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The effect of censoring on cancer risk estimates based on the Canadian National Dose Registry of occupational radiation exposure

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Cohort studies represent an important epidemiological tool for exploring the potential adverse health effects of low-dose exposure to ionizing radiation in the workplace. Analyses of data from the National Dose Registry of Canada have suggested that occupational radiation exposure leads to increased risk of several specific types of cancer, as well as increased overall risk of cancer. An important aspect of such studies is the censoring in recorded exposures induced by dosimetry detection limits. Such a censoring effect can lead to significant underestimation of cumulative doses which, in turn, can result in overestimation of the excess cancer risk associated with occupational radiation exposure. In this article, we present analytic results, supported by a simulation study, on the magnitude of overestimation of risk based on the additive relative risk model used in the analysis of the NDR data that can occur due to censoring. Our results indicate that overestimation of risk is modest, being less than 20% in all situations considered here. Because censoring also results in ovestimation of the precision of the risk estimates, the significance levels of Wald-type statistical tests for increased risk based on the ratio of the estimate to its standard error are virtually unaffected by censoring. These results suggest that although the application of the additive excess relative risk model in the presence of censoring may lead to some overestimation of risk, the model does not lead to invalid conclusions regarding the association between occupational radiation exposure and cancer risk based on data from the NDR.
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Introduction

Cohort studies represent an important epidemiological tool for estimating mortality rates associated with occupational and environmental exposures (Krewski et al., 2003b). For example, Pope et al. (1995) used the American Cancer Society's (ACS) Cancer Prevention Survey, a large cohort involving 1.2 million subjects in the United States followed since its inception in 1982, to link particulate air pollution less than 2.5 μm in aerodynamic diameter ($PM_{2.5}$) to mortality.

Cohort mortality studies are subject to a number of sources of error. In the ACS cohort, the exposure of all individuals in the same city was approximated by the average $PM_{2.5}$ concentration measured at one or more fixed site ambient monitors located with the urban area (Krewski et al., 2003a, leading to exposure misclassification (Armstrong et al., 1992). Using data from a similar study conducted by (Dockery et al., 1993; Mallick et al., 2002) showed that adjusting for this type of exposure measurement error using regression calibration resulted in a notable increase in the mortality rates associated with particulate air pollution. Errors can also occur when vital status is determined by computerized record linkage (CRL) with mortality records maintained in national databases (Krewski et al., 2001). Morrison et al. (1997) used CRL to determine vital status of Canadian farm operators in a large-scale cohort mortality study focusing on the use of agricultural chemicals. Linkage error rates (false links and false nonlinks) were estimated to be in the range of 5–10% in this study.

Ashmore et al. (1998) and Sont et al. (2001) used data from the National Dose Registry (NDR) of Canada to estimate mortality and cancer incidence associated with occupational exposure to ionizing radiation. The NDR is a large cohort containing dose records for over 600,000 workers dating back to 1950 (Ashmore et al., 1997). Vital status and cancer incidence were determined by linking the NDR to the Canadian Mortality Database and the Canadian Cancer Incidence Database, respectively. Occupational exposures are monitored using radiation dosimeters worn by workers, and read at intervals ranging from 2 weeks to 3 months. Cumulative exposure at a given time is determined by adding all prior exposure measurements.

An important source of exposure measurement error in the NDR is the occurrence of a large number of readings below

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the detection limit of the radiation dosimeters: nearly half of the dosimeter readings fall in this category, leading to left censoring of radiation exposure measurements (Ashmore et al., 1998). Exposure measurement error of this type is augmented as periodic radiation exposure measurements are summed to obtain cumulative exposure measurements for individuals in the NDR. Censoring of radiation exposure data also occurs in other studies of this type, including a pooled study of radiation workers in Canada, the United States, and the United Kingdom (Cardis et al., 1995).

Individual dosimeter measurements are also subject to a number of other sources of error, both random and systematic. In particular, the dosimeter measurement itself is a proxy for the internal exposure of relevant organs to ionizing radiation. A comprehensive discussion of bias and uncertainty associated with using personal dosimeters to estimate cumulative exposure to radiation can be found in Gilbert et al. (1996).

Although statistical methods for addressing censoring of radiation exposure data have been proposed by Gilbert et al. (1996), Mitchell et al. (1997) and Xue and Shore (2003), a formal analysis of the effects of censoring in large-scale studies of occupational radiation carcinogenesis has not been reported to date. The purpose of this paper is to investigate the effect of censoring of occupational radiation exposure measurements on cancer risk estimates derived from the NDR of Canada. Specifically, computer simulation is used to determine the bias and imprecision in excess relative risk of mortality due to censoring. In order to make our simulation study as realistic as possible, data from the NDR are used to guide the design of our simulation experiments.

