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A Nested Case-Control Study of Leukemia Mortality and Ionizing Radiation at the Portsmouth Naval Shipyard

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A nested case-control study using conditional logistic regression was conducted to evaluate the exposure–response relationship between external ionizing radiation exposure and leukemia mortality among civilian workers at the Portsmouth Naval Shipyard (PNS), Kittery, Maine. The PNS civilian workers received occupational radiation exposure while performing construction, overhaul, repair and refueling activities on nuclear-powered submarines. The study age-matched 115 leukemia deaths with 460 controls selected from a cohort of 37,853 civilian workers employed at PNS between 1952 and 1992. In addition to radiation doses received in the workplace, a secondary analysis incorporating doses from work-related medical X rays and other occupational radiation exposures was conducted. A significant positive association was found between leukemia mortality and external radiation exposure, adjusting for gender, radiation worker status, and solvent exposure duration (OR = 1.08 at 10 mSv of exposure; 95% CI = 1.01, 1.16). Solvent exposure (including benzene and carbon tetrachloride) was also significantly associated with leukemia mortality adjusting for radiation dose, radiation worker status, and gender. Incorporating doses from work-related medical X rays did not change the estimated leukemia risk per unit of dose. © 2005 by Radiation Research Society

INTRODUCTION

In 1978, Najarian and Colton (*1*) reported elevations in proportionate mortality from leukemia and from all cancers combined for civilian workers at the Portsmouth Naval Shipyard (PNS) in Kittery, Maine. In response to these findings, Rinsky *et al.* (*2*) conducted a cohort mortality study of 24,545 civilian workers (white males only) employed from January 1, 1952, through August 15, 1977, but found no excess of leukemia or overall cancer mortality.

After the cohort mortality studies, Stern *et al.* (*3*) conducted a leukemia case-control study that did not find a statistically significant association between external ionizing radiation or possible solvent exposure and leukemia. However, elevated leukemia risk was seen in workers with cumulative equivalent doses of at least 10 mSv.

In 2004, Silver *et al.* (*4*) studied the mortality of an expanded PNS cohort of 37,853 male and female workers ever employed between January 1, 1951, and December 31, 1992, with vital status follow-up through 1996. At the end of vital status follow-up, 32.7% of the cohort was classified as deceased. Leukemia mortality was as expected based on U.S. population rates [standardized mortality ratio (SMR) = 1.01; 95% confidence interval (CI) = 0.84, 1.22] in the full cohort, but it showed a statistically nonsignificant elevation among non-radiation-monitored workers (SMR = 1.08, 95% CI = 0.86, 1.35). While the SMR did not indicate an excess, internally standardized rate ratios (SRRs) showed a significant trend of increasing leukemia risk with increased radiation exposure among radiation workers ($P = 0.01$). The leukemia SRRs were 2.06 (95% CI = 0.77, 5.50), 2.94 (95% CI = 1.10, 7.86), and 5.08 (95% CI = 1.35, 19.20) among radiation workers who had cumulative doses between 1–<10 mSv, 10–<50 mSv, and greater than or equal to 50 mSv when compared to workers in the baseline group (0–<1 mSv). No evaluation of potential confounding by solvent exposure was conducted (*4*).

The positive dose–response pattern for leukemia reported by Silver *et al.* was also observed in a recent analysis of the 13,468 radiation-monitored PNS workers by Yiin *et al.* (*5*). Using a linear relative risk model, Yiin *et al.* reported a statistically nonsignificant excess relative risk (ERR) of 10.9% (95% CI = −0.09%, 38.0%) per 10 mSv of external radiation exposure (*5*). However, Yiin *et al.* were not able to consider detailed confounding, such as from potential occupational exposure to solvents, or to evaluate the impact on risk estimates by the inclusion of doses from work-related medical X rays with doses resulting from exposures common to the workplace.

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TABLE 1
Frequency of Cases by International Classification of Diseases (ICD) Code Revisions

ICD revision	Years	Leukemia ICD codes	Number of CLL cases[a]	Total number of cases (n = 115)
9th	1979 to 1999	204.0–208.9	9	65
8th	1968 to 1978	204.0–207.9	5	35
6th and 7th	1949 to 1967	204.0–204.4	0	15

[a] The 6th and 7th revisions to the International Classification of Diseases (ICD) do not specify chronic lymphocytic leukemia (CLL).

The purpose of the current study was to investigate associations between external ionizing radiation exposure and leukemia mortality among civilian workers employed for at least 1 day between January 1, 1952, and December 31, 1992, at the Portsmouth Naval Shipyard (PNS). This study employed a nested case-control design to analyze that association while controlling for confounding and evaluating potential effect modifiers not available in the full cohort.

MATERIALS AND METHODS

PNS Study Subjects

The study population from which the cases and controls were selected is described by Silver *et al.* (*4*) and consists of 37,853 civilian workers ever employed between 1952 and 1992 whose vital status and cause of death were obtained through 1996. Of the total cohort, 13,468 workers were monitored for external ionizing radiation.

All deaths occurring between 1952 and 1996 among the entire cohort with an underlying cause of death classified as leukemia under the revision of the International Classification of Diseases in effect at the time of death were selected as cases (n = 115) (Table 1).

For each case, four controls were randomly selected from each risk set using incidence density sampling methods described by Beaumont *et al.* (*6*). A risk set consists of all workers who were under observation at the age of the index case at the time of failure (that is, were hired at an earlier age than the case's death age and lived longer than the case). Cases and controls were matched on attained age because it is a strong predictor of leukemia mortality and is therefore an important potential confounder of the associations of interest in these analyses.

