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# Risk of Lung Cancer and Leukemia from Exposure to Ionizing Radiation and Potential Confounders among Workers at the Portsmouth Naval Shipyard

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**Significantly elevated lung cancer deaths and statistically significantly positive linear trends between leukemia mortality and radiation exposure were reported in a previous analysis of Portsmouth Naval Shipyard workers. The purpose of this study was to conduct a modeling-based analysis that incorporates previously unanalyzed confounders in exploring the exposure–response relationship between cumulative external ionizing radiation exposure and mortality from these cancers among radiation-monitored workers in this cohort. The main analyses were carried out with Poisson regression fitted with maximum likelihood in linear excess relative risk models. Sensitivity analyses varying model components and using other regression models were conducted. The positive association between lung cancer risk and ionizing radiation observed previously was no longer present after adjusting for socioeconomic status (smoking surrogate) and welding fume and asbestos exposures. Excesses of leukemia were found to be positively, though not significantly, associated with external ionizing radiation, with or without including potential confounders. The estimated excess relative risk was 10.88% (95% CI −0.90%, 38.77%) per 10 mSv of radiation exposure, which was within the ranges of risk estimates in previous epidemiological studies (−4.1 to 19.0%). These results are limited by many factors and are subject to uncertainties of the exposure and confounder estimates.** 

## INTRODUCTION

A number of epidemiological studies have been conducted to determine whether radiation exposure at the Portsmouth Naval Shipyard (PNS) is associated with increased risks of various cancers including lung cancer and leukemia (*1–4*). In a recent analysis examining standardized mortality ratios (SMRs) and internally adjusted standardized rate ratios (SRRs) using an expanded cohort of all PNS workers employed between 1952 and 1992, regardless of radiation monitoring status, Silver and colleagues (*5*) found significantly elevated SMRs for deaths from lung cancer and all cancers combined. While the overall SMR for leukemia was not elevated, a statistically significant positive linear trend between leukemia and cumulative external dose was observed in SRR analyses of radiation-monitored workers. Potential confounders such as asbestos and welding fumes for lung cancers, organic solvents for leukemia, and smoking status (or its surrogate), however, could not be analyzed simultaneously with the main exposure of interest, external radiation, in the full cohort study. The factors identified in the previous study might be incorporated in internal analyses of an occupational cohort to obtain an undistorted estimate of radiation exposure effect on cancer risk. The purpose of the current study was to conduct a modeling-based analysis of the cohort that incorporates multiple covariates to explore the dose–response relationship between external radiation exposure and the causes of death including lung cancer and leukemia.

## MATERIALS AND METHODS

### *Cohort Description*

The details of the full study cohort have been described in a previous report (*5*). In brief, the previous study population comprises 37,853 males and females of all races employed as civilian workers at PNS for at least 1 day between January 1, 1952 and December 31, 1992, with a subcohort of 13,468 workers monitored for radiation at PNS. The current study focuses on this radiation-monitored subcohort. These workers had more detailed computerized work history information to allow assessment of confounding exposures. For all workers, person-years at risk were started on the first date that monitoring at the shipyard was performed on or after January 1, 1952. Person-years at risk were considered to have ended on the date of death or December 31, 1996 (end of the study), whichever came first. There were 3,217 (23.9%) subjects without race recorded.

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Since 99.7% of workers with known race were white, those of unknown race were assumed to be white.

*Vital Status Ascertainment*

Vital status for these workers was ascertained through December 31, 1996. Sources were primarily the National Death Index (NDI) Plus service (including underlying cause of death) of the National Center for Health Statistics and the Social Security Administration (SSA), as described by Silver *et al.* (*5*). When vital status remained uncertain ($n$ = 170, 1.3%), subjects were considered to be alive. Underlying cause of death was coded to the revision of the International Classification of Diseases (ICD) in effect at the time of death.

*Outcome of Interest*

Cancers of *a priori* interest included lung cancer (ICD code 162 or 163 in 6th or 7th revision; 162 in 8th or 9th revision) and leukemia (ICD code 204 in 6th or 7th revision; 204–207 in 8th revision; 204–208 in 9th revision).

*Analytic Variables*

The work history file, with annual data for years monitored, contained a sequence of jobs that included year, job code and shop (a location surrogate). On-site and off-site external radiation exposures were recorded for each monitored year. Socioeconomic status (a surrogate for smoking habits) was based on job title. Asbestos and welding fume exposures and status of solvent exposure for each worker were determined based on the job codes and shops. The construction of each variable is described below.

*External Radiation Exposure—Main Effect of Study Factor*

The predominant exposure at PNS was external whole-body penetrating $\gamma$ radiation emitted by activation products deposited in reactor systems and components (*6*). Personal dosimeters for monitoring radiation exposures were worn by workers entering radiological areas or handling radioactive materials. Early dosimeters used film emulsions that were processed biweekly through 1959 and extended to monthly between 1960 and 1974. Thermoluminescent dosimeters (TLDs) replaced film badges in 1974, allowing for daily assessment of worker exposures. After processing, the dosimetry results were compared to administrative limits to ensure that worker exposures remained below accepted levels. Workers with radiation exposures approaching or surpassing time-dependent exposure control levels had their rights to access radiation areas removed.

When dosimetry information was not available from other employment, an overestimate of off-site dose was assigned by shipyard radiological protection staff to avoid exceeding lifetime dose limits at the shipyard. These ''administrative'' doses have been adjusted for this analysis to minimize potential bias due to the overestimation (*6*). Adjustments to dose estimates from the shipyard records for prior dose and administrative dose assignments resulted in a reduction in collective dose of 7.35 person-Sv.

PNS annual exposure reports were tabulated by shipyard personnel by summing the results of each monitoring cycle for each worker within the monitoring year. Annual exposures were reported in quantities of dose equivalent to the whole body. These annual reports were obtained for the radiation exposure assessment. Cumulative external radiation exposure for each worker was the sum of the annual exposures for each year monitored. Radiation exposure was treated as a time-dependent continuous variable in the main analysis, and person-year weighted means of radiation exposure were calculated based on the categories used by Silver *et al.*: 0–<1 (baseline), 1–<10, 10–<50 and ≥50 mSv. Total radiation exposures including off-site exposures and PNS exposures prior to the onset of the dosimetry program in 1950 (*6*) were used in the primary analyses.

