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A Nested Case-Control Study of Lung Cancer Risk and Ionizing Radiation Exposure at the Portsmouth Naval Shipyard

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Results have been inconsistent between studies of lung cancer risk and ionizing radiation exposures among workers at the Portsmouth Naval Shipyard (PNS). The purpose of this nested case-control study was to evaluate the relationship between lung cancer risk and external ionizing radiation exposure while adjusting for potential confounders that included gender, radiation monitoring status, smoking habit surrogates (socioeconomic status and birth cohort), welding fumes and asbestos. By incidence density sampling, we age-matched 3,291 controls selected from a cohort of 37,853 civilian workers employed at PNS between 1952 and 1992 with 1,097 lung cancer deaths from among the same cohort. Analyses using conditional logistic regression were conducted in various model forms: log-linear (main), linear excess relative risk (ERR), and categorical. Lung cancer risk was positively associated with occupational dose (OR = 1.02 at 10 mSv; 95% CI 0.99–1.04) but flattened after the inclusion of work-related medical X-ray doses (OR = 1.00; 95% CI 0.98–1.03) in multivariate analyses. Similar risk estimates were observed in the linear ERR model at 10 mSv of cumulative exposure with a 15-year lag.

INTRODUCTION

Results have been inconsistent among a number of epidemiological studies of cancer risk from exposure to ionizing radiation among workers at the Portsmouth Naval Shipyard (PNS) and all-cancer and lung cancer mortality (*1–5*). Najarian and Colton reported a twofold increase in proportional mortality due to all cancers combined among workers with low levels of ionizing radiation exposure at PNS (*1*), but a follow-up cohort mortality study by the National Institute for Occupational Safety and Health (NIOSH) did not find excess mortality from all cancers combined or any other cause (*2*). Excess lung cancer deaths, however, were observed among workers with at least 10 mSv (1 rem) cumulative radiation dose. A subsequent nested lung cancer case-control study found a significant elevation among workers with cumulative doses between 10–50 mSv. Further analysis showed that risk estimates were lower at all levels of radiation exposure after controlling for exposures to asbestos and welding fumes (*3*). It suggested that these potential confounders were at least partially responsible for the increased lung cancer risk.

To pursue this finding, NIOSH researchers conducted an expanded cohort mortality study and found elevated standardized mortality ratios (SMRs) for lung cancer of 1.11 (95% CI 1.05–1.18) among the entire cohort, 1.13 (1.01–1.25) among 11,791 exposed radiation workers, and 1.12 (1.04–1.21) in 24,385 non-monitored workers (*4*). Internal comparison of radiation-monitored workers resulted in standardized rate ratios (SRRs) of 1.30 (0.90–1.88) and 1.35 (0.97–1.89) for dose categories 1–<10 mSv and 10–<50 mSv, respectively, compared with doses 0–<1 mSv (baseline). The SRR was closer to the baseline at 1.04 (0.69–1.56) in the highest dose category (>50 mSv). The slope for the Rothman Trend Test was positive but nonsignificant at 5.10×10^{-7} (*6, 7*). Due to data limitations, researchers were unable to control for potential confounding exposures at the full cohort level.

In a subsequent study restricted to the radiation-monitored subset of 13,468 workers, Yiin *et al.* (*5*) reported a nonsignificant excess relative risk (ERR) of 1.08% for lung cancer with every 10 mSv of lagged external radiation dose, without adjusting for potential confounders. In contrast, when adjusted for socioeconomic status (SES) as a surrogate for smoking, welding fumes, and asbestos exposure, the positive exposure–response relationship became negative at −0.53%. Similar to what was observed by Silver and colleagues, lung cancer rate ratios in categorical analyses increased with greater exposure categories initially but then dropped closer to the baseline in the group with the highest exposures. Due to data constraints, the confounder adjustments in this study were limited to portions of the work histories during which the workers were monitored for radiation exposure.

The current nested case-control study was undertaken to assess the relationship between lung cancer risk and exter-

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nal ionizing radiation exposure while adjusting for potential confounders that included gender, radiation monitoring status, smoking habit surrogates (SES and birth cohort), welding fumes and asbestos. The study design, which included detailed reconstructions of historical exposures to ionizing radiation, asbestos and welding fumes, facilitated a more complete assessment of exposures to the study population as well as an evaluation of the role of occupational medical X-ray examinations.