Radiation Exposure

Personal radiation monitoring was conducted for all employees and visitors entering radiological areas or handling radioactive materials. In 1950, PNS began using personal dosimetry for recording worker doses to penetrating γ radiation. The monitoring program was expanded and improved in 1958 for work related to nuclear-powered submarines. After medical and training qualifications as radiation workers, shipyard employees were issued personal radiation dosimeters when accessing radiation-controlled areas of the shipyard, both on board submarines and in support buildings. Non-radiation workers were restricted from accessing these areas and did not require personal monitoring. For this study, non-radiation workers were assumed to be unexposed to ionizing radiation from shipyard sources other than work-related medical X-ray examinations. Work-related medical X-ray doses were calculated for each worker, including those not monitored for occupational sources, as described below.

Nearly all worker radiation exposure occurred while performing tasks within the shielded reactor compartment on nuclear-powered submarines during overhaul and repair activities. Workers were predominantly exposed to whole-body penetrating γ radiation emitted by activation products deposited in reactor systems and components, principally ^{60}Co (half-life 5.27 years). Observed photon energies typically ranged between 100 and 3,000 keV, with lower-energy photons (<100 keV) from scattered radiation and X rays contributing less than 5% to worker radiation dose. Except for limited exposures involving X-ray generating equipment and sealed sources, exposure profiles do not vary greatly for shipyard workers due to the similar nature of work. Approximately 65% of the radiation field was anterior to posterior, 25% was rotational, and the remaining 10% was isotropic (*7*). Details of the radiation exposures at PNS and the procedures for assembling and validating dosimetry data for this study are described elsewhere (*7, 8*).

Shipyard employees were also exposed to penetrating radiation from work-related medical X rays (*8*). Pre-employment and periodic chest X-ray examinations were performed throughout the period addressed by this study. Early routine chest examinations were conducted frequently and used photofluorographic equipment, which resulted in significantly higher exposures than those from the direct radiographic techniques employed today. Additionally, shipyard radiation workers were required to participate in routine examinations more frequently than non-radiation workers, resulting in a potential association between the level of dose from work-related medical X rays and the level of occupational dose (*8*).

Workplace exposure data were gathered from personal dosimetry records. For most workers, exposure data were available for each dosimeter processing period. However, computer reports of annual personal exposure reports were used to supplement data collection when interval data were not available. Exposure records included estimates for shallow, deep, X-ray and neutron exposures.

Information describing medical X-ray examinations was abstracted from the medical records of each study subject. Data regarding examination date, reason (i.e., work-related medical X rays or nonroutine), type of projection (i.e., body part and orientation), and imaging equipment used (i.e., photofluorographic or direct radiographic) were coded into a relational database. Dose estimates also required specific knowledge of X-ray geometry, accelerating voltage and current, exposure time, beam filtration, and patient sex, age and anatomy. X-ray equipment and operating parameters were abstracted from available historical documents. The physical arrangement of the X-ray beam and patient were described by U.S. Navy technical procedures (*8*). Other parameters necessary for modeling were adopted from average values reported by the National Council on Radiation Protection (NCRP) (*9, 10*).

Dosimetry

External ionizing radiation exposure was the primary exposure variable. Three radiation dose metrics are considered in the study analysis. First, the cumulative whole-body equivalent dose for each case and control was calculated by summing the worker's reported dose from each monitoring period recorded in shipyard dosimetry records. The cumulative whole-body dose was limited to X-ray and γ-ray exposures, since there was no evidence of significant neutron or internal exposures to workers within the study population (*7*). Second, reported whole-body doses were adjusted to account for recognized biases in the measurement process that arise from exposure to heterogeneous radiation fields, calibration methods, dosimeter design, and dosimeter energy response (*8*). Dosimeter-specific bias factors were applied to the adjusted whole-body doses to obtain an estimate of equivalent dose to the active bone marrow. The bias factors were derived as described by Thierry-Chef *et al.* (*11*) using dose conversion coefficients recommended by the International Commission on Radiological Protection (ICRP) (*12*). Third, the equivalent dose to bone marrow from work-related medical X rays was calculated using methods described by Daniels *et al.* (*8*). The cumulative equivalent dose to active bone marrow was then determined by summing doses from work-related medical X rays and traditional occupational sources. For controls, all dose metrics were assessed from date of first

exposure to the cutoff date (i.e., the date at which they reached the age at death of the matched case).

Some exposures were not detected as a result of limitations in measurement sensitivity. Given the dosimetry methods used at PNS, the amount of ''missed dose'' from measurement sensitivity is expected to be small in comparison to recorded doses (*7*). In general, missed-dose values were imputed from the distribution of recorded values grouped by worker (preferred) or by dosimeter type and monitoring period. These grouped data, including left-censored placeholders, were fitted to a log-normal distribution to impute substitution values for reported less-than values. Distribution fitting was performed using maximum likelihood estimation or by probability plotting using least-squares regression of the log of exposures as a function of the normal score (*13*).

Because most leukemia subtypes have a relatively short latent period, lag assumptions of 0, 2, 5 and 7 years were tested, first with each radiation dose term individually (unadjusted) and then in the final regression model. From log likelihood testing, the 2-year lag was determined to be the most appropriate lag period and was employed for all radiation dose variables (*14*). The 2-year lag period for leukemia is also consistent with analyses of leukemia mortality in other populations (*15*). All radiation exposure assessment was done by those blind to case status.

Solvent Exposure

Solvent exposure was considered because of the possible increased risk of leukemia among workers exposed to benzene or carbon tetrachloride (*16–18*). Jobs and shops determined to have exposure potential were abstracted from work history records for each study subject. Duration of employment in those jobs and shops was chosen as a surrogate for exposure magnitude because monitoring records were sparse.

Information for the evaluation of chemical exposures was found in records kept by the PNS medical clinic and, beginning in the early 1980s, the industrial hygiene (IH) department. These records contained limited information on chemical use during shipyard construction, overhaul and maintenance activities. The documents included manufacturing process descriptions, production flow charts, plant production inventories, and routine inspection and accident reports. The IH department also kept records of environmental monitoring results for airborne contaminants within the shipyard complex.