The statistical model used to estimate the excess relative risk, the NDR data set, and the simulation study protocol are outlined in the next section. Results and conclusions are given in the subsequent sections, respectively. A rigorous proof that, asymptotically, the Wald t-statistic used to test the significance of the radiation effect in the additive excess relative risk (ERR) model is not affected by censoring is given in Appendix A.

Methods

The ERR Model

The additive ERR model (Breslow and Day, 1994) postulates that exposure to a given risk factor increases the risk of an adverse health outcome by a linear additive factor β. In this paper, the risk factor of primary interest is radiation exposure and the adverse health outcome of concern is lung cancer. Covariates such as age, calendar year, and gender are controlled for by fitting the model separately in different cells defined by specific values of these covariates. For purposes of illustration, we will assume that the model is being applied to a population of males exposed to radiation in the workplace, and consider cells defined by 5-year age intervals and 5-year calendar periods.

Let Y_i be the cancer incidence of the ith cell. Let t_i and $\bar{D}_i$ denote the total number of person-years and mean cumulative exposure in the ith cell, respectively. Thus, if the ith cell is defined to include all subjects aged from 30 to 35 years during the period 1970 to 1975, t_i counts the number of person-years spent in that cell by subjects in the data set, and $\bar{D}_i$ is the average cumulative exposure experienced by those people at the time of leaving that cell. If the risk of an unexposed individual in that cell developing lung cancer during the course of a year is λ_i, then the ERR model postulates that the number of lung cancer cases observed in the ith cell, Y_i, is Poisson distributed with expected value

$$E(Y_i) = t_i\lambda_i(1 + \beta\bar{D}_i). \quad (1)$$

The parameter β, referred to as the ERR due to radiation exposure, measures the effect of one unit of radiation on the relative risk of lung cancer. If $\beta = 0$, there is no exposure effect on cancer risk; if $\beta > 0$, radiation exposure increases the risk of lung cancer.

Censoring and the NDR Data

The NDR of Canada contains occupational radiation exposure records for a cohort of over 600,000 Canadian workers dating back to 1951. Through linkage with the Canadian Cancer Incidence Database and the Canadian Mortality Database, vital status, cause of death (for deceased individuals) and cancer incidence data are also available for most of the cohort. Only annual cumulative doses for each individual are recorded in the NDR, although these were originally obtained by summing individual dosimetry measurements taken several times annually.

Sont et al. (2001) investigated the relationship between cancer incidence and occupational radiation exposures based on the cohort of the NDR. They used a subset of 191,333 subjects with nearly equal numbers of males and females from various jobs, which were classified into four broad occupational groups: dental workers (42,194 subjects, representing 22% of the cohort), medical workers (67,650 subjects, 35%), industrial workers (59,544 subjects, 31%), and nuclear power workers (21,945 subjects, 12%). The nuclear power group, of which 89% is male, showed both the highest overall rate of cancer (2.6%) and the largest average cumulative exposure (39.98 mSv). Lung cancer was the most common type of cancer in both males and females.

There has been discussion in the literature (Xue and Shore, 2003) about the lower limit of detection of dosimeters, specifically film badge dosimeters. The detection limit, together with other sources of exposure measurement error, represent sources of uncertainty in the recorded annual doses. Typically, the recorded dose is obtained by rounding the observed dose to the nearest detectable scale, and doses below the detection limit are recorded as zero. Detection limits of 0.20, 0.30, and from 0.05 to 0.5 mSv have been reported in Canada (Sont et al., 2001), the US (Mitchell

et al., 1997), and the UK (Inskip et al., 1987), respectively; all exposures below these limits are censored. Although censoring may confer an appreciable error in a single measurement of dose, it can result in important downward biases in cumulative dose measurements. As an extreme example, consider a male nuclear power worker who has worked for ten years and whose film badge was evaluated bi-weekly. If every bi-weekly dose was exactly 0.19 mSv, but was reported as zero, the reported cumulative dose would be zero, rather than 45 mSv.

In general, this type of censoring of occupational radiation exposure measurements is expected to lead to overestimation of risk. To explore the degree of overestimation, we conducted a simulation study in which both actual doses and reported doses are known, so that the effect of censoring can be evaluated. Techniques proposed by Inskip et al. (1987), Gilbert et al. (1996), Mitchell et al. (1997), and Xue and Shore (2003) for correcting censored measurements depend on knowledge about individual recorded doses. Since only annual cumulative doses are available for subjects in the NDR, such methods cannot be applied in our case.

Simulation Strategy

Our strategy for empirically exploring the effect of censoring in the NDR data was to simulate a population of 96,000 males with known exposure measurements (not subject to censoring) and with lung cancer incidence generated by the ERR model with known ERR. By repeatedly simulating data from this population and fitting the ERR model to the censored data (obtained by setting any exposure measurements below the detection limit) and the uncensored data separately, it is possible to determine the effect of censoring on the estimated ERR. To explore the impact of our simulation assumptions on the censoring effect, we varied three factors in the model and data: the ERR coefficient, the dose-lag factor (the lag time between exposure and effect), and the frequency of measurement. The choice of values for these factors was motivated by the data for males in the study conducted by Sont et al. (2001) based on the NDR.