MATERIALS AND METHODS

Study Subjects

Cases and controls were from a cohort mortality study of 37,853 male and female civilian workers of all races employed at PNS for at least 1 day between January 1, 1952 and December 31, 1992 whose vital status was followed through December 31, 1996 (*4*). The protocol was approved and reviewed annually by the Institutional Review Board of the Centers for Disease Control and Prevention (CDC) to ensure that the research project was conducted in an ethical manner and was consistent with CDC's policies and procedures for protection of human research participants. Cases had an underlying cause of death classified as lung cancer under the revision of the International Classification Diseases (ICD) in effect at the time of death. There were 699 (63.7%), 257 (23.4%) and 141 (12.9%) cases classified under the 9th (ICD = 162; 1979–1999), 8th (ICD = 162; 1968–1978), and 6th and 7th (ICD = 162 or 163; 1949–1967) revisions, respectively. For each case, a risk set was developed comprising all workers who were at risk of dying from lung cancer and who lived to at least the age attained by the index case at the time of death. Three controls were randomly selected from each risk set using an incidence density sampling program (*8*).

Occupational Radiation Exposures

Individual occupational radiation exposures were characterized as the sum of equivalent doses from radiation exposures from on-site, prior employment/off-site, and administrative adjustments. Details of the radiation exposures at PNS and the procedures for assembling and validating dosimetry data are described elsewhere (*9*). After medical and training qualifications as radiation workers, shipyard employees were issued dosimeters when accessing radiation-controlled areas of the shipyard, both on board submarines and in support buildings. These dosimeters were processed routinely, and the results were compared to administrative limits to ensure that worker exposures remained below accepted levels. Workers with radiation exposures approaching or surpassing control levels had their rights to access radiation areas removed.

Recorded doses resulted primarily from external exposures to low-LET penetrating radiation; there was no evidence of significant neutron or internal exposures to workers within the study population (*9*). Given the dosimetry methods used at PNS, the amount of nondetectable or ''missed'' dose from measurement sensitivity is expected to be small in comparison to recorded doses. In general, missed dose values were imputed from the distribution of recorded values grouped by dosimeter type and monitoring period (*10*). Radiation doses were adjusted to account for recognized biases in the dosimetry process that arise from exposures to heterogeneous radiation fields, calibration methods, dosimeter design, and dosimeter energy response. Dose variables were quantified in terms of tissue equivalent dose (H_T), where tissue (T) was limited to the lung. Equivalent dose was chosen as the exposure metric to be consistent with other recent PNS studies (*4, 5*). Given that exposures primarily resulted from external sources of γ radiation, such as cobalt-60 (*9*), a radiation weighting factor of unity is assumed and dose estimates are considered reasonable approximations of absorbed dose. The methods used for adjusting film badge measurements between 1950 and 1974 are described elsewhere (*11*). Similar methods were used for adjusting the results from thermoluminescence dosimetry used since October 1974.

Cumulative external radiation doses from all years monitored were calculated for each worker by summing the results from each monitoring cycle. As in the previous cohort mortality study (*5*), a lag of 15 years was employed to discount any exposure that occurred 15 years prior to death or end of study, while other lags (10, 20 and 25 years) were tested in sensitivity analyses. Radiation workers were reclassified as non-radiation workers if all their exposures were recorded in the lagged years. Exposures were truncated for each control when he or she reached the age at death of the matched case, minus the lag period. For this study, non-radiation workers were assumed to be unexposed to ionizing radiation from occupational sources other than work-related medical X-ray examinations, since they were restricted from the radiological areas.

Work-Related Medical X-Ray Examinations

Shipyard employees were also exposed to penetrating radiation from work-related medical X-ray examinations (*12*). Information describing work-related X rays was abstracted from the medical records for each study subject. 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 had significantly higher exposures than those used 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 levels of work-related X rays and workplace external ionizing radiation exposures. While the main analyses were restricted to occupational doses, additional analyses were conducted with the inclusion of work-related X rays in radiation exposures (i.e., occupational dose + work-related X rays as one exposure variable).