Additionally, the shipyard IH department had records detailing work practices and process improvements. The work practice records describe the use of personal protective equipment during sand blasting, welding and painting activities, and local exhaust ventilation while working in confined spaces. Other records indicated that the shipyard reduced potential exposures by replacing hazardous chemicals with less toxic substitutes when possible. For example, in 1948 the shipyard began phasing out the use of carbon tetrachloride. Also, the shipyard substantially decreased the use of benzene by discontinuing the purchase of bulk benzene by February 1958; however, it remained as a contaminant in petroleum distillates (2–5%) such as gasoline and in some solvents (11–15%) such as toluene, xylene and naphthas. Records detailing new construction, refueling and overhaul at the shipyard were also kept by the IH and Public Affairs offices. These records identify specific periods when significant changes in work activity occurred at the shipyard (*14*).

Job titles and shop assignments for each case and control throughout their employment at PNS were gathered from available personnel records. All work history information was coded by staff who were unaware of case status to avoid potential bias. A total of 1,372 job title and shop combinations were identified and solvent exposure potentials were related to these combinations. Shops were grouped by (1) function of the shop (e.g., production, administrative, support), (2) types of chemicals and materials used, and (3) whether the employees performed work on submarines. The job titles were grouped by (1) type of work tasks performed and (2) type of potential chemical exposures.

Given the limited availability of relevant monitoring data and chemical use information, the intensity and frequency of potential exposures could not be quantified. Job titles and shops identified for potential benzene and carbon tetrachloride exposures were painting, welding, machining, woodworking, electrician and transportation groups. Individuals working in these jobs who were assigned to a production or support shop were classified as exposed to benzene or carbon tetrachloride. In contrast, workers assigned to administrative job/shop functions were not considered solvent-exposed.

Sparse benzene monitoring data available from the late 1970s and early 1980s did not reveal any exposures above 0.15 parts per million (ppm). Therefore, a last exposure date of December 31, 1980, was assigned to all of the exposure job groups except the transportation group. The transportation job group was still considered potentially exposed until January 1, 1990, when benzene in gasoline was reduced to less than 1% in response to requirements enacted by the U.S. Environmental Protection Agency (*19*). Therefore, a worker employed in the transportation group would not accumulate exposure time after January 1, 1990, and all other workers' exposure time contributions were considered to have ceased after December 31, 1980.

Time Since Radiation Exposure

Time since radiation exposure (TSRE) was analyzed using time windows of exposure as described by Rothman (*20*). The total radiation exposure accrued by each case and control in the periods 0–<2.5 years prior to case failure (or, for controls, prior to the cutoff date), 2.5–<5 years prior, 5–<10 years prior, and ≥10 years prior was determined. The association between leukemia mortality and total exposure accrued in each window was examined.

Radiation Monitoring Status

The results of the PNS cohort mortality study suggest that radiation-monitored and non-monitored PNS workers had very different occupational and non-occupational exposure histories, with radiation-monitored workers showing a strong healthy worker effect while their non-monitored colleagues do not. The average employment duration also differed substantially among the radiation-monitored and non-monitored workers in the PNS cohort. The non-monitored workers have a much shorter average duration of employment, with fewer than half employed as long as 5 years. SMR and SRR results for many causes of death, including leukemia, differed between these two groups (*4*). Thus the potential impact of the healthy worker survivor effect (*21, 22*) would differ substantially in the two groups. Many other nuclear worker studies have accounted for this by stratifying on radiation monitoring status or restricting the study to monitored workers. Non-monitored workers were included in the study to evaluate the influence on risk of work-related medical X rays (which could be evaluated in both groups of workers). In recent studies of Mayak workers (*23*), a dichotomous variable was used to differentiate monitored and unmonitored radiation workers given evidence of different mortality risks between the two groups. Consistent with the Mayak study approach, the radiation monitoring status of each worker was incorporated as a dichotomous variable.

Gender

Gender was included in the analysis because males have a higher risk of leukemia than females (*24*) and males were expected to receive more exposure than females. The analysis of this variable is limited because the PNS cohort is predominantly male (93%).

Statistical Analysis

Conditional logistic regression was used to evaluate any exposure–response relationship between external ionizing radiation exposure and leukemia mortality. The full conditional logistic regression model used was log-linear with parameters estimated for radiation exposure, solvent duration, TSRE, radiation monitoring status, and gender. The incidence density design ensures that the OR approximates the rate ratio in the cohort. Given that the linear excess relative risk (ERR) model is often

TABLE 2
Temporal Variables for all Leukemia Cases and Matched Controls between 1952 and 1996

Temporal variables	Cases (n = 115)	Controls (n = 460)	P value[a]
Mean year of birth	1912	1914	0.24
Mean age at date first employed (years)	34.2	35.3	0.30
Mean duration of employment (years)	19.6	17.6	0.13
Mean year first employed	1947	1949	0.06
Mean year last employed	1966	1967	0.46
Percentage employed at least 5 years	79%	76%	0.52
Mean time since last employed (years)	13.6	14.5	0.47
Mean age at cutoff date (years)	67.5	67.4	0.98

[a] Student's t test of difference in mean values between case and control groups.

used in radiation epidemiological studies (*25*), a linear ERR model was developed using a software package (PECAN module of EPICURE) designed for matched case-control analysis (*26*). Because the induction period for leukemia from radiation exposure was suspected to be as short as several years (*15*), a lag period of 2 years was selected. Radiation doses and solvent exposure duration were truncated for each control when they attained the age at death of their matched case, minus the lag period.

