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Healthy Worker Survivor Bias in the Colorado Plateau Uranium Miners Cohort

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Cohort mortality studies of underground miners have been used to estimate the number of lung cancer deaths attributable to radon exposure. However, previous studies of the radon–lung cancer association among underground miners may have been subject to healthy worker survivor bias, a type of time-varying confounding by employment status. We examined radon-mortality associations in a study of 4,124 male uranium miners from the Colorado Plateau who were followed from 1950 through 2005. We estimated the time ratio (relative change in median survival time) per 100 working level months (radon exposure averaging 130,000 mega-electron volts of potential α energy per liter of air, per working month) using G-estimation of structural nested models. After controlling for healthy worker survivor bias, the time ratio for lung cancer per 100 working level months was 1.168 (95% confidence interval: 1.152, 1.174). In an unadjusted model, the estimate was 1.102 (95% confidence interval: 1.099, 1.112)—39% lower. Controlling for this bias, we estimated that among 617 lung cancer deaths, 6,071 person-years of life were lost due to occupational radon exposure during follow-up. Our analysis suggests that healthy worker survivor bias in miner cohort studies can be substantial, warranting reexamination of current estimates of radon's estimated impact on lung cancer mortality.

cohort studies; dose-response; G-estimation; lung neoplasms; mortality; occupational exposure; radon; structural nested model

Abbreviations: SNAFT, structural nested accelerated failure time; TR, time ratio; WLM, working level months.

Radon is a ubiquitous gas that concentrates in indoor air and is a leading cause of lung cancer in the United States. The burden of lung cancer attributable to residential radon exposure is of considerable interest, given the costs of compliance with the current Environmental Protection Agency action level and the public health impacts of the lower action level recommended by the President's Cancer Panel (1–3). Radon exposure is protracted and may have persistent effects, so researchers frequently model radon–lung cancer associations using a cumulative metric of radon exposure. Occupational cohort mortality studies of underground miners have contributed to risk assessment, providing influential estimates of radon–lung cancer associations (3–7). Occupational studies are better suited than residential studies for estimating precise dose-response parameters and exploring time-related aspects of the exposure-outcome association, because variation in long-term exposures is better characterized and occupational exposures often reflect a broader dose range (5). However, occupational studies are subject to unique biases that impact their utility for characterization of dose-response functions.

One of the biases particular to occupational settings is healthy worker survivor bias. This bias results when workers at higher risk for the outcome of interest tend to leave the job at higher rates than workers at lower risk. When the exposure of interest is aggregated over time, this phenomenon can result in higher exposures among healthier individuals (8). Consequently, the disease rates of employed and unemployed persons are generally not comparable, even among those with identical cumulative exposures. Thus, healthy worker survivor bias can be conceptualized as a form of confounding by employment status (9).

Regression methods can be used to control confounding by employment status in some cases, and they are typically used to estimate exposure-response metrics for radon, often stratified by proxies of employment status, such as employment

duration (3, 5, 7, 10, 11). However, regression methods cannot completely control this bias when past exposure affects subsequent employment (Figure 1) (12). To our knowledge, the potential for this bias has not yet been evaluated in miner studies, despite the availability of relevant methodological advances (13, 14). Herein, we apply methods for controlling confounders affected by past exposure to estimate dose-response parameters between radon and lung cancer mortality and all-cause mortality.

METHODS

Study population

The Colorado Plateau uranium miners' cohort includes 4,137 miners who agreed to participate in a health study conducted by the US Public Health Service, completed at least 1 health examination and interview between January 1, 1950, and December 31, 1959, and were currently mining or started mining during follow-up (15).

Follow-up for mortality was assessed through December 31, 2005 (16, 17). Cause-of-death information was obtained directly from death certificates before 1979 and from the National Death Index for deaths occurring thereafter. We defined death from lung cancer using the code for the underlying cause of death indicating malignant neoplasm of the trachea, bronchus, or lung (according to the revision of the *International Classification of Diseases* in use at the time of death).