Welding Fumes and Asbestos

Employment histories including job titles, shop assignments, and dates of employment for study subjects found in PNS personnel records (*2*) were entered into an employment history database. Shops are occupational groups describing major shipyard tasks, while job titles describe specific functions. A total of 1,174 standardized shop and job-title combinations from 1945 to 1996 in 3-year periods were used to create exposure matrices for asbestos and welding fumes (iron oxide fume). Only shop/job title/3-year period combinations (n = 3,519 cells) occupied by study subjects were included in each exposure matrix.

Industrial hygiene monitoring records collected from PNS comprised an air monitoring database and a subset of these air samples was used to create numerical values for asbestos exposure intensity categories. The paucity of welding fume air sampling data did not allow for the same approach, and numerical values for welding fume exposure intensity categories were based on consensus occupational exposure guidelines.

In addition to asbestos and welding fume exposure intensity, exposure frequency (number of days exposed per year at the estimated exposure intensity), and respirator use/type (for asbestos only) were estimated in the exposure matrices. A three-member panel of experienced PNS industrial hygienists (each with 25+ years of experience) independently estimated these metrics for all 3,519 cells in the exposure matrices for asbestos and welding fumes. The panel's estimates were compared for agreement. Estimates that differed among the three panelists were divided into identical/small differences and discordant (for larger differences) categories. Rules were defined to resolve the small differences and discordant estimates were resolved by the industrial hygiene panel through consensus. Each exposure matrix cell's final exposure estimate was the product of exposure intensity (in fibers/cm^3 for asbestos or mg/m^3 for welding fume) and frequency, divided by a protection factor, if a respirator was required, plus the product of background intensity and frequency of unexposed days (background adjustment).

Cumulative exposures for asbestos (fiber-days/cm^3) and welding fume (mg-days/m^3) were calculated for each study subject by summing all

TABLE 1
Assumed Smoking Category and Corresponding Socioeconomic Status Assignment and Estimated Pack-Years

Smoking category	Pack-years[a]	No. of subjects	SES	Skill category	No. of subjects
Lower smoking probability	29.5	302	1	Professional	117
			2	Technical	185
Intermediate smoking probability	32.3	2,193	3	Skilled Labor	2,193
Higher smoking probability	35.1	1,891	4	Administrative Support	796
			5	Unskilled Labor	1,095

[a] Based on data obtained from 365 subjects with detailed smoking histories.

matching shop/job/time combinations in their employment histories with the final exposure estimates in the corresponding exposure matrices.

Gender

Gender was included in the analyses because of the historical differences between males and females in lung cancer risk, smoking habits, levels of occupational exposures, and the resulting potential for confounding or effect modification.

Radiation-Monitoring Status

The results of the PNS cohort mortality study suggested considerable differences between radiation-monitored and non-monitored workers, with the former showing a strong healthy worker effect while the latter did not. The non-monitored workers had a much shorter average duration of employment (10 years compared to 19 years), and fewer lasted 5 or more years (50 compared to 88%) than the exposed radiation workers (*4*). In recent studies of lung cancer in Mayak workers, monitoring status was used with the inclusion of non-monitored workers for a more powerful assessment of external exposure effects (*13*). We adopted a dichotomous radiation-monitoring status for each worker to account for these differences.

Smoking Habit and its Surrogates

Findings of the PNS cohort mortality study suggested the possibility of differential smoking habits by radiation worker status and, perhaps, by radiation dose (*4*). Given the possibility of non-random distribution of smoking within the cohort, and the potential for confounding of any observed relationship between radiation and lung cancer mortality by smoking, we requested to review medical records for all study subjects, regardless of case or control status, to avoid biasing data collection and coding. Imputation of smoking status for nuclear facility workers, including PNS workers, proved feasible in a recent multi-site leukemia case-control study; however, this study was restricted to radiation-monitored workers.

Different forms were used in different years, so the level of detail about smoking habits and in particular smoking history varied over time. The Navy Environmental Health Center (NEHC) provided access to a database containing smoking data from the voluntary asbestos medical surveillance program (AMSP). These data were appended to the electronic database after a comparison with hard-copy records.

1. Smoking ascertainment

Unfortunately, data sufficient to support assessment of historical smoking to the level of pack-years by specific dates were very limited. With 15-year lags used, detailed data were available for 26.8% (277 out of 1,166) of the monitored risk-set members but only 1.3% (42 of 3,222) of the non-monitored risk-set members. A number of limited single-point-in-time data were available from the 1960s. However, these data were only available for an additional 0.2% (8 of 3,222) of the non-monitored risk-set members. Even with a zero lag, smoking data were available for less than 10% of the non-monitored members.