Odds ratios (ORs) and the corresponding 95% CI were derived from parameter estimates and the associated standard errors of the conditional logistic regression model. A two-tailed test of significance with a significance level (α) of 0.05 was used to determine the statistical significance of the OR and exposure–response relationships. Assessment of possible interactions between radiation exposure variables (e.g., reported cumulative equivalent dose, cumulative bone marrow equivalent dose excluding work-related medical X-ray contribution, and cumulative bone marrow equivalent dose with work-related medical X-ray contribution) and other covariates (e.g. solvent exposure duration, radiation worker status, and gender) was performed using a hierarchically formulated approach in which all interaction terms except those of *a priori* interest (e.g. TSRE) were evaluated simultaneously (*27*). Statistical testing of interaction (cross product) terms was performed using the log likelihood ratio test assuming a χ^2 distribution for the nested models. Potential confounding variables are independent risk factors that are correlated with both radiation exposure and leukemia mortality and were considered for exclusion from the analysis if their removal changes the relative value of the radiation exposure coefficient by less than 10%.

RESULTS

Descriptive Statistics

For each of the 115 cases, four controls were selected for a total of 460, five of which were selected twice. Of the 444 (78%) cases and controls with known race, 99% were white. Mean values of the temporal variables for the cases and controls are shown in Table 2. All temporal values were computed as of the cutoff date for each case/control set. There were no statistically significant differences in the mean values of the temporal variables between the cases and controls.

Radiation Exposure

Of the 575 cases and controls, 201 (35%) were radiation-monitored; 173 (87%) of the radiation-monitored cases and controls had reported exposure greater than zero. Among the 115 cases, 34 (30%) were monitored for radiation exposure; all were male. Of the 81 non-radiation-monitored cases, only three were female. Among the 460 controls, 167 (36%) were radiation-monitored (all male) and 293 (63%) were not monitored (253 male and 40 female). Five radiation-monitored cases (15%) and 23 radiation-monitored controls (14%) had zero recorded exposure (Table 3).

The mean and median reported cumulative equivalent doses for the case-control study group from onsite exposures were 23.2 mSv and 4.52 mSv, respectively. The mean dose for the cases (39.0 mSv) was nearly twice that (20.0 mSv) for the controls. Similarly, the median dose for cases (10.4 mSv) was about 2.5 times that (3.82 mSv) for the controls. Doses were estimated for 175 workers to account for exposures below the measurement sensitivity of the different dosimetry devices. The ''missed dose'' increased the collective dose by 87.6 mSv (1.84%).

Work-related medical X-ray dose estimates were assigned to 555 (96.5% of) cases and controls. The collective cumulative equivalent dose to active bone marrow from all occupational sources was approximately 6.1 person-Sv, of which 2.6 person-Sv (43%) was from work-related medical X rays. Radiation-monitored cases and controls received 2.3 times the number of work-related medical X rays of non-monitored cases and controls (*8*). However, the mean

TABLE 3
Radiation Monitoring Status among Cases and Controls (%)

Radiation monitoring status	Cases (n = 115)	Controls (n = 460)	Total (n = 575)
Monitored with reported exposure >0	29 (17)	144 (83)	173
Monitored with no reported exposure	5 (18)	23 (82)	28
Not monitored	81 (22)	293 (78)	374

TABLE 4
Equivalent Dose to Active Bone Marrow from Occupational Sources and Work-Related Medical X Rays Combined

	Equivalent dose to active bone marrow (mSv)								
	Occupational sources only			Work-related medical X rays only			Occupational sources and work-related medical X rays combined		
Statistic	Cases (n = 34)	Controls (n = 167)	Total (n = 201)	Cases (n = 111)	Controls (n = 440)	Total (n = 551)	Cases (n = 111)	Controls (n = 444)	Total (n = 555)
Mean	29.1	14.6	17.1	5.13	4.68	4.78	14.1	10.1	10.9
Median	7.88	2.82	3.45	4.50	4.50	4.50	6.00	4.54	4.62
Minimum	0	0	0	0.04	0.04	0.04	0.04	0.04	0.04
Maximum	145	145	223	16.5	15.1	16.5	147	236	236
Collective dose (person-Sv)	0.99	2.44	3.43	0.57	2.06	2.63	1.56	4.50	6.06

bone marrow dose value from work-related medical X rays for radiation-monitored cases and controls (5.97 mSv) was only moderately higher than for the non-monitored cases and controls (4.10 mSv). The 111 exposed cases had a collective dose of 1.6 person-Sv, of which 0.6 person-Sv (37%) was from work-related medical X rays (Table 4). Only four cases and 16 controls were not exposed to radiation from any source considered in this study.

Solvent Exposure

Sixty-three cases and 244 controls were identified as employed in job and shop categories likely to involve benzene or carbon tetrachloride exposure. The mean and median values for cumulative employment duration in any of the exposed groups were 14.5 and 14.3 years for the cases and 10.0 and 7.7 years for the controls. The machining group included more cases (30) and controls (112) than any of the other exposed groups. The mean and median cumulative employment duration in the machining group was 15.6 and 16.1 years for the cases and 10.7 and 10.1 years for the controls (Table 5).

Regression Analysis

The log-linear regression model shows a significant positive exposure–response relationship between leukemia mortality and external ionizing radiation (OR = 1.08 at 10 mSv of exposure; 95% CI = 1.01, 1.16), adjusting for solvent exposure duration, radiation worker status, and gender. When the analysis is conducted without the radiation monitoring status variable, the non-adjusted risk estimate is lower (OR = 1.04 at 10 mSv of exposure; 95% CI = 0.97, 1.10). When the analysis is conducted without the solvent exposure duration variable, there is only a slight change in the 95% confidence interval of the risk estimate (OR = 1.08 at 10 mSv of exposure; 95% CI = 1.01, 1.15).

The interaction between attained age and radiation exposure was assessed and was found to be nonsignificant (P = 0.07). Also, a birth cohort analysis was conducted and revealed no differences in leukemia mortality among birth cohort groups and no effect on the radiation risk coefficients.

