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Evidence of Confounding by Smoking of Associations Between Radiation and Lung Cancer Mortality Among Workers at the Savannah River Site

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Background *This study investigates confounding by cigarette smoking of associations between occupational exposure to ionizing radiation and lung cancer mortality among workers at the Savannah River Site (SRS).*
Methods *Thirteen thousand two hundred sixty-five white males hired at SRS between 1950 and 1986 were followed through 2002 to ascertain causes of death. Estimates of radiation doses from external sources and internal tritium uptakes were derived from dosimetry records. Logistic regression methods were used to derive discrete-time estimates of rate ratios. An indirect approach to control for unmeasured confounding by smoking was employed that involves joint modeling of lung cancer and chronic obstructive pulmonary disease (COPD) mortality.*
Results *Prior to indirect adjustment for smoking, there was minimal evidence of association between lung cancer mortality and cumulative radiation dose under a 10-year lag assumption (RR at 100 mSv = 0.90; 90% CI: 0.80–1.01). Subsequent to indirect adjustment for smoking, the association between lung cancer mortality and cumulative radiation dose under a 10-year lag was positive (RR at 100 mSv = 1.33; 90% CI: 1.01–1.77).*
Conclusions *In this cohort, there is evidence of negative confounding of radiation dose–lung cancer mortality associations by cigarette smoking.* Am. J. Ind. Med. 54: 421–427, 2011. *© 2011 Wiley-Liss, Inc.*

KEY WORDS: bias (epidemiology); lung neoplasms/epidemiology/*etiology; occupational exposure/*adverse effects; smoking/*adverse effects; ionizing radiation

INTRODUCTION

Cigarette smoking is a potentially important confounder in analyses of associations between occupational lung carcinogens and lung cancer mortality. However, individual smoking history information is rarely available in occupational cohort mortality studies; therefore, direct adjustment for confounding by smoking is rarely possible. Richardson recently described an approach to control for unmeasured confounding by smoking that involves joint modeling of lung cancer and chronic obstructive pulmonary disease (COPD) mortality [Richardson, 2010]. In this study, we use this method to analyze lung cancer mortality in a large cohort of nuclear industry workers employed at the Savannah River Site (SRS).

There are reasons to expect positive confounding of occupational exposure–lung cancer mortality associations by smoking in some U.S. occupational cohort studies.

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Over the last half century, US blue-collar workers have tended to smoke more and experience higher exposures to respiratory carcinogens than white-collar workers [Sheridan et al., 1993; Shi, 1998]. In addition, the prevalence of smoking among US men has diminished in more recent birth cohorts, as has the magnitude of occupational exposure to many established carcinogens. Upward bias in occupational exposure–lung cancer associations may occur when adjustment for occupational status and birth cohort does not fully control confounding by smoking.

On the other hand, negative confounding by smoking in analyses of associations between occupational exposure and lung cancer mortality could also occur in certain occupational settings. For example, at US Department of Energy nuclear weapons plants, prohibition of smoking in radiologically controlled areas was enforced in order to reduce hand-to-mouth behavior that might lead to internal contamination by radionuclides as well as to reduce potential for ignition of flammable or combustible materials. Therefore, workers could smoke on-the-job in areas with little or no radiation exposure potential but were prohibited from smoking on-the-job in areas where there was high radiation exposure potential [Petersen et al., 1990]. More generally, smoking may contribute to the healthy worker survivor effect [Robins, 1987]. Smokers tend to have poorer health than non-smokers and therefore may tend to terminate employment earlier than non-smokers [Siemiatycki et al., 1988]. Consequently, over time the prevalence of smoking among employed workers in a defined occupational cohort may tend to diminish while non-smokers may remain employed and accrue higher cumulative exposures than smokers.

This study examines the association between ionizing radiation and lung cancer mortality among SRS workers and assesses confounding of this association by cigarette smoking.

MATERIALS AND METHODS

This study was approved by an Institutional Review Board at the University of North Carolina at Chapel Hill.

The SRS, located near Aiken, South Carolina, was constructed in 1950 by the E.I. du Pont Nemours and Company (DuPont) to produce materials for the US nuclear weapons program. We enumerated a cohort of 18,883 people who were hired by DuPont to work at the SRS prior to January 1, 1987, who worked at least 90 days, and who had complete information on name, social security number, date of birth, and date of first hire.