For the remainder of workers, medical files either could not be located by the National Personnel Record Center (NPRC) in St. Louis, MO or they were located and reviewed by NIOSH staff, but no smoking data were found. Data were disproportionately available for cases due to notations in medical records made around the time or after diagnosis; thus the availability of suitable data for controls, who were to serve as the basis for any imputations, was even more limited. Because smoking data were so scarce, the decision was made to examine two other variables, socioeconomic status and birth cohort, as proxies for smoking status and to use the smoking data we had collected to evaluate these proxy measures.

2. Socioeconomic status (SES) and birth cohort

The methodology for SES assignment in the previous cohort mortality study (*5*) was used. Briefly, SES was coded based on collapsed job title series and ranged from 1 to 5, with 1 being the highest and 5 the lowest: (1) Professional, (2) Technical, (3) Skilled Labor, (4) Administrative Support, and (5) Unskilled Labor. These five categories were further collapsed into three (1/2, 3 and 4/5) for the analyses due to limited numbers in some assigned SES levels. SES based on occupation and/or educational attainment has shown a strong inverse association with smoking (*14–16*); i.e., subjects with higher SES have lower smoking probability. We found that for those with historical data, average pack years had an inverse relationship with SES (Table 1). Birth cohort is also a plausible surrogate for smoking. Studies investigating trends in smoking by birth cohort showed that the proportion of young men who smoked generally fell in each birth cohort since the 1920s (*17–19*). Birth cohort was also used as a likelihood of smoking in our analyses, and the limited data in our study showed a similar trend (Table 2).

TABLE 2
Cases and Controls and Estimated Pack-years in each Birth Cohort

Birth cohort	No. of cases	No. of controls	Total	Cases	Pack-years[a]
≤1900	158	615	773	20.4%	32.7 (29.9)
>1900–1910	249	731	980	25.4%	56.8 (13.9)
>1910–1920	376	1,025	1,401	26.8%	32.6 (29.5)
>1920–1930	240	687	927	25.9%	36.8 (30.1)
>1930	74	233	307	24.1%	23.9 (29.6)
Total	1,097	3,291	4,388	25.0%	33.1 (29.9)

[a] Means (standard deviations) of pack-years based on data obtained from 365 subjects with detailed smoking histories.

TABLE 3
Frequency (%) of Radiation Monitoring Status[a] among Cases and Controls

Radiation monitoring status	Cases	Controls	Total
Monitored	321 (29.3%)	845 (25.7%)	1,166 (26.6%)
Not monitored	776 (70.7%)	2,446 (74.3%)	3,222 (73.4%)
Total	1,097	3,291	4,388

[a] With a 15-year lag; workers monitored within 15 years of date of death or study end date were classified as non-monitored.

Statistical Analyses

Conditional logistic regression using PECAN in Epicure (*20*) was used to evaluate any dose–response relationship between lung cancer mortality and external ionizing radiation dose, with adjustment for potential confounders such as gender, radiation monitoring status, smoking habit surrogates (SES and birth cohort), welding fumes and asbestos. The main regression model was log-linear. Odds ratios (ORs) and the corresponding 95% profile likelihood-based confidence intervals (CIs) were derived from parameter estimates and the associated standard errors of the regression model. In addition, linear ERR per 10 mSv and log-linear categorical models (1–<10, 10–<50 and ≥50 mSv compared to baseline 0–<1 mSv) for radiation exposure were also assessed. The ERR model is often used in radiation epidemiological studies (*21*), and categorical analyses are useful for detecting the shape of the exposure response (*22*).

Analyses with categorized welding fume and asbestos exposures were conducted to examine risk trends of these two variables based on their distributions of cumulative exposure estimates within the study population. To establish exposure categories, the ACGIH Threshold Limit Values (TLVs) (*23*) were cumulated over time. Reference values equaling the TLVs for 1 year and 10 years were computed, assuming 240 working days per year for welding fume and asbestos, respectively. A TLV-1 is the exposure at the TLV for 240 working days, and a TLV-10 is the TLV-1 multiplied by 10. Five exposure categories were determined for welding fume (iron oxide) using fractions of its associated TLV-1 value [i.e., <0.5 (baseline), 0.5−, 1−, 2− and 4+ TLV-1 units, where TLV-1 = 1,200 mg-days/m^3). Similarly, four asbestos exposure categories were defined using a TLV-10 value of 240 fiber/cm^3 per day. A lag of 15 years for radiological and chemical exposures was used in the main analyses, although longer lags (20 and 25 years) for asbestos were also evaluated.