Some analyses of leukemia risk in nuclear workers have shown an increase in the risk estimate when chronic lymphocytic leukemia (CLL) cases are excluded (*25*). The significant exposure response remained unchanged when all 14 of the cases identified as CLL and their controls were excluded from the analysis. Only three of the 14 cases of CLL had a history of radiation exposure, and their collective exposure was only 0.05 person-Sv. CLL cases prior to 1968 could not be identified since an International Classi-

TABLE 5
Frequency of Cases and Controls by Job/Shop with Likely Solvent Exposure Including Benzene and Carbon Tetrachloride

Solvent-exposed group	Cases	Controls	Mean duration (years) (cases)	Median duration (years) (cases)	Mean duration (years) (controls)	Median duration (years) (controls)
Painting group	2	12	13.0	13.0	9.2	8.8
Welding group	11	34	14.0	13.1	11.4	7.8
Transportation group	9	27	9.3	5.8	5.2	3.0
Electrical group	19	44	8.0	6.1	9.9	5.5
Machining group	31	113	15.6	16.1	10.7	10.1
Woodworking group	3	28	4.1	2.5	5.9	2.1
Totals within a solvent-exposed group (no duplicates)[a]	63	244	14.5	14.3	10.0	7.7

[a] There were 26 cases and controls that were included in more than one job/shop group.

TABLE 6
Final Model (Log-Linear): Cumulative Whole-Body Equivalent Dose with 2-Year Lag

Variable	Parameter estimate	Standard error	Odds ratio	95% confidence limits	
Equivalent dose (10 mSv)	0.076	0.035	1.08	1.01	1.16
Solvent duration exposed, lagged 2 years	0.0323	0.0115	1.03	1.01	1.06
Radiation worker (1 = Yes, 0 = No)	−0.7283	0.2632	0.48	0.29	0.81
Gender	−1.194	0.6112	0.30	0.09	1.00

fication of Diseases (ICD) code was not assigned to this leukemia subtype at that time.

When the radiation exposure variable in the log-linear model includes only measured exposure from occupational sources and no estimated missed exposure, there remained a significant positive exposure–response relationship between leukemia mortality and radiation exposure, and the odds ratio and confidence limits remain essentially unchanged (OR = 1.08 at 10 mSv of exposure; 95% CI = 1.01, 1.16). The analysis was also conducted using a linear excess relative risk model adjusting for solvent exposure duration, radiation worker status, and gender. This model yielded higher risk estimates (23% ERR per 10 mSv; 95% likelihood-based CI = 3%, 88%) at low dose than the log-linear model.

Both the linear excess relative risk model and the log-linear model detect a significant trend of increasing risk with increasing exposure. These models predict similar relative risk (6.7 with a log-linear and 6.9 with a linear ERR model) at a cumulative dose of about 250 mSv, which corresponds to the top 1% of the doses among the 13,468 radiation-monitored workers in the PNS workers in the cohort. Below 250 mSv, the linear ERR model estimates higher relative risks, while the log-linear model estimates higher relative risks above that level. Given that recent studies have suggested the dose response in the lower-dose range appears to be linear-quadratic (*15*), the log-linear model may be the preferred model because it provides a reasonable approximation of the linear-quadratic dose–response curve in the low-dose range (*15*). The addition of a quadratic term to the linear ERR analyses used in this case-control study was not significant ($P = 0.23$).

Time since Radiation Exposure

The time windows categorical approach shows slightly heterogeneous risk of leukemia mortality with time after radiation exposure. While the effect estimate is elevated in the 2.5- to 5-year exposure window (OR = 1.32 at 10 mSv; 95% CI = 0.56, 3.12), the total radiation dose between 5 and 10 years appears to have the greatest effect on leukemia mortality (OR = 1.42 at 10 mSv; 95% CI = 1.04, 1.95), and the effect estimate declines for previous exposures 10 years or greater (OR = 1.06 at 10 mSv; 95% CI = 0.99, 1.15).

Radiation-Monitored Workers

The parameter estimate for radiation worker status in the log-linear model was negative (Table 6), indicating that radiation-monitored workers had a lower overall leukemia risk than non-monitored workers. This result is consistent with the overall cohort analysis (*4*). Because leukemia mortality was greater among non-monitored workers, an analysis including only radiation-monitored workers was conducted using both log-linear and linear ERR models. Gender was dropped from these models because only three female radiation-monitored workers would be included.

The log-linear model shows a significant positive exposure–response relationship between leukemia mortality and external ionizing radiation exposure (OR = 1.20 at 10 mSv of exposure; 95% CI = 1.05, 1.37), adjusting for solvent exposure duration. The solvent exposure duration is elevated but is no longer statistically significant (OR = 1.05 at 1 year of exposure; 95% CI = 0.99, 1.10). The relative risk (RR) using a linear excess relative risk model indicated greater risk (RR = 1.40 at 10 mSv; 95% likelihood-based CI = 1.05, 2.89) than the log-linear model.

Analyses were conducted using both the log-linear and linear ERR models, excluding all cases and controls with more than 100 mSv of cumulative external ionizing radiation dose to examine the influence of highly exposed subjects on the point estimates. Although the point estimates of both models remained essentially unchanged, neither model yielded statistically significant results when highly exposed subjects were excluded (*14*).

Solvent Exposure Duration

The log-linear model also shows a significant positive exposure response between leukemia mortality and solvent exposure duration (OR = 1.03 at 1 year of exposure; 95% CI = 1.01, 1.06). When the analysis is restricted to non-radiation-monitored workers, there is only a slight change in the 95% confidence interval of the risk estimate (OR = 1.03 at 1 year of exposure; 95% CI = 1.01, 1.07).