Monthly radon exposures, measured in working level months (WLM; defined as radon exposure averaging 130,000 mega-electron volts of potential α energy per liter of air, per working month), were derived from raw data files (17). These exposure data were originally derived from a job-exposure matrix using area measurements and extrapolations from nearby mine shafts/mines or regional averages. Estimated radon exposure due to previous work in hard-rock (i.e., non-uranium) mines was also recorded. Three miners who had lifetime cumulative exposures greater than 10,000 WLM were excluded.

Information on individual smoking histories was obtained from surveys conducted in 1985 or from prior surveys (for decedents or nonrespondents). We excluded 10 miners with unknown smoking status. Employment status (active vs. inactive) was assumed to be continuously active employment between the dates of hire and termination.

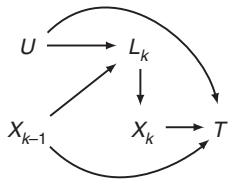

Figure 1. Hypothesized relationships underlying healthy worker survivor bias in the Colorado Plateau uranium miners cohort. Confounding of the association between radon exposure X_k and age at death T occurs through employment status L_k in month k, possibly by an unmeasured predictor of leaving employment and death, U. Stratifying on L_k in a regression model induces bias in the coefficient for prior radon exposure X_{k-1}.

Our analytical data set included a record for every person-month between study enrollment and the earliest of the date of death, the date of loss to follow-up, or December 31, 2005.

Statistical methods

We used an accelerated failure time model to estimate the change in the expected age at death due to an increment of cumulative radon exposure under a linear dose-response assumption. This quantity is expressed as the time ratio (TR) and is reported along with associated 95% confidence intervals for a 100-WLM increase in cumulative radon exposure. With respect to time-varying cumulative exposures, the TR can be interpreted as the relative change in the median remaining survival time after a 1-unit increase in the exposure of interest. For example, if an individual would survive to age 70 years in the absence of exposure but only to age 60 years if exposed at age 20, then the TR for a unit increase in cumulative exposure would be $(70 - 20)/(60 - 20) = 1.25$.

Inference in accelerated failure time models is similar to that in models for hazard ratios or disease rate ratios. Under an exponential survival time distribution, the TR (transformed so that TR > 1 indicates harmful exposure) and the hazard ratio will be identical, though this equivalence does not hold for other distributions (18). Our exposure of interest was the radon exposure that accumulated after study enrollment, and we defined employment history as cumulative time at work after enrollment. We estimated TRs for lung cancer mortality and all-cause mortality.

We estimated TRs using a structural nested accelerated failure time (SNAFT) model fitted by G-estimation (13). Here we provide a basic explanation of use of the SNAFT model in a study in which age at death is known for all individuals. In Web Appendix 1 (available at http://aje.oxfordjournals.org/), we fully describe our approach with the miner data, in which some of the deaths are censored.

We used age as the analytical time scale, and we defined entry into the study as age at first health examination. Some entry examinations were conducted long after hire, because uranium mining in the Colorado plateau began before 1950. This can be problematic because any deaths occurring before 1950 would not have been recorded, leading to study entry criteria that depended on remaining alive and employed. Robins refers to this process as "selection bias by cohort definition" (9, p. 1435), which is not addressed by treating employment status as a time-varying confounder. Following Robins, we considered exposure estimates and employment duration before study entry to be time-fixed covariates. Other approaches are considered below. Cumulative exposure and employment duration were defined as zero at entry. Cumulative radon exposure began accruing only after a 5-year lag from study entry, while employment status was not lagged.

Our SNAFT model was

$$T^0 = m + \int_m^T (1 + \phi \overline{X}_{k-60})\, dk, \qquad (1)$$

where T is observed age at death (in months), m is age at study entry (in years), $\overline{X}_{k-60}$ is cumulative radon exposure with a

60-month (5-year) lag, ϕ is the parameter of interest, and T^0 is the survival time that would be expected under no radon exposure during follow-up. Time is denoted by k. T^0 is an individual-level variable that can be deterministically derived from the model shown in equation 1, a value of ϕ, and the following observed quantities: age at death, cumulative exposure, and age at study entry.