RESULTS

Demographics

A total of 1,097 workers had died from lung cancer as of December 31, 1996. For each of these cases, three controls were selected, for a total of 3,291. Cases and controls had very similar averages for year of birth (1914 and 1913), age at date first employed (33.3 and 33.2 years), year first employed (1947 and 1946), year last employed (both 1966), employment duration (19.0 and 20.2), and time since last employed (14.9 and 13.8 years). More cases (96.8%) than controls (92.4%) were male. Of the 4,388 cases and controls, 1,166 (26.6%) were monitored for external radiation exposure at PNS, after discounting any exposure that occurred 15 years prior to death or end of study. Slightly more of the cases (29.3%) than controls (25.7%) were radiation workers (Table 3).

Exposures

The average cumulative on-site dose was 19.2 mSv among radiation-monitored workers (*n* = 1,152), and rose slightly to 19.5 mSv when off-site exposures and missing/administrative dose were added in (*n* = 1,166). The mean equivalent dose from work-related X rays was of the same order of magnitude, 17.5 mSv, and affected far more workers (*n* = 3,263). In addition, while the mean cumulative occupational dose from sources other than work-related X rays was higher in cases (22.6 mSv) than in controls (18.4 mSv), the mean cumulative dose from work-related X rays was somewhat higher in controls (17.8 mSv) than in cases (16.4 mSv). When exposures from all sources were combined, the mean equivalent doses were closer, 23.6 mSv in controls (*n* = 2,481) and 24.2 mSv in cases (*n* = 876). When the non-radiation workers (who were assigned zero doses from shipyard sources) were included, the average cumulative dose, as expected, dropped drastically for on-site/off-site/administrative doses combined and was about 20% lower for all sources combined (Table 4).

Cumulative welding fume exposure (with a 15-year lag) was higher in cases, with a mean of 919 mg-days/m^3 than in controls at 776 mg-days/m^3. As shown in Table 4, asbestos exposure was also higher in cases (456 fiber-days/cm^3) than in controls (361 fiber-days/cm^3). From available detailed smoking histories, pack-years peaked at 56.8 in birth cohort >1900–1910, then dropped to 32.6–36.8 in the 1910s and 1920s birth cohort. The most recent birth cohort (>1930) had the lowest average pack-years at 23.9 (Table 2).

TABLE 4
Mean (and standard deviation) of Cumulative Exposures[a] with a 15-Year Lag among all Cases and Controls

Exposures	Cases (*n* = 1,097)	Controls (*n* = 3,291)	Total (*n* = 4,388)
Occupational dose[b]	6.6 (30.8)	4.7 (24.0)	5.2 (25.9)
Occupational dose + work-related X rays	19.3 (36.1)	17.8 (30.3)	18.2 (31.9)
Welding fume	919 (2455)	776 (2322)	812 (2356)
Asbestos	456 (1617)	361 (1389)	384 (1450)

[a] Non-radiation workers were assigned zero ionizing radiation from shipyard sources.
[b] Occupational doses include on-site, prior/off-site and administrative doses.

TABLE 5
Individual Risk Factor Effects: Conditional Logistic Regression of Lung Cancer Risk at the Portsmouth Naval Shipyard