Vital status was ascertained through December 31, 2002 via records of the Social Security Administration (SSA) and the National Death Index. We obtained underlying and contributing causes of death for deceased workers. For deaths occurring prior to 1979, cause of death information was coded according to the Eighth revision of the International Classification of Diseases (ICD); for deaths occurring in 1979 and later, cause of death information was coded to the ICD revision in effect at the time of death. If there was no death indication for a worker and they were confirmed to be alive on January 1, 1979 or later by the SSA or by the Site's employment records then they were assumed to be alive as of December 31, 2002. The analyses examine the following categories of underlying cause of death: lung cancer (ICD8–ICD9 code 162, ICD10 codes C33–C34); and, COPD including bronchitis and emphysema (ICD8 codes 490–492, ICD9 codes 490–492 and 496, ICD10 codes J40–J44). Sensitivity analyses were conducted using the subgroup of COPD including emphysema (ICD8 codes 492, ICD9 codes 492 and 496, ICD10 codes J43–J44).

Smoking patterns in the United States are highly structured by sex and race, with different patterns of prevalence of smoking by birth cohort for white males, non-White males, white females, and non-White females (2–3). Since 88% of the lung cancer deaths in this cohort occurred among white men, and white males received 85% of recorded occupational radiation dose, to simplify this investigation we restricted analysis to the 13,265 white men in the study cohort.

The exposure of interest was defined as cumulative whole body radiation dose equivalent in milliSievert (mSv) from external sources and tritium received during employment at the Site. Personal monitoring data were available for the period 1950–1999 from Site records. External ionizing radiation exposure monitoring began with film badge dosimeters as well as neutron nuclear track emulsion dosimeters; in more recent years, external exposures were monitored via thermoluminescent dosimeters. Radiation dose estimates from tritium depositions were derived via bioassay monitoring. Whole body radiation doses were estimated for work-years with missing dose data using dose estimates in adjacent time periods and average values for similar workers. Estimated annual doses constituted 4% of employment years for males [Richardson et al., 2007a].

Workers were classified by pay code, defined as monthly, weekly, or hourly, based upon the worker's pay code at time of hire. This information was derived from employment history records that were available in hard copy form and were computerized for the purposes of this research project. Monthly paid workers were primarily engineers, chemists, physicists, and supervisors. Weekly paid workers were primarily clerical and kindred workers, security personnel, analysts, and technicians. Hourly paid workers were primarily employed as operators and skilled manual workers.

Statistical Methods

We created a person-year data set with one record for each person-year of observation from age at study entry to: age at death, loss to follow up, or administrative censoring on December 31, 2002. For purposes of notation, the members of the cohort are indexed by i, with contiguous time periods (i.e., years of age) indexed by j. Let P_{ij} denote the probability that person i at age j will die from lung cancer during that time interval, conditional on their survival up to the start of time interval j. Since P_{ij} is bounded by 0 and 1, it can be modeled as having a logistic dependence on a set of predictors as,

$$\log\left(\frac{P_{ij}}{1-P_{ij}}\right) = \alpha_1 t_{1ij} + \alpha_2 t_{2ij} + \ldots + \alpha_J t_{Jij} + \beta_1 x_{1ij} + \beta_2 x_{2ij} + \ldots + \beta_{\mathrm{M}} x_{\mathrm{M}ij} + \delta \mathrm{dose}_{ij}$$

where t_{1ij}–t_{Jij} are binary indicator variables representing the J observed age intervals, x_{1ij}–$x_{\mathrm{M}ij}$ are covariates of interest, and dose_{ij} is the radiation dose estimate for person i at age j. This model allows for a parametric description of the baseline discrete time hazard function via the parameters α_1–α_J and estimation of the impact of the explanatory variables on the log odds of disease via the parameters β_1–β_{M} and δ. In the current analysis, the primary time scale was attained age; and, the baseline hazard was constrained to be a function of the time scale by assigning a score to each period (the natural log of attained age, centered at 70 years) and modeling this as a linear-quadratic function. This pooled logistic regression analysis provides a discrete time hazard approximation of the continuous time Cox proportional hazards model [Langholz and Goldstein, 1996]. The value $\hat{\delta}$ provides an estimate of the log relative hazard rate (log[RR]) per 100 mSv dose.

