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BIOLOGICALLY BASED ANALYSIS OF LUNG CANCER INCIDENCE IN A LARGE CANADIAN OCCUPATIONAL COHORT WITH LOW-DOSE IONIZING RADIATION EXPOSURE, AND COMPARISON WITH JAPANESE ATOMIC BOMB SURVIVORS

William D. Hazelton[1], Suresh H. Moolgavkar[1], Stanley B. Curtis[1], Jan M. Zielinski[2], J. Patrick Ashmore[3], Daniel Krewski[4]

[1]Fred Hutchinson Cancer Research Center, Seattle, Washington, USA
[2]Healthy Environments and Consumer Safety Branch, Health Canada, Ottawa, Ontario, and Department of Epidemiology and Community Medicine, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada
[3]Radiation Protection Bureau, Health Canada, Ottawa, Ontario, Canada
[4]Department of Epidemiology and Community Medicine, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, and McLaughlin Centre for Population Health Risk Assessment, University of Ottawa, Ottawa, Ontario, Canada

Lung cancer incidence is analyzed in a large Canadian National Dose Registry (CNDR) cohort with individual annual dosimetry for low-dose occupational exposure to gamma and tritium radiation using the two-stage clonal expansion model (TSCE) and extensions of the model with up to 10 initiation steps. Models with clonal expansion turned off provide very poor fits and are rejected. Characteristic and distinct temporal patterns of excess relative risk (ERR) are found for dose response affecting early, middle, or late stages of carcinogenesis, that is, initiation with one or more stages, clonal expansion, or malignant conversion. Both fixed lag and lag distributions are used to model time from first malignant cell to incidence. Background rates are adjusted for gender and birth cohort. Lacking individual smoking data, surrogate annual smoking doses based on U.S. annual per capita cigarette consumption appear to account for much of the birth cohort effect, leaving radiation dose response relatively unchanged. The mean cumulative exposure for males receiving nonzero cumulative doses of gamma and tritium radiation was 18.2 mSv. The males have a significant dose response with 33 out of a total of 322 lung cancer cases attributable to radiation. There were 78 incident lung cancer among females, (with mean cumulative exposure of 3.8 mSv among females with nonzero exposure). The dose response for females appears smaller than for males but does not differ significantly from zero or from the male dose response. Findings for males include significant dose-response relationships

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Address correspondence to William D. Hazelton, Fred Hutchinson Cancer Research Center, Public Health Sciences Division, M2-B500, 1100 Fairview Avenue North, Box 19024 Seattle, WA 98109-1024, USA. E-mail: hazelton@fhcrc.org

for promotion and malignant conversion, but not initiation, and a protraction effect (sometimes called an inverse-dose-rate effect, where risk increases with protraction of a given dose). The dose response predicted by our analysis appears consistent with the risk for lung cancer incidence in the Japanese atomic bomb survivors cohort, provided that proper adjustments are made for duration of exposure and differences in background rate parameters.

Little is known about the effects of human exposure to low levels of gamma, beta, x-ray, or tritium radiation. These particles deposit energy relatively sparsely along their tracks as they penetrate biological tissue, and are classified as low-linear-energy-transfer (low-LET) radiation.

U.S. regulatory guidelines for low-LET exposure (National Council on Radiation Protection and Measurement, 2001) rely heavily on analysis of incidence and mortality among atomic bomb survivors (Thompson et al., 1994; Pierce et al., 2005). This practice raises several questions. Can risk be reliably extrapolated from the generally high-dose acute exposures of the Japanese atomic-bomb survivors to the low-dose, often protracted exposures, seen among some Western working populations? Also, should one use the excess relative risk (ERR) or some other quantity when attempting to extrapolate risk between high and low doses or from one population to another?

The Canadian radiation workers cohort analyzed here for lung cancer incidence is particularly interesting because of its size (over 190,000 individuals) and because the low mean radiation exposures received by the workers are in the range of interest for regulatory agencies.

Previous analysis of this cohort (with some difference in exclusions) by Sont et al. (2001) led to estimates for ERR that appear at first glance to be approximately an order of magnitude higher than estimates based on extrapolation from the atomic bomb survivors. Some authors (Gilbert, 2001) have raised questions about the possibility of confounding in the Canadian cohort because of this apparent discrepancy. However, we show in this article that the dose-response estimates for the Canadian cohort are not inconsistent with the atomic-bomb data.

