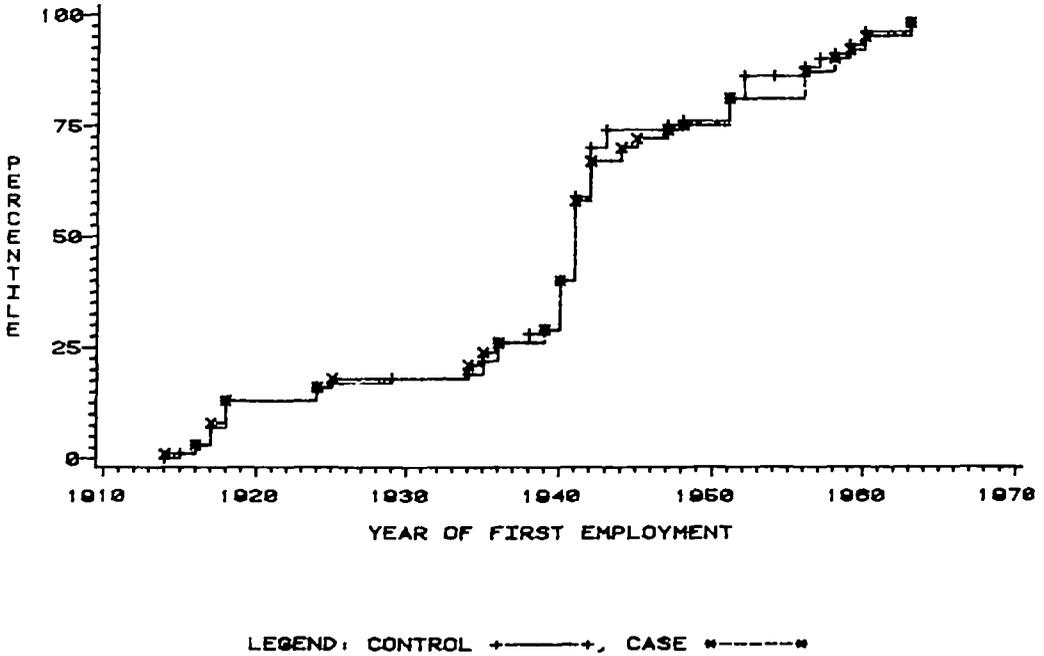


FIGURE 2. Agreement on percentile of year of first employment between 53 leukemia cases and their matched controls at a naval nuclear shipyard: Portsmouth Naval Shipyard, New Hampshire, January 1, 1952-August 15, 1977. Cases: mean = 1940; range = 1914-1963. Controls: mean = 1940; range = 1914-1963.