Consistent with much of the prior radon literature, in which the excess relative rate (rate ratio − 1) is modeled on a linear scale (19), the parameter ϕ is defined as the excess relative time (where TR = 1 + ϕ). Our novel approach contrasts with previous uses of SNAFT models, which are typically log-linear (e.g., see Hernán et al. (20)). In contrast with a log-linear model, our model is a linear rather than multiplicative model for the TR. As a technical note, our model places no bounds on ϕ and thus does not exclude negative-value increments of baseline survival time (the integrand term in model 1) in the case of beneficial exposures. Consequently, use of our model is best suited to associations between health outcomes and agents with known deleterious effects, such as radon. As long as ϕ multiplied by the maximum observed exposure is less than 1, this condition will not bias the estimate of ϕ. Thus, studies in which exposures are low (as in residential studies of radon) may not be subject to this caveat even when some studies may be expected to yield estimates below the null by sampling variability.

In SNAFT models, the baseline time, T^0, can be interpreted as a potential outcome representing the time of death we would observe if we intervened to prevent exposure at work (e.g., by mandating the use of 100% efficient respirators). This interpretation allows one to easily calculate the number of years of life lost (among cases) due to occupational radon exposure as $T - T^0$, which we use to supplement the TR as an estimate of the impact of radon exposure (21). We calculated years of life lost due to exposure for all-cause mortality and lung cancer mortality.

We estimated ϕ using G-estimation. G-estimation is an iterative search for the value of ϕ at which T^0 is independent of monthly radon exposure X_k, conditional on covariates. Testing the conditional independence of T^0 and X_k can be done by including the potential outcome, T^0, as an individual-level covariate in a model that predicts monthly exposures (the "exposure model"), conditional on prior covariates. The coefficient for T^0 in the exposure model can be used to test this conditional independence. At the estimate of ϕ, monthly radon exposure within groups of similar individuals should not be associated with T^0. A point estimate and associated 95% confidence interval for ϕ were obtained using a grid search over a range of values for ϕ (20). Grid-search values are given in Web Appendix 1 (Web Figures 1 and 2). Under our model, a TR greater than 1 indicates a harmful exposure.

We modeled exposure using a log-linear model with modifications to account for unexposed individuals. Our exposure model included terms for employment status, previous radon exposure during follow-up, race/ethnicity, year of birth, radon exposure before follow-up, duration of employment (years) before follow-up, and year of hire. Covariate coding for our exposure model is given in Web Table 1, and further technical details regarding our approach to estimating the TR are shown in Web Appendix 1.

Assessing the presence of healthy worker survivor bias

SNAFT models can adjust for time-varying confounding due to current employment status and history of prior employment and exposure, which we hypothesized would control healthy worker survivor bias. Following the methods of previous investigators, we controlled for current employment status by restricting the exposure model to periods of active employment (i.e., $L_k = 1$) (22, 23), and we also adjusted for exposure and employment history $(\overline{X}_k, \overline{L}_k)$ by including terms for the history variables described in Web Table 1, up to and including time k. The exposure model may be restricted to specific time periods (such as employed person-time) without placing the same restriction on the SNAFT model (24). We refer to this model as our "adjusted" SNAFT model.

We also fitted an "unadjusted" SNAFT model that does not adjust for time-varying confounding. The exposure model for the "unadjusted" SNAFT model was used to estimate the expected cumulative exposure (rather than monthly exposures), conditional only on age and the covariates fixed at the beginning of follow-up.

To quantify the magnitude of the healthy worker survivor bias in all models, we calculated the percent difference between "adjusted" and "unadjusted" models as $(\phi_{\text{adjusted}} - \phi_{\text{unadjusted}})/\phi_{\text{adjusted}} \times 100$. A negative value was interpreted as evidence that the radon-mortality association was underestimated due to healthy worker survivor bias.

We also characterized variation in the radon–lung cancer association with time since exposure, similar to previous analyses. Using the model shown in equation 2, we estimated the TR for particular windows of exposure from the model preferred by the Committee on the Biological Effects of Ionizing Radiation (5).

$$T^0 = m + \int_m^T (1 + \phi_1 \overline{X}_{k1} + \phi_2 \overline{X}_{k2} + \phi_3 \overline{X}_{k3})\, dk. \qquad (2)$$

In model 2, we let $\overline{X}_{k1}$, $\overline{X}_{k2}$, and $\overline{X}_{k3}$ correspond to the exposure accrued (since follow-up began) 5–14 years prior, 15–24 years prior, and ≤25 years prior. This approach utilizes the same exposure model as we used in our primary analysis. Note that model 1 is a special case of model 2 when $\phi_1 = \phi_2 = \phi_3$.