All regression models included indicator variables for categories of year of birth (classified as born before 1915, 1915 to <1920, 1920 to <1925, 1925 to <1930, 1930 to <1935, or after 1935) and pay code (monthly, weekly, or hourly paid), which were time-fixed covariates measured at study entry. All regression models also included indicator variables for employment status (classified as actively employed, terminated within the last 2 years or terminated 2 or more years ago, cross-classified by age at termination <62 years and 62+ years), which was a time-varying covariate used to control for the healthy worker survivor effect [Steenland and Stayner, 1991; Arrighi and Hertz-Picciotto, 1994; Steenland et al., 1996]. The primary exposure variable of interest, dose_{ij}, was a time-varying measure of cumulative radiation dose under a 5-, 10-, or 20-year lag. Since some prior analyses have suggested that the effect of ionizing radiation on lung cancer risk may be greater for doses accrued at older adult ages [Richardson and Wing, 1999; Wing and Richardson, 2005; Preston et al., 2007], we also conducted analyses in which the exposure variable of interest, dose_{ij}, was a time-varying measure of cumulative radiation dose accrued at ages 50 years and older.

We classified each person-year of observation according to an outcome variable with 3 levels (0 = event of interest did not occur during the person-period, 1 = lung cancer death occurred, 2 = COPD death occurred). A polytomous logistic regression model for this multilevel outcome variable estimates the log of the probability that outcome category is 1 divided by the probability that the outcome category is 0 and simultaneously estimates the log of the probability that outcome is 2 divided by the probability that the outcome category is 0. Let δ_{11} denote the parameter representing the estimate of the radiation–lung cancer association under this model and δ_{21} denote the parameter representing the estimate of the radiation–COPD association. Under the assumption that the relationship between radiation and COPD is due to differences in smoking between radiation dose groups, the quantity of interest, $\exp(\delta_{11}–\delta_{21})$, provides an estimate of the relative rate of lung cancer that is adjusted for confounding by smoking [Abbott, 1985; Richardson, 2010]. We to refer to this adjustment obtained by joint modeling of lung cancer and COPD mortality as "indirect adjustment" for confounding by smoking, noting the distinction between this phrase and the phrase "indirect standardization" which is often employed in occupational cohort studies that report standardized mortality ratios. The variance for $(\delta_{11}–\delta_{21})$ was derived via the equation $\mathrm{Var}(\delta_{11}–\delta_{21}) = \mathrm{Var}(\delta_{11}) + \mathrm{Var}(\delta_{21}) - 2\mathrm{Cov}(\delta_{11}, \delta_{21})$ and 90% Wald-type confidence intervals were derived as $\exp[(\delta_{11}–\delta) \pm 1.645\ (\mathrm{Var}(\delta_{11}–\delta_{21}))^{(1/2)}]$. The LOGISTIC procedure of the SAS statistical package (version 9.2) was used to fit all regression models [SAS Institute Inc., 2007]. Linear excess relative risk models are often fitted in radiation epidemiology; at low-dose ranges, the linear excess relative risk and exponential risk (i.e., log-linear) model lead to similar quantitative results. Log-linear models were fitted in this analysis due to our interest in assessment of confounding by smoking; the indirect method employed in the current analysis requires the multiplicative assumptions implied by the log-linear model form [Gail et al., 1988].

RESULTS

With follow-up through 2002, 32% of the study cohort was deceased (4,261 workers), 65% of the cohort was alive at the end of follow-up (8,942 workers), and <1% was lost to follow-up (62 workers). Table I reports the distribution of deaths due to lung cancer and COPD

TABLE I. Distribution of Person-Time and Deaths Due to Lung Cancer and COPD by Age, Pay Code, Birth Cohort, and Dose Category Among White Males Employed at the Savannah River Site, South Carolina, 1950–2002

	Person-years	Lung cancer	COPD
Attained age (years)			
<35	108,562	1	0
35–39	58,333	2	0
40–44	58,895	8	0
45–49	54,359	9	0
50–54	48,788	34	3
55–59	43,566	50	10
60–64	38,217	84	16
65–69	31,571	113	21
70–74	20,623	86	47
75–79	9,277	46	26
80–84	3,340	23	16
85+	1,017	7	5
Pay code			
Monthly paid	127,328	75	15
Weekly paid	120,174	92	40
Hourly paid	229,046	296	89
Birth cohort (year of birth)			
<1915	28,226	82	23
1915 to 1919	32,860	60	30
1920 to 1924	68,209	98	37
1925 to 1929	117,831	135	36
1930 to 1934	97,500	74	15
1935+	131,922	14	3
Dose category (mSv)			
0	113,256	47	22
>0 to <5	166,879	144	38
5 to <10	45,750	65	28
10 to <20	39,295	40	13
20 to <40	36,057	44	11
40 to <80	30,320	37	15
80 to <160	25,835	46	8
160 to <320	17,177	35	9
320+	1,979	5	0
Total	476,548	463	144