Worker studies do have limitations, often including large exposure uncertainties and potential confounders. However, they have a significant role to play in ascertaining the effects of protraction of exposure that cannot be addressed through analysis of the atomic bomb survivors' data.

MATERIAL AND METHODS

The Radiation Protection Bureau of Health Canada maintains the National Dose Registry (NDR), containing personal dosimetry records for Canadian workers exposed to ionizing radiation dating back to 1951, with current records for over 500,000 individuals. These records were linked by computer to the Canadian Cancer Data Base (CCDB) with records covering the period from 1969 to 1988, providing incidence information for lung cancer as well as

other outcomes. In linkage, pairs of records were assigned probabilistic link weights based on agreement, partial agreement, or discrepancies in phonetically coded surname, first and second given names (or initials), the year, month, and day of birth, sex, and the relation between data such as the year of death and year of last monitoring, place of death, and place of last monitoring. Miners were excluded from the linkage because records for gamma exposure were available for them only after 1980. We expect soon to have incidence information updated to include follow-up through 1996.

The Canadian National Dose Registry (CNDR) cohort we analyze consists of 191,042 individuals with complete records in the NDR database for radiation exposure between 1951 and 1988, who were successfully linked to the CCDB databases providing lung cancer incidence information between 1969 and 1988. Further information on dosimetry and linkage of incidence with the NDR database is available in other sources (Sont et al., 2001; Ashmore et al., 1998). Individual records contain requisite personal information and annual exposure values for several categories of ionizing radiation. The personal information consists of a unique identification number, gender, job category (dental, medical, industrial, or nuclear power), birth year, diagnosis year (if applicable), death year (if applicable), cancer incidence flag (lung, other cancer, or none), death flag (alive, lung cancer, other death), and a flag indicating possible exposure to neutron radiation at any time during employment. Annual exposure information is based on personal badge dosimetry and includes cumulative annual values for whole-body and skin exposure to gamma and tritium radiation. Tritium dose equivalents make up 9.0% of the collective dose. Individuals flagged for possible exposure to neutrons have additional flags indicating each year with possible neutron exposure.

There are 95,439 males in the CNDR cohort, with mean cumulative radiation exposures to combined whole-body gamma and tritium radiation of 18.2 mSv for the 60,677 males with nonzero exposure. The cohort includes 95,603 females, with mean combined exposure of 3.8 mSv for the 44,238 females with nonzero exposure. During follow-up, 322 males and 78 females were diagnosed with lung cancer. During the same period, 231 males and 42 females died from lung cancer.

Models

The two-stage clonal expansion (TSCE) and the extended models are stochastic models of stem cell kinetics and "mutation," corresponding closely to the initiation, promotion, malignant conversion, and progression paradigm of carcinogenesis (see, e.g., Moolgavkar & Venzon, 1979; Moolgavkar & Lubeck, 1990; Lubeck & Moolgavkar, 1996; Kopp-Schneider, 1997; Heidenreich et al., 1997; Hazelton et al., 2001; Little, 1995). We assume a normal stem-cell population of fixed size X. In the TSCE model, any of these cells may undergo Poisson initiation at rate v to become initiated. In the extended model with n initiation steps, each normal cell may undergo up to n sequential heritable transitions at rates $v_1, v_2, \ldots, v_n$. This initiation process is similar to the Armitage–Doll (AD) multistage cancer model (Armitage & Doll, 1961), except

that the endpoint is an initiated cell (rather than a malignant cell as in the AD model). Subsequent steps are as follows for either the TSCE or extended model. Each initiated cell may divide symmetrically at rate α (or asymmetrically to an initiated and a differentiated cell, but this has no effect since the number of initiated cells remains the same), die or terminally differentiate at rate β, and mutate further to malignant status at rate μ. A fixed lag or lag distribution (a two-parameter gamma distribution) is utilized to represent the time from occurrence of the first malignant cell to lung cancer incidence.