*Covariates*

Selection of covariates or confounders for analyses was based mainly on the strength of prior epidemiological evidence of cancer hazards (*1, 4, 7–12*). Factors including sex, attained age, and calendar years were stratified, while socioeconomic status, asbestos, welding fumes and solvent exposures were modeled parametrically in analyses. Race was not used in the analyses since the majority of the subjects were assumed to be white.

*Sex, attained age and calendar year*. Sex, attained age and calendar year may affect the background cancer risk and need to be adjusted in the analyses. Analyses were conducted primarily with stratification on these factors to model the background rates. Attained age was categorized in 13 groups: <25, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79 and ≥80. Calendar years were grouped into nine intervals: 1952–1954, 1955–1959, 1960–1964, 1965–1969, 1970–1974, 1975–1979, 1980–1984, 1985–1989 and 1990–1996. Stratification on these factors was applied to each cause of death of interest in regression modeling.

*Asbestos and welding fume exposures*. As noted by Silver *et al.* (*5*), the lack of detailed work histories in an electronic format as well as limited data on chemical exposures prevented a quantitative assessment of non-radiological exposures for the full PNS cohort. However, a dosimetry file created by the shipyard for 13,468 workers monitored for external radiation exposure did include fields indicating the shops where workers were assigned and a code for the type of job held for the years in which they were monitored. The job codes used in this file were determined to be based on the classifications used in the U.S. Office of Personnel Management's ''Handbook of Occupational Group and Families''. Using this resource, the job codes were converted to more descriptive job titles using the corresponding classifications for Federal general schedule (GS) or wage grade (WG) employees. Potential asbestos and welding fume exposures were determined qualitatively by a panel of industrial hygienists familiar with shipyard operations using a list of assigned shop/job title combinations generated from this file. Previous studies have shown that an expert panel approach can be used successfully for historical occupational exposure assessments (*13–15*). Based on the assigned shops and job titles, a code of 0 (not exposed), 1 (possible exposure), or 2 (probable exposure) was assigned to each work record to represent the likelihood of welding fume exposure. Similarly, a code of 0 (not exposed), 1 (possible exposure), 2 (probable moderate or infrequent exposure), or 3 (probable higher or frequent exposure) was assigned for asbestos exposure. These codes indicating the intensity of potential asbestos or welding fume exposures were summed over the observed duration of exposure. A worker with an exposure value of 5 indicates exposure at level 1 for 5 years, exposure at level 2 for 2 years plus 1 for 1 year, or other combinations. The product of duration and intensity category is not a continuous variable and the total exposures (based on intensity and duration) were arbitrarily classified into three categories (0, >0–5 and >5), although different exposure categories were also tested. These exposure categories were used as time-dependent variables in the regression modeling. Asbestos and welding fume exposures were evaluated for lung cancer, smoking-related cancers, and all cancers combined.

*Solvent exposure*. Due to the limited availability of quantitative chemical exposure information for the shipyard during the study period, it was determined that a qualitative chemical exposure assessment method would be implemented. As in the asbestos and welding fume assessments, the solvent exposure assessment also used the dosimetry file information that listed shop number, job title, and other vital job characteristics. The original unique job/shop combinations were collapsed into 1,301 unique job/shop combinations to be considered for solvent exposures. A list of these job/shop combinations was given to each of two industrial hygienists with historical knowledge of shipyard chemical inventories, practices and protocols for qualitative solvent exposure assessment. For solvent exposure, each unique shop/job was assigned a dichotomous variable of 0 (not exposed) or 1 (possible solvent exposure) based on the potential exposure to carbon tetrachloride, benzene or mixtures containing benzene

(e.g. aromatic hydrocarbons, petroleum distillates, gasoline). The final solvent exposure was classified as a dichotomous variable of ever or never having any potential exposure to solvents throughout the entire work history. Dichotomous solvent exposure was used in regression modeling for leukemia.

*Socioeconomic status (SES).* Since the smoking history for members of the cohort is not available, an indicator of SES based on the job title information in the dosimetry file was used as a surrogate for possible smoking habits. SES has been assessed based on occupation and/or educational attainment and has shown a strong inverse association with smoking (*16–18*). Therefore, workers with higher SES were assumed to be less likely to be smokers, while those with lower SES more likely. SES was coded based on collapsed job title series and ranged from 1 to 5, with 1 being the highest and 5 the lowest SES category. These predefined categories were 1 (professional), 2 (technical), 3 (skilled labor), 4 (administrative support), and 5 (unskilled labor). Due to limited numbers in some assigned SES levels, these categories were further collapsed into three for the regression analyses: higher smoking probability (SES = 4 or 5), intermediate smoking probability (SES = 3), and lower smoking probability (SES = 1 or 2). Because of promotions and job changes, job category for some workers varied over time. A decision was made to use the first available job category to define SES, since it may be more likely to represent a worker's smoking habit. An exception was when a worker changed his or her job within 1 year of entering the Navy work force and then kept the same SES for the rest of the work history. In this case, the job category following the entry category was used to represent the worker's SES. The reason was that a worker might have entered the Navy work force in a level different from his or her skill level but changed to the matching skill level once a position opened up. SES was evaluated for each cause of death in regression analyses.

### *Statistical Methods*

The analyses were conducted using Poisson regression modeling for causes of death suspected to be associated with external whole-body penetrating $\gamma$ radiation. Multivariate modeling using Poisson regression has the advantage over SMR or SRR analysis of allowing the incorporation of multiple covariates simultaneously with radiation exposure. In addition, it is flexible in specifying the form of the risk function for exposure (*19*). Using grouped cohort survival data analysis with Poisson regression, the number of cases and the total time at risk (person-years) have been cross-classified using categories described previously on sex, attained age and calendar time, along with external radiation exposure and other categorized factors such as SES, asbestos, welding fumes and solvent exposure.

Lags of 0, 2, 3, 5 and 7 years were employed for leukemia analyses and lags of 0, 5, 10, 15 and 20 years for lung cancer and other cancers of longer latency. Any exposure that occurred in the years lagged prior to death or end of study was discounted. Lags with the best fit to the data based on likelihood ratio statistics of different regression models were selected for subsequent analyses to test the effects of various covariates and in modeling cancer risk.