Our analytical data set included both prevalent hires (miners who were already employed at study entry) and incident hires (miners who were enrolled in the study at the time they started mining). Because prevalent and incident hires may have differed with respect to health status at the time of entry into follow-up (25), we assessed the impact of including long-term prevalent hires by restricting models to miners who had worked for <20, <10, <5, <2.5, or 0 years before enrollment. In these models, we collapsed the birth cohort variable from 8 time periods to 4 time periods: before 1910 (referent), 1910–1919, 1920–1929, and after 1929.

SNAFT models are one valid approach for cohort analyses of cumulative exposure-mortality associations under certain conditions, namely when prior exposure affects employment status and employment affects subsequent exposure and disease. Following previous reports (23), we assessed whether these conditions hold by fitting 2 standard proportional

Table 1. Demographic and Follow-up Characteristics and Radon Exposures of 4,124 Male Uranium Miners, Colorado Plateau, 1950–2005

Characteristic	Race/Ethnicity[a]					
	White ($n = 3,355$)			Nonwhite ($n = 769$)		
	No.	%	Median (IQR)	No.	%	Median (IQR)
Vital status[b]						
Alive	790	23.5		214	27.8	
Deceased (unknown cause)	51	1.5		20	2.6	
Deceased (known cause)	2,514	74.9		535	69.6	
Deceased (lung cancer)	554	16.5		63	8.1	
Birth cohort						
<1900	171	5.1		20	2.6	
1900–1909	460	13.7		75	9.8	
1910–1919	857	25.2		131	17.0	
1920–1929	890	26.5		278	36.2	
1930–1939	890	26.5		256	33.3	
1940–1949	87	2.6		9	1.2	
Date of hire, year						
Cases[c]			1953 (1950–1956)			1953 (1951–1956)
Noncases			1955 (1952–1957)			1954 (1951–1957)
Total			1954 (1951–1957)			1954 (1951–1957)
Duration of follow-up, years						
Cases			28.0 (18.7–37.4)			31.1 (24.7–40.3)
Noncases			35.9 (19.8–45.6)			39.8 (26.3–48.5)
Total			34.1 (19.5–45.5)			38.6 (26.2–47.1)
Duration of active employment during follow-up, years						
Cases			7.4 (3.6–10.9)			10.8 (7.5–12.5)
Noncases			3.5 (0.8–7.7)			5.6 (1.5–8.9)
Total			4.0 (1.0–8.2)			5.6 (1.5–9.6)
Duration of active employment at study entry, years[d]						
Cases			2.4 (0.79–6.0)			2.5 (1.1–4.0)
Noncases			1.3 (0.30–3.9)			1.2 (0.21–3.0)
Total			1.5 (0.29–4.0)			1.4 (0.29–3.0)
Monthly radon exposure during active work time, WLM						
Cases			4.5 (2.4–9.0)			3.8 (2.5–8.1)
Noncases			3.1 (1.4–6.6)			2.6 (1.1–5.8)
Total			3.4 (1.6–7.2)			2.9 (1.2–6.1)
Cumulative radon exposure during follow-up, 100 WLM[d]						
Cases			4.6 (1.8–9.5)			6.2 (3.3–11.1)
Noncases			1.6 (0.44–4.1)			2.0 (0.6–5.2)
Total uranium mining			1.9 (0.55–4.9)			2.4 (0.65–5.8)
Cumulative radon exposure at study entry, 100 WLM[d]						
Cases			2.7 (0.59–8.6)			1.7 (0.47–6.7)
Noncases			1.0 (0.15–3.9)			0.68 (0.11–2.3)
Total uranium mining			1.2 (0.19–4.6)			0.76 (0.13–2.7)
Hard-rock mining			0.00 (0.00–0.18)			0.00 (0.00–0.00)

Abbreviations: IQR, interquartile range; WLM, working level months.
[a] The total number of person-years was 107,626 for whites and 27,343 for nonwhites.
[b] Vital status as of December 31, 2005.
[c] Cases were defined as persons who died during follow-up with the underlying cause of death listed as lung cancer.
[d] Entry into follow-up was defined as the date of first interview by the US Public Health Service.