Factor	No. of cases	No. of controls	Risk estimate (95% CI)
SES			
Professional/technical	67	235	Baseline
Skilled labor	597	1,596	RR = 1.33 (1.00, 1.79)
Adminastrative support/unskilled labor	433	1,458	RR = 1.05 (0.79, 1.42)
Birth cohort			
≤1900	158	615	Baseline
>1900–1910	249	731	RR = 1.34 (1.07, 1.69)
>1910–1920	376	1,025	RR = 1.47 (1.18, 1.84)
>1920–1930	240	687	RR = 1.42 (1.11, 1.81)
>1930	74	233	RR = 1.30 (0.91, 1.85)
Welding fume (at 1,000 mg-days/m^3)	N/A	N/A	RR = 1.03 (1.00, 1.05)
Welding fume TLV-1[a] categories			
<0.5	807	2,603	Baseline
0.5−	116	277	RR = 1.35 (1.07, 1.70)
1−	86	178	RR = 1.58 (1.20, 2.07)
2−	40	108	RR = 1.20 (0.82, 1.72)
4+	48	125	RR = 1.26 (0.88, 1.76)
Asbestos (at 1,000 fiber-days/cm^3)	N/A	N/A	RR = 1.04 (1.00, 1.09)
Asbestos TLV-10[b] categories			
<0.5	865	2,724	Baseline
0.5−	40	92	RR = 1.35 (0.92, 1.95)
1−	49	117	RR = 1.33 (0.93, 1.86)
2+	143	358	RR = 1.26 (1.02, 1.55)
Occupational dose[c]			
Log-linear (at 10 mSv)	N/A	N/A	RR = 1.03 (1.00, 1.05)
Linear ERR (per 10 mSv)	N/A	N/A	ERR = 3.6% (0.2%, 8.9%)
Categorical			
<1 mSv	889	2,794	Baseline
≥1–<10 mSv	104	264	RR = 1.23 (0.97, 1.56)
≥10–<50 mSv	69	141	RR = 1.54 (1.14, 2.07)
≥50 mSv	35	92	RR = 1.21 (0.80, 1.77)

[a] Welding fume TLV-1 = 1,200 mg-days/m^3 (5 mg/m^3 day^{-1} × 240 working days/year × 1 year).
[b] Asbestos TLV-10 = 240 fiber-days/cm^3 (0.1 fiber/cm^3 day^{-1} × 240 working days/year × 10 years).
[c] With a 15-year lag.

Individual Risk Factor Effects

The individual effects of occupational dose and the risk factors potentially associated with lung cancer mortality are listed in Table 5. Each of the two lower SES categories had nonstatistically significantly higher lung cancer risk compared to the highest SES. Using birth cohort as a surrogate for smoking habit, lung cancer risks were statistically significantly higher for workers born in each decade from the 1900s to 1930s than those born before 1900. The odds ratio dropped to 1.30 and was not statistically significantly higher for workers born after 1930.

Lung cancer risk increased positively with increased welding fume (OR = 1.03 at 1,000 mg-days/m^3) or asbestos (OR = 1.04 at 1,000 fiber-days/cm^3) exposures. Categorical analyses showed that each of the higher welding fume exposure categories had higher lung cancer risk than the baseline, although the risk trend tailed off after the third category. Similarly, all asbestos exposure categories had higher risk than the baseline, but the risk estimates slightly decreased with increasing exposure categories. The risk estimates increased with longer lag periods (OR = 1.05 and 1.06 at 1,000 fiber-days/cm^3 for 20 and 25 years, respectively) for continuous asbestos exposure but showed a similar tail-off trend for categorized exposures (data not shown).

Without considering any potential confounders, lung cancer risks increased with increased occupational dose (with a 15-year lag) in either the log-linear model (OR = 1.03 at 10 mSv; 95% CI 1.00–1.05) or the ERR model (ERR = 3.6% per 10 mSv; 95% CI 0.2–8.9%). In the categorical model, the odds ratios of lung cancer mortality compared to workers with 0–<1 mSv (baseline) of cumulative exposure increased from 1.23 to 1.54 for workers in dose categories 1–<10 and 10–<50 mSv, respectively, then

TABLE 6
Multivariate Analysis: Conditional Logistic Regression of Lung Cancer Risk with Radiation Exposure (with a 15-year lag) and Potential Confounders at the Portsmouth Naval Shipyard

