ORIGINAL ARTICLE

Investigating time patterns of variation in radiation cancer associations

D B Richardson, J P Ashmore

Occup Environ Med 2005;**62**:551–558. doi: 10.1136/oem.2004.017368

See end of article for authors' affiliations

Correspondence to: Professor D Richardson, Department of Epidemiology, School of Public Health, University of North Carolina, Chapel Hill, NC 27599-8050, USA; david_richardson@unc.edu

Accepted 15 February 2005

Aims: In occupational settings, carcinogenic exposures are often repeated or protracted over time. The time pattern of exposure accrual may influence subsequent temporal patterns of cancer risk. The authors present several simple models that may be used to evaluate the influence of time since exposure or age at exposure on cancer incidence or mortality in an occupational cohort.

Methods: A cohort of 40 415 nuclear industry workers was identified via the Canadian National Dose Registry. Vital status and cause of death were ascertained through 1994. Associations between ionising radiation and mortality due to lung cancer, leukaemia, and cancers other than lung and leukaemia were quantified using conditional logistic regression models with risk sets constructed by incidence density sampling. A step function, a bilinear function, and a sigmoid function were used to evaluate temporal variation in exposure effects.

Results: Step and sigmoid functions were used to explore latency and morbidity periods. For analyses of lung cancer, leukaemia, and other cancers the best fitting models were obtained when exposure assignment was lagged by 13, 0, and 5 years, respectively. A bilinear function was used to evaluate whether exposure effects diminished with time since exposure. In analyses of lung cancer and leukaemia, there was evidence that radiation effects attenuated with protracted time since exposure. In analyses of age at exposure, there was evidence of variation in radiation mortality associations for analyses of lung cancer and leukaemia; discounting radiation doses accrued at younger ages (for example, 15–35 years) led to significant improvements in model fit.

Conclusions: This paper illustrates empirical approaches to evaluating temporal variation in the effect of a protracted exposure on disease risk.

In occupational settings, carcinogenic exposures are often repeated or protracted over time. In this paper we present methods for evaluating the influence of exposure time patterns on disease risk. We illustrate these methods using an example from a cohort study of the effects of occupational exposures to ionising radiation in the nuclear industry.

We start by examining the influence of time since exposure. When deriving estimates of association between cumulative exposure to an occupational carcinogen and cancer mortality, investigators often lag exposure assignment by several years. Lagging of exposure assignment is done under the assumption that exposures accrued in the period immediately before death are unlikely to be aetiologically relevant because of a period of induction, latency, and morbidity between exposure and resultant cancer mortality.[1] The validity of an exposure lag assumption is a potential determinant of the validity of a cumulative exposure mortality estimate, because if an exposure lag assumption is incorrect estimates of cumulative exposure mortality associations may be biased as a result of exposure misclassification.[2]

In addition to considerations about induction, latency, and morbidity periods, a researcher might postulate that the relative risk of disease following exposure to a hazardous agent varies with continued time since exposure.[3 4] For example, in studies of the association between ionising radiation exposure and mortality due to acute lymphatic and myeloid forms of leukaemia there is typically evidence of a brief induction, latency, and morbidity period, after which the relative risk of leukaemia peaks and then diminishes with continued time since exposure.[5] Accounting for such variation may be important for deriving reliable estimates of exposure disease trends.

The carcinogenic effect of an agent may also vary with age at exposure or attained age. In occupational settings, workers tend to accrue exposures over a wide range of ages. At young ages, sensitivity to exposure effects might vary due to developmental processes. With older age there are declines in the accuracy and efficiency of most biological systems, including those involved in immune and cellular repair processes.[6] Therefore, the ages at which exposures occur may also be important to understanding patterns of disease risk.

A standard approach used for evaluating heterogeneity in the effects of exposures accrued at different points in time is the method of time window analysis.[7–9] This approach may be viewed as the application of a time dependent exposure weighting function.[4] A weight of 1 is applied to exposures accrued within the critical time window of exposure and a weight of zero is applied to exposures accrued at all other times. A standard summary measure of an exposure history, such as a cumulative measure of exposure, can be calculated using this weighted exposure information. Multiple exposure time windows may be included simultaneously in a regression analysis in order to evaluate the effect of exposures accrued in one time period while adjusting for the effect of exposures accrued at other time periods.[10]

However, one limitation of this approach is that an investigator has to, a priori, define boundaries for time windows, and epidemiological risk estimates may be sensitive to decisions about boundary values.[11] Another limitation of the time window approach is that the boundaries of windows are typically defined by step functions. The

Abbreviations: AECL, Atomic Energy of Canada Ltd; CLL, chronic lymphocytic leukaemia; CMDB, Canadian Mortality Data Base; ICD, International Classification of Diseases; NDR, National Dose Registry

assumption that the effect of an exposure is uniform within a window, and changes abruptly at the boundary of this window, is less plausible than the assumption that effects transition gradually over time. Finally, time window specific dose-response trend estimates tend to be statistically unstable as doses may be accrued within relatively narrow windows of exposure and exposure levels for adjacent windows may be correlated.[12]

These limitations led us to consider alternative methods to describe variation over time in sensitivity to the effects of an exposure. In this paper, we propose a series of models that may be used to empirically evaluate the influence of time since exposure and age at exposure on ionising radiation cancer mortality associations. We apply these models to analyses of data derived from a large nuclear worker cohort study.

METHODS

A roster was constructed of all radiation monitored nuclear workers identified through the Canadian National Dose Registry (NDR), a federally operated, centralised occupational radiation dose record keeping system.[13 14] The Registry includes records for individuals employed by the three Canadian companies involved in nuclear power generation (New Brunswick Power, Quebec Hydro, and Ontario Power Generation) and for individuals employed by Atomic Energy of Canada Ltd (AECL) which is a nuclear power research and development company.

In order to ensure reliable linkage with death records, workers included in the study cohort had to have complete information on sex, surname, and either first initials and date of birth, or first names and year of birth. In addition, workers in the study cohort were required to be over 15 years of age at hire, to have been monitored for radiation exposure in more than one calendar year, and to be less than 100 years old at end of follow up.