Solutions for the extended model survival and hazard with piecewise constant parameters are given in the Appendix. Exact, easily programmable solutions are known for the TSCE model for piecewise constant exposures (Heidenreich et al., 1997). The TSCE model has fewer identifiable parameters than biological parameters, providing some freedom to rescale background parameters (Hazelton et al., 2001).

Construction of Likelihood

Assuming independence between individuals, the cohort likelihood is the product of individual likelihoods over all subjects j, $L = \Pi L_j$. Individual likelihoods $L_j = L_j(s_j, t_j, (\ldots))$ depend on time of entry into the study s_j, censoring or failure time t_j, birth cohort, and on detailed exposure histories in conjunction with general dose-response models for the biological parameters in the two-stage or extended model, and on the lag time or lag time distribution.

Let $P(t)$ represent the probability of death from lung cancer at time t, with survival $S(t) = 1 - P(t)$ and density $P'(t)$. The individual likelihoods for cases and survivors, including left truncation, are given by

$$L_j(t_j, s_j) = \begin{cases} P'(t_j)/S(s_j) & \text{if diagnosed with lung cancer} \\ S(t_j)/S(s_j) & \text{otherwise} \end{cases} \quad (1)$$

Furthermore, let $h_m(u)$ represent the individual two-stage or extended model hazard and $S_m(u)$ represent the two-stage or extended model survival at time u. For a fixed lag time from first malignant cell to lung cancer incidence t_{lag}, individual likelihoods in Eq. (1) are calculated using $S(t_j) = S_m(t_j - t_{lag})$; $S(s_j) = S_m(s_j - t_{lag})$; $P'(t_j) = h_m(t_j - t_{lag})\, S_m(t_j - t_{lag})$. For a lag time distribution, the density $P'(t_j)$ in Eq. (1) is given by the convolution of the TSCE or extended model density, $P'_m(u) = h_m(u)S_m(u)$ with a lag time distribution $f(t_j - u)$, $P'(t_j) = \int_0^{t_j} h_m(u)S_m(u)f(t_j - u)\, du$.

The survival $S(t_j)$ is calculated by convolving the two-stage or extended model probability $(1 - S_m(u))$, with the lag time distribution up to the time of censoring, $S(t_j) = 1 - \int_0^{t_j} (1 - S_m(u))f(t_j - u)\, du$.

Left truncation requires calculation of the survival $S(s_j)$ at entrance into the study.

A gamma distribution, $f(x,a,b) = \frac{1}{b^a \Gamma(a)} x^{a-1} e^{-x/b}$, with mean $\mu_{lag} = ab$, variance $\sigma^2_{lag} = ab,^2$ and lag time argument $x = t_j - u$ is used with the fully parameterized models. Gauss–Legendre quadrature (with variable number of Gauss points to check convergence) is used for numerical integration and convolution, with likelihood optimization in High Performance Fortran for parallel computation.

Birth Cohort Effect

In modeling lung cancer incidence without individual smoking data, a birth cohort effect may primarily reflect smoking trends. Previous analyses of lung cancer mortality using the TSCE model (Hazelton et al., 2001; Lubeck et al., 1999; Moolgavkar et al., 1993) with individual smoking data available indicate that smoking may significantly affect several steps in the initiation, promotion, and malignant conversion process. In searching for the best representation for birth cohort effect, we test a number of functional forms, including linear, logarithmic, exponential, power law, and sigmoidal functions affecting only initiation, promotion, or malignant conversion, followed by all combinations. Multiplicative as well as additive forms are also compared. The best likelihoods with fewest parameters are found for the birth cohort effect acting as an exponential factor added to promotion, and multiplying the background malignant transformation and initiation rates in equal amounts, as shown in Table 1.

To see if the male birth cohort effect is related to smoking trends, we use surrogate dose information based on annual apparent per capita cigarette consumption among U.S. males between 1900 and 1990 (Psoter & Morse, 2001). A dose-response model is introduced assuming each individual receives a cigarette dose appropriate to the calendar year beginning at a given age to replace the birth cohort effect. The surrogate dose is allowed to affect initiation, promotion, and malignant transformation. This model gives the best fits with the surrogate smoking dose beginning between ages 13–15 (Armitage & Doll, 1961; Lubeck et al., 1999; Moolgavkar et al., 1993). The likelihood improves over no adjustment by about two-thirds of the improvement seen with a birth cohort effect. The results presented here utilize the nonspecific birth cohort effect.