Table 1 summarizes the lifetime cumulative doses observed in the four occupational groups among the male subjects analyzed by Sont et al., and compares these doses to those observed in our synthetic population. The synthetic population summarized in Table 1 was generated with an ERR of 0.31%, a dose-lag of 10 years, and monthly radiation exposure measurements. Although our simulation was not designed to mimic the NDR population precisely, we were guided by a number of observed characteristics of the NDR data set. Consequently, the average censored lifetime doses in the simulated population are similar to those in the NDR.

In the NDR study, the minimum detectable dose was 0.2 mSv and the estimated ERR for lung cancer in males was 0.31% per mSv. To determine whether the censoring effect is more or less pronounced for smaller (and therefore more difficult to detect) risks, we ran simulations with the observed value for the ERR, as well as simulations with both substantially larger (3.1%) and substantially smaller (0.031%) risks. Following Sont et al. (2001), exposure data were lagged by 10 years. To see whether the censoring effect depends on the dose-lag factor, we also conducted simulations with larger (15 years) and smaller (5 years) lag times.

In the early years of the NDR, nuclear power workers had their dosimeters read and recorded every 2 weeks. Later, the recording frequency was reduced to monthly. Canadian dental workers, on the other hand, have always been subject to quarterly monitoring. Industrial worker exposures are typically measured monthly. To see how measurement frequency affected censoring-induced bias, we chose to measure workers from each group with the same frequency. However, we conducted simulations with biweekly, monthly, and quarterly measurements. Since more frequent measurement must inevitably result in smaller individual measurements, it is to be expected that greater measurement frequency would result in greater overestimation of cancer-induced risk.

Simulation Algorithm

Our baseline study, summarized in the first row of Table 2, used the NDR ERR of 0.31%/mSv,. with monthly measurements and doses lagged by 10 years. Using these parameters, we simulated 100 populations of 96,000 males each. In addition, we simulated 100 populations for each of six other combinations of the parameters. We varied each parameter individually, using the baseline values for the other

Table 1. Comparision of mean lifetime doses (in mSv) in the NDR and the synthetic data for the first simulation in Table 2.

Category	*N*	Cases	Person-years	NDR	Simulated	
					Censored	Uncensored
Dental	8400	41	99,740	0.65	0.63	2.69
Medical	23,500	114	279,621	5.30	3.66	5.95
Industrial	44,500	189	525,670	6.19	5.85	8.26
Nuclear	19,600	97	232,633	36.54	48.19	49.90

Table 2. Percent change (with 95% confidence interval) in cancer risk assessment induced by censoring.

	Simulation factors			Censoring effect	
	ERR (%)	Lag (years)	Dosimeter frequency	Change in risk estimate (%)	Change in *t*-statistic (%)
	0.31	10	Monthly	16 ± 1.3	0.87 ± 1.6
	3.10	10	Monthly	17 ± 0.1	0.02 ± 0.02
	0.03	10	Monthly	17 ± 1.0	−0.06 ± 0.9
	0.31	5	Monthly	16 ± 1.0	0.90 ± 1.3
	0.31	15	Monthly	16 ± 1.1	0.40 ± 1.0
	0.31	10	Quarterly	6 ± 0.2	0.04 ± 0.2
	0.31	10	Bimonthly	20 ± 2.4	−1.60 ± 7.9
Sensitivity analysis	0.31	10	Monthly	18 ± 0.0	−1.0 ± 1.2

Each row summarizes 100 synthetic populations. For each dataset, the ERR model was fit before and after censoring all doses below the minimum detectible limit of 0.2 mSv.

parameters as the point of reference. Our procedure for generating a simulated male population for the NDR involved six steps.

(1) *Date of first exposure* In the first step, we independently generated 96,000 years of entry into the study using the empirical distribution derived from the actual NDR data. The NDR data span the 38-year period from the beginning of 1951 until the end of 1988. Once the calendar year of entry was established, the precise date of entry was randomly chosen within that year according to a uniform distrubution. This step resulted in 96,000 simulated subjects, each with a date of entry chosen so that the distribution matched the empirical distribution in the NDR.

(2) *Age* In the second step, an (integer) age at first exposure was generated for each individual. The age was chosen from the empirical distribution of age at entry, conditional on year of entry. Once the age at first exposure was established, each individual was assigned a date of birth. Note that even though an individual entering the study in 1951 may well have experienced some unrecorded occupational exposure before the beginning of the study, it was assumed that there was no exposure prior to entry into the study.