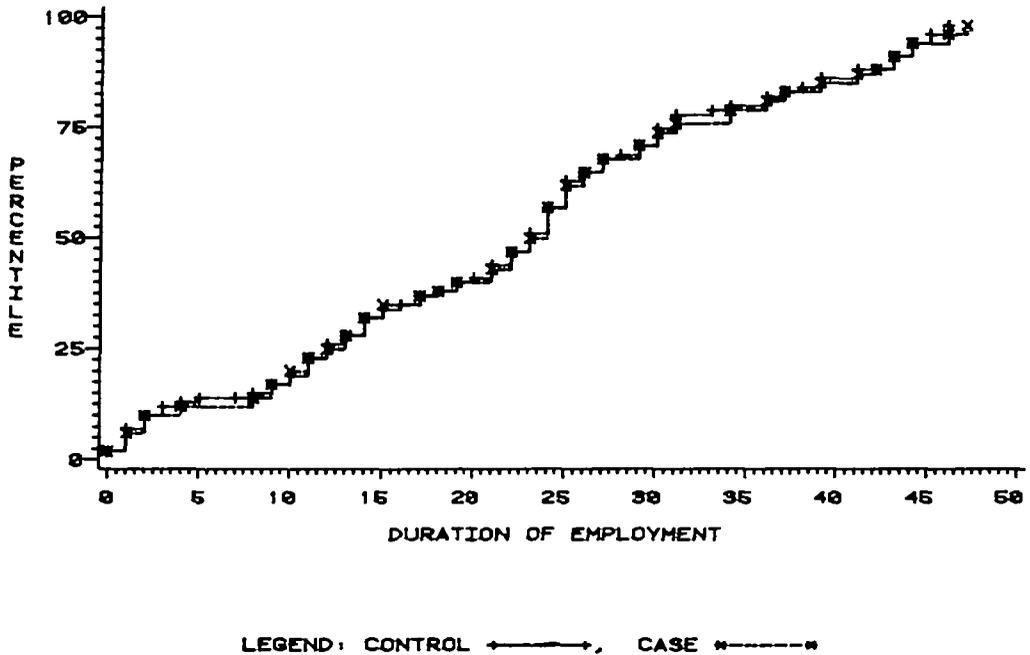


FIGURE 3. Agreement on percentile of duration of employment (years) between 53 leukemia cases and their matched controls at a naval nuclear shipyard: Portsmouth Naval Shipyard, New Hampshire, January 1, 1952–August 15, 1977. Cases: mean = 22; range = 0–47. Controls: mean = 22; range = 0–46.

(26 per cent) had a history of being monitored for radiation exposure at the Portsmouth Naval Shipyard, including 11 who had accumulated a radiation dose of at least 1 rem. Only one case (15.29 rem) and no controls had accumulated a radiation dose of more than 5 rem during their employment at the shipyard. For all leukemia combined, an odds ratio above 1.0 was seen only for those workers who had accumulated at least 1.0 rem of exposure; this odds ratio, however, was not statistically significant (table 1). For lymphatic leukemia, no evidence of an association with radiation exposure was observed at any level. For myeloid leukemia, an odds ratio of 2.24 was obtained for workers who had accumulated at least 1.0 rem of exposure, but, again, this ratio was not statistically significant. When this latter group was further compared with those workers who had been in the radiation program but who had no measurable radiation dose (0.0 rem), no statistically significant result was obtained (odds ratio = 5.33, 95 per cent confidence interval = 0.61–45.99).

Solvents. Odds ratios were elevated, al-

though not significantly so, for persons ever employed in jobs with potential for organic solvent exposures (table 2). This elevation was seen both for duration of employment of less than 10 years as well as for duration of employment of 10 years or more. Odds ratios were consistently above 1.0 for both myeloid and lymphatic leukemia, but, again, none was statistically significant and there was no significant association for either cell type with duration of employment. Review of work histories indicated that all nine leukemia cases who worked in jobs with potential for organic solvent exposure had been employed during the 1940s and early 1950s when benzene was still in use at the Portsmouth Naval Shipyard. Carpentry was the job category for seven of these nine cases. An analysis conducted for carpentry showed elevated odds ratios for all leukemia, myeloid leukemia, and lymphatic leukemia; none was statistically significant (table 3). Interestingly, five of the seven carpenters had been employed in the maintenance and supply shops, not in the woodworking shop.

Other jobs and shops. An examination

TABLE 1

Univariate analysis of leukemia by cell type and cumulative amount of radiation dose among cases and controls at a naval nuclear shipyard: Portsmouth Naval Shipyard, New Hampshire, January 1, 1952–August 15, 1977

Amount of radiation (rem)	All leukemias			Myeloid leukemia			Lymphatic leukemia		
	No. of cases	Odds ratio*	95% confidence interval	No. of cases	Odds ratio	95% confidence interval	No. of cases	Odds ratio	95% confidence interval
Not in radiation program	42			23			17		
In radiation program									
0.0	2	0.40	0.09–1.75	1	0.38	0.05–2.92	1	0.52	0.06–4.36
0.001–0.999	3	0.42	0.11–1.57	1	0.25	0.03–2.03	2	0.70	0.12–4.05
1.0+	6	1.40	0.42–4.70	4	2.24	0.49–10.16	1	0.50	0.04–6.75
Total cases	53			29			21		

* Mantel-Haenszel odds ratio compared to employees not in the radiation program.