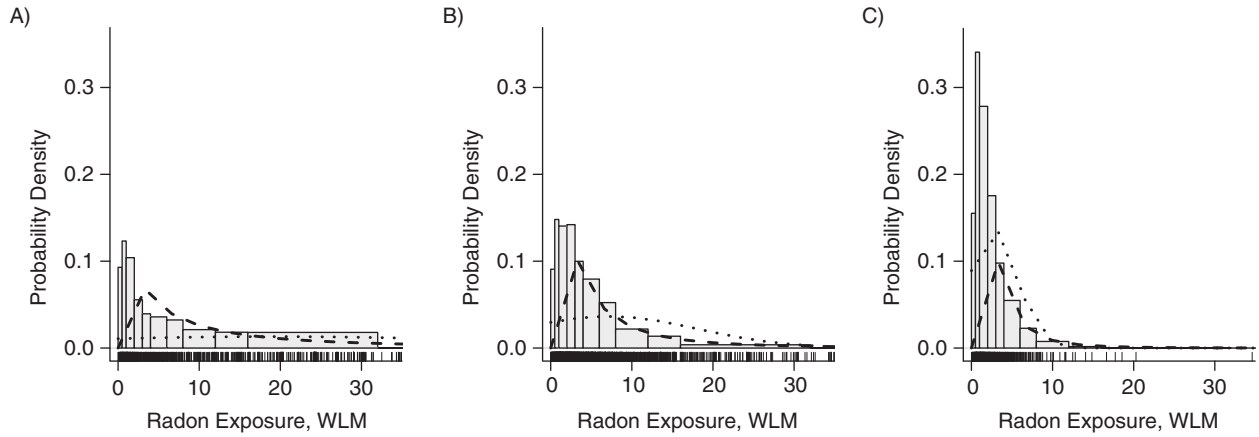

Figure 2. Distributions of monthly radon exposure for white male uranium miners born during 1920–1929, Colorado Plateau, 1950–2005. Months selected represent the 95th (A), 50th (i.e., median) (B), and 5th (C) percentiles of the mean monthly exposure (in working level months (WLM)) incurred from 1950 to 1969, respectively. The graph shows histograms with cutpoints at 0, 1, 2, 3, 4, 6, 8, 12, 16, 32, and ≥32 WLM and normal (dashed lines) and log-normal (dotted lines) curves fitted to the data. Lines below the histograms represent monthly exposures for individual miners. Exposures were truncated at 35 WLM.

hazards models. First, we estimated whether prior exposure affects current employment status by fitting a model adjusted for baseline covariates and employment history. Second, we fitted a model to compare the hazard of death between person-time not employed as a uranium miner and person-time employed as a uranium miner (referent) with adjustment for covariates, including cumulative exposure with a lag of 2 years.

RESULTS

Demographic characteristics and exposure distribution

Our cohort comprised 4,124 white and nonwhite miners with over 130,000 person-years of follow-up (Table 1). No cause of death could be determined for 22 miners, and 14 were lost to follow-up before 1979. A majority of the miners died before December 31, 2005, and a higher proportion of whites than of nonwhites died of lung cancer (a difference previously attributed to differences in smoking patterns) (26). Nonwhite miners were followed up for a longer period of time and worked longer during follow-up than white miners, despite similar employment time before follow-up. In both racial/ethnic groups, employment duration (as well as duration of radon exposure), median monthly exposure (in WLM) among employed person-months, and cumulative exposure (in 100 WLM) at baseline and during follow-up were higher in persons who eventually died of lung cancer than in noncases. Median cumulative exposure was higher during follow-up than prior to first interview. Monthly exposure distributions were highly right-skewed and varied with calendar period (Figure 2).