(3) *Length of exposure* In the third step, each subject was assigned a period of exposure. This exposure period was uniformly distributed on the interval from zero to the maximum logically admissible exposure, determined by the conditions that there could be no exposure after the end of 1988 and that no individual was exposed after the age of 65. The period of exposure represents the length of time from entry into the study to the point at which the individual was no longer working in a NDR-monitored occupation. We assumed that all individuals were subject to occupational radiation exposure throughout this period.

(4) *Death and cancer incidence* Each subject was assigned a time of death and a time of cancer diagnosis, based on historical Canadian mortality and lung cancer incidence rates. The historical rates were obtained from Statistics Canada for 5-year time periods (1950–1955, 1956–1960,…,1986–1990), stratified by 5-year age groups. The precise times of death and cancer incidence were determined using the respective hazard functions defined by a subject's date-of-birth, the subject's lagged cumulative exposure, and the historical mortality and cancer incidence rates. If a subject either died or developed lung cancer before the end of 1988, that subject was considered to have left the study at the time of death or cancer occurrence.

(5) *True doses* In the final step, radiation exposure measurements were generated to span each subject's total period of exposure. For example, if dosimeter measurements were taken monthly, a subject with 9.5 years of exposure would receive 114 exposure measurements. Based on the observation that about 40% of the people in the actual NDR data set had measured lifetime exposures of zero, it was assumed that some proportion of individuals were never exposed to any radiation during their working career. Thus, the simulated individuals were allocated to one of two groups: the nonexposed group or the exposed group. For people in the nonexposed group, all exposures were set to zero; for those in the exposed group, the monthly exposures were independently and identically sampled from a truncated lognormal distribution. The truncated lognormal distribution was defined by the mean, standard deviation, and the assumption that no monthly exposure could exceed 10 mSv.

We note here that the monthly dose distribution described above is a slight modification of the distribution used in the study of dose censoring among the ORNL workers study of dose censoring, in which no subjects received zero doses (Mitchell et al., 1997). Our assumption that some subjects received zero doses is based on our belief that, even in the nuclear power sector, many jobs do not involve radiation exposure. For example, administrative staff would not normally be exposed to radiation at work.

(6) *Measured doses* Measurement error was added to each exposure value based on the measurement error distribution used in a study of workers in the Oak Ridge Nuclear

Laboratories conducted by Mitchell et al. (1997). The measurement error was defined as follows. Suppose that x is the true exposure and that $\tilde{x}$ is the measured exposure. Then $\log(\tilde{x})$ is modeled as a lognormal variable with mean equal to $\log(x)$ and standard deviation depending on x through the following relationship (in mSv – based on empirical results from Morgan, 1961):

$$\mathrm{SE}[\log(\tilde{x})] = \begin{cases} -0.088 - 0.265\log(x) & 0 < x \leq 0.30 \\ 0.047 - 0.153\log(x) & 0.30 < x \leq 1.0 \\ 0.047 - 0.006\log(x) & 1.0 < x \leq 10.0 \end{cases}$$

Rounding error was also imposed on these values, with each measurement rounded to two decimal places. Finally, a censored data set was created by setting each measured dose of less than 0.2 mSv equal to zero.

The end result of this procedure was the creation of two data sets: one containing the 'true' uncensored data, and the other containing the censored data. Comparisons between these two data sets then provide a basis for evaluation of the effect of censoring on estimates of risk, as well as the precision of these estimates.

Sensitivity Analysis

An important assumption in our simulation study is that the dose distribution did not change over the study period. In fact, it is known that the dose distribution within the NDR has changed over this period. Owing to more stringent safety measures introduced in the 1960s, exposures tended to be lower in the latter part of the study. Figure 1, showing the annual average dose of the four job categories in the NDR, illustrates this phenomenon.

To see whether or not the assumption of a constant dose distribution within each occupational group was leading us to a false conclusion, we conducted a sensitivity analysis in which the dose distributions were modified to have the same expected value as was empirically observed by year and occupational group in the NDR. We set the ERR to be 0.31% for this analysis, chose a dose-lag of 10 years, and simulated monthly dosimeter measurements. (A sensitivity analysis of this type was not needed to support the asymptotic results on the accuracy of the Wald t-statistic presented in Appendix A, since these results are independent of the dose distribution within the occupational groups.)