A computer software package, DATAB in Epicure (*20*), was used to generate files for Poisson regression analysis. Person-years were counted from when a worker was monitored until he or she was lost to follow-up, died or reached the end of follow-up. AMFIT, a Poisson regression program in Epicure that was designed specifically for use with grouped cohort survival data, was used for regression modeling.

### *Main Analyses*

A linear excess relative risk (ERR) model, which is commonly seen in radiation epidemiology (*7, 21, 22*), was used as the main model. In this model, the relative risk is described as a linear function of external radiation exposure $d$, while the rest of the covariates are stratified or modeled log linearly with risk. The model fit has the form of

$$\lambda(\underline{x}, d) = \lambda_0(\underline{x})(1 + \beta d),$$

where $\lambda_0(\underline{x})$ represents the background risk, $\underline{x}$ is a vector of covariates, and $\beta d$ describes the ERR at cumulative exposure $d$. The parameter $\beta$ associated with radiation exposure is the change in the excess relative risk per unit change in cumulative exposure. Confidence intervals (CI) in terms of the profile likelihood were calculated. The excess relative risk is not significant if its 95% likelihood-based CI includes zero.

Stratified covariates used in adjusting the background rates included sex, attained age, and calendar year. Any of these variables was excluded from analyses if its removal changed the radiation exposure coefficient by less than 10%. Potential confounding variables modeled explicitly (including SES and welding fume, asbestos and solvent exposures) were assumed to have a log linear relationship with cancer risk. To evaluate the impact of each variable on the cancer risk, 95% likelihood-based CI of the risk estimates (rate ratios) for these model parameters were calculated. A covariate was considered to have significant influence on cancer risk and was kept in the analyses if the range between lower and upper bounds did not include 1. Due to limited cases and power, a covariate that failed to show significant impact on cancer risk was kept in the analyses if its exclusion affected the risk coefficient of external radiation exposure by more than 10%.

### *Sensitivity Analyses*

The final main analysis model, developed as described above, formed the basis of the sensitivity analysis modeling.

*Regression models*. Additional multiplicative relative risk models were tested for the exposure–response relationship of external radiation exposure and cancer risk. In the categorical relative risk model, the relative risk in each higher dose category to the baseline (lowest exposure category) was estimated by $\lambda(\underline{x}, d) = \lambda_0(\underline{x})e^{\rho_d}$, $d = 1, \ldots, 4$, where $d$ is the dose category index, and the $\rho_d$ parameters are the log relative risks for the dose category. In the log linear model, relative risk is estimated by $\lambda(\underline{x}, d) = \lambda_0(\underline{x}) \cdot e^{\beta d}$, where $\beta$ is the log of the relative risk per unit change in cumulative exposure.

*Cutoff dates and external radiation exposure*. Date last observed (DLO) was used as an alternative for end of study date (EOS). Additional analyses were conducted using on-site PNS exposure only without off-site or prior exposure. The main analyses included radiation-monitored workers with both zero and non-zero exposures. Because a number of subcohort differences were reported in the analyses by Silver *et al.* (*5*), sensitivity analyses were conducted excluding unexposed radiation-monitored workers (those with zero PNS recorded exposure).

*Background rates*. Alternative to stratification, a parametric model using log(age/60) as the background rates (*23*) was specified in regression analyses, where the person-year weighted means of age categories were used. With the use of log(age/60), the intercept in the regression model is the maximum likelihood estimate of the log of the background rate for a 60-year-old worker. Additionally, score tests for nonlinearity in the age trend were carried out by including the quadratic term of log age in the model and the likelihood ratio statistic for its effect was computed.

*Welding fume and asbestos categories*. Total exposures (based on intensity and duration) of welding fumes and asbestos were arbitrarily classified into three categories (value of 0, >0–5 and >5). More categories (0, >0–3, >3–10 and >10) were considered in lung cancer sensitivity analyses to explore the impact of different groupings.

*Other cancers*. Although not considered *a priori*, analyses were conducted to compare lung cancer results with smoking-related cancers other than lung as a group (including malignancies of the oral cavity and pharynx, larynx, esophagus, bladder, kidney and pancreas), which showed elevated risk for the full cohort. In addition, risk of deaths from all cancers was investigated, because of reported increase among PNS workers with relatively low doses of ionizing radiation (*2*).

## RESULTS

There were 13,468 civilian workers who were monitored for radiation exposure at PNS for at least 1 day between

**TABLE 1**
**Assumed Smoking Category and Corresponding Socioeconomic Status Assignment**

| Smoking category | No. of subjects | SES | Skill category | No. of subjects |
|---|---|---|---|---|
| Lower smoking probability | 2,701 | 1 | Professional | 1,448 |
| | | 2 | Technical | 1,253 |
| Intermediate smoking probability | 9,335 | 3 | Skilled labor | 9,287 |
| | | N/A | Unknown | 48 |
| Higher smoking probability | 1,432 | 4 | Administrative support | 63 |
| | | 5 | Unskilled labor | 1,369 |

January 1, 1952 and December 31, 1992. The majority of the workers were white males (97.4%), with only 2.3% females ($n$ = 315) and 0.3% non-white ($n$ = 38). As of December 31, 1996, 3,861 (28.7%) were known to be deceased. Among the deceased, 411 (10.6%) died of lung cancer and 34 (0.9%) died of leukemia.

*Descriptive Statistics of Analytic Variables*

Included in the analyses were 11,791 exposed radiation workers, 1,627 unexposed radiation workers (those who were monitored but had no detectable PNS exposure), and 50 unexposed radiation workers with prior or offsite exposures.

Daniels *et al.* compared the cumulative dose distribution for PNS with those of radiation worker cohorts employed in the U.S. (Hanford Site, Oak Ridge National Laboratory, and the Rocky Flats Nuclear Weapons plant), United Kingdom (Atomic Energy Authority, Atomic Weapons Establishment, and the British Nuclear Fuels plant of Sellafield), and Canada (Atomic Energy of Canada Chalk River plant). The cumulative dose distributions share similarities typically associated with low-dose protracted occupational radiation exposure at these sites, except for workers at Sellafield. The distribution at PNS is highly skewed with more than half of the workers (65.4%) having cumulative doses $<$10 mSv and $>$95% having doses $<$100 mSv (*6*).