Dose-response analyses

Using a model for all-cause mortality under a 5-year cumulative radon exposure lag, the adjusted TR was higher than the unadjusted TR by 74% (Table 2). Based on our adjusted model, we estimate that among 3,120 miners who died during follow-up, occupational radon exposure after enrollment was associated with 10,118 person-years of life lost due to premature death (not shown).

For lung cancer mortality, the adjusted TR was higher than the unadjusted TR by 39% (Table 2). Based on our adjusted model, we estimate that among 617 lung cancer cases, exposure accounted for 6,071 person-years of life lost (not shown). The adjusted TR for lung cancer decreased with time since exposure (Table 3).

After exclusion of people who had long durations of employment prior to entering the cohort, the adjusted TR decreased relative to the TR in the full cohort (Table 4).

Table 2. Time Ratio for the Radon-Mortality Association, Lagged 5 Years, Among 4,124 Male Uranium Miners, Colorado Plateau, 1950–2005

Model	Time Ratio, per 100 WLM[a]	95% CI	Difference, %[b]
Lung cancer mortality			
Adjusted[c]	1.168	1.152, 1.174	0[d]
Unadjusted	1.102	1.099, 1.112	−39
All-cause mortality			
Adjusted[c]	1.054	1.041, 1.068	0[d]
Unadjusted	1.014	1.013, 1.015	−74

Abbreviations: CI, confidence interval; WLM, working level months.

[a] Adjusted for time-fixed covariates: exposure from uranium mining before enrollment, exposure from hard-rock mining before enrollment, race/ethnicity, birth cohort, and date of hire.

[b] Percent difference in ϕ from adjusted model (defined in text).

[c] Also adjusted for time-varying covariates: annual exposure during follow-up (from 1, 2, 3, 4, and 5 years prior), cumulative exposure (from 6–9 years prior and ≥10 years prior), current employment status, and cumulative time at work during follow-up.

[d] Referent.

Table 3. Time Ratio for the Radon–Lung Cancer Mortality Association According to Window of Radon Exposure Among 4,124 Male Uranium Miners, Colorado Plateau, 1950–2005

Exposure Window, years[a]	Time Ratio, per 100 WLM[b]	95% CI
5–14	1.188	1.116, 1.230
15–24	1.128	1.050, 1.294
≥25	1.022	0.950, 1.198

Abbreviations: CI, confidence interval; WLM, working level months.
[a] Exposure accrued within the noted period following study enrollment.
[b] Adjusted for radon exposure from uranium mining before enrollment, exposure from hard-rock mining before enrollment, race/ethnicity, birth cohort, date of hire, annual exposure during follow-up (from 1, 2, 3, 4, and 5 years prior), cumulative exposure (from 6–9 years prior and ≥10 years prior), current employment status, and cumulative time at work during follow-up.

The hazard for terminating employment was lower in workers with cumulative radon exposure above the median value (1.2 × 100 WLM) than in those with cumulative exposure less than the median (referent) (hazard ratio = 0.90, 95% confidence interval: 0.84, 0.98; not shown). The direction of this association agrees with previous analyses of occupational cohorts using similar or identical statistical models (9, 23, 27). The adjusted hazard of death was higher among person-time not employed as a uranium miner than among person-time employed as a uranium miner (hazard ratio = 3.3, 95% confidence interval: 2.4, 4.3). Thus, regression models adjusting for employment history would be biased, and SNAFT models are needed to appropriately adjust for time-varying confounding by employment status.

Table 4. Sensitivity Analysis of the Impact of Including Prevalent Hires in the Study Cohort (4,124 Male Uranium Miners) on the Adjusted Time Ratio for the Radon–Lung Cancer Mortality Association, Colorado Plateau, 1950–2005

Maximum Duration of Employment Prior to Study Enrollment, years[a]	Time Ratio, per 100 WLM[b]	95% CI
Full cohort[c]	1.095	1.087, 1.117
20	1.092	1.087, 1.112
10	1.094	1.085, 1.114
5	1.086	1.075, 1.089
2.5	1.082	1.074, 1.088
Incident hires only	1.070	1.063, 1.076

Abbreviations: CI, confidence interval; WLM, working level months.
[a] In each row, workers were excluded if they had worked longer than the specified number of years before study enrollment.
[b] Adjusted for baseline exposure from uranium mining, race/ethnicity, prior hard-rock mining exposure, birth cohort, date of hire, annual exposure during follow-up (from 1, 2, 3, 4, and 5 years prior) cumulative exposure (from 6–9 years prior and ≥10 years prior), active employment status, and cumulative time at work during follow-up.
[c] Birth cohort was represented by 4 groups (before 1910 (referent), 1910–1919, 1920–1929, and after 1929), resulting in different time ratios between the analysis with no exclusions and the results from Table 3 (where birth cohort was represented by 8 groups).