Monitoring for external radiation exposure was primarily conducted using personal radiation dosimeters. Over time the types of dosimeters, monitoring frequencies, and recording thresholds changed, although the impact of these changes on the accuracy of historical radiation dose estimates is believed to be small.[15] Radiation dose estimates from tritium deposition were derived via bioassay monitoring. Estimates of whole body ionising radiation dose are expressed as equivalent doses in milliSievert (mSv) and reflect the sum of estimates of external penetrating radiation dose and internal tritium dose; quality factors for *x* ray, gamma, and beta were assumed equal to 1.0, and the quality factor for neutrons was assumed to be 10.0. The NDR is an inclusive repository for all available information on radiation exposures accrued by Canadian workers; consequently, doses received by cohort members in other industrial or medical settings were also included in these analyses. Dosimetry records for AECL workers for the period before 1956 were destroyed in a fire but were subsequently reconstructed for the purposes of epidemiological research and also reviewed and updated as part of an intercomparison study of NDR and nuclear facility dose records.[16] Historical records, notably memoranda, were used to reconstruct doses for AECL workers for the period before 1956; estimated doses greater than 3 mSv in a monitoring period were reported by memorandum to the worker's department head (these memoranda were not destroyed in the fire). In addition, original dosimetry records for monitoring during a 1953 reactor cleanup effort were not lost in the fire; these records permitted reliable reconstruction of what are believed to be the most significant doses accrued during this period. Similar to most,[13 14 16 17] but not all,[18] previous epidemiological studies that have included AECL workers, we have included employees hired since the start of AECL operations by incorporating these reconstructed dose estimates. Inclusion of information on workers employed in the early years of operation of the industry was important for this investigation because our focus is on temporal variation in radiation exposure effects.

Vital status as of 31 December 1994, was determined by linking NDR records with the Canadian Mortality Data Base (CMDB) and tax summary records in order to confirm both alive and deceased vital status. The CMDB includes death records from 1950 for all Canadians, including those who died while residing in the United States, and is routinely used to ascertain mortality in a number of cohort studies.[19] Underlying causes of death was coded to the version of the International Classification of Diseases (ICD) in use at time of death. We examined the following three causes of death: lung cancer (ICD6 and 1CD7 codes 162 and 163, ICD8 and ICD9 code 162); leukaemia excluding chronic lymphocytic leukaemia (ICD6 and 1CD7 code 204, ICD8 codes 204–207 excluding 204.1, and ICD9 codes 204–208 excluding 204.1); and all cancers (ICD6 and ICD7 codes 140–205, ICD8 codes 140–207, and ICD9 codes 140–208) other than lung cancer and leukaemia. Although ICD6 and ICD7 did not include a separate code for chronic lymphocytic leukaemia (CLL), this did not pose a problem for identifying the category of leukaemia excluding CLL in these analyses because no deaths due to lymphatic leukaemia (acute or chronic) were recorded in this population during the period when ICD6 and ICD7 were in use.

Statistical methods

Analyses were conducted using a nested case control approach. Risk sets were formed by incidence density matching of cases (cancer deaths) to non-cases on attained age.[20] For each case, a risk set was formed that included all workers who were alive and eligible to be in the study at the attained age of the index case. For analyses of lung cancer and all cancers other than lung and leukaemia, controls were also matched to cases on sex, calendar year at risk (defined in five year categories from <1960 to 1990+), facility (AECL or other facility), socioeconomic status (based upon the worker's most recent occupation, and defined in the following categories: professional white collar, other white collar, skilled blue collar, other blue collar, and unknown), duration of monitoring (<5, 5 to <10, 10 to <15, 15 to <20, and 20+ years), and monitoring status (radiation monitored in the last five years or not). For analyses of leukaemia mortality, risk sets were matched on attained age, with the other covariates controlled for as main effects in the regression model. Twenty five controls were selected for each case by random sampling without replacement from all members of the risk set (excluding the index case itself).[21]

Conditional logistic regression was used to evaluate associations between case status and radiation exposure history. Let us say that y_j denotes the case status of individual j in a risk set that is matched on attained age A. The radiation exposure history for each worker was recorded as a radiation dose estimate for each calendar year of observation. We assigned an age-at-exposure, a, to each calendar year based on the worker's age at the midpoint of the calendar year. Therefore, the array $x_j(a)$ indexes the radiation dose accrued by individual j at age, a. The summation of these doses up to attained age A

$$\sum_{a=1}^{A} x_j(a)$$

is the total cumulative dose accrued by individual j.

Name	Parameters	Weighting function
Step function	η	$w(t) = I[t >= \eta]$
Sigmoid function	σ_1, σ_2	$w(t) = \dfrac{\left(\frac{t}{\sigma_2}\right)^{\sigma_1}}{\left(\frac{t}{\sigma_2}\right)^{\sigma_1} + \left(\frac{t}{\sigma_2}\right)}$
Bilinear function	ϕ_1, ϕ_2	$w(t) = \left[\left(\frac{t}{\phi_1} I[t <= \phi_1]\right) + \left(\frac{\phi_2 - t}{\phi_2 - \phi_1} I[\phi_1 < t <= \phi_2]\right)\right]$

Figure 1 Weighting functions. The function *I*["logical expression"] equals 1 if "logical expression" is true and 0 if it is false. The value *t* is the timescale over which weights vary. For analyses of age at exposure *t*= *a* and denotes the age at the midpoint of each calendar year of exposure. For analyses of time since exposure *t*= *A*-*a* and denotes the difference between the attained age and the age at the midpoint of each calendar year of exposure.

We begin by evaluating whether the relative effect of exposure varies with time since exposure. An exposure weighting function, $w(t)$, was used to express this variation, with the timescale, t, defined as the difference between a worker's attained age, A, and their age when an increment of exposure occurred, a. We evaluated three simple parametric forms for the exposure weighting function (fig 1). The most parsimonious model was a step function. A step function can be defined by a single parameter, η; a weight of zero is applied to doses that occurred less than η years in the past, and a weight of one is applied to all other doses.