Exposure from Work-Related Medical X Rays

When bone marrow doses from work-related medical X rays and the other occupational sources were combined, the association with leukemia mortality (adjusting for gender,

TABLE 7
Log-Linear Model: Equivalent Dose to Bone Marrow from All Occupational Sources and Work-Related Medical X Rays Combined with 2-Year Lag

Variable	Parameter estimate	Standard error	Odds ratio	95% Confidence limits	
Equivalent dose (10 mSv)	0.108	0.046	1.11	1.02	1.22
Solvent duration exposed, lagged 2 years	0.0312	0.0115	1.03	1.01	1.06
Radiation worker (1 = Yes, 0 = No)	−0.7581	0.2660	0.47	0.28	0.79
Gender	−1.198	0.6110	0.30	0.09	1.00

radiation worker status, and solvent exposure duration) is significant (OR = 1.11 at 10 mSv equivalent dose to active bone marrow; 95% CI = 1.02, 1.22) (Table 7). Without work-related medical X-ray dose contributions, the association of leukemia risk with bone marrow dose remains essentially unchanged (OR = 1.11 at 10 mSv; 95% CI = 1.01, 1.22).

DISCUSSION

A statistically significant positive association was found between leukemia mortality and increasing external ionizing whole-body radiation exposure, after adjusting for radiation worker status, gender and solvent exposure duration (log-linear OR = 1.08 at 10 mSv; 95% CI = 1.01, 1.16). When including only PNS recorded dose (i.e., excluding estimated missed radiation exposure), the odds ratio and confidence limits remained unchanged. Missed doses accounted for less than 2% of the collective dose estimated for the cases and controls. Radiation doses received in the 5- to 10-year period before death showed the strongest association with leukemia risk. The window-of-exposure method accounts for the fact that radiation exposures at PNS were not single, acute exposures (in which time since exposure is easily defined) but are protracted exposures over time. The finding of a significant dose–response relationship between leukemia mortality and radiation dose is consistent with the most recent cohort analyses of PNS workers (*4, 5*). Also, categorical risk estimates for this case-control study reported previously (*14*) are similar to those reported for the entire PNS cohort by Silver *et al.* (*4*)

The linear ERR model estimated an excess relative risk of 23% (95% CI = 3%, 88%) per 10 mSv of external radiation exposure from occupational sources after solvent exposure was included. When solvent exposure was excluded from the model an ERR of 21% (95% CI = 2%, 77%) per 10 mSv was estimated. The excess relative risk has been estimated in previous studies at between −4.1% and 19.0% at 10 mSv for workers exposed to penetrating ionizing radiation (*28*) and approximately 4% at that dose for A-bomb survivors who were exposed instantaneously as adults and developed leukemia less than 25 years after exposures (*15, 25, 29*). In contrast, workers in this study received fractionated exposures over periods that were often several decades long. A linear-quadratic model is often used in analyses for A-bomb survivors because it fits these data better than a simple linear model (*15, 30*). The fit in the linear ERR analyses used in this case-control study was not significantly different with the addition of a quadratic term ($P = 0.23$).

A statistically significant positive relationship was found between leukemia mortality and duration of employment in the six PNS job categories (machining, transportation, welding, electrical, painting and woodworking) classified as having potential exposure to benzene or carbon tetrachloride. Yiin *et al.* reported an elevated but nonsignificant leukemia risk among 13,468 radiation-monitored workers ever exposed to solvents compared to those never exposed (RR = 1.14; 95% CI = 0.56, 2.34) (*5*). However, unlike in this case-control study, the solvent exposure metric used by Yiin *et al.* was dichotomous (ever/never worked in a potentially exposed job). When the dichotomous solvent exposure metric was used in this case-control study, it also was not significant.

It is unlikely that the solvent exposure duration variable is a confounder because there was less than a 10% change in the relative value of the radiation exposure parameter estimate when the solvent variable was removed from the regression model; additionally, the solvent variable is not significantly correlated with the radiation exposure variable ($P = 0.14$). There was also no evidence of effect modification on a multiplicative scale of radiation by solvent exposure ($P = 0.35$).

The leukemia risk estimate in the regression model of equivalent dose to bone marrow is slightly higher (OR = 1.11 at 10 mSv; 95% CI = 1.01, 1.22) compared to the model of whole-body equivalent dose (OR = 1.08 at 10 mSv; 95% CI = 1.01, 1.16) because attenuation of radiation by the body results in less dose to active bone marrow per unit exposure. However, in this study, incorporation of dose from work-related medical X rays did not change the leukemia risk estimate. When the regression model includes bone marrow dose from both occupational sources and work-related medical X rays, a significant dose response remains.

There are several possible reasons why the inclusion of work-related medical X rays made no difference in the leukemia risk estimate despite the fact that work-related med-

ical X rays were not randomly distributed among the cases and controls. First, these results may provide evidence that the effects produced by work-related medical X rays were of similar magnitude per unit dose as other occupational radiation exposure, since many more radiation-exposed study subjects were added by considering medical X-ray exposures. Second, although radiation-monitored workers received more work-related medical X rays than non-radiation-monitored workers, the mean bone marrow doses are only moderately higher for the radiation-monitored cases and controls (5.97 mSv) than for the non-radiation-monitored cases and controls (4.10 mSv) because monitored workers received greater numbers of X rays using the lower-dose direct radiographic technique (*8*). After 1966, nearly all work-related medical X rays documented in the medical records indicate that direct radiographic techniques were used, which lowered the estimated average equivalent dose to active bone marrow from 1.5 mSv per examination to 0.04 mSv per examination.

LIMITATIONS

In evaluating these findings, it is important to consider the relatively small number of study subjects who were radiation-monitored. However, the radiation risk estimates seem robust; the addition of medical X-ray bone marrow doses (which greatly increased the radiation-exposed percentages) changed risk estimates very little.