Results

The results of our simulation study are summarized in Table 2. Each row summarizes the results from 100 independent simulated populations of 96,000 males. The first three columns show the values of the ERR, dose-lag, and measurement frequency used to construct the synthetic populations. The final two columns summarize the effect of

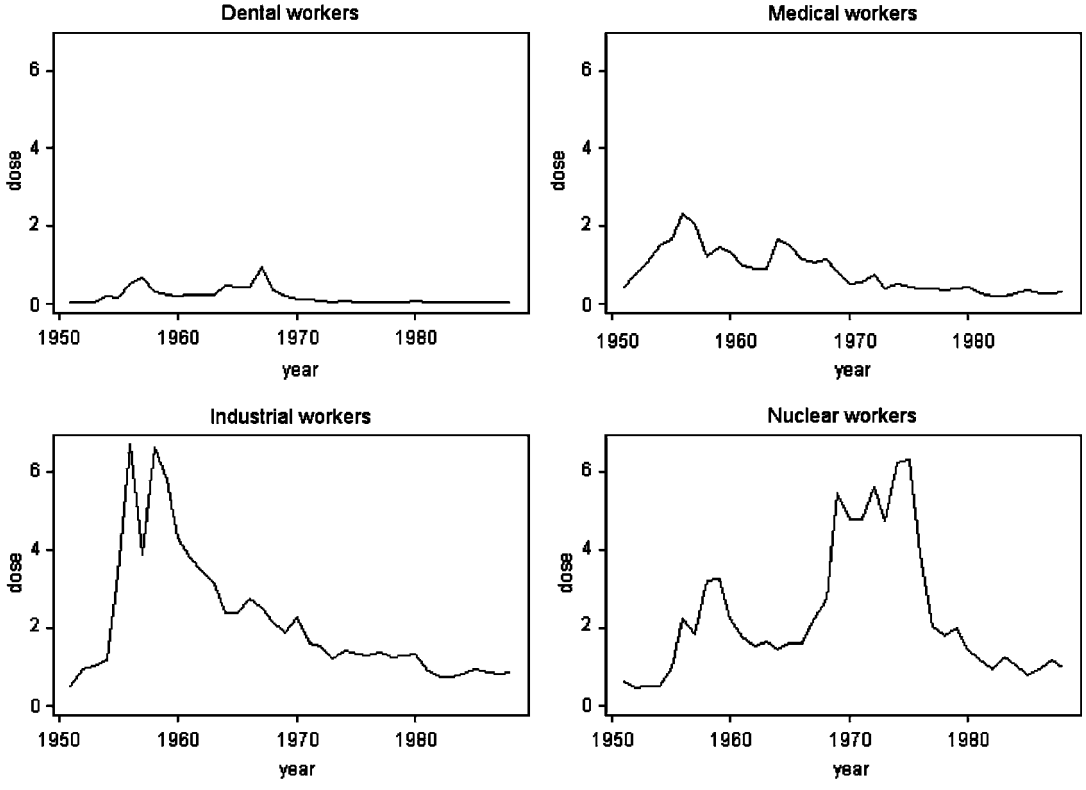

Figure 1. Mean observed monthly dose by year and occupational group.

censoring on the estimated ERR and on the *t*-statistic for testing the significance of the estimated relative risk. The numbers in the last two columns represent estimates, with 95% confidence intervals, of the increase in estimated ERR and the increase in the *t*-statistics induced by censoring. For example, the first row shows the results for the baseline model, with an ERR of 0.31%, a lag of 10 years, and monthly measurements. On average, censoring leads to an increase of 16% in the estimated risk, but only increases the *t*-statistic by about 1%. The confidence intervals for the estimated censoring effects are quite narrow and none contains zero. On the other hand, all of the confidence intervals for the increase in the *t*-statistic do include zero.

From Table 2, we can observe that all combinations of the three model factors resulted in some censoring-induced overestimation of the ERR of lung cancer due to occupational radiation exposure. As expected, overestimation increased with increasing measurement frequency. The other two factors, the dose-lag factor and the true value of the ERR, did not seem to exert much influence on the degree of overestimation. In all cases with monthly dose measurements, the censored estimate of ERR was about 16% to 17% greater than the uncensored estimate. For the simulation set with bi-monthly measurements, the degree of overestimation rose to about 20%; for quarterly measurements, overestimation was only about 6%.

In all cases examined, the standard error of the estimated ERR was overestimated to virtually the same extent as the estimated risk itself. As these two biases are essentially equal, the statistical significance of the estimated ERR was not overstated. In other words, although censoring consistently lead to overestimation of the ERR, it did not lead to an inflated *t*-statistic for testing the significance of the ERR. This is reassuring, as it implies that it is still possible to perform unbiased tests of whether or not there is a significant ERR associated with occupational radiation exposure, even when the dose measurements are censored.

In Appendix A, we prove that this result will always hold (asymptotically) under the assumptions of our simulation study. Specifically, under the assumptions that time spent in a given cell (defined by 5-year age intervals and 5-year calendar year periods) is independent of a subject's exposure measurements in that cell, given that the subject spends some time in that cell, and that exposures are independently and identically distributed within each of a finite number of strata, we prove that the *t*-statistics derived from censored data and from uncensored data will, asymptotically, be the same if the sample size is sufficiently large.