A sigmoid function is a simple alternative to a step function that allows for a more gradual transition in the relative effect of exposure over time. The sigmoid function was defined by the following parameters: σ_1 defines the shape of the function and σ_2 specifies the inflection point for the curve. If the value of σ_1 is greater than unity then this describes a situation in which the effect of exposure increases with increasing time since exposure. The sigmoid function approximates the step function at large values of σ_1 (for example, 50). If the value of σ_1 is less than unity then this describes a situation in which the effect of exposure decreases with increasing time since exposure.

The bilinear exposure weighting function is an alternative parametric form that allows evaluation of the assumption that the relative effect of exposure increases to some maximal value and then diminishes with additional time since exposure.[12] It consists of two attached lines that form a triangular function. For the first ϕ_1 years after exposure, the relative effect of exposure increases linearly to its maximum value, ϕ_1 years after exposure; then, the effect diminishes linearly with additional time since exposure, reaching a relative effect of zero (no effect) ϕ_2 years in the past.[12]

The sum of the time weighted exposures,

$$\sum_{a=1}^{A} w(t)x_j(a)$$

describes the cumulative effective dose accrued by individual j at attained age A. We examined the relation between this effective dose metric and mortality using a conditional logistic regression model of form

$$\text{logit Pr}(y_j = 1 \mid x_j(a)) = \beta_0 + \beta_1 \sum_{a=1}^{A} w(t)x_j(a)$$

The value $[1000(\hat{\beta}_1)]$ provides an estimate of the (log) per cent change in mortality risk per 10 mSv dose under an exponential relative risk model. At low doses, this value approximates the estimate of excess relative risk per Sv (ERR/Sv) that would be derived under an additive relative risk model.[22] One advantage of using an exponential relative risk model is that parameter estimates are not constrained (as they are when using an additive relative risk model), thereby reducing problems with model convergence and estimation of confidence intervals.

An SAS program was written in order to calculate the cumulative effective dose for each study member at specified values for the parameter(s) defining $w(t)$.[23] Conditional logistic regression models were fit to these data using SAS PHREG in order to estimate the association between cumulative effective dose and cancer mortality.[24] The search algorithm involved estimating the dose-response parameter over a grid of weighting function parameters (for example, α_1, α_2), tabulating the residual deviances, and then recentering the grid for the next iteration of the search. Intervals between grid points were progressively reduced; in this way the maximum likelihood estimates for the weighting function parameter(s) were determined by identifying the model that produced the minimal residual deviance.

Analyses were also conducted using a piecewise constant model (that is, a model for time window analysis), in order to provide a non-parametric description of the pattern of variation in radiation exposure effects with time since exposure. In analyses of time since exposure, a separate regression parameter is included for the cumulative dose accrued within each of the following exposure time windows: 0 to <10 years, 10 to <30 years, and 30+ years before the age at which risk is being estimated. Specifically, we applied a piecewise constant model of the form

$$\text{logit Pr}(y_j = 1 \mid z_j, x_j(a)) = \beta_0 + \beta_1 \sum_{a=1}^{A} I[t < 10]x_j(a) + \beta_2 \sum_{a=1}^{A} I[10 <= t < 30]x_j(a) + \beta_3 \sum_{a=1}^{A} I[t >= 30]x_j(a)$$

where *I*["logical expression"] which equals 1 if "logical expression" is true and 0 if it is false. Parameter estimates β_1, β_2, and β_3 describe the change in the log of the relative risk per 10 mSv dose, for cumulative radiation doses accrued in time windows defined by <10, 10 to <30, and 30+ years since exposure, respectively.

The same exposure weighting functions (fig 1) were used to evaluate variation in exposure effects with age at exposure. In these analyses the timescale, t, for the exposure weighting function was age at exposure (that is, the age when an increment of exposure occurred, a). A piecewise constant model of age at exposure effects was developed for doses accrued in time windows defined by ages <35, 35 to <50, and 50+ years, respectively. In order to allow for an induction, latency, and morbidity period before radiation induced mortality, exposure assignment was lagged by 10 years for analyses of lung cancer and all cancers other than lung and leukaemia, and by two years for analyses of leukaemia mortality.

Table 1 Number of workers, vital status, and number of deaths due to all cancers, lung cancer, and leukaemia by sex

Vital status	Male	Female	Total
Alive	32922 (94.9)	5661 (98.8)	38583 (95.5)
Dead	1761 (5.1)	71 (1.2)	1832 (4.5)
All cancer	537	39	576
Lung	203	3	206
Leukaemia	15	1	16
Total	34683	5732	40415

Our primary interest in these analyses was in evaluation of whether exposure effects were influenced by the time pattern of exposure. Therefore, each model was compared to a ''null'' model under which there was no variation in exposure effect over the timescale of interest.

RESULTS

Table 1 shows the vital status of the workers in the study cohort at the end of follow up. The percentage of deceased male workers (5.1%) was greater than for females (1.2%). The number of all cancers, lung cancers, and leukaemia deaths is also presented in table 1. Whole body radiation doses tended to be relatively low among the workers in this study cohort. The average cumulative whole body dose was 14 mSv, while the 90th percentile of the cumulative whole body dose distribution was 35 mSv and the maximum cumulative whole body dose was 952 mSv.

Time since exposure

Lung cancer

Figure 2A shows the profile likelihood estimation of the step function parameter, η, in analyses of radiation lung cancer mortality associations. The best fitting regression model (indicated by the minimal residual deviance in fig 2A) was derived under a 13 year exposure lag assumption, although the fit of models was very similar under values for η ranging from 5–20 years.

Analyses of radiation lung cancer mortality associations under the piecewise constant function (fig 2B) suggest that lung cancer mortality is positively associated with radiation doses accrued in the periods 10–30 years prior (3.25%/10 mSv, 90% CI 1.52 to 4.98), and negatively associated with doses accrued <10 years prior (−1.77%/10 mSv, 90% CI −6.03 to 2.49) and 30+ years prior (−0.54%/10 mSv, 90% CI −4.92 to 3.83).