TABLE 2

Univariate analysis of leukemia by cell type and by duration of employment in solvent-exposed jobs among cases and controls at a naval nuclear shipyard: Portsmouth Naval Shipyard, New Hampshire, January 1, 1952–August 15, 1977

Solvent jobs (years worked)	All leukemias			Myeloid leukemia			Lymphatic leukemia		
	No. of cases	Odds ratio*	95% confidence interval	No. of cases	Odds ratio	95% confidence interval	No. of cases	Odds ratio	95% confidence interval
Never	44			25			17		
<10	5	1.65	0.60–4.57	2	1.77	0.39–8.13	2	1.14	0.26–5.02
10+	4	1.86	0.44–7.81	2	1.37	0.27–6.92	2	4.67	0.18–119.96
Ever	9	1.88	0.79–4.44	4	1.87	0.58–6.03	4	1.50	0.39–5.77

* Mantel-Haenszel odds ratio compared to employees never in a solvent job.

was made of all jobs ever held and all shops ever worked, in which at least three or more cases were employed (table 3). Analysis by job category revealed a statistically significant odds ratio for all leukemias for the job category of electrician. This association was greater for lymphatic leukemia than for myeloid leukemia. Statistically significant odds ratios were also found for lymphatic leukemia for the category of supervisor (without regard of job) and for myeloid leukemia for that of welder. A review of the work history records of the 13 leukemia cases which occurred among supervisors revealed that five at some time had been employed as either an electrician or welder. None had accumulated a lifetime radiation dose at the Portsmouth Naval Shipyard of at least 1.0 rem or had ever worked in a solvent-exposed job. Analysis by shop category revealed statistically significant odds ratios for lymphatic leukemia

among employees of the electrical shop and for myeloid leukemia among employees of the welding shop. Nine of the ten cases in the electrical shop had the job classification of electrician and all seven cases in the welding shop had the job classification of electrical welder.

Conditional logistic regression analysis

Interactions between exposure variables and between matching and exposure variables were checked in the models with exposures entered as continuous variables. Based on the a priori hypotheses, the exposure variables examined in the model were radiation and organic solvents. Based on the results of the univariate analyses, electrical and welding jobs were also placed into the model. None of the interactions was found to be statistically significant ($p > 0.05$), nor did the exclusion of these terms appreciably alter estimates of the odds ra-

TABLE 3

Univariate analysis of leukemia by jobs and shops in which three or more cases ever worked in descending order of odds ratio for all leukemias at a naval nuclear shipyard: Portsmouth Naval Shipyard, New Hampshire, January 1, 1952–August 15, 1977

Job or shop category	All leukemias			Myeloid leukemia			Lymphatic leukemia		
	No. of exposed cases	Odds ratio*	95% confidence interval	No. of exposed cases	Odds ratio	95% confidence interval	No. of exposed cases	Odds ratio	95% confidence interval
Jobs ever held									
Electrician	11	3.00	1.29–6.98	6	2.33	0.77–7.06	5	6.00	1.47–24.45
Carpenter	7	2.50	0.91–6.90	4	2.50	0.71–8.83	3	3.33	0.56–19.83
Supervisor	13	2.36	0.95–5.86	8	1.53	0.54–4.40	5	13.00	1.31–28.96
Welder	7	2.25	0.92–5.53	6	3.83	1.28–11.46	0		
Sheetmetal	4	2.14	0.64–7.19	2	3.50	0.49–24.96	2	2.00	0.41–9.83
Shipfitter	11	1.54	0.67–3.54	8	1.71	0.62–4.72	3	2.00	0.41–9.76
Engineer	6	1.40	0.53–3.70	3	1.00		3	2.20	0.51–9.44
Outside machinist	6	0.91	0.38–2.22	3	1.75	0.19–2.66	2	0.88	0.17–4.40
Rigger	5	0.81	0.28–2.34	1	0.20	0.02–1.75	3	1.67	0.34–8.13
Pipefitter	5	0.70	0.27–1.84	3	0.86	0.25–2.93	2	0.64	0.13–3.14
Inside machinist	10	0.54	0.24–1.22	6	0.82	0.25–2.70	3	0.30	0.09–0.97
Shops ever worked									
Electrical	10	2.57	1.11–5.96	5	2.12	0.64–7.10	5	3.80	1.13–12.76
Welding	7	2.25	0.92–5.53	6	3.83	1.28–11.46	0		
Public works	3	2.40	0.60–9.61	1	4.00	0.31–51.79	2	2.67	0.48–14.89
Sheetmetal	4	2.08	0.64–7.19	2	3.50	0.49–24.69	2	2.00	0.35–12.35
Shipfitting	14	1.53	0.71–3.31	8	1.21	0.46–3.18	4	1.83	0.39–8.54
Woodworking	4	1.30	0.37–4.41	2	1.00		2	3.00	0.27–33.35
Outside machine	7	1.04	0.43–2.50	4	1.00		2	0.75	0.13–4.27
Planning	5	1.00		2	0.70	0.15–3.39	3	1.38	0.35–5.47
Rigging	6	1.00		1	0.22	0.02–1.75	4	2.60	0.57–11.86
Electrical fabrication	7	0.89	0.37–2.11	4	1.44	0.38–5.55	2	0.40	0.10–1.53
Inside machine	6	0.68	0.26–1.75	2	0.37	0.08–1.75	3	0.91	0.26–3.26
Supply	4	0.68	0.24–1.95	2	0.88	0.21–3.83	2	0.64	0.13–3.06
Maintenance	6	0.64	0.26–1.69	4	0.96	0.24–2.48	1	0.28	0.05–1.57
Pipefitting	3	0.55	0.16–1.87	2	0.70	0.14–3.38	1	0.50	0.07–3.62