DISCUSSION

Healthy worker survivor bias can occur in occupational studies when exposure accrues over time and workers with stronger health (and therefore better cancer prognosis) remain employed longer. The estimates of the TR were lower in unadjusted models than in the models adjusted for healthy worker survivor bias for both lung cancer mortality (39%) and all-cause mortality (74%). These findings support previous speculation on the possibility of substantial survivor bias in the Colorado Plateau uranium miner data set (28). We observed that prior radon exposure was associated with leaving employment, which multivariable regression models cannot address. SNAFT models can adequately control healthy worker survivor bias in this scenario because the models achieve confounder control without stratification (13). We show that this bias leads to underestimation of the slopes of the dose-response relationships between radon and both lung cancer mortality and all-cause mortality, which underlie projections of population excess mortality due to radon exposure.

Previous analyses of miner data may be subject to uncontrolled or improperly controlled healthy worker survivor bias. For example, in its most recent report, the Committee on the Biological Effects of Ionizing Radiation based risk estimates on the so-called "exposure-age-duration" and "exposure-age-concentration" Poisson regression models. These models estimate the relative rate per 100 WLM of radon exposure, stratified on age at exposure, attained age, and duration (or concentration) of exposure. Exposure duration is a strong proxy for employment history. Under our hypothesis, risk parameters from both the "exposure-age-concentration" model and the "exposure-age-duration" model may be biased downward. Our findings suggest a stronger healthy worker survivor bias among all causes of death, perhaps because of the inclusion of causes of death in which healthy worker survivor bias is stronger.

Our estimate of the TR and hazard ratios/rate ratios from previous analyses of this cohort are not directly comparable because mortality rates are not constant over time. Accordingly, we compared adjusted and unadjusted models to assess the magnitude of bias. Other investigators have assessed this bias by transforming the TR from SNAFT models to a hazard ratio to compare it with results from proportional hazards regression models (22) or parametric accelerated failure time models (29). Our novel approach allows a straightforward comparison of 2 SNAFT models. However, our approach may be more sensitive to misspecification of exposure models, which are needed for G-estimation. Previous examples have used simpler exposure models than our own, by fitting models for binary exposures (20, 22, 30–35) or exposure quantiles (29). In contrast, we report results from SNAFT models under a parametric model for the unbinned exposure (36). In Web Appendix 2, we also fitted SNAFT models under alternative exposure models and noted that results were somewhat sensitive to the choice of model (Web Table 2), though findings were robust to specification of the SNAFT model (Web Table 3). We also compared a log-linear SNAFT model to a baseline adjusted parametric accelerated failure

time model, which yielded a similar magnitude for healthy worker survivor bias as our approach (Web Appendix 3, Web Table 4). SNAFT results had narrower confidence intervals than the parametric model, reflecting different parametric assumptions made by the 2 approaches. These results and a set of simulations outlined in Web Appendix 4 suggested that our approach provides a valid estimate of bias from time-varying confounding (Web Table 5).

An innovation of this study was our use of SNAFT models to explore variation in the TR by exposure windows. Such models have been previously proposed in principle (e.g., see model 23.10 in the paper by Robins and Hernán (37)) but have not been used in analysis. The TR for each window of exposure can be interpreted as a direct effect of exposure within that time period, not mediated by subsequent exposure (38).