The fitted sigmoid function ($\hat{\sigma}_1 = 10$, $\hat{\sigma}_2 = 15$) describes a situation in which the effect of exposure gradually increases with time since exposure, attaining a maximum effect more than 15 years after exposure. Under the fitted bilinear function (fig 2C), exposure effects progressively increase for the first 32 years since exposure and subsequently diminish in a rapid monotonic fashion ($\hat{\phi}_1 = 32$, $\hat{\phi}_2 = 33$). The fit of the regression model under the bilinear weighting function was substantially better than the fit of models under the step and sigmoid weighting functions (table 2).

Leukaemia

Figure 3A shows the profile likelihood estimation for the step function parameter for analyses of leukaemia mortality. The best fitting association was derived under a 0 year exposure lag assumption; therefore, the best fitting estimate is identical to the ''null'' model, $\eta = 0$, for lifetime cumulative dose (table 2).

Exposure time windows analyses of radiation leukaemia mortality associations suggest that the association between leukaemia mortality and cumulative radiation dose is positively associated with radiation doses accrued in the periods <10 years prior (12.59%/10 mSv, 90% CI −0.78 to 25.96) and 10–30 years prior (8.72%/10 mSv, 90% CI 0.73 to 16.71), but there is essentially no association with doses accrued in the period 30+ years prior (0.02%/10 mSv, 90% CI −16.22 to 16.25). All of these time window specific estimates of association, however, are highly imprecise (fig 2B).

The fitted sigmoid function ($\hat{\sigma}_1 = -50$, $\hat{\sigma}_2 = 31$) describes a situation in which the effect of radiation exposure on leukaemia rates occurs promptly after exposure, but diminishes in the period 30+ years after exposure (fig 3C). Under the fitted bilinear function, exposure effects progressively decrease in magnitude with increasing time since exposure ($\hat{\phi}_1 = 0$, $\hat{\phi}_2 = 52$). The fit of the regression model under the bilinear function was very similar to the fit of the model under the sigmoid function, and neither was significantly better than the null model (table 2).

Cancers other than lung and leukaemia

Figure 4A shows the profile likelihood for the step function parameter, η in analyses of cancers other than lung and leukaemia. The best fitting association was derived when exposure assignment was lagged by five years (fig 4A). While discounting the most recently accrued radiation doses improved model fit, the null hypothesis, $\eta = 0$, was not rejected (table 2).

Figure 4B illustrates the piecewise constant model under which lifetime cumulative dose is partitioned into three windows. Mortality from cancers other than lung and leukaemia is positively associated with cumulative radiation doses accrued 10–30 years prior (1.71%/10 mSv, 90% CI 0.28 to 3.14) and 30+ years prior (2.56%/10 mSv, 90% CI −0.19 to 5.31), and negatively associated with doses accrued <10 years prior (−0.70%/10 mSv, 90% CI −4.29 to 2.89) although the radiation risk estimate for the most recent time window of exposure is highly imprecise.

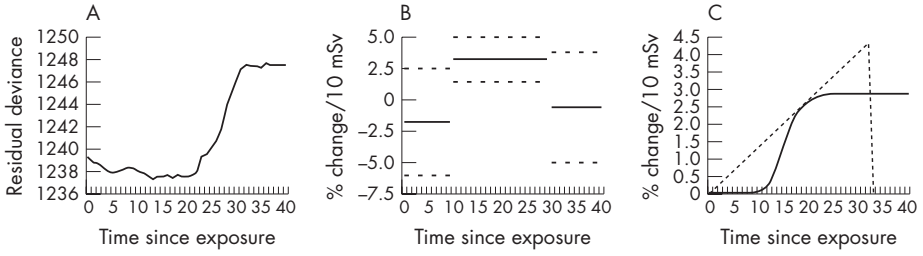

Figure 2 Lung cancer mortality. Evaluation of variation in radiation dose lung cancer mortality association with time since exposure. (A) Profile search for step function parameter, η. (B) Time window estimates. Dashed lines indicate 90% confidence interval. (C) Fitted sigmoid (solid line) and bilinear (dashed line) functions. Risk sets were matched on attained age, and analyses were adjusted for sex, calendar year at risk, facility, socioeconomic status, duration of monitoring, and monitoring status.

Table 2 Evaluation of variation in exposure effect with time since exposure under three exposure weighting functions. Canadian nuclear industry workers study

Exposure weight function	Residual deviance	Likelihood ratio statistic*	Degrees of freedom	p Value
Lung cancer				
Step function	1237.25	1.91	1	0.17
Sigmoid function	1237.41	1.75	1	0.19
Bilinear function	1233.89	5.27	2	0.07
Leukaemia				
Step function	83.16	0.00	1	1.00
Sigmoid function	82.12	1.04	1	0.31
Bilinear function	82.54	0.62	2	0.73
Cancers other than lung and leukaemia				
Step function	2049.00	1.40	1	0.24
Sigmoid function	2049.07	1.33	1	0.25
Bilinear function	2049.16	1.24	2	0.54

*Test for variation in exposure effect with time since exposure. Model fit is compared to the model for total cumulative dose (that is, $\eta = 0$ for the step function; $\sigma_1 = 1$ for the sigmoid function; and, $\phi_1 = \phi_2 = 0$ for the bilinear function with ϕ_2 parameterised as a slope). Analyses of lung cancer, and cancers other than lung and leukaemia, were matched on attained age, sex, calendar year at risk, facility, socioeconomic status, duration of monitoring, and monitoring status; analyses of leukaemia were matched on attained age and adjusted for sex, calendar year at risk, facility, socioeconomic status, duration of monitoring, and monitoring status.

The sigmoid function allows for a more gradual transition in exposure effect with time since exposure than the step function; the inflection point of the sigmoid function is at four years time since exposure ($\hat{\sigma}_1 = 42$, $\hat{\sigma}_2 = 4$). Under the fitted bilinear function ($\hat{\phi}_1 = 15$, $\hat{\phi}_2 = 196$), exposure effects progressively increase for the first 15 years since exposure and do not appear to diminish with continued time since exposure (fig 4C). Use of the step exposure weighting function led to better model fit than use of the sigmoid or bilinear weighting functions (table 2).