Estimates for background parameters (with either the birth cohort or surrogate doses) do not differ significantly between optimizations for the subcohort of unexposed workers as compared to optimizations with the full cohort subject to radiation dose-response parameterization.

Dose-Response Modeling

Initiation, promotion, and malignant conversion are each parameterized as $c_0(1 + c_1 d_r^{c_2})$, with c_0 representing the corresponding background rate, c_1 a dose-response coefficient, and c_2 a power of the total radiation dose rate, d_r =

TABLE 1. Two-Stage Clonal Expansion Model (TSCE) With Birth Cohort, Background Parameters, and Full or Reduced Dose-Response Models for the Influence of Combined Gamma and Tritium Radiation, Using Six Dose-Response Parameters in the Full Model (p_6–p_{11}) and Three in the Reduced Model (p_6, p_7, p_{10})

TSCE model and parameter estimates using fixed lag or gamma distribution lag	Comment
Background parameterization:	Allowable rescaling: (using constants c_1, c_2 such that X, ν_0, μ_0, α_0 positive definite, $\alpha_0 \geq g_0$)[a] (normal stem cells) $X \rightarrow X \times c_1$ (bkg. cell division) $\alpha_0 \rightarrow \alpha_0 \times c_2$ (bkg. net cell proliferation) $g_0 \rightarrow g_0$ (bkg. initiation, birth cohort) $\nu_0 \rightarrow \nu_0 \times c_2/c_1$ (bkg. conversion, birth cohort) $\mu_0 \rightarrow \mu_0/c_2$
$X = 10^7$	
$\alpha_0 = p_1$	
$g_0 = p_2$	
$\nu_0 = p_3 \times f_{bc}$	
$\mu_0 = \nu_0$ (before rescaling)	
$f_{bc} = \exp\{p_4 \times (\text{birth year} - 1930)\}$	(birth cohort effect)
$\alpha_{bc} = g_{bc} = p_5 \times f_{bc}$	(promotion birth cohort effect)
Dose-response: $d_r = d_{gamma} + d_{tritiam}$	(combined gamma, tritium dose units of 1 mSv)
Full model: Reduced model:	
$g_r = p_6 \times d_r^{p_7}$ $g_r = p_6 \times d_r^{p_7}$	(radiation effect on net cell proliferation)
$\alpha_r = g_r$ $\alpha_r = g_r$	(net cell division [no significant difference from g_r])
$\nu_r = p_8 \times d_r^{p_9}$ $\nu_r = 0$	(radiation effect on initiation [not significant])
$\mu_r = p_{10} \times d_r^{p_{11}}$ $\mu_r = p_{10}$	(malignant conversion [dose power not significant])
Lag: $f_{lag}(x,a,b) = \frac{1}{b^a \Gamma(a)} x^{a-1} e^{-x/b}$ $t_{lag} = p_{12}$	(gamma distribution with x as lag, or fixed lag)
$\mu_{lag} = p_{12} = a \times b$ $\sigma_{lag} = p_{13} = \sqrt{a \times b^2}$	(mean, std. dev. for gamma distribution)
$\alpha_i = \alpha_0 \times (1 + \alpha_{bc} + \alpha_r)$ $\nu_i = \nu_0 \times (1 + \nu_r)$	(combined cell division, combined initiation)
Identifiable parameters:	
$y_i = u_i X/\alpha_i$	(tissue initiation scaled by cell division rate)
$g_i = g_0 \times (1 + g_{bc} + g_r)$	(approximate net cell proliferation rate)
$r_0 = \alpha_0 \mu_0$	(background cell division, malignant conversion)
$\alpha_i = (1 + \alpha_{bc} + \alpha_r)$	(cell division relative to background)
$m_i = (1 + \mu_r)$	(malignant conversion relative to background)