Variability of dosimetry practices, exposure conditions, and other factors such as the sex, age and anatomy of the exposed worker all result in uncertainty in the recorded whole-body radiation doses resulting from occupational exposure (*7, 31*). Also, a number of factors affect the actual dose to workers from a diagnostic X-ray procedure (*8*). Although efforts to reduce sources of dose uncertainty were maximized, differences between actual values and reference values used for dose reconstruction may have resulted in some bias in dose estimates.

The number of work-related medical X rays may have been underestimated for the cases and controls. Information about the type and frequency of X rays was gathered from existing medical records, and, although records were available for 90% of the cases and controls, the amount of pertinent information in the medical records varied considerably. This variation was due in part to differences in recording practices by attending physicians and changes in record management policies throughout the years.

To evaluate the impact of work-related medical X rays on leukemia risk, bone marrow doses from both medical X rays and occupational exposures were estimated. Many generalizations were required in the development of the dose conversion factors that were applied to estimate the equivalent dose to bone marrow. Therefore, uncertainty is likely when estimating a worker's bone marrow dose, given the variability of several critical parameters over the period of the study. These parameters include, but are not limited to, X-ray procedures and equipment, exposure geometry, incident photon energies, and worker age, sex and anatomy (*8*). Radiation exposures from non-occupational medical therapeutic and diagnostic sources as well as natural sources have not been evaluated in the radiation exposure assessment for this study. The impact of these exposures is unknown. However, there is no reason to expect that they are correlated with occupational dose.

Because the PNS civilian worker cohort and the cases and controls included in this study were overwhelmingly white and male, direct interpretation of leukemia risk for either females or non-whites was not possible. However, these results may be generalized to other occupational cohorts that are predominately white and male and receive low-level protracted exposures to low-linear energy transfer (LET) radiation.

Misclassification of workers exposed to benzene and carbon tetrachloride is likely. Subjective determinations, based on examination of sparse industrial hygiene data supplemented by field surveys and discussions with Portsmouth Naval Shipyard personnel, had to be used to designate the various shops and jobs with possible benzene or carbon tetrachloride exposure. Since benzene and carbon tetrachloride exposures were not known, duration of employment in potentially exposed jobs was selected as a surrogate for cumulative solvent exposure. Despite these limitations, there is no evidence of confounding by these solvents of the radiation dose–response relationship observed in this study.

Smoking was not included as a study variable in the analysis because of the lack of readily available individual smoking information in the PNS medical records. There is evidence suggesting that certain forms of adult leukemia, i.e. non-lymphocytic, may be associated with cigarette smoking (*32, 33*). However, since that association is weak, it is not likely that the increased risk estimate seen in this study is a result of confounding by smoking (*34*).

CONCLUSIONS

This study of a workforce exposed to both radiation and known or potential chemical leukemogens provides an estimate of leukemia risk in an occupational context in contrast to the extrapolation of risk from high-dose-rate exposures. The findings support other nuclear worker studies that collectively observe slight elevations in mortality from leukemia subtypes other than CLL that appear to be related to increases in low-LET radiation exposure (*25, 35, 36*). The current study explored the role of chemical exposures on leukemia risk in greater detail than previous studies involving PNS workers and observed a significant exposure response between leukemia mortality and the amount of time workers were employed in job categories where these exposures were probable.

Unlike previous PNS studies, this case-control study provides an in-depth analysis of work-related medical X rays

on leukemia risk using detailed information from worker medical records. The study observed that incorporating dose from work-related medical X-ray exposures had essentially no effect on the magnitude of the radiation-related risk estimate for leukemia in the PNS workers.

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REFERENCES

1. T. Najarian and T. Colton, Mortality from leukaemia and cancer in shipyard nuclear workers. *Lancet* **1**, 1018–1020 (1978).

2. R. A. Rinsky, R. D. Zumwalde, R. J. Waxweiler, W. E. Murray, P. J. Bierbaum, P. J. Landrigan, M. Terpilak and C. Cox, Cancer mortality at a Naval Nuclear Shipyard. *Lancet* **1**, 231–235 (1981).

3. F. B. Stern, 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.* **123**, 980–992 (1986).

4. S. R. Silver, R. D. Daniels, T. D. Taulbee, D. D. Zaebst, G. M. Kinnes, J. R. Couch, T. L. Kubale, J. H. Yiin, M. K. Schubauer-Berigan and P. H. Chen, Differences in mortality by radiation monitoring status in an expanded cohort of Portsmouth Naval Shipyard workers. *J. Occup. Environ. Med.* **46**, 677–690 (2004).

5. J. H. Yiin, M. K. Schubauer-Berigan, S. R. Silver, R. D. Daniels, G. M. Kinnes, D. D. Zaebst, J. R. Couch, T. L. Kubale and P. H. Chen, Risk of lung cancer and leukemia from exposure to ionizing radiation and potential confounders among workers at the Portsmouth naval shipyard. *Radiat. Res.* **163**, 603–613 (2005).

6. J. J. Beaumont, K. Steenland, A. Minton and S. Meyer, A computer program for incidence density sampling of controls in case-control studies nested within occupational cohort studies. *Am. J. Epidemiol.* **129**, 212–219 (1989).

7. R. D. Daniels, T. D. Taulbee and P. Chen, Radiation exposure assessment for Portsmouth Naval Shipyard health studies. *Radiat. Prot. Dosim.* **111**, 139–150 (2004).

8. R. D. Daniels, T. L. Kubale and H. B. Spitz, Radiation exposure from work-related medical X-rays at the Portsmouth Naval Shipyard. *Am. J. Ind. Med.* **47**, 206–216 (2005).

9. NCRP, *Exposure of the U.S. Population From Diagnostic Radiation.* Report No. 100, National Council on Radiation Protection and Measurements, Bethesda, MD, 1989.

10. NCRP, *Medical X-Ray and Gamma-Ray Protection for Energies Up to 10 MeV, Equipment Design and Usage.* Report No. 33, National Council on Radiation Protection and Measurements, Washington, DC, 1968.