Age at exposure

Lung cancer

Under a step function, the best fitting radiation lung cancer model is obtained when discounting doses accrued at ages less than 34 years. Figure 5A shows the profile likelihood estimation of the parameter for this simple exposure weighting function. There is substantial support for rejection of the ''null'' model under which exposure effects are uniform with age at exposure (table 3).

When cumulative dose is partitioned into three time windows defined by age at exposure (fig 5B) there is evidence which suggests that the association between lung cancer mortality and radiation dose is primarily limited to associations with doses accrued in the period of older ages at exposure. The association between lung cancer mortality and cumulative radiation dose accrued at ages less than 35 years was negative but imprecise (−2.23%/10 mSv, 90% CI −6.75 to 2.33), the association with radiation doses accrued at ages 35 to <50 years was positive (2.97%/10 mSv, 90% CI 0.73 to 5.21), and the association with radiation doses accrued at 50+ years of age was of largest magnitude (3.65%/10 mSv, 90% CI 0.57 to 6.73).

Under the sigmoid exposure weighting function, the best fitting radiation exposure lung cancer mortality model is obtained via a sigmoid function that is centered at age 34 years with steepness that approximates a step function ($\hat{\sigma}_1 = 50$, $\hat{\sigma}_2 = 34$). The sigmoid and step functions provide similar goodness of fit to these data; the bilinear function, in contrast, does not fit these data well (table 4).

Leukaemia

Under a step function in which we discount doses accrued in early adulthood, the best fitting model is obtained when discounting doses accrued at ages less than 31 years. Figure 6A shows the profile likelihood estimation of the parameter for the step exposure weighting function. There is significant empirical support for rejection of the ''null'' model, $\eta = 0$, under which exposure effects are uniform with age at exposure (table 3).

Under the piecewise constant model, we estimated the association between radiation dose and leukaemia mortality. The cumulative radiation dose accrued at ages less than 35 years is positively associated with cancer mortality (3.22%/10 mSv, 90% CI −6.04 to 12.48), and the radiation dose accrued at ages 35 to <50 years exhibits a positive association of larger magnitude but little precision (15.16%/10 mSv, 90% CI −1.54 to 31.86); in contrast, the radiation dose accrued at 50+ years of age exhibits a smaller association with extremely poor precision (8.88%/10 mSv, 90% CI −10.78 to 28.54).

We estimated parameters for the sigmoid model for age at exposure effects. The best fitting model is obtained for an age at exposure model that is centred at age 31 years ($\hat{\sigma}_1 = 50$, $\hat{\sigma}_2 = 31$).

Cancers other than lung and leukaemia

Figure 7A shows the profile likelihood estimation of the parameter for this simple exposure weighting function. The ''null'' model, under which radiation exposure effects are uniform with age at exposure, provided the best fitting model (table 3).

Using the piecewise constant function to explore age at exposure effects (fig 7B), the cumulative radiation dose accrued at ages less than 35 years was positively associated with mortality from these cancer causes (2.23%/10 mSv, 90% CI −0.81 to 5.27), as was cumulative radiation dose accrued at ages 35 to <50 years (2.11%/10 mSv, 90% CI 0.22 to 4.00)

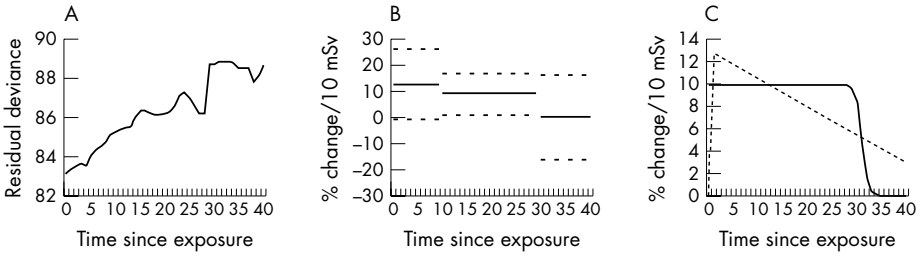

Figure 3 Leukaemia mortality. Evaluation of variation in radiation dose leukaemia mortality association with time since exposure. (A) Profile search for step function parameter, η. (B) Time window estimates. Dashed lines indicate 90% confidence interval. (C) Fitted sigmoid (solid line) and bilinear (dashed line) functions. Risk sets were matched on attained age, and analyses were adjusted for sex, calendar year at risk, facility, socioeconomic status, duration of monitoring, and monitoring status.

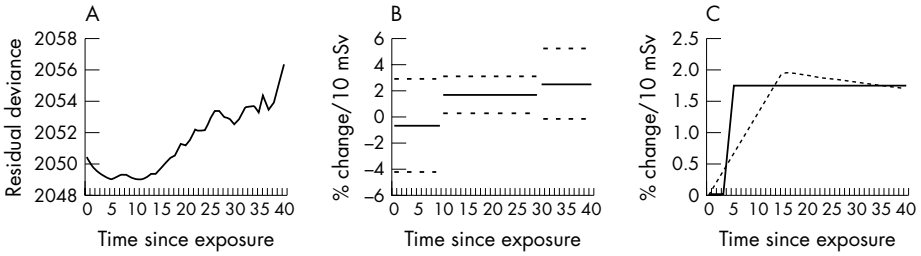

Figure 4 Cancers other than lung and leukaemia. Evaluation of variation in radiation dose leukaemia mortality association with time since exposure. (A) Profile search for step function parameter, η. (B) Time window estimates. Dashed lines indicate 90% confidence interval. (C) Fitted sigmoid (solid line) and bilinear (dashed line) functions. Risk sets were matched on attained age, and analyses were adjusted for sex, calendar year at risk, facility, socioeconomic status, duration of monitoring, and monitoring status.

and cumulative radiation dose accrued at 50+ years of age (1.22%/10 mSv, 90% CI −1.31 to 3.75).