Furthermore, we show that this result does not depend on our choice of distribution for the individual doses. In particular, the accuracy of the *t*-statistic does not depend on the fact that we chose the lognormal distribution to generate our simulated doses. The results of the sensitivity analysis presented in the bottom row of Table 2 suggest that, even though the asymptotic result depends on the assumption that the occupation group dose distributions remain constant throughout the study period, this result is not highly sensitive to moderate departures from this assumption.

Although we cannot use the results of this study to estimate directly the amount by which the ERR was overestimated in the NDR study as reported by Ashmore et al. (1998) and Sont et al. (2001), our results do suggest that the degree of overestimation is likely to be modest. Of the three factors varied in the simulations (ERR, dose-lag, and measurement frequency), only measurement frequency appeared to have a strong effect on the degree of overestimation.

Discussion

Epidemiological studies of the type considered in this article are an important source of information on the health risks of occupational exposure to ionizing radiation. With the establishment of centralized occupational radiation exposure registries similar to the NDR of Canada in a number of countries (Boyle et al., 1997), and the trend toward pooling of such data at the international level (cf. Cardis et al., 1995), it is important that sources of uncertainty in risks estimates derived from exposure data in such registries be understood. In this paper, we have examined an important source of uncertainty, common to all dose registries, due to the detection limits of radiation dosimeters used to monitor worker exposures.

Our asymptotic results, supported by extensive simulations, strongly suggests that censored exposure measurements below the detection limit of radiation dosimeters are unlikely to affect the statistical significance of tests for increased risk in the ERR model used to analyze the occupational radiation exposure data in the NDR of Canada. In other words, if a significant cancer effect is found by fitting the ERR model to the censored data, then that effect would also have been found to be significant if the model had been fit to the uncensored data. This implies that censoring does not affect our ability to detect an increased risk of cancer caused by occupational radiation exposure in the NDR.

This finding may appear to be be counter-intuitive, since measurement error usually leads to greater uncertainty and a concomitant loss of power. This apparent contradiction is due to the fact our intuition is shaped by results concerning random measurement error, not deterministic error such as the truncation of observations below a fixed limit.

The results of our study also suggest that although the cancer effects are likely overestimated due to censoring, estimates of excess cancer risk obtained by fitting the ERR model to occupational radiation exposure data are unlikely to be overestimated by more than 15% to 20% percent. We base this conclusion on the fact that the main factor affecting

the censoring bias appears to be measurement frequency. The fact that more frequent measurements lead to greater overestimation is to be expected, since taking measurements more frequently means that the individual doses will be smaller, and hence more likely to fall below the censoring threshold. Except for nuclear power workers in the early period of the NDR study, who constitute a small subset of the NDR data set analyzed by Sont et al. (2001), all the measurements for the NDR were monthly or quarterly. In all six of our simulations with monthly or quarterly exposure monitoring, the censoring bias was no greater than 17%. Although the ERR for lung cancer in males due to occupational radiation exposure was estimated to be 3.1% per 10 mSv in the NDR, our study suggests that the true ERR may be as low as 2.7%.

Our proof that the asymptotic distribution of the *t*-statistic is unaffected by left-censored data depends on simplifying assumptions that are unlikely to be strictly true in practice. In particular, we assume that within each occupational group, the individual dose measurements are independently and identically distributed over all cells. In other words, the dose distribution does not vary from subject to subject and does not change over time. In fact, exposures earlier in the study were likely to be higher than exposures later in the study, when radiation protection measures became more stringent. Our sensitivity analysis suggest that the asymptotic result remains valid even though the assumption of constant dose distributions within occupational groups is not strictly true. This may be due, at least in part, to the fact that most of the data in the NDR were collected in the latter half of the study period, during which it is more reasonable to assume that for most people the dose distribution would not change much with time.

It is important to note that the results of our study are particular to the additive ERR model discussed by Breslow and Day (1994). It is not generally true that censoring induced by detection limits on radiation dosimeters will never result in a reduction of power. For example, Inskip et al. (1987) fit a Poisson regression model to occupational exposure data after stratifying not only by age and study year, but also by cumulative exposure. In this case, the authors show that correcting for censored and missing dose measurements alters the significance of the estimated relative risk, resulting in reduced power to detect an increased risk of cancer associated with occupational radiation exposure.

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Appendix A. Proof of asymptotic result

Notation

Each of the observed cases of cancer used to fit the ERR model falls into one cell of a two-way table. Each of the C cells is defined by a 5-year time period and a 5-year age group; any individual who was in a given age group during a given time period contributes person-years to that cell. We assume that the subjects are partitioned into S strata $(S_1, \ldots, S_s)$ defined by the occupational group, and that the individual dose measurements of individuals in a given stratum are independently and identically distributed. We will use the subscripts i, j, k, and l to index cells, people, individual measured doses, and strata, respectively.