* Mantel-Haenszel odds ratio compared to employees never in that job or shop.

tios. Therefore, only main effects of radiation, solvents, electrician, and welder were included in the models. Odds ratios mentioned in this section were controlled for other main effects.

Radiation. For all leukemias, when cumulative radiation was examined as a categorical variable, the only elevation in the odds ratio was observed for those workers with at least 1.0 rem of radiation dose (table 4). This elevation was also observed for myeloid leukemia, but not for lymphatic leukemia. As in the univariate analysis, none of the odds ratios was found to be statistically significant.

When cumulative radiation was exam-

ined as a continuous variable, results similar to those seen in the categorical analysis were noted (table 5). Elevations in the odds ratios were observed for all leukemias as well as myeloid leukemia. A separate analysis, in which radiation doses received in the last five years prior to the date of death of each case were eliminated, resulted in small and nonsignificant increases in the odds ratio of no more than 2 per cent and produced no statistically significant findings (results not shown).

Solvents. The odds ratios for ever having worked in an organic solvent-exposed job were in excess of unity for all leukemias, myeloid leukemia, and lymphatic leukemia

TABLE 4
 Conditional logistic regression for leukemia by exposure category among cases and controls at a naval nuclear shipyard: Portsmouth Naval Shipyard, New Hampshire, January 1, 1952-August 15, 1977

Radiation or job category	All leukemias				Myeloid leukemia				Lymphatic leukemia			
	β^*	SE†	Odds ratio	95% confidence interval	β	SE	Odds ratio	95% confidence interval	β	SE	Odds ratio	95% confidence interval
Amount of radiation (rem)												
0.0	-0.95	0.81	0.39	0.08-1.89	-0.84	1.16	0.43	0.04-4.19	-0.67	1.15	0.51	0.05-4.89
0.001-0.999	-0.94	0.70	0.39	0.10-1.54	-1.14	1.18	0.32	0.03-3.23	-0.78	0.94	0.46	0.07-2.89
1.0+	0.71	0.66	2.03	0.56-7.42	1.37	0.92	3.94	0.65-23.88	-0.18	1.37	0.84	0.06-12.25
Solvent job‡	0.84	0.51	2.32	0.85-6.29	0.94	0.76	2.56	0.59-11.35	0.69	0.75	1.99	0.46-8.67
Electrician†	1.22	0.45	3.39	1.40-8.18	1.11	0.61	3.03	0.92-10.03	1.81	0.76	6.11	1.38-27.10
Welder‡	1.16	0.55	3.19	1.09-9.37	1.83	0.68	6.23	1.64-23.64				
Model (p value)		0.01				0.02						

* β , regression coefficient.
 † SE, standard error of regression coefficient.
 ‡ Ever worked in job.

TABLE 5
 Conditional logistic regression for leukemia using continuous exposure variables among cases and controls at a naval nuclear shipyard: Portsmouth Naval Shipyard, New Hampshire, January 1, 1952-August 15, 1977

Radiation or years worked category	All leukemias				Myeloid leukemia				Lymphatic leukemia			
	β^*	SE†	Odds ratio‡	95% confidence interval	β	SE	Odds ratio	95% confidence interval	β	SE	Odds ratio	95% confidence interval
Radiation (rem)	0.29	0.18	1.26	0.95-1.66	0.45	0.30	1.43	0.89-9.68	-0.21	0.91	0.84	0.29-4.83
Years in a solvent job	0.07	0.04	1.82	0.93-3.58	0.09	0.06	2.16	0.79-5.95	0.05	0.06	1.53	0.56-4.22
Years as an electrician	0.08	0.04	1.67	1.01-2.78	0.07	0.05	1.57	0.83-2.96	0.10	0.06	1.90	0.89-4.07
Years as a welder	0.08	0.04	2.86	1.02-8.04	0.13	0.05	5.53	1.52-20.09				
Model (p value)		0.01				0.01						