Of the 13,468 naval shipyard employees, 11,825 (88%) had the same SES assigned over all the years being monitored. There were 124 workers with assigned SES that was different from entry SES. The SES for 48 workers could not be determined (due to the lack of sufficient work history information) so category 3 (skilled labor) was assigned. Table 1 lists the number of subjects in each skill category, as well as in each smoking category used in regression analysis.

Welding fume and asbestos exposures were modeled as time-dependent variables, so a worker shifted to a higher exposure category when accumulating more exposures over time. There were 53.2% ($n$ = 7,163) workers without potential exposures to welding fumes and 38.1% ($n$ = 5,125) without asbestos exposure potential. At the end of study, about 28.5% ($n$ = 3,833) of the workers had total exposures (based on intensity and duration) less than or equal to 5 for welding fumes, and 33.7% ($n$ = 4,543) had total $\leq$5 for asbestos. Only 18.4% ($n$ = 2,472) had total welding fume exposure exceeding 5, but 28.2% ($n$ = 3,800) had lifetime asbestos exceeding that level.

A total of 59.4% ($n$ = 8,006) of the workers had no known solvent-exposed jobs at PNS. The duration of 5,462 workers involved in potentially solvent-related jobs ranged from 1 to 32 years, with an average of 5.1 years and a median of 3.0 years.

Based on plausibility and likelihood ratio statistic tests of various regression models (data not shown), a lag of 15 years was used in subsequent analyses for cancers with longer latency such as lung, smoking-related and all cancers, while a lag of 3 years was selected for leukemia analyses.

*Lung Cancer ERR Model*

Stratifying on sex, age and calendar time and without adjusting for SES, welding fumes, or asbestos exposure, the lung cancer excess relative risk per 10 mSv of lagged external radiation exposure increased by 1.13% (95% CI $-$1.44%, 4.56%). The change in exposure coefficient was only 4% when sex was removed from the model. Therefore, all the subsequent analyses were based on stratification on age and calendar time only.

The effects of covariates potentially associated with lung cancer are listed in Table 2. When each of the covariates was tested separately, lung cancer risks increased with lower SES or higher welding fume exposure categories, and both exposed asbestos categories showed increased lung cancer risk compared with the nonexposed (baseline). The rate ratios (RR) for skilled labor (intermediate smoking probability) and administrative support/unskilled labor (higher smoking probability) relative to baseline (professional/technical; lower smoking probability) indicated increased risks with increasing smoking probability. RR also increased with increased welding fume exposure but was not substantively different between the two exposed categories. Workers with any asbestos jobs also had higher risks (RR = 1.32–1.30) than those without any potential asbestos jobs. When all the factors were included in a model, the effects of asbestos were less strong than those of SES and welding fume exposure.

The positive exposure–response relationship between lagged external radiation exposure and lung cancer risk ob-

**TABLE 2**
**Poisson Regression of Lung Cancer Risk with Radiation Exposure (with a 15-Year Lag) and Potential Confounders, Radiation-Monitored Workers at the Portsmouth Naval Shipyard, 1952–1996**

| Factor | No. of cases (total PY)[a] | Risk estimate (95% CI)[b] |
|---|---|---|
| External radiation exposure only | | |
| Dose coefficient (per 10 mSv) | | ERR = 1.08% (−1.47%, 4.49%) |
| SES only | | |
| SES professional/technical | 25 (54,061) | Baseline |
| SES skilled labor | 331 (219,645) | RR = 1.69 (1.14, 2.61) |
| SES administrative support/unskilled labor | 55 (30,186) | RR = 2.14 (1.35, 3.50) |
| Welding fume only | | |
| Welding fume: never | 174 (226,772) | Baseline |
| Welding fume: >0–5 | 125 (44,459) | RR = 1.60 (1.24, 2.06) |
| Welding fume: >5 | 112 (32,661) | RR = 1.65 (1.26, 2.15) |
| Asbestos only | | |
| Asbestos: never | 242 (247,081) | Baseline |
| Asbestos: >0–5 | 100 (37,839) | RR = 1.32 (1.03, 1.68) |
| Asbestos: >5 | 69 (18,972) | RR = 1.30 (0.97, 1.72) |
| SES, welding fume and asbestos[c] with external radiation exposure | | |
| SES professional/technical | | Baseline |
| SES skilled labor | | RR = 1.31 (0.87, 2.07) |
| SES administrative support/unskilled labor | | RR = 1.75 (1.08, 2.90) |
| Welding fume: never | | Baseline |
| Welding fume: >0–5 | | RR = 1.45 (1.10, 1.92) |
| Welding fume: >5 | | RR = 1.50 (1.09, 2.06) |
| Asbestos: never | | Baseline |
| Asbestos: >0–5 | | RR = 1.11 (0.85, 1.46) |
| Asbestos: >5 | | RR = 1.10 (0.78, 1.54) |
| Dose coefficient (per 10 mSv)[d] | | ERR = −0.53% (−3.06%,[e] 2.59%) |

*Notes.* All models stratified on age group (13 strata) and calendar time (9 strata). Factors within each are adjusted for all other factors in that model.
[a] Total PY: Total person-years for all subjects in the category.
[b] RR: rate ratio, ERR = excess relative risk, and CI: likelihood-based confidence intervals.
[c] The coefficients and 95% CI for these three covariates in this model are very similar to those in the model without the linear radiation exposure term.
[d] ERR changed to −0.39% (95% CI −2.57%, 2.62%) when asbestos term was dropped.
[e] Estimated. There may be no feasible value for this bound.

served without considering any other covariates became negative (although not significantly different from zero) after adjusting for SES and welding fume and asbestos exposures (Table 2). Lung cancer risk among PNS workers remained increased with elevated smoking probability (lower SES) and increased welding fume exposures. Workers with any asbestos-exposed jobs also showed elevated lung cancer risk, although the effect was not significant (Table 2). Removing asbestos from the model, however, resulted in a 26% change in the coefficients of external radiation exposure from −0.53% to −0.39%. Therefore, asbestos along with SES and welding fume exposure was kept in the final model and in the sensitivity analyses.