The best fitting regression model under a sigmoid exposure weighting function ($\hat{\sigma}_1 = 34$, $\hat{\sigma}_2 = 14$) is one in which that the effect of radiation exposure on cancer mortality is uniform with age at exposure (fig 7C). The bilinear function suggests a small decline in exposure effects with age at exposure (fig 7C).

DISCUSSION

A cumulative measure of exposure is commonly used in epidemiological studies to summarise a potentially long history of exposures.[25] Implicit in the use of a cumulative measure of exposure is the assumption that the effects of exposures accrued at different points in time are additive and remain constant over time. In this paper we illustrate methods that may be used to evaluate departures from this assumption; these methods use time dependent exposure weighting functions under which the relative effect of exposures may vary with time.

Our findings provide support for the standard approach of using a step weighting function to lag exposure assignment (table 2). We found no empirical support for use of the more complicated sigmoid function that allows for a more gradual transition in exposure effect over an induction, latency, and morbidity period. The bilinear function, which allows for diminishing effects of exposure with protracted time since exposure, provided a somewhat better regression model fit for analyses of lung cancer than a simple exposure lag model (that is, a step weighting function). Evidence of attenuation of radiation dose lung cancer associations with protracted time since exposure has been reported in previous studies of the effects of acute and protracted radiation exposures.[12 26–28] In our analyses of leukaemia excluding CLL, the best fitting models for time since exposure effects are consistent with an extremely short lag period. While an estimate of a 0 year exposure lag for leukaemia is implausible, these analyses had relatively little power to discriminate between similar models given the small numbers of leukaemia cases. The results of model development using the sigmoid and bilinear weighting functions suggest a diminishing effect of radiation exposure with time since exposure. Again, such a pattern is consistent with temporal patterns of leukaemia risk following radiation exposure observed in other populations.[29 30]

Our ability to investigate variation in radiation effects with time since exposure is constrained, however, by the fact that entrance into the cohort was relatively recent for most cohort members. Fifty per cent of the workers were first monitored after 1980, and 25% of the workers were first monitored after 1987. Consequently, analyses that investigate variation in exposure effects with protracted time since exposure are limited by sparse data. In addition, dosimetry information for the early years of the nuclear industry plays a greater role in estimates exposure effects in the longest period time since exposure. Although the observed trends of diminishing radiation exposure effects for lung cancer and leukaemia are consistent with findings from other studies, an alternative possibility is that exposure misclassification is greater for doses accrued in the more distant past (and therefore risk estimates for periods of greater time since exposure are increasingly biased towards the null).

Our analyses of the influence of age at exposure suggest stronger radiation dose lung cancer associations at older ages at exposure. These findings are of interest given similar patterns of association observed in several other nuclear worker cohorts.[7 8 31 32] Interestingly, there was minimal evidence of variation in exposure effects for cancers other than lung and leukaemia (table 3). Similarly, in the Lifespan Study of atomic bomb survivors, for most solid cancers estimates of ERR/Sv are greater for people who were exposed at younger ages than for people exposed at older ages; however, the opposite pattern is observed for lung cancer.[33] One possibility is that the temporal patterns of variation in radiation lung cancer mortality associations reflect temporal patterns of confounding, for example by smoking. Spurious

Table 3 Evaluation of variation in exposure effect with age at exposure under three exposure weighting functions. Canadian nuclear industry workers study

Exposure weight function	Residual deviance	Likelihood ratio statistic*	Degrees of freedom	p Value
Lung cancer				
Step function	1234.12	3.86	1	0.05
Sigmoid function	1234.73	3.25	1	0.07
Bilinear function	1237.26	0.72	2	0.70
Leukemia				
Step function	79.67	3.82	1	0.05
Sigmoid function	79.93	3.56	1	0.06
Bilinear function	82.64	0.85	2	0.65
Cancers other than lung and leukemia				
Step function	2049.07	0.00	1	1.00
Sigmoid function	2049.07	0.00	1	1.00
Bilinear function	2048.83	0.24	2	0.89

*Test for variation in exposure effect with age at exposure. Model fit is compared to the model for total cumulative (that is, $\eta = 0$ for the step function; $\sigma_1 = 1$ for the sigmoid function; and, $\phi_1 = \phi_2 = 0$ for the bilinear function with ϕ_2 parameterised as a slope). Exposure assignment is lagged 10 years for analyses of lung cancer and cancers other than lung and leukaemia, and two years for analyses of leukaemia. Analyses of lung cancer, and cancers other than lung and leukaemia, were matched on attained age, sex, calendar year at risk, facility, socioeconomic status, duration of monitoring, and monitoring status; analyses of leukaemia were matched on attained age and adjusted for sex, calendar year at risk, facility, socioeconomic status, duration of monitoring, and monitoring status.

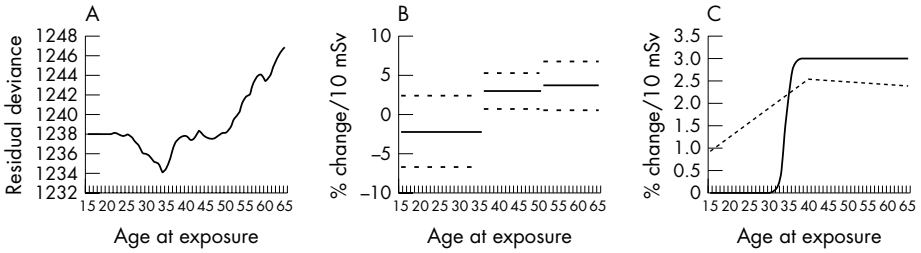

Figure 5 Lung cancer mortality. Evaluation of variation in radiation dose leukaemia mortality association with age at exposure. (A) Profile search for step function parameter, η. (B) Time window estimates. Dashed lines indicate 90% confidence interval. (C) Fitted sigmoid (solid line) and bilinear (dashed line) functions. Risk sets were matched on attained age, and analyses were adjusted for sex, calendar year at risk, facility, socioeconomic status, duration of monitoring, and monitoring status.