* β , regression coefficient.
 † SE, standard error of regression coefficient.
 ‡ The odds ratios were calculated using the average exposure for all controls in the study who were exposed. The averages were as follows: radiation, 0.79 rem; solvent jobs, 8.59 years; electricians, 6.46 years; welders, 13.16 years. The odds ratios were calculated as an exponential value of X , where β was the regression coefficient and X was the average exposure.

in both the categoric analysis (table 4) and the continuous analysis (table 5). The ratios were highest for myeloid leukemia, but none of the odds ratios reached statistical significance. It should be noted, however, that a one-sided 95 per cent confidence limit would have resulted in 1.04 for all leukemias in the continuous analysis.

Electricians and welders. For the job title "electrician," the odds ratio for lymphatic leukemia was significantly elevated in the categoric analysis (table 4), and very similar to the odds ratio obtained in the univariate analysis. Statistically significant results for electricians were also observed in the continuous analysis for all leukemias (table 5). All other odds ratios for electricians in both the categoric and continuous analyses were elevated, but not statistically significant. For the job title "welder," odds ratios in both the categoric and continuous analyses were statistically significant for all leukemias as well as for myeloid leukemia (tables 4 and 5).

DISCUSSION

Although a retrospective cohort mortality study of employees at the Portsmouth Naval Shipyard (2, 3) revealed no overall excess risk of leukemia, this case-control analysis was undertaken to evaluate the potential association of leukemia with specific work-environment exposures at the Portsmouth Naval Shipyard. No statistically significant positive association of leukemia with either radiation or solvent exposures was found. Of the numerous relationships examined, the only statistically significant associations with leukemia occurred among electricians and welders.

The study was somewhat limited in its ability to detect an association between radiation exposure and leukemia because of two factors: 1) worker cumulative lifetime radiation exposures received at the Portsmouth Naval Shipyard were very low; and 2) only a few workers had received any detectable radiation dosage. Out of 53 cases, only six had accumulated a lifetime radiation dose of at least 1.0 rem and only

one had accumulated a lifetime radiation dose of more than 5.0 rem. While previous epidemiologic investigations have demonstrated a causal association between leukemia and exposure to ionizing radiation mainly in high-dose radiation studies (21-30), the effects of low-dose radiation exposures have not been clearly established (21, 31-34). When nuclear work began at the Portsmouth Naval Shipyard in 1958, the International Commission on Radiological Protection recommended that occupational whole-body dosage to radiation be limited to 3.0 rem per 13-week period and that cumulative lifetime dose not exceed an amount calculated as five times (age - 18 years) rem (15). In 1965, the International Commission on Radiological Protection deleted its age requirement and stated that the annual radiation dose not exceed 5 rem (15). This recommendation was derived from estimates of risk obtained from various human epidemiologic investigations. The Portsmouth Naval Shipyard has always established administrative dose limits below those recommended by the International Committee on Radiological Protection. This procedure was reflected in the relatively small annual radiation doses received among all cases and controls in the present study, which averaged less than 13 millirem (mrem) per year.

Although various jobs at the Portsmouth Naval Shipyard required the use of organic solvents, the elevated odds ratio observed was mainly due to only one job category—carpenter. The specific solvents to which carpenters have been potentially exposed included benzene, xylene, toluene, acetone, methylene chloride, tetrachloroethane, and methyl ethyl ketone. Although benzene was not observed during the 1980 industrial hygiene survey carried out at the Portsmouth Naval Shipyard by the National Institute for Occupational Safety and Health (2), benzene was known to have been utilized at the Portsmouth Naval Shipyard in the past.

The statistically significant elevated risk of leukemia found among electricians and

welders in our study was noteworthy. Electricians may frequently encounter exposures from metal fumes (i.e., nickel, chromium, iron, or lead, etc.), solvents (including benzene), fluxes, chlorinated biphenyls, epoxy resins, chlorinated naphthalenes, and electrical current. All seven welders who were identified as having leukemia had the job classification of electrical welder and may have had potential for some of the same exposures as those of electricians. Similar observations of elevated risk of leukemia among persons employed in "electrical" jobs, including those of "electrician" and "welder," have been reported in recent years (35-38).