### *Leukemia ERR Model*

Excess relative risk of dying from leukemia among PNS workers with every 10 mSv increase of lagged external radiation exposure was 10.52% (95% CI −1.22%, 40.19%) in the ERR model with stratification on sex, age and calendar time. The excess relative risk was essentially unchanged when sex and calendar time were dropped from the model. Stratifying on attained age only, an excess relative risk estimate of 10.88% (Table 3) was observed. Because of the small change in risk estimates, sex and calendar time were not included in the subsequent analyses.

The leukemia rate ratios increased from 0.88 for workers with intermediate smoking probability to 1.03 for those with higher smoking probability compared with professional and technical employees with lower smoking probability (Table 3). The effect, however, was not significant. Similarly, workers with any potential solvent-exposed jobs showed elevated but not significant leukemia risk. Analyses with both covariates in a model showed a similar trend to those with each tested individually (Table 3).

Adjusting for SES and dichotomous solvent exposure, the excess relative risk of leukemia mortality slightly increased from 10.88% to 10.97% (0.8%; Table 3). Therefore, SES and solvent exposure were excluded from subsequent analyses.

**TABLE 3**
**Poisson Regression of Leukemia Risk with Radiation Exposure (with a 3-Year Lag) and Potential Confounders, Radiation-Monitored Workers at the Portsmouth Naval Shipyard, 1952–1996**

| Factor | No. of cases (total PY)[a] | Risk estimate (95% CI)[b] |
|---|---|---|
| External radiation exposure only | | |
| Dose coefficient (per 10 mSv) | | ERR = 10.88% (−0.90%, 38.77%) |
| SES only | | |
| SES professional/technical | 4 (54,061) | Baseline |
| SES skilled labor | 26 (219,645) | RR = 0.88 (0.34, 3.00) |
| SES administrative support/unskilled labor | 4 (30,186) | RR = 1.03 (0.24, 4.40) |
| Solvent exposure only | | |
| Solvent: never | 17 (176,157) | Baseline |
| Solvent: ever | 17 (127,735) | RR = 1.19 (0.60, 2.35) |
| SES and solvent exposure | | |
| SES professional/technical | | Baseline |
| SES skilled labor | | RR = 0.79 (0.28, 2.82) |
| SES administrative support/unskilled labor | | RR = 0.92 (0.20, 4.10) |
| Solvent: never | | Baseline |
| Solvent: ever | | RR = 1.24 (0.61, 2.59) |
| SES and solvent exposure with external radiation exposure | | |
| SES professional/technical | | Baseline |
| SES skilled labor | | RR = 0.72 (0.26, 2.59) |
| SES administrative support/unskilled labor | | RR = 0.78 (0.17, 3.57) |
| Solvent: never | | Baseline |
| Solvent: ever | | RR = 1.19 (0.58, 2.49) |
| Dose coefficient (per 10 mSv) | | ERR = 10.97% (−0.96%, 39.89%) |

*Notes.* All models stratified on age group (13 strata). Factors within each are adjusted for all other factors in that model.
[a] Total PY: total person-years for all subjects in the category.
[b] RR: rate ratio, ERR: excess relative risk, and CI: likelihood-based confidence intervals.

*Sensitivity Analyses*

''Lagging'' excludes exposures that may not have had sufficient latency to be of etiological importance. Analyses conducted with lags of 0, 5, 10, 15 and 20 years showed little difference in risk estimates in the log linear model for lung cancer (data not shown). Lagging 15 years in categorical model had the best fit to the data. Therefore, a 15-year lag was chosen for lung cancer analyses given the long latency required for developing and dying from lung cancer. Many epidemiological studies have considered a 2-year lag in analyzing leukemia risk and radiation exposure (*21, 24–27*). Our analyses with a 3-year lag fit the data the best. Therefore, a 3-year lag was used in the main leukemia analyses.

*Lung cancer log linear model*. In the log linear model, the rate ratios and associated 95% confidence intervals of lung cancer mortality for the three covariates were identical to those in the main analyses (Tables 2 and 4). Workers with higher welding fume or asbestos exposures or higher smoking probability (lower SES) also showed higher lung cancer mortality. The rate ratio for cumulative external radiation exposure was 0.99 at 10 mSv (Table 4), which is consistent with the risk estimate of −0.0053 per 10 mSv in the ERR model.

*Leukemia log linear model*. As shown in Table 4, analyses of leukemia mortality and lagged external radiation exposure using the log linear model also showed a nonsignificantly positive exposure–response trend, although the risk estimate of 1.05 at 10 mSv is lower than that in the ERR model.

*Lung cancer categorical model*. When the cumulative radiation exposures were divided into four groups in the categorical model, the rate ratios of lung cancer mortality comparing to workers with 0–<1 mSv (baseline) of cumulative exposure increased from 1.18 to 1.31 for workers in dose categories 1–<10 and 10–<50 mSv, respectively, then dropped to 1.02 for those exposed to ≥50 mSv (Table 4). Further dividing the ≥50 mSv category into two, the rate ratios for 50–<100 and ≥100 mSv as a function of baseline were 0.84 (95% CI 0.46, 1.44) and 1.18 (0.71, 1.87), respectively. The risk estimate for the highest exposure category (≥100 mSv) was higher than that for 50–<100 mSv but lower than that for 10–<50 mSv. Consistent with the results in the ERR model, lung cancer mortality increased accordingly with increased smoking probability. In addition, workers with any welding fume or asbestos exposures also showed higher lung cancer risk than the nonexposed.