with respect to categories of dose as well as age, pay code, and birth cohort. In total, 463 lung cancer and 144 COPD deaths were observed. There are substantial differences in lung cancer rates by pay code; age- and cohort-adjusted lung cancer rates were 51% higher among weekly paid workers (RR = 1.51; 90% CI: 1.17–1.95), and 131% higher among hourly paid workers (RR = 2.31; 90% CI: 1.86–2.86), when contrasted with monthly paid workers.

Prior to adjustment for confounding by smoking there was minimal evidence of association between lung cancer mortality and radiation dose under a 5-, 10-, or 20-year exposure lag assumption (Table II). Among monthly paid workers, prior to adjustment for confounding by smoking, the estimated association between lung cancer mortality and radiation dose (under a 10-year lag) was positive (RR at 100 mSv = 1.43; 90% CI: 0.79–2.59). Among hourly and weekly paid workers this association was negative (RR at 100 mSv = 0.95; 90% CI: 0.83–1.09 and RR at 100 mSv = 0.64; 90% CI: 0.46–0.91, respectively).

There was a negative association between radiation dose and COPD (RR at 100 mSv = 0.79; 90% CI: 0.61–1.01). This was primarily due to the association among hourly paid workers (RR at 100 mSv = 0.68; 90% CI: 0.50–0.91) and weekly paid workers (RR at 100 mSv = 0.63; 90% CI: 0.37–1.09). There was little evidence of association between COPD mortality and radiation dose among monthly paid workers (RR at 100 mSv = 1.07; 90% CI: 0.21–5.38).

After indirect adjustment for smoking there was a positive association between cumulative radiation dose and lung cancer mortality under 5-, 10-, and 20-year lag assumptions (Table II). With indirect adjustment for smoking the estimated association was similar for monthly paid workers (RR at 100 mSv = 1.34; 90% CI: 0.11–15.76) and hourly paid workers (RR at 100 mSv = 1.40; 90% CI: 1.03–1.92). The estimate was small and imprecise for weekly paid workers (RR at 100 mSv = 1.02; 90% CI: 0.31–3.39). Relative rates were larger but less precise for doses accrued at ages 50 years and older. The association between lung cancer mortality and radiation doses accrued

TABLE II. Estimated Association Between Cumulative Radiation Dose (Under 5-, 10-, and 20-Year Lag Assumptions) and Lung Cancer Mortality Among White Male Workers at Savannah River Site, South Carolina, 1950–2002

	Unadjusted for confounding by smoking	Adjusted for confounding by smoking
	RR at 100 mSv (90% CI)	RR at 100 mSv (90% CI)
5-Year exposure lag	0.90 (0.80–1.01)	1.32 (1.01–1.73)
10-Year exposure lag	0.90 (0.80–1.01)	1.34 (1.01–1.77)
20-Year exposure lag	0.91 (0.79–1.05)	1.59 (1.13–2.24)

All estimates are adjusted for attained age, pay code, birth cohort, and employment status.

TABLE III. Indirectly Adjusted Relative Risk Estimates for Lung Cancer in SRS Workers Based on Several Modifications of the Analytical Approach

	5-Year lag	10-Year lag	20-Year lag
	RR at 100 mSv (90% CI)	RR at 100 mSv (90% CI)	RR at 100 mSv (90% CI)
Modification in analytical approach			
1. None	1.32 (1.01–1.73)	1.34 (1.01–1.77)	1.59 (1.13–2.24)
2. As in 1, but without adjustment for birth cohort	1.28 (0.98–1.68)	1.30 (0.98–1.71)	1.49 (1.07–2.09)
3. As in 2, but without adjustment for pay code	1.22 (0.95–1.58)	1.23 (0.95–1.61)	1.40 (1.01–1.93)
4. As in 3, but without adjustment for employment status	1.25 (0.97–1.62)	1.26 (0.97–1.64)	1.42 (1.03–1.97)

at ages 50 years and older was positive under 5-year (RR at 100 mSv = 1.61; 90% CI: 0.71–3.69), 10-year (RR at 100 mSv = 1.95; 90% CI: 0.79–4.79), and 20-year (RR at 100 mSv = 3.30; 90% CI: 0.89–12.22) lag assumptions.