This study was limited by a number of factors. First, with the exception of radiation exposure, actual exposure levels of the various agents used were not known. Consequently, length of employment in the various shops and jobs was used as an index for exposure. Second, while an attempt was made to identify and classify shops and jobs by similar processes and exposures into broad functionally identifiable groups for analytic purposes, there were overlapping processes and exposures between categories. Third, because of job mobility, some of the cases and controls were classified into multiple occupational categories. Fourth, due to the relatively small number of cases in this study, most of the exposure categories had very few cases. By subdividing the cases into myeloid and lymphatic leukemia, the number of cases in each exposure category was reduced even further. Consequently, the power of our study to detect significant associations was limited, as evidenced by the wide confidence intervals on the odds ratios. Even the use of one-sided 95 per cent confidence intervals, however, would not have changed our non-significant findings except for the category of solvent exposures for all leukemias. Finally, tests were performed on a large number of shops and jobs for which there were no a priori hypotheses which could have introduced chance significant findings.

In conclusion, this case-control analysis

among Portsmouth Naval Shipyard workers who died from leukemia, and their matched controls, was conducted in an attempt to ascertain associations between leukemia and specific exposures and occupations. No statistically significant associations with leukemia were found among workers exposed to ionizing radiation; however, an increase in the odds ratio for myeloid leukemia was observed among persons who had accumulated a lifetime radiation dose of at least 1.0 rem. For organic solvent-exposed workers, the odds ratios were elevated for all of the leukemia cell types, but none of the odds ratios reached statistical significance. However, statistically significant excess risks of leukemia were noted for those persons employed at the Portsmouth Naval Shipyard as electricians and welders; these results were observed in the univariate analysis as well as in the conditional logistic regression analysis.

REFERENCES

1. Najarian T, Colton T. Mortality from leukemia and cancer in shipyard nuclear workers. *Lancet* 1978;1:1018-20.
2. Rinsky RA, Zumwalde RD, Waxweiler RJ, et al. Epidemiological study of civilian workers at the Portsmouth Naval Shipyard. Report to the Director of the National Institute for Occupational Safety and Health, December 1980. Cincinnati, OH: NIOSH, 1980.
3. Rinsky RA, Zumwalde RD, Waxweiler RJ, et al. Cancer mortality at a naval nuclear shipyard. *Lancet* 1981;1:231-5.
4. Greenberg ER, Rosner B, Hennekens C, et al. An investigation of bias in a study of nuclear shipyard workers. *Am J Epidemiol* 1985;121:301-8.
5. Aksoy M, Dincol K, Erdem S, et al. Acute leukemia due to chronic exposure to benzene. *Am J Med* 1972;52:160-6.
6. Aksoy M, Erdem S, Dincol G. Types of leukemia in chronic benzene poisoning: a study of thirty-four patients. *Acta Haematol (Basel)* 1976;55:65-72.
7. Arp EW, Wolf PH, Checkoway H. Lymphatic leukemia and exposures to benzene and other solvents in the rubber industry. *J Occup Med* 1983;25:598-602.
8. Ott MG, Townsend JC, Fishbeck WA, et al. Mortality among individuals occupationally exposed to benzene. *Arch Environ Health* 1978;33:3-10.
9. Rinsky RA, Young RJ, Smith AB. Leukemia in benzene workers. *Am J Ind Med* 1981;2:217-45.
10. Vigliani EC. Leukemia associated with benzene exposure. *Ann NY Acad Sci* 1976;271:143-51.
11. International Agency for Research on Cancer.

- IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Vol 29. Lyon: IARC, 1982.
12. NIOSH. Revised recommendation for an occupational exposure to benzene. Washington, DC: US GPO, 1977. (DHEW publication no 757-009/8).
 13. Flodin U, Andersson L, Anjou C, et al. A case-referent study on acute myeloid leukemia, background radiation, and exposure to solvents and other agents. *Scand J Work Environ Health* 1981;7:169-78.
 14. McMichael AI, Spirtas R, Kupper LL, et al. Solvent exposures and leukemia among rubber workers: an epidemiologic study. *J Occup Med* 1975;17:234-9.
 15. Murray WE, Terpilak MS. The radiological control program of the Portsmouth Naval Shipyard. Unpublished report. Cincinnati, OH: NIOSH; Rockville, MD: Food and Drug Administration, Bureau of Radiological Health, 1982.
 16. University of North Carolina, Occupational Health Studies Group. Case-control analysis program. Chapel Hill, NC: University of North Carolina, 1977.
 17. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *JNCI* 1969;22:719-48.
 18. Conditional logistic regression for matched sets. In: Breslow NE, Day NE. *Statistical methods in cancer research*. Vol 1. The analysis of case-control studies. Lyon: IARC, 1980:248-79.
 19. Kleinbaum DG, Kupper LL, Morgenstern H. Applications of modeling: conditional likelihood estimation. In: Beal C, ed. *Epidemiologic research*. Belmont, CA: Lifetime Learning Publications, 1982:492-507.
 20. Day NE, Byar DP. Testing hypotheses in case-control studies. Equivalence of Mantel-Haenszel statistics and logit score tests. *Biometrics* 1979;35:623-30.
 21. Committee on the Biological Effects of Ionizing Radiation (BEIR III). *The effects on populations of exposure to low levels of ionizing radiation*. Washington, DC: National Academy of Sciences, 1980.
 22. Folley JH, Borges W, Yamawaki T. Incidence of leukemia in survivors of the atomic bomb in Hiroshima and Nagasaki, Japan. *Am J Med* 1952;13:311-21.
 23. Bizzozero OJ Jr, Johnson KG, Ciocco A, et al. Radiation-related leukemia in Hiroshima and Nagasaki, 1946-1964. *Ann Intern Med* 1967;66:522-30.
 24. Beebe GW, Kato H, Land CE. Life span study report 8: Mortality experience of atomic bomb survivors, 1950-1974. Technical report 1077. Hiroshima: Radiation Effects Research Foundation, 1978.
 25. Court-Brown WM, Doll R. Mortality from cancer and other causes after radiotherapy for ankylosing spondylitis. *Br Med J* 1965;2:1327-32.
 26. Matanoski GM, Seltser R, Sartwell PE, et al. The current mortality rates of radiologists and other physician specialists: specific causes of death. *Am J Epidemiol* 1975;101:199-210.
 27. Hempelmann LH, Hall WJ, Phillips M, et al. Neoplasms in persons treated with x-ray in infancy: fourth survey in 20 years. *JNCI* 1975;55:519-30.
 28. Shore RE, Albert RE, Pasternack BS. Follow-up study of patients treated by x-ray epilation of tinea capitis. *Arch Environ Health* 1976;31:21-8.
 29. Gibson R, Graham S, Lilienfeld A, et al. Irradiation in the epidemiology of leukemia among adults. *JNCI* 1972;48:301-11.
 30. Ichimaru M, Ichimaru T, Belsky J, et al. Incidence of leukemia in atomic bomb survivors, Hiroshima and Nagasaki 1950-1971, by radiation dose, years after exposure, age, and type of leukemia. Technical report 1076. Hiroshima: Radiation Effects Research Foundation, 1976.
 31. Archer VE. Effects of low-level radiation: a critical review. *Nuclear Safety* 1980;21:68-82.
 32. Caldwell GG, Kelley DB, Heath CW. Leukemia among participants in military maneuvers at a nuclear bomb test. *JAMA* 1980;244:1575-8.
 33. Caldwell GG, Kelley DB, Zack M, et al. Mortality and cancer frequency among military nuclear test (Smoky) participants, 1957-1979. *JAMA* 1983;250:620-4.
 34. Bross IDJ, Ball M, Falen S. A doseage response curve for the one rad range: adult risks from diagnostic radiation. *Am J Public Health* 1979;69:130-6.
 35. Milham S. Mortality from leukemia in workers exposed to electrical and magnetic fields. (Letter to the Editor.) *N Engl J Med* 1982;307:249.
 36. Wright WE, Peters JM, Mack TM. Leukemia in workers exposed to electrical and magnetic fields. *Lancet* 1982;2:1160-2.
 37. McDowall ME. Leukemia mortality in electrical workers in England and Wales. *Lancet* 1983;1:246-7.
 38. Coleman M, Bell J, Skeet R. Leukemia incidence in electrical workers. *Lancet* 1983;1:982-3.