*Leukemia categorical model*. Stratifying on age, a positive trend showing monotonically elevated leukemia mor-

**TABLE 4**
**Poisson Regression of Cancer Risks using Alternative Models, Radiation-Monitored Workers in the Portsmouth Naval Shipyard, 1952–1996**

| | Loglinear model | Categorical | Model |
|---|---|---|---|
| Cancer type factor | RR (95% CI)[a] | No. of cases (PY)[b] | RR (95% CI) |
| Lung cancer[c] | | | |
| SES professional/technical | Baseline | | Baseline |
| SES skilled labor | 1.31 (0.87, 2.07) | | 1.31 (0.86, 2.07) |
| SES administrative support/unskilled labor | 1.75 (1.08, 2.90) | | 1.76 (1.08, 2.91) |
| Welding fume: Never | Baseline | | Baseline |
| Welding fume: >0–5 | 1.45 (1.10, 1.92) | | 1.41 (1.06, 1.87) |
| Welding fume: >5 | 1.50 (1.09, 2.06) | | 1.38 (0.99, 1.92) |
| Asbestos: Never | Baseline | | Baseline |
| Asbestos: >0–5 | 1.11 (0.85, 1.46) | | 1.11 (0.85, 1.46) |
| Asbestos: >5 | 1.10 (0.78, 1.54) | | 1.06 (0.75, 1.48) |
| Dose coefficient (at 10 mSv) | 0.99 (0.97, 1.02) | | — |
| Dose 0–<1 mSv | | 197 (227,339) | Baseline |
| Dose 1–<10 mSv | | 100 (37,028) | 1.18 (0.89, 1.55) |
| Dose 10–<50 mSv | | 75 (26,181) | 1.31 (0.95, 1.79) |
| Dose ≥50 mSv | | 39 (13,345)[d] | 1.02 (0.67, 1.51) |
| Leukemia[e] | | | |
| Dose coefficient (at 10 mSv) | 1.05 (0.98, 1.11) | | — |
| Dose 0–<1 mSv | | 7 (139,877) | Baseline |
| Dose 1–<10 mSv | | 10 (77,531) | 2.03 (0.78, 5.60) |
| Dose 10–<50 mSv | | 10 (57,784) | 3.16 (1.21, 8.71) |
| Dose ≥50 mSv | | 7 (28,700) | 3.39 (1.16, 9.91) |

*Note.* Factors within each are adjusted for all other factors in that model.

[a] RR: rate ratio and CI: likelihood-based confidence intervals.

[b] Number of cases and total person-years in each category for categorical model.

[c] Dose with a 15-year lag; models stratified on age group (13 strata) and calendar time (nine strata).

[d] Subdividing this category to two, the RR (95% CI) relative to baseline are 0.84 (0.46, 1.44) and 1.18 (0.71, 1.87) for 50–<100 (15 cases; 6,993 total person-years) and ≥100 mSv (24 cases and 6,352 total person-years) dose categories, respectively.

[e] Dose with a 3-year lag; models stratified on age group (13 strata).

tality with increasing cumulative exposure categories was observed. The rate ratios of leukemia mortality compared to workers in the 0–<1 mSv exposure category were 2.03, 3.16 and 3.39 for those in the 1–<10, 10–<50, and ≥50 mSv categories, respectively (Table 4).

*Alternative cutoff date*. Little differences in risk estimates for either lung cancer or leukemia were observed between the use of end of study date (EOS) or date last observed (DLO), as the gap in person years between EOS and DLO was only 0.26 years on average.

*Onsite PNS exposure only*. The average lifetime cumulative PNS radiation exposure among 13,468 radiation-exposed workers was 19.94 mSv, which accounted for 96.8% of total exposures (20.59 mSv; including offsite or prior). Using PNS exposure only in the regression analyses, there were small changes in risk estimates of SES, welding fumes and asbestos exposure for lung cancer. The radiation exposure coefficient changed from 10.88% to 11.56% (95% CI −0.65%, 40.56%) in leukemia analyses, and from −0.53% to −0.11% (95% CI −2.32%, 3.11%) in lung cancer analyses. The general trends of the exposure–response relationship remained unchanged.

*Radiation-monitored workers with non-zero exposures*. Analyses were also conducted with only exposed radiation workers due to reported subcohort differences (*5*). As a result, 1,677 unexposed radiation workers (including 55 lung cancer and 5 leukemia deaths) were excluded. The general trends in analyses for lung cancer remained unchanged and the ERR changed from −0.53% to −0.42% (95% CI −2.66%, 2.78%). Similarly, the results for leukemia analyses were consistent with those in the main analyses. The ERR increased from 10.88% to 12.87% (95% CI −0.61%, 50.73%) per 10 mSv of radiation exposure when radiation-monitored workers without PNS or offsite exposures were excluded from analyses.

*Alternative background rates*. The score test for nonlinearity of the background rates in log(age/60) is −4.56 ($P < 0.01$) for lung cancer, which suggests that the rate of increase in the background rates was lower for workers over the age of 60. This model fits worse than the stratified model, and the estimated ERR per 10 mSv with only log(age/60) in the model is very different from that in the main analyses. Adding a quadratic term for log age to the model improved the model fit, as likelihood ratio (LR) statistic showed significant effect (LR = 29.43; $P < 0.01$), and the estimated ERR of −0.41% (95% CI −2.64%, 2.77%) is close to that in the main analyses with stratification on age. Adding a quadratic term in exposure–re-

**TABLE 5**
**Poisson Regression of Smoking-Related Cancers and All Cancers with Radiation Exposure (with a 15-Year Lag) and Potential Confounders, Radiation-Monitored Workers in the Portsmouth Naval Shipyard, 1952–1996**

| | Smoking-related[a] | All cancers[b] |
|---|---|---|
| Factor | Risk estimate (95% CI)[c] | Risk estimate (95% CI) |
| External radiation exposure only | | |
| Dose coefficient (per 10 mSv) | ERR = −1.68% (−4.87%[d], 2.45%) | ERR = 0.14% (−1.26%, 1.84%) |
| SES only | | |
| SES professional/technical | Baseline | Baseline |
| SES skilled labor | RR = 1.12 (0.69, 1.96) | RR = 1.35 (1.09, 1.70) |
| SES administrative support/unskilled labor | RR = 1.09 (0.55, 2.16) | RR = 1.50 (1.14, 1.97) |
| Welding fume only | | |
| Welding fume: never | Baseline | Baseline |
| Welding fume: >0–5 | RR = 1.68 (1.19, 2.36) | RR = 1.32 (1.14, 1.54) |
| Welding fume: >5 | RR = 1.16 (0.77, 1.71) | RR = 1.31 (1.12, 1.54) |
| Asbestos only | | |
| Asbestos: never | Baseline | Baseline |
| Asbestos: >0–5 | RR = 1.30 (0.91, 1.83) | RR = 1.26 (1.08, 1.46) |
| Asbestos: >5 | RR = 0.97 (0.60, 1.50) | RR = 1.24 (1.04, 1.47) |
| SES, welding fume and asbestos with external radiation exposure | | |
| SES professional/technical | Baseline | Baseline |
| SES skilled labor | RR = 0.93 (0.55, 1.66) | RR = 1.16 (0.91, 1.48) |
| SES administrative support/unskilled labor | RR = 0.92 (0.46, 1.85) | RR = 1.35 (1.01, 1.79) |
| Welding fume: Never | Baseline | Baseline |
| Welding fume: >0–5 | RR = 1.69 (1.15, 2.48) | RR = 1.21 (1.02, 1.43) |
| Welding fume: >5 | RR = 1.27 (0.78, 2.05) | RR = 1.20 (0.99, 1.45) |
| Asbestos: Never | Baseline | Baseline |
| Asbestos: >0–5 | RR = 1.07 (0.72, 1.58) | RR = 1.16 (0.98, 1.36) |
| Asbestos: >5 | RR = 0.93 (0.53, 1.59) | RR = 1.16 (0.94, 1.43) |
| Dose coefficient (per 10 mSv) | ERR = −1.79% (−5.26%,[d] 2.96%) | ERR = −0.07% (−0.22%,[d] 0.09%) |