We suppose that our sample consists of dose records for N individuals, with the jth subject's measurements constituting a time series of exposure measurements for that individual. If the jth individual contributes person-years to the ith cell, his/her cumulative uncensored and censored doses upon leaving that cell will be denoted by D_{ij} and C_{ij}, respectively. The number of person-years contributed by subject j to cell i will be denoted by t_{ij}, and the total number of dose measurements obtained for subject j before he/she leaves cell i will be denoted by m_{ij}. We assume that for some non-negative constant c (the minimum detection limit), the jth individual's kth censored dosimeter measurement c_{jk} is defined by

$$c_{jk} = \begin{cases} 0 & d_{jk} < c, \\ d_{jk} & d_{jk} \geq c. \end{cases}$$

Define Φ_i to be the set of individuals who contribute person-years to the ith cell and $n_i = |\Phi_i|$ to be the number of individuals in Φ_i. For example, the expression $\Phi_i = \{3,4,7\}$ means that the third, fourth, and seventh subjects (and no others) contribute person-years to the first cell, so that $n_1 = 3$. Define t_i and $\bar{D}_i$ to be the total number of person-years and the weighted average of the cumulative dose (weighted by the number of person-years t_{ij}) in the ith cell, respectively. Define y_i to be the observed number of lung cancer cases in the ith cell and λ_i to be the baseline lung cancer rate (cases per person-year for the population of interest) for the ith cell. Although we used historical values for λ_i in our study, λ_i can also be estimated as part of the model-fitting procedure. The ERR model then implies that, for some constant β, the expected number of cancer cases for cell i is given by the expression

$$E[Y_i] = t_i \lambda_i (1 + \beta \bar{D}_i).$$

The parameter β measures the ERR due to radiation exposure. Suppose that the jth subject contributes t_{ij} person-years to the ith cell, and has an average cumulative dose of D_{ij} in cell i. Then the weighted average $\bar{D}_i$ is estimated by

$$\bar{D}_i = \sum_{j \in \Phi_i} \frac{t_{ij} D_{ij}}{\sum_{j \in \Phi_i} t_{ij}}$$

We assume that the probability that a given individual is in stratum l is $p(l)$. Furthermore, we assume that for a subject in the lth stratum, either all of that subject's exposure measurements are zero, or that all of that subject's exposure measurements are independently and identically distributed (iid) random variables with density function f_l. The probability that a subject's dose distribution is identically zero is $p_l(0)$. Furthermore, assume both that the stratum memberships of different individuals are independent and that the number of person-years contributed to a given cell by different individuals are iid. Given that an individual is in stratum l, the expected value of his/her censored reading is a constant multiple of the expected value of an uncensored dose measurement:

$$E[c_{jk} | j \in S_l] = \alpha_l E[d_{jk} | j \in S_l]$$

where the constant α_l is defined as

$$\alpha_l = \frac{\int_c^\infty u f_l(u) \mathrm{d}u}{\int_0^\infty u f_l(u) \mathrm{d}u}$$

Fitting the ERR model

The iterative Gauss–Newton algorithm used to fit the excess relative risk model can be very compactly described in matrix notation. Define the vectors

$$\mathbf{Y} = \begin{bmatrix} y_1 \\ \vdots \\ y_C \end{bmatrix}, \quad \mathbf{V} = \begin{bmatrix} t_1 \lambda_1 \bar{D}_1 \\ \vdots \\ t_C \lambda_C \bar{D}_C \end{bmatrix}, \quad \text{and} \quad \mathbf{1} = \begin{bmatrix} 1 \\ \vdots \\ 1 \end{bmatrix}$$

The fitting algorithm proceeds as follows.

Initialization step:

(1) Choose initial estimate $\hat{\beta}_0$.
(2) Define the $C \times C$ diagonal matrix $\hat{\mathbf{W}}_0$ with ith diagonal entry equal to $[t_i \lambda_i (1 + \hat{\beta}_0 \bar{D}_i)]^{-1}$.

mth Iterative step:

(1) Compute updated estimate $\hat{\beta}_m = \hat{\beta}_{m-1} + (\mathbf{V}^t \mathbf{W}_{m-1} \mathbf{V})^{-1} \mathbf{V}^t \mathbf{W}_{m-1} [\mathbf{Y} - \mathbf{W}_{m-1}^{-1} 1]$.
(2) Update the $C \times C$ diagonal matrix $\hat{\mathbf{W}}_\mathbf{m}$ so that ith diagonal entry equals $[t_i \lambda_i (1 + \hat{\beta}_m \bar{D}_i)]^{-1}$.