Factor	Risk estimate (95% CI)
Potential confounders	
Sex - female compared to male	RR = 0.42 (0.28, 0.60)
Radiation monitoring status - yes compared to no	RR = 0.99 (0.83, 1.18)
SES - skilled labor compared to professional/technical	RR = 1.30 (0.97, 1.77)
SES - administrative support/unskilled labor compared to professional/technical	RR = 1.15 (0.86, 1.57)
Birth cohort →1900–1910 compared to ≤1900	RR = 1.36 (1.08, 1.71)
Birth cohort →1910–1920 compared to ≤1900	RR = 1.49 (1.19, 1.88)
Birth cohort →1920–1930 compared to ≤1900	RR = 1.48 (1.15, 1.92)
Birth cohort →1930 compared to ≤1900	RR = 1.35 (0.92, 1.96)
Welding fume (at 1,000 mg-days/m^3)	RR = 1.01 (0.98, 1.04)
Asbestos (at 1,000 fiber-days/cm^3)	RR = 1.02 (0.98, 1.07)
Occupational dose	
Log-linear[a] (at 10 mSv)	RR = 1.02 (0.99, 1.04)
Linear[a] (per 10 mSv)	ERR =1.9% (−0.9%, 6.6%)
Categorical[a]	
Occupational dose ≥1–<10 compared to <1 mSv	RR = 1.17 (0.86, 1.60)
Occupational dose ≥10–<50 compared to <1 mSv	RR = 1.45 (1.01, 2.09)
Occupational dose ≥50 compared to <1 mSv	RR = 1.13 (0.72, 1.75)

[a] Model with all potential confounders listed above. RR and the corresponding 95% C.I. for these potential confounders (from the log-linear model) are very similar whether occupational dose is modeled log-linearly, linearly or categorically.

dropped to 1.21 in the highest exposed category (≥50 mSv). Using longer lag years (20 and 25 years) did not improve the model fit, and the differences in terms of coefficients or model deviances were negligible when a 10-year lag was used.

Multivariate Analysis

Table 6 shows multivariate analyses of lung cancer risk with occupational dose and all potential confounders (gender, radiation monitoring status, SES, birth cohort, welding fume, and asbestos exposure). The risk estimates increased slightly for birth cohort but decreased for welding fume and asbestos exposures when compared with those in individual risk factor effect analyses. The dose–response relationship between occupational dose and lung cancer risk was weakly positive, because the risk estimates were attenuated in both the log-linear (OR = 1.02 at 10 mSv) and linear ERR (ERR = 1.9% per 10 mSv) models. Occupational dose categories showed the same tail-off trend but with lower risk estimates (OR = 1.17, 1.45 and 1.13, respectively, for 1–<10, 10–<50 and ≥50 mSv compared to baseline). The risk estimates for occupational dose were similar when categorized welding fume and asbestos exposures were used in the analysis. Using longer lag periods for asbestos had no impact on the risk estimates for occupational dose. The results changed little when different lags (10, 20 and 25 years) in occupational dose were used.

Work-Related Medical X-Ray Examinations

There was a reduction in risk estimates when work-related medical X-ray doses were added to occupational dose in univariate analyses: OR = 1.02 at 10 mSv (95% CI 0.99–1.04) in the log-linear model and ERR = 1.6% per 10 mSv (95% CI −0.6%–4.8%) using the linear model (data not shown). In the categorical model, the odds ratios of lung cancer mortality compared to baseline decreased from 1.46 (95% CI 1.19–1.78) to 1.21 (95% CI 0.99–1.47), then increased to 1.31 (95% CI 0.95–1.78) for workers in dose categories 1–<10, 10–<50 and ≥50 mSv, respectively. When all potential confounders were included, the risk estimates were 1.00 at 10 mSv (95% CI 0.98–1.03) in the log-linear model and ERR = 0.2% per 10 mSv (95% CI −1.5%–3.0%) in the linear model and showed a decreasing trend in the categorical model (OR = 1.31, 1.03 and 0.95, respectively, for 1–<10, 10–<50 and ≥50 mSv compared to baseline).

DISCUSSION

Yiin and colleagues (*5*) found an excess relative lung cancer risk of 1.08% (95% CI −1.47–4.49%) per 10 mSv increase of lagged external ionizing radiation exposure among all radiation-monitored workers. This positive relationship became nonsignificantly negative after adjusting for potential confounders such as smoking surrogates (SES and birth cohort) and welding fume and asbestos exposures (ERR = −0.53% per 10 mSv; 95% CI −3.06–2.59%). In the current study, the excess risk estimate of 3.6% also attenuated (to 1.9%) when all potential confounders were included in the multivariate analysis. Rinsky *et al.* (*3*) concluded that exposures to the by-products of asbestos and/or welding fumes were in large part responsible for the excess relative risk. We found that the risk estimates for ionizing radiation and all confounders except birth cohort were lower in the multivariate analysis than in individual risk factor effect analysis. In fact, the effect of birth cohort, a possible surrogate for one of the strongest risk factors of lung cancer, was not affected by other variables in the analysis.