*Note.* Factors within each are adjusted for all other factors in that model.
[a] Models stratified on age group (13 strata).
[b] Models stratified on sex, age group (13 strata), and calendar time (nine strata).
[c] RR: rate ratio, ERR: excess relative risk, and CI: likelihood-based confidence intervals.
[d] Estimated. There may be no feasible value for this bound.

sponse analyses for leukemia did not improve the model fit (LR = 0.07; $P = 0.79$), and the score test for nonlinearity of the background rates in log age is not significant ($P > 0.5$). Therefore, a quadratic term was removed from leukemia analyses with alternative background rates. The estimated leukemia ERR per 10 mSv of radiation exposure in a model without the quadratic term was 11.45% (95% CI −0.67%, 39.94%), a small proportional increase over 10.88% in the main analyses.

*Considerations of other welding fume and asbestos categories*. The general trends of risk estimates for welding fume exposure using different categories were similar to those in the main model. All welding fume categories showed significantly higher risk than the baseline. The rate ratios were 1.47 (95% CI 1.09, 1.98), 1.40 (1.02, 1.92), and 1.61 (1.08, 2.38), respectively, for welding fume exposure values of >0–3, >3–10 and >10. With different asbestos categories, the rate ratios relative to baseline (no potential asbestos exposure) were 0.98 (0.71, 1.34) for asbestos values >0–3, 1.25 (0.92, 1.69) for >3–10, and 1.00 (0.59, 1.63) for asbestos >10. The ERR estimate changed from −0.53% in the main analyses to −0.45% (95% CI −3.07%, 2.72%) with different welding fume and asbestos categories.

*Smoking-related cancers*. There were 179 smoking-related (other than lung) cancer deaths (4.6% of all deaths). Sex and calendar time were not stratified in analyses for these smoking-related cancers because their removal affected the exposure coefficient by only 8.9%. No excess relative risk of smoking-related cancer mortality was observed in ERR model with a 15-year lag and stratified by age (Table 5). None of the covariates showed overall significant effect on smoking-related cancer risk, although the risk of 1.68 (95% CI 1.19, 2.36) for workers with welding fume values >0–5 was higher than that for those with no potential welding fume exposure. Adjusting for SES, welding fume and asbestos exposures only resulted in a 6.5% change in the exposure coefficient (Table 5; ERR changed from −1.68% to −1.79%).

*All cancers*. A total of 1,123 (29.1% of all deaths) deaths were due to cancers. When the covariates were tested individually, workers with lower SES (intermediate and high-

er smoking probabilities), or any welding fume or asbestos exposures had significantly higher all-cancer mortality than those without. The risks were still higher, though not all significant, when combining all three covariates in a model. With stratification on sex, age and calendar time, and adjustment for SES, welding fume and asbestos in regression analyses, the estimated ERR per 10 mSv of radiation exposure was −0.07% (Table 5). Removing any of the stratified variables or modeled covariates would cause the estimated ERR to change by more than 10%. Therefore, all these variables were kept in the analyses for all cancer risks.

## DISCUSSION

In the previous study by Silver *et al.*, exposed radiation workers had an elevated lung cancer SMR of 1.13 (95% CI 1.01, 1.25) compared to the U.S. population and SRR of 1.25 (0.91, 1.72) compared to non-monitored workers (*5*). The current study found an excess relative lung cancer risk of 0.81% (95% CI −1.69%, 4.20%) per 10 mSv increase of lagged external radiation exposure among exposed radiation workers. The excess relative risk is higher at 1.08% (Table 2) when unexposed radiation workers were also included in analyses. These results, however, did not consider potentially confounding risk factors that were known or suspected lung carcinogens such as smoking, asbestos and constituents of welding fumes (*9–12, 28, 29*).

The application of complex models using Poisson regression methods incorporates multiple covariates in evaluating risk patterns for the cohort (*30*). After adjusting for SES, welding fume and asbestos exposures, no excess lung cancer risk was observed in relationship to external ionizing radiation. Instead, elevated lung cancer mortality may be attributed to increased smoking probability or having any welding fume or asbestos exposures (Table 2), although the effects of asbestos as estimated for this analysis seem less strong than those of the other two covariates. These findings are consistent with a study of lung cancer mortality at the PNS by Rinsky *et al.* (*1*). They concluded that exposures to the by-products of asbestos and/or welding fumes were in large part responsible for the excess relative risk and confounded the observed association between radiation exposure and lung cancer.

Categorical analyses are useful for detecting the shape of exposure response (*31*). In lung cancer categorical analyses, rate ratios increased with increased exposure categories initially but then dropped at the highest exposure group. This pattern has often been seen for lung cancer in occupational cohort studies. Possible reasons for this phenomenon include misclassification of high exposures, depletion of susceptible workers at high exposures, and bias resulting from the healthy worker survivor effect (*31, 32*).