Termination step:

Stop when $||\hat{\beta}_m - \hat{\beta}_{m-1}|| < \varepsilon$

Output:

$\hat{\beta} := \hat{\beta}_m$, $\hat{\mathbf{W}} := \hat{\mathbf{W}}_m$

Regardless of the starting value $\hat{\beta}_0$, $\hat{\beta}_m$ converges to the maximum likelihood estimate of β and $(\mathbf{V}^t \hat{\mathbf{W}} \mathbf{V})^{-1/2}$ converges to the standard error of $\hat{\beta}$.

Effect of censoring on $\hat{\beta}$

Let $\hat{\beta}$ and $\hat{\beta}^{(c)}$ denote, respectively, the estimates of β fit using uncensored and censored dose measurements. Asymptotically, the t-statistics $\hat{\beta}/\mathrm{SE}(\hat{\beta})$ and $\hat{\beta}^{(c)}/\mathrm{SE}(\hat{\beta}^{(c)})$ for testing $H_0{:}\beta = 0$ are equal. The proof of this fact involves two steps. First, we will show that the average cumulative censored dose for the ith cell, $\bar{C}_i$, approaches $\alpha\bar{D}_i$, for some constant α that is independent of i. This will be true when $n_i = |\Phi_i|$, the number of people contributing to cell i, approaches infinity. Next, we show that this fact implies that censoring does not affect the value of the t-statistic.

We now show that censoring results in the average dose $\bar{D}_i$ for the ith cell being multiplied by a constant which is independent of i. The average cumulative dose $\bar{D}_i$ for the ith cell is calculated using the expression

$$\bar{D}_i = \frac{\sum_{j\in\Phi_i} t_{ij} D_{ij}}{\sum_{j\in\Phi_i} t_{ij}} = \frac{\sum_{j\in\Phi_i} t_{ij} \sum_{k=1}^{m_{ij}} d_{jk}}{\sum_{j\in\Phi_i} t_{ij}}.$$

Let $\bar{t}_i = E[t_{ij}]$, $\bar{m}_i = E[m_{ij}]$, and $\bar{d}_l$ be the expected value of one measurement for a subject with nonzero dose in the lth stratum. The independence of t_{ij} and d_{jk} implies that

$$\begin{aligned} D_i &\to \frac{n_i \bar{m}_i \bar{t}_i \sum_{l=1}^{S} p(l)[1 - p_l(0)]\bar{d}_l}{n_i \bar{t}_i} \\ &= \bar{m}_i \sum_{l=1}^{S} p(l)[1 - p_l(0)]\bar{d}_l \end{aligned}$$

as $n_i \to \infty$. A parallel argument for the convergence of $\bar{C}_i$ shows that the average cumulative dose computed from the censored measurements converges in probability to that computed from the uncensored dose as $n_i \to \infty$, with the constant α defined by

$$\alpha = \frac{\sum_l \alpha_l p(l)[1 - p_l(0)]\bar{d}_l}{\sum_l p(l)[1 - p_l(0)]\bar{d}_l}$$

Finally, we show that, at least asymptotically, censoring does not change the value of the t-statistic for testing the significance of $\hat{\beta}$. At the mth iterative step, the updated estimate $\hat{\beta}_m$ is

$$\begin{aligned} \hat{\beta}_m = \hat{\beta}_{m-1} + &\left[\sum_i \frac{t_i \lambda_i \bar{D}_i^2}{\left(1 + \hat{\beta}_{m-1}\bar{D}_i\right)}\right]^{-1} \\ &\sum_i \left[\frac{\bar{D}_i y_i}{\left(1 + \hat{\beta}_{m-1}\bar{D}_i\right)} - \bar{D}_i t_i \lambda_i\right] \end{aligned} \qquad (A.1)$$

The estimate for $\hat{\beta}^{(c)}$ is obtained from this expression by substituting $\hat{\beta}_{m-1}^{(c)}$ for $\hat{\beta}_{m-1}$ and $\bar{C}_i$ for $\bar{D}_i$. If we choose both the starting values $\hat{\beta}_0$ and $\hat{\beta}_0^{(c)}$ to be 0, Eq. (1) implies that $\hat{\beta}_1^{(c)}$ converges in probability to $\hat{\beta}_1/\alpha$ when $n_i \to \infty$. By induction on m, we see that $\hat{\beta}_m^{(c)}$ converges in probability to $\hat{\beta}_m/\alpha$ for all m and, therefore, that

$$\hat{\beta}^{(c)} \to \frac{\hat{\beta}}{\alpha} \qquad (A.2)$$

Similarly, one can show that

$$\mathrm{SE}(\hat{\beta}^{(c)}) \to \frac{\mathrm{SE}(\hat{\beta})}{\alpha} \qquad (A.3)$$

It follows that

$$\frac{\hat{\beta}^{(c)}}{\mathrm{SE}(\hat{\beta}^{(c)})} \to \frac{\hat{\beta}}{\mathrm{SE}(\hat{\beta})}$$

as $n_i \to \infty$.