Birth cohort showed statistically significant elevations in lung cancer mortality for workers born in three subsequent decades from 1900 to 1930 compared to those born prior to 1900. The elevations peaked in the 1920–1930 cohort and then fell slightly in workers born after 1930 (still elevated but not statistically significant). This pattern is consistent with published data about historical likelihood of smoking in males, who comprise the bulk of cases and controls. SES was used in the radiation-monitored cohort mortality study and showed a reasonably good fit as a surrogate for smoking probability (*5*). Our data from a limited number of subjects with detailed smoking histories also showed that estimated smoking pack-years increased with increased smoking probabilities based on SES (Table 1). SES, however, was a less strong surrogate for smoking probability than birth cohort in this case-control study (Table 5).

Incorporation of work-related X rays in the analyses attenuated the risk estimates. In fact, the risk estimates were nearly flat in multivariate analyses. These results are not surprising since the inclusion of work-related X rays diluted the exposure differences between cases and controls. The case to control ratio with regard to average occupational doses was 1.4 (6.6 compared to 4.7 mSv), while the ratio decreased to 1.1 (19.3 compared to 17.8 mSv) with combined sources (Table 4). The impact of work-related X rays on lung cancer mortality is the opposite of what was reported by Kubale *et al.*, where no change in leukemia risk estimate was observed after including work-related X rays (*24*). However, the dose to the target organ (hematopoietic bone marrow) per X-ray examination in that study is much less than the equivalent dose to the lung given the exposure geometry of chest X-ray examinations.

As in the previous cohort mortality study, lung cancer risk estimates in the categorical analyses again increased with increased exposure categories initially and then dropped in the highest exposure group. This tail-off pattern was seen in the cohort mortality study among radiation-monitored workers and has often been seen for lung cancer in occupational cohort studies. Misclassification of high exposures, data scarcity of the highest category, the possibility of increased residual confounding, depletion of susceptible workers with high exposures, and bias resulting from the healthy worker survivor effect are possible explanations for this phenomenon (*22, 25*).

LIMITATIONS

Our analyses were limited by a number of factors. First, although we made extensive efforts to collect smoking data for all cases and controls, almost no information was available for non-radiation workers. This non-random information deficit precluded implementation of the backup strategy of using available data to predict the smoking habits of workers lacking data. Instead, we examined SES and birth cohort as potential surrogates, and birth cohort appeared to be the more robust surrogate. However, it accounted for $<35\%$ of the variation of smoking quantity among controls with detailed smoking data. Gender was included as well to increase the level of control for smoking. In addition, results of the PNS cohort study suggested that smoking habits may have differed by radiation monitoring status. The available data did not allow assessment of this hypothesis here, but monitoring status was included in the models for this and other reasons. However, some residual confounding or effect modification likely results from use of these surrogates in place of actual smoking data.

The scarcity of usable air monitoring data for asbestos and welding fumes forced reliance on an expert panel to develop exposure estimates based on job and shop for particular periods. Moderate to high initial panel estimates were identical or had small differences. Discordant estimates were resolved in consensus meetings that were quite successful. Although the methods used to reconstruct exposures to asbestos and welding fumes were rigorous, without monitoring data to validate the panel estimates, exposure misclassification remains a possibility.

Variations in dosimetry practices, equipment and exposure conditions all result in uncertainty in the recorded whole-body radiation doses used as a basis for the radiation exposure estimates. These and other factors, such as the sex, age and anatomy of the exposed worker, add to the uncertainty in the subsequent use of recorded doses in the estimation of the worker's equivalent dose to the lung. Larger dose uncertainties are likely from exposures during medical X-ray examinations given the limited data available concerning X-ray procedures and equipment. 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 radiation exposure assessment methods included considerations for unmonitored PNS exposures and exposures occurring elsewhere. However, it is likely that some relevant occupational exposures remain undiscovered. Likewise, 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.

CONCLUSIONS

We found that birth cohort, SES, welding fume and asbestos exposures along with occupational dose to external ionizing radiation were positively associated with lung cancer mortality. The association between lung cancer mortality and ionizing radiation exposure remained positive but was not statistically significant after adjusting for the potential confounders. Control for potential confounders and effect modifiers, while incomplete, did attenuate the radiation risk estimates.

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