SES is often used as a surrogate for smoking probability in epidemiological studies. Our classification of SES based on job categories indicated that it is a reasonably good surrogate of smoking probability. Despite the fact that most of the subjects (69%) were classified into intermediate smoking probability (skilled labor and unknown categories) and only limited numbers of subjects were in the lower (professional and technical) or higher smoking probability categories (administrative support and unskilled labor), our results suggested increased lung cancer risk with increased smoking probability. This is in agreement with reported relationship between lung cancer and smoking in many epidemiological studies.

Silver *et al.* found a significantly positive linear exposure–response trend between leukemia mortality and ionizing radiation exposure in internal analyses of monitored workers (*5*). We found a similar increasing exposure–response trend in our categorical analysis and a nonsignificantly elevated excess relative leukemia risk of 10.88% per 10 mSv of exposure. The excess relative risk has been estimated at between −4.1% and 19.0% at 10 mSv in other epidemiological studies of workers exposed to penetrating ionizing radiation (*33*) as well as in the Japanese Life Span Study with various ages at exposure and times after exposure (*34*). A linear-quadratic model is often used in analyses for the Life Span Study because it fits data better than a simple linear model (*34, 35*). The addition of a quadratic term, however, did not improve the model fit in our analyses.

In leukemia categorical analyses, a monotonically increasing risk trend with increasing exposure categories was observed. A similar monotonic trend for leukemia mortality with similar risk estimates was also reported in the study by Silver *et al.* (*5*). Overall, the results from both studies support our findings of positive linear trend between leukemia mortality and ionizing radiation exposure in ERR model.

Confounders such as age, sex, calendar year and SES have often been adjusted in analyses of leukemia mortality in nuclear workers monitored for ionizing radiation exposure (*22, 26, 33, 36–40*). Suspect chemical leukemogens such as solvents have been mentioned as a potential biasing factor in epidemiological studies (*22, 39*), but rarely have they been controlled in the analyses of the relationship between external radiation and leukemia, mainly due to the complexity of the exposure measurement for a large cohort study and the lack of available exposure records (*41*). Potential solvent exposure was adjusted in our analyses, and it was positively, though not significantly, associated with leukemia mortality. Solvent exposure was not a confounder in this study. One possible explanation was misclassification due to lack of specificity in categorizing solvent exposure. A case–control study with more refined classification is under way to further explore the confounding issues of solvent exposure in the relationship of ionizing radiation and leukemia mortality.

It is noteworthy that the overall trend in risk estimates for lung cancer or leukemia in relation to ionizing radiation did not change substantially in various sensitivity analyses

for exposure calculations. The results using only PNS exposure also followed the general trends of those using total exposure. This latter result was not surprising since PNS exposure accounted for about 97% of total exposure. Silver and colleagues reported differences for lung cancer and leukemia risks between exposed and unexposed radiation workers (*5*). We did not report the results for the unexposed radiation workers separately, but excluding them (12% of all radiation monitored workers) had minimal impact on the regression results.

Silver and colleagues reported no elevation in smoking-related cancers except lung among exposed radiation workers (SMR = 1.00; 95% CI 0.84, 1.18) or unexposed radiation workers (SMR = 0.96; 95% CI 0.81, 1.14) (*5*). Our results showed a deficit in excess relative risk per 10 mSv of ionizing radiation among radiation-monitored workers, with or without adjusting for SES or welding fume or asbestos exposures. Workers with higher doses may have spent more time in confined spaces on the submarines, and this may have an impact on lifestyle or occupational exposures. It is possible that the negative ERR for smoking-related cancers other than lung reflects an inverse relationship between radiation dose and cigarette smoking or some as-yet unexplored confounding occupational exposure. Slightly elevated all-cancer deaths were observed among exposed radiation workers (SMR = 1.07; 95% CI 1.00, 1.14) and unexposed radiation workers (SMR = 1.01; 95% CI 0.87, 1.18) in the study by Silver *et al.* (*5*). In our study using Poisson regression analyses with adjustment for potential confounders (SES, welding fume and asbestos exposures) failed to demonstrate a positive exposure–response relationship between all-cancer mortality and ionizing radiation, although all three confounding variables were positively associated with all-cancer mortality (Table 5).

## LIMITATIONS

Our analyses were limited by a number of factors. First, as previously noted by Silver *et al.* (*5*), underascertainment of cause of death or of primary sites of malignancies is an issue in this cohort. Neoplasms of unspecified site were more likely to have been listed as cause of death in earlier years. If primary sites of these fatal malignancies were known, the risk estimates for the corresponding cancer outcomes might have been higher. Second, the number of leukemia cases was relatively small. That resulted in wide confidence intervals on the odds ratios, and lack of power to detect significant associations between ionizing radiation and leukemia mortality (or other cancer sites). Third, this study did not differentiate chronic lymphocytic leukemia (CLL) from other types, i.e., all leukemia deaths were used for the analyses, although CLL is not considered to be related to ionizing radiation exposure (*42*). Fourth, missed dose due to higher detection limits can lead to misclassification of exposed workers into lower cumulative dose groups or as unexposed radiation workers. Fifth, actual smoking data were not available for the cohort. SES was a crude surrogate that may not have adequately controlled for smoking in our study. Finally, we did not have the actual exposure levels of welding fumes, asbestos or solvents. Exposure estimates were not quantitative, were based on years of employment, shops and job codes/titles and were subject to misclassification. Misclassifications on either ionizing radiation or the confounders could lead to attenuation of a linear exposure response seen in our analyses. These limitations are being addressed in lung cancer and leukemia case–control studies with more detailed exposure assessment for these and other factors.

## CONCLUSIONS

In this study, we found that SES, welding fume and asbestos exposures were positively associated with lung cancer risk. The positive association between lung cancer risk and ionizing radiation exposure observed previously was no longer present after adjusting for these potential confounders.

Excesses of leukemia in the radiation-monitored workers at PNS were found to be positively associated with external ionizing radiation, with or without including potential confounders. The estimated excess relative risk of 10.88% per 10 mSv of cumulative radiation exposure is within the ranges of risk estimates from previous epidemiological studies. The National Council on Radiation Protection and Measurements estimates that 1.5 million U.S. workers are occupationally exposed to ionizing radiation each year, including approximately 120,000 workers being monitored each year for radiation exposure at DOE facilities. Further analyses with more specific classification for other exposures are being conducted within this cohort to study the joint effect of ionizing radiation and potential confounders on leukemia and lung cancer mortality.

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