Our analysis was concerned mainly with reducing healthy worker survivor bias, which we conceptualized as a specific instance of time-varying confounding. We also addressed other sources of variation in the TR in occupational studies, such as left-truncation (39). Within our data, miners hired before study inception in 1950 may have been systematically different from the miners who were hired after the study began. As one way to address these possible differences, we adjusted for preenrollment exposure and employment history as time-fixed covariates and used them only for control of confounding. Additionally, we did not consider individuals to have been at risk during preenrollment person-time, which should be considered immortal person-time (40). To illustrate the potential bias, we repeated our SNAFT analysis with lung cancer but included immortal person-time and preenrollment exposure in the cumulative exposure metric. This change resulted in a 34% decrease in the value of ϕ for the adjusted model (not shown).

Another way to address concerns about including data from the period before study enrollment is to consider differences between "prevalent" and "incident" hires (39). As shown in Table 4, the apparent magnitude of the radon–lung cancer exposure-response decreases after exclusion of workers with long periods of employment before follow-up. This result runs counter to expectation under the assumption that susceptible individuals will be underrepresented in the full cohort. The result may reflect exposure measurement quality changes over time or modification by exposure concentration. We also observed stronger apparent healthy worker survivor bias among prevalent hires (not shown). Both observations may be partly explained by the longer duration of employment during follow-up among prevalent hires (median, 4.5 years; not shown) than among incident hires (median, 3.8 years). Incident hires comprised only 10% of the workforce ($n = 389$; 34 lung cancer deaths; not shown), so inference regarding biases in this group is subject to greater uncertainty.

Confidence intervals were narrower in analyses excluding miners with 5 or more years of employment before enrollment than in analyses with fewer excluded miners (Table 3). This observation may be due to a reduction in the variation of other risk factors for lung cancer that vary by year of hire, such as smoking. In the miner data, we observed that never smokers were more prevalent among miners hired after 1955 (27%) than among miners hired before 1940 (14%) or those hired between 1940 and 1955 (22%; not shown). We did not have access to dates of initiation or cessation of smoking (17) and could not evaluate the role of smoking as a time-varying confounder. Previous analyses have suggested that smoking may modify the radon–lung cancer association (41) but is not a source of strong time-fixed (17, 42) or time-varying (43) confounding. In our context, smoking may affect both employment status and the outcomes under study (44). SNAFT models can adequately control this bias through adjustment for employment history, if we assume that smoking is not associated with exposure, independent of employment history and the baseline covariates. This assumption may be violated if persons who start smoking are preferentially placed in less exposed (or more highly exposed) jobs within the mine. This phenomenon would probably appear as apparent time-fixed confounding by smoking, as well, which suggests that any residual confounding by smoking is small.

We have mainly addressed issues of confounding by time-varying factors in this analysis. However, the effects of cumulative exposure to radon may be heterogeneous over other time-varying covariates, such as exposure concentration or time since exposure (43, 45). As we have shown, SNAFT models are well suited to addressing questions regarding time-varying covariates. Unfortunately, our algorithm for a SNAFT model with which to quantify modification of the TR by exposure concentration did not converge, so we were unable to assess the TR over levels of exposure concentration (not shown). Recent analyses have suggested that apparent modification by exposure concentration may be partially due to changes in exposure measurement quality over time (46), which we address in Web Appendix 2. Allowing for modification of the TR would be essential for comparing hypothetical interventions (37), such as more stringent occupational exposure limits (47). This problem echoes previous difficulties with addressing modification in SNAFT models raised by Joffe et al. (48) and may be a shortcoming of the use of SNAFT models in practice. However, results from our models using time windows of exposure agreed qualitatively with those of previous analyses (49, 50), suggesting that SNAFT models may be useful for estimating more complex dose-time-response relationships in epidemiologic data.

While we addressed 1 kind of bias, any study using miner data is subject to other biases from 1) exposure measurement error that reduces the ability to control confounding (51) and biases the dose response (52); 2) coexposure to other lung carcinogens such as arsenic (53), diesel exhaust (54), or silica (54); and 3) reliance on death certificate data. The relative impact of these issues for SNAFT models (as compared with regression) is unknown. Further refinement of analyses to include possible dose-response modification by exposure concentration, possibly using pooled data, may better inform risk projection. We show evidence of healthy worker survivor bias in a cohort that plays a key role in risk projection models, and improved handling of employment history as a confounder is a necessary step in reducing this bias.

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