To evaluate the need for other covariates following indirect adjustment for smoking, we estimated the radiation–lung cancer relative rate sequentially omitting birth cohort, paycode, and employment status (Table III). Omission of direct adjustment for birth cohort, pay code, and employment status had only a modest effect on the magnitudes of the estimated associations.

DISCUSSION

This study provides evidence of negative confounding of occupational radiation dose–lung cancer mortality associations by smoking. Ideally, in this type of observational study, we would directly control for confounding by smoking by adjusting for smoking history. Unfortunately, we lack individual information on smoking histories in this cohort study of SRS workers; therefore, we have employed an indirect method of adjustment for unmeasured confounding by smoking that draws upon estimates of the association between radiation dose and COPD. Our aim was to reduce residual confounding by smoking of the radiation–lung cancer association.

The results provide evidence of negative confounding by smoking of the radiation dose–lung cancer mortality association in analyses that adjusted for attained age, birth cohort, pay code, and employment status. After indirect adjustment for smoking, the estimated coefficient for the radiation dose–lung cancer association was only modestly impacted by subsequent adjustment for birth cohort, pay code, and employment status (Table III). However, it is important to note that these variables are not simply proxies for smoking; therefore, adjustment for birth cohort, pay code, and employment status may help to reduce confounding in analyses that indirectly adjust for smoking. Failure to directly adjust for pay code effects, for example, led to modest changes in the estimated coefficient for the smoking-adjusted radiation dose–lung cancer association (Table III). It is also worth noting that although indirect adjustment reduces the impact of these covariates on the estimated coefficient for the radiation dose–lung cancer association this does not imply that these parameters are no longer important independent predictors of mortality in the regression analysis.

Smoking is a plausible concern as a confounder of occupational radiation exposure–mortality associations at SRS. We have previously reported substantial differences in lung cancer and non-malignant respiratory disease mortality between monthly, weekly, and hourly paid male workers at SRS [Richardson et al., 2007b]. The standardized mortality ratios for lung cancer were 0.52 (90% CI: 0.43–0.64), 0.75 (90% CI: 0.63–0.89), and 1.12 (90% CI: 1.02–1.22) among monthly, weekly, and hourly paid men. The standardized mortality ratios for non-malignant respiratory disease were 0.39 (90% CI: 0.30–0.50), 0.77 (90% CI: 0.62–0. 93), and 0.83 (90% CI: 0.73–0.94) among monthly, weekly, and hourly paid men. Such observations are consistent with national survey data on occupational status and smoking among US workers [Axelson and Steenland, 1988]. Stratification of radiation dose–lung cancer mortality associations by pay status (or statistical adjustment for pay code) should minimize the potential for confounding by differences in smoking between pay code groups. However, our analyses show that within a pay code group, radiation dose may still be related to smoking, leading to residual confounding.

Steenland et al. [1984] and Axelson [1989] have argued that substantial confounding of occupational exposure–mortality associations by cigarette smoking is unlikely. However, in the current study, we found that cumulative radiation dose was negatively associated with COPD mortality rates, an observation suggestive of lower smoking prevalence among workers with higher cumulative radiation doses. Smoking-related diseases, such as COPD, may result in early termination of employment and occupational exposure accrual. In such settings, smoking may result in biased estimates of occupational exposure–mortality associations by contributing to an overall healthy worker survivor effect. Adjusting for potential confounding by smoking should reduce this bias [Richardson, 2010].

While cigarette smoking is a very strong risk factor for COPD, there are other risk factors for the disease including silica and asbestos (which are also lung carcinogens). Excesses of COPD among workers with lower cumulative radiation doses, therefore, could be indicative of negative confounding of the radiation dose–lung cancer association by factors additional to smoking. Industrial hygiene reports from the early 1970s indicate that occupational asbestos exposure was a problem at SRS, particularly in the Maintenance Department [Du Pont de Nemours and Co. and Savannah River Plant]. If asbestos exposure does confound the radiation–lung cancer mortality association then the approach of joint modeling of COPD and lung cancer may reduce this source of confounding. However, the smoking attributable fraction of COPD cases among US males is in excess of 90%, suggesting that smoking is the most plausible explanation for the association between COPD mortality and radiation even in the SRS cohort, which has evidence of asbestos-related disease [Richardson et al., 2007b]. Furthermore, the same selection factors that would tend to preferentially remove smokers from occupational exposure to radiation would also tend to remove them from exposure to other occupational hazards such as asbestos and silica.