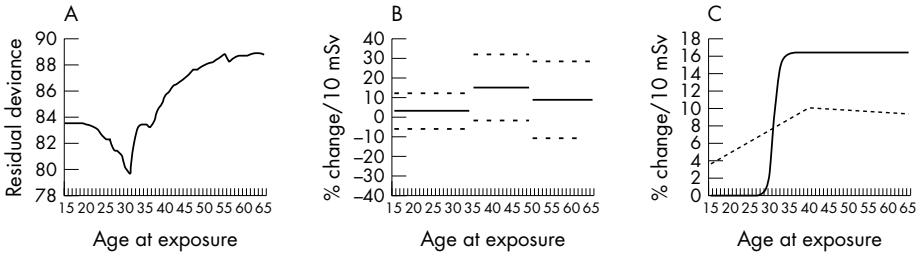

Figure 6 Leukaemia mortality. Evaluation of variation in radiation dose leukaemia mortality association with age at exposure. (A) Profile search for step function parameter, η. (B) Time window estimates. Dashed lines indicate 90% confidence interval. (C) Fitted sigmoid (solid line) and bilinear (dashed line) functions. Risk sets were matched on attained age, and analyses were adjusted for sex, calendar year at risk, facility, socioeconomic status, duration of monitoring, and monitoring status.

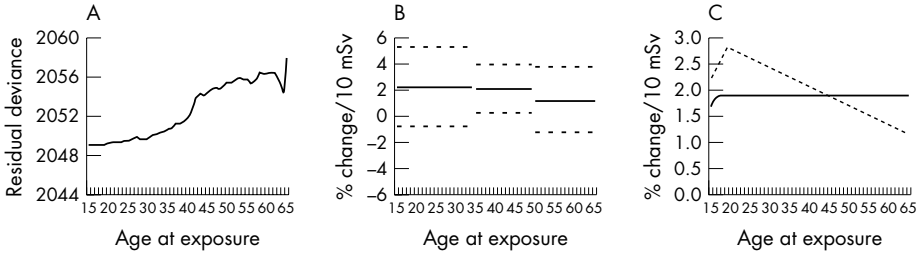

Figure 7 Cancers other than lung and leukaemia. Evaluation of variation in radiation dose leukaemia mortality association with age at exposure. (A) Profile search for step function parameter, η. (B) Time window estimates. Dashed lines indicate 90% confidence interval. (C) Fitted sigmoid (solid line) and bilinear (dashed line) functions. Risk sets were matched on attained age, and analyses were adjusted for sex, calendar year at risk, facility, socioeconomic status, duration of monitoring, and monitoring status.

evidence of association between radiation doses accrued at older ages and lung cancer could arise due to confounding if smoking were positively associated with radiation doses accrued at older age, but not with radiation doses accrued at younger ages. Alternatively, birth cohort trends in smoking could lead to apparent age at exposure effects if regression analyses assume multiplicative relations involving birth cohort effects yet the interaction between smoking and radiation is sub-multiplicative.[33 34]

In this paper we examined patterns of radiation risk with time since exposure and age at exposure singly, rather than jointly. The joint estimation of weighting functions for these time related factors would stretch the limits of these data. One way to address this issue is to conduct analyses that make use of a theoretical model of carcinogenesis, such as the Armitage-Doll model. We explored the use of relatively simple parametric forms for exposure weighting functions to describe temporal variation in exposure effects. We used these models for testing simple hypotheses about temporal variation in exposure effects. Hauptmann *et al* have proposed an alternative regression modelling approach in which cubic splines are used to describe latency effects.[26 35] Cubic splines provide a highly flexible approach to modelling exposure time response associations. However, similar to considerations about using cubic splines to model dose response trends, a limitation of the approach is that it uses a relatively large number of degrees of freedom to produce model forms that are not necessarily easy to interpret. For these analyses, we have favoured the use of simpler parametric models to address questions about whether exposure effects tended to increase or decrease over time.

We found that we had a limited ability with these data to discriminate between models that provide similar goodness of fit. However, these analyses illustrate how exposure weighting functions may be applied in order to empirically evaluate hypotheses about variation in the relative effect of a protracted exposure with time since exposure and/or age at exposure.

Main message

Simple parametric models may be used to empirically evaluate the influence of time since exposure or age at exposure on cancer incidence or mortality in occupational and environmental cohort studies.

ACKNOWLEDGEMENTS

The authors are grateful to Geoffrey Howe at the Mailman School of Public Health, Columbia University for his valuable comments on this work. Funding for record linkage and other resources were provided by Health Canada and Statistics Canada. The authors are also grateful to Kathy Gale of AECL, Martha Fair, and Dores Zucharini of Statistics Canada. Dr Richardson was supported, in part, by grant RO3-OH0721-01 from the National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention.

Authors' affiliations

D B Richardson, Department of Epidemiology, School of Public Health, University of North Carolina, Chapel Hill, NC, USA
J P Ashmore, McLaughlin Centre for Population Health Risk Assessment, Institute of Population Health, University of Ottawa, Ottawa, ON, Canada