11. I. Thierry-Chef, F. Pernicka, M. Marshall, E. Cardis and P. Andreo, Study of a selection of 10 historical types of dosemeter: Variation of the response to Hp(10) with photon energy and geometry of exposure. *Radiat. Prot. Dosim.* **102**, 101–113 (2002).

12. ICRP, *Conversion Coefficients for Use in Radiological Protection Against External Radiation.* Publication 74, *Annals of the ICRP*, Vol. 26, No. 3–4, Pergamon Press, Oxford, 1996.

13. D. R. Helsel, Statistical treatment of data below the detection limit. *Environ. Sci. Technol.* **24**, 1766–1774 (1990).

14. T. L. Kubale, R. D. Daniels, J. H. Yiin, G. M. Kinnes, J. Couch, M. K. Schubauer-Berigan, S. R. Silver, S. J. Nowlin and P. H. Chen, *A Nested Case-Control Study of Leukemia and Ionizing Radiation at the Portsmouth Naval Shipyard.* HHS (NIOSH) Publication No. 2005-104, Division of Surveillance, Hazard Evaluations, and Field Studies, National Institute for Occupational Safety and Health, Cincinnati, OH, 2004.

15. National Research Council, Committee on the Biological Effects of Ionizing Radiation, *Health Effects of Exposure to Low Levels of Ionizing Radiation (BEIR V).* National Academy Press, Washington DC, 1990.

16. IARC, *IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Wood, Leather, and Some Associated Industries,* Vol. 25. International Agency for Research on Cancer, Lyon, 1981.

17. H. Checkoway, T. Wilcosky, P. Wolf and H. Tyroler, An evaluation of the associations of leukemia and rubber industry solvent exposures. *Am. J. Ind. Med.* **5**, 239–249 (1984).

18. T. C. Wilcosky, H. Checkoway, E. G. Marshall and H. A. Tyroler, Cancer mortality and solvent exposures in the rubber industry. *Am. Ind. Hyg. Assoc. J.* **45**, 809–811 (1984).

19. R. E. Kirk, D. F. Othmer, J. I. Kroschwitz and M. Howe-Grant, *Encyclopedia of Chemical Technology,* 4th ed. Wiley, New York, 1991.

20. K. J. Rothman and S. Greenland, *Modern Epidemiology,* 2nd ed., pp. 675–709. Lippincott-Raven, Philadelphia, 1998.

21. U. Siebert, D. Rothenbacher, U. Daniel and H. Brenner, Demonstration of the healthy worker survivor effect in a cohort of workers in the construction industry. *Occup. Environ. Med.* **58**, 774–779 (2001).

22. J. Baillargeon and G. S. Wilkinson, Characteristics of the healthy survivor effect among male and female Hanford workers. *Am. J. Ind. Med.* **35**, 343–347 (1999).

23. E. S. Gilbert, N. A. Koshurnikova, M. E. Sokolnikov, N. S. Shilnikova, D. L. Preston, E. Ron, P. V. Okatenko, V. F. Khokhryakov, E. K. Vasilenko and S. A. Romanov, Lung cancer in Mayak workers. *Radiat. Res.* **162**, 505–516 (2004).

24. American Cancer Society, *Cancer Facts & Figures 2002.* American Cancer Society, Atlanta, GA, 2002.

25. M. K. Schubauer-Berigan and T. B. Wenzl, Leukemia mortality among radiation-exposed workers. *Occup. Med.* **16**, 271–287 (2001).

26. D. L. Preston, J. H. Lubin, D. A. Pierce and M. E. McConney, EPICURE Version 2.10. Hirosoft International Corporation, Seattle, WA, 1998.

27. D. G. Kleinbaum and M. Klein, *Logistic Regression a Self-Learning Text,* 2nd ed. Springer-Verlag, New York, 2002.

28. P. Fraser, L. Carpenter, N. Maconochie, C. Higgins, M. Booth and V. Beral, Cancer mortality and morbidity in employees of the United Kingdom Atomic Energy Authority, 1946–86. *Br. J. Cancer* **67**, 615–624 (1993).

29. E. Cardis, M. Vrijheid, M. Blettner, E. Gilbert, M. Hakama, C. Hill, G. Howe, J. Kaldor, C. R. Muirhead and K. Veress, Risk of cancer after low doses of ionising radiation: retrospective cohort study in 15 countries. *Br. Med. J.* **331**, 77–82 (2005).

30. E. Ron, Ionizing radiation and cancer risk: Evidence from epidemiology. *Radiat. Res.* **150** (Suppl.), S30–S41 (1998).

31. R. D. Daniels and M. K. Schubauer-Berigan, Bias and uncertainty of penetrating photon dose measured by film dosemeters in an epidemiological study of US nuclear workers. *Radiat. Prot. Dosim.* **113**, 275–289 (2005).

32. H. Austin and P. Cole, Cigarette smoking and leukemia. *J. Chronic Dis.* **39**, 417–421 (1986).

33. R. R. Williams and J. W. Horm, Association of cancer sites with tobacco and alcohol consumption and socioeconomic status of patients: Interview study from the third national cancer survey. *J. Natl. Cancer Inst.* **58**, 525–547 (1977).

34. O. Axelson and K. Steenland, Indirect methods of assessing the effects of tobacco use in occupational studies. *Am. J. Ind. Med.* **13**, 105–118 (1988).

35. D. L. Cragle, J. P. Watkins and K. Robertson-Demers, Mortality among workers at the Savannah River Nuclear Fuels Production Facility. In *Proceedings of the Section on Statistics in Epidemiology*. American Statistical Association, Alexandria, VA, 1999.

36. A. J. Douglas, R. Z. Omar and P. G. Smith, Cancer mortality and morbidity among workers at the Sellafield plant of British Nuclear Fuels. *Br. J. Cancer* **70**, 1232–1243 (1994).