External exposure to ionizing radiation has been associated with lung cancer mortality in studies of other radiation-exposed populations [United Nations Scientific Committee on the Effects of Atomic Radiation, 2006]. In the current analysis, the estimated dose–lung cancer mortality association is positive after adjustment for smoking (RR at 100 mSv = 1.31), but imprecisely estimated (Table II). The magnitude of this estimated association is slightly larger than the estimated association between occupational radiation dose and lung cancer in the IARC 15-country study (RR at 100 mSv = 1.19; 90% CI: not reported), although in the IARC 15-country study no adjustment was made for confounding by smoking.

Although caution is warranted when extrapolating from these findings to other studies of nuclear industry workers, prior work has suggested that similar patterns of negative confounding by smoking of radiation dose–lung cancer associations may arise among UK nuclear workers. McGeoghegan et al. [2008] investigated mortality among Sellafield workers, noting substantial deficits of non-malignant respiratory disease mortality compared to the general population with industrial (blue-collar) workers having 1.9-fold higher non-malignant respiratory disease mortality rates (SMR = 0.72) than non-industrial (white-collar) workers (SMR = 0.38). Within the group of male industrial workers, radiation workers had lower SMRs for non-malignant respiratory disease (0.69) than non-radiation workers (0.78). The pattern was similar, but less pronounced among white-collar workers, where SMRs were very low regardless of radiation exposure status. McGeoghegan et al. [2008] noted that "The somewhat more marked 'healthy worker' effect for respiratory disease, together with the reduced mortality from respiratory disease in radiation workers compared with non-radiation workers, suggests that the restriction placed on smoking in the workplace for radiation workers has been a significant factor in reducing the mortality of the cohort." Subsequently, Muirhead et al. [2009] reported a highly significant negative association was observed between radiation doses and mortality from bronchitis, emphysema, and chronic obstructive disease (ERR/Sv = −1.04; 90% CI: −1.35 to −0.59) in the most recent analysis of the UK National Registry for Radiation Workers (NRRW).

This study reports dose–response analyses overall and with stratification by pay code. One reason for interest in differences in dose–response relationships by pay code is consideration of the possibility that smoking modifies associations between radiation and lung cancer. The RR at 100 mSv was similar for monthly and hourly paid workers (1.34 and 1.40, respectively). These are the SRS pay code groups with the lowest and highest rates of lung cancer and COPD, which correspond to differences in smoking prevalence between white- and blue-collar workers reported in surveys. The similarity of dose–response coefficients for these groups may be an indication a lack of modification of radiation risk by smoking on a multiplicative relative risk scale. In contrast, we found no association between radiation and lung cancer among weekly paid workers (RR at 100 mSv = 1.02; 90% CI: 0.31–3.39); however, the estimated association was highly imprecise for this group.

This study reports dose–response analyses for cumulative dose under 5-, 10-, and 20-year lags, and also reports analyses for radiation doses accrued at ages 50 years and older. We found suggestive evidence that radiation–lung cancer dose–response relationships are greater for doses accrued after age 50. Increased relative risks for lung and some other cancers at older ages of exposure have been reported among older compared to younger adults among A-bomb survivors and several cohorts of nuclear workers [Richardson et al., 2001; Preston et al., 2007]. One possible explanation for this age pattern is that the confounding effects of smoking differ by age. It is therefore noteworthy that a similar pattern is observed among SRS workers in analyses that indirectly adjust for smoking.

The current analysis suggests that cigarette smoking may be an important negative confounder of radiation dose–lung cancer mortality associations in this cohort. We observe positive associations between radiation dose and lung cancer mortality after indirectly adjusting for unmeasured confounding by smoking. While attention is often focused primarily on the possibility of positive confounding by smoking in occupational studies, these findings suggest the importance of giving equal attention to the possibility for negative confounding by smoking of occupational exposure–lung cancer associations.

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