REFERENCES

1 **Rothman KJ**. Induction and latent periods. *A J Epidemiol* 1981;**114**:253–9.
2 **Salvan A**, Stayner L, Steenland K, *et al*. Selecting an exposure lag period. *Epidemiology* 1995;**6**:387–90.
3 **Pearce N**. Methodological problems of time-related variables in occupational cohort studies. *Rev Epidemiol Sante Publique* 1992;**40**(Suppl 1):S43–S54.
4 **Checkoway H**, Pearce N, Hickey JL, *et al*. Latency analysis in occupational epidemiology. *Arch Environ Health* 1990;**45**:95–100.
5 **Darby SC**, Nakashima E, Kato H. A parallel analysis of cancer mortality among atomic bomb survivors and patients with ankylosing spondylitis given X-ray therapy. *J Natl Cancer Inst* 1985;**75**:1–21.
6 **Richardson DB**, Wing S, Hoffmann W. Cancer risk from low-level ionizing radiation: The role of age at exposure. *Occup Med* 2001;**16**:191–218.
7 **Richardson DB**, Wing S. Radiation and mortality of workers at Oak Ridge National Laboratory: positive associations for doses received at older ages. *Environ Health Perspect* 1999;**107**:649–56.
8 **Ritz B**, Morgenstern H, Moncau J. Age at exposure modifies the effects of low-level ionizing radiation on cancer mortality in an occupational cohort. *Epidemiology* 1999;**10**:135–40.
9 **Cardis E**, Gilbert E, Carpenter L, *et al*. Combined Analyses of Cancer Mortality Among Nuclear Industry Workers in Canada, the United Kingdom and the United States of America. Lyon, France: World Health Organization, International Agency for Research on Cancer, 1995.
10 **National Research Council, Committee on the Biological Effects of Ionizing Radiation (BEIR IV)**. *Health risks of radon and other internally deposited alpha-emitters*. Washington, DC: National Academy Press, 1988.
11 **Richardson DB**, Wing S. Greater sensitivity to ionizing radiation at older age: follow-up of workers at Oak Ridge National Laboratory through 1990. *Int J Epidemiol* 1999;**28**:428–36.
12 **Langholz B**, Thomas D, Xiang A, *et al*. Latency analysis in epidemiologic studies of occupational exposures: application to the Colorado Plateau uranium miners cohort. *Am J Ind Med* 1999;**35**:246–56.
13 **Ashmore JP**, Krewski D, Zielinski JM, *et al*. First analysis of mortality and occupational radiation exposure based on the National Dose Registry of Canada. *Am J Epidemiol* 1998;**148**:564–74.
14 **Sont WN**, Zielinski JM, Ashmore JP, *et al*. First analysis of cancer incidence and occupational radiation exposure based on the National Dose Registry of Canada. *Am J Epidemiol* 2001;**153**:309–18.
15 **Thierry-Chef I**, Pernicka F, Marshall M, *et al*. Study of a selection of 10 historical types of dosemeter: variation of the response to Hp(10) with photon energy and geometry of exposure. *Radiat Prot Dosimetry* 2002;**102**:101–13.
16 **Gribbin MA**, Weeks JL, Howe GR. Cancer mortality (1956–1985) among male employees of Atomic Energy of Canada Limited with respect to occupational exposure to external low-linear-energy-transfer ionizing radiation. *Radiat Res* 1993;**133**:375–80.
17 **Cardis E**, Gilbert ES, Carpenter L, *et al*. Effects of low doses and low dose rates of external ionizing radiation: cancer mortality among nuclear industry workers in three countries. *Radiat Res* 1995;**142**:117–32.
18 **Zablatoska LB**, Ashmore JP, Howe GR. Analysis of mortality experience amongst Canadian nuclear power industry workers. *Radiat Res* 2004.
19 **Howe GR**. Use of computerized record linkage in cohort studies. *Epidemiol Rev* 1998;**20**:112–21.
20 **Richardson D**. An incidence density sampling program for nested case control analyses. *Occup Environ Med* 2004;**61**:e59.
21 **Robins JM**, Gail MH, Lubin JH. More on ''Biased selection of controls for case-control analyses of cohort studies''. *Biometrics* 1986;**42**:293–9.
22 **Frome EL**, Cragle DL, Watkins JP, *et al*. A mortality study of employees of the nuclear industry in Oak Ridge, Tennessee. *Radiat Res* 1997;**148**:64–80.
23 **SAS**. *Version 8.01*. Cary, NC: SAS Institute, 1999.
24 **SAS Institute Inc**. SAS Technical Report P-229, SAS/STAT Software: Changes and Enhancements, Release 6.07. Cary, NC: SAS Institute, Inc, 1992.
25 **Checkoway H**, Rice CH. Time-weighted averages, peaks, and other indices of exposure in occupational epidemiology. *Am J Ind Med* 1992;**21**:25–33.
26 **Hauptmann M**, Berhane K, Langholz B, *et al*. Using splines to analyse latency in the Colorado Plateau uranium miners cohort. *J Epidemiol Biostat* 2001;**6**:417–24.
27 **National Research Council, Committee on the Biological Effects of Ionizing Radiation (BEIR V)**. *Health effects of exposure to low levels of ionizing radiation (BEIR V)*. Washington, DC: National Academy Press, 1990.
28 **Weiss HA**, Darby SC, Doll R. Cancer mortality following X-ray treatment for ankylosing spondylitis. *Int J Cancer* 1994;**59**:327–38.
29 **Weiss HA**, Darby SC, Fearn T, *et al*. Leukemia mortality after X-ray treatment for ankylosing spondylitis. *Radiat Res* 1995;**142**:1–11.
30 **Preston DL**, Kusumi S, Tomonaga M, *et al*. Cancer incidence in atomic bomb survivors. Part III. Leukemia, lymphoma and multiple myeloma, 1950–1987 [published erratum appears in *Radiat Res* 1994;**139**:129]. *Radiat Res* 1994;**137**(2 Suppl):S68–97.
31 **Ritz B**. Radiation exposure and cancer mortality in uranium processing workers. *Epidemiology* 1999;**10**:531–8.
32 **Kneale GW**, Stewart AM. Factors affecting recognition of cancer risks of nuclear workers. *Occ Environ Med* 1995;**52**:515–23.
33 **Pierce DA**, Sharp GB, Mabuchi K, Department of Statistics RERFHPHJprj. Joint effects of radiation and smoking on lung cancer risk among atomic bomb survivors. *Radiat Res* 2003;**159**:511–20.
34 **Pierce DA**, Radiation Effects Research Foundation HJprj. Age-time patterns of radiogenic cancer risk: their nature and likely explanations. *J Radiol Prot* 2002;**22**:A147–54.
35 **Hauptmann M**, Wellmann J, Lubin JH, *et al*. Analysis of exposure-time-response relationships using a spline weight function. *Biometrics* 2000;**56**:1105–8.