p_1	α_0	0.2888	(0.113	0.737)	0.3110	(2.10^{-8}	0.78)	$1.0\ 10^{-3}$ [b]	(~0	4.110^{2})
p_2	g_0	0.2715	(0.216	0.341)	0.2683	(0.044	0.325)	0.2042	(0.180	0.231)
p_3	ν_0,μ_0	2.19×10^{-9}	$(7.8 \times 10^{-10}$	$6.1 \times 10^{-9})$	2.26×10^{-9}	$(7 \times 10^{-10}$	$9 \times 10^{-9})$	1.37×10^{-10}	$(7.2 \times 10^{-11}$	$2.6 \times 10^{-10})$
p_4	bc	0.0405	(0.025	0.066)	0.0405	(0.034	0.046)	0.0251	(0.021	0.030)
p_5	g_{bc},α_{bc}	0.1664	(0.053	0.526)	0.1601	(0.072	0.238)	0.9978	(0.867	1.115)
p_6	g_{r1},α_{r1}	0.0135	$(3.7 \times 10^{-4}$	0.498)	0.0255	$(5 \times 10^{-4}$	3.55)	4.73×10^{-4}	$(4.3 \times 10^{-7}$	0.047)
p_7	g_{r2},α_{r2}	0.6943	(0.138	3.414)	0.6699	(~0	1.50)	0.6266		
p_8	ν_{r1}	0.5840	(~0	10.49)				0.3461		
p_9	ν_{r2}	0.0031						0.0033		
p_{10}	μ_{r1}	0.4219	(0.144	1.237)	0.5133	(0.12	1.02)	0.3316	(0.074	1.0)
p_{11}	μ_{r2}	0.4012	(0.112	1.431)				0.4328		
p_{12}	μ_{lag},t_{lag}	5.3313	(5.264	5.400)	5.007	(2.99	5.67)	3.5840	(0.379	33.82)
p_{13}	σ_{lag}	0.1630	(0.135	0.196)				0.2753	(~0	835.8)

[a] Background parameters may be rescaled as in reference (Hazelton et al., 2001).
[b] Parameter at lowest possible rescalable value.

$d_{gamma} + d_{tritium}$ with units of millisieverts per year. We also compare dose-responses with adjustable dose rate threshold, but this does not significantly improve the fit. Gamma and tritium exposures are combined as already described on an annual basis with no adjustment for background radiation exposure. Testing shows marginal likelihood improvement with separate dose-response parameterization. Combining gamma and tritium doses with an adjustable biological effectiveness factor for the tritium does not improve the likelihood significantly.

The fitting of parameters proceeds as follows. First background parameters are fitted using the subcohort with no radiation exposure. Then preliminary TSCE models are optimized assuming dose response only on initiation, promotion, or malignant conversion steps. Subsequently, combined dose response is introduced affecting all combinations of these steps. Table 1 presents a full model for combined gamma and tritium doses and a reduced or simplified dose-response model where parameters are eliminated as possible on the basis of likelihood ratio tests, while keeping biological plausibility in mind. In particular, we assume a two-parameter dose-response form for promotion that allows saturation of response at high dose rates. Estimation while forcing dose response on promotion to be linear gives somewhat poorer likelihoods but is not rejected statistically at the 95% confidence level. However, this leads to a very high excess relative risk (ERR) at large dose rates. For females, the likelihood surface for background birth rate α_0 is very flat, allowing this parameter to drift to implausibly low values, even when rescaling of parameters (Hazelton et al., 2001) is taken into account. Thus we set a lower bound for this parameter during estimation (causing almost no difference in likelihood estimates). The dose response for females is consistent with no effect and also with the male dose response. Joint analysis of male and female dose response with separate birth cohort and background rates gives estimates for dose response almost identical to those for males.

RESULTS

Lung cancer incidence among the 95,430 males in the cohort is strongly associated with whole-body gamma radiation. Dose response for gamma radiation or combined gamma and tritium is significant for promotion and malignant conversion as shown in Table 1. Whole-body tritium exposures are generally small in comparison with gamma exposures, and the dose response for tritium considered separately is marginally significant.

Figure 1 shows the temporal patterns of ERR for several doses, durations of exposure, and ages at exposure, for three preliminary TSCE models optimized for the male cohort with dose response affecting only initiation, promotion, or malignant conversion. The solid lines assume dose response only on initiation, dashed lines have dose response only on promotion, and dotted lines have dose-response only on malignant conversion. Plots of ERR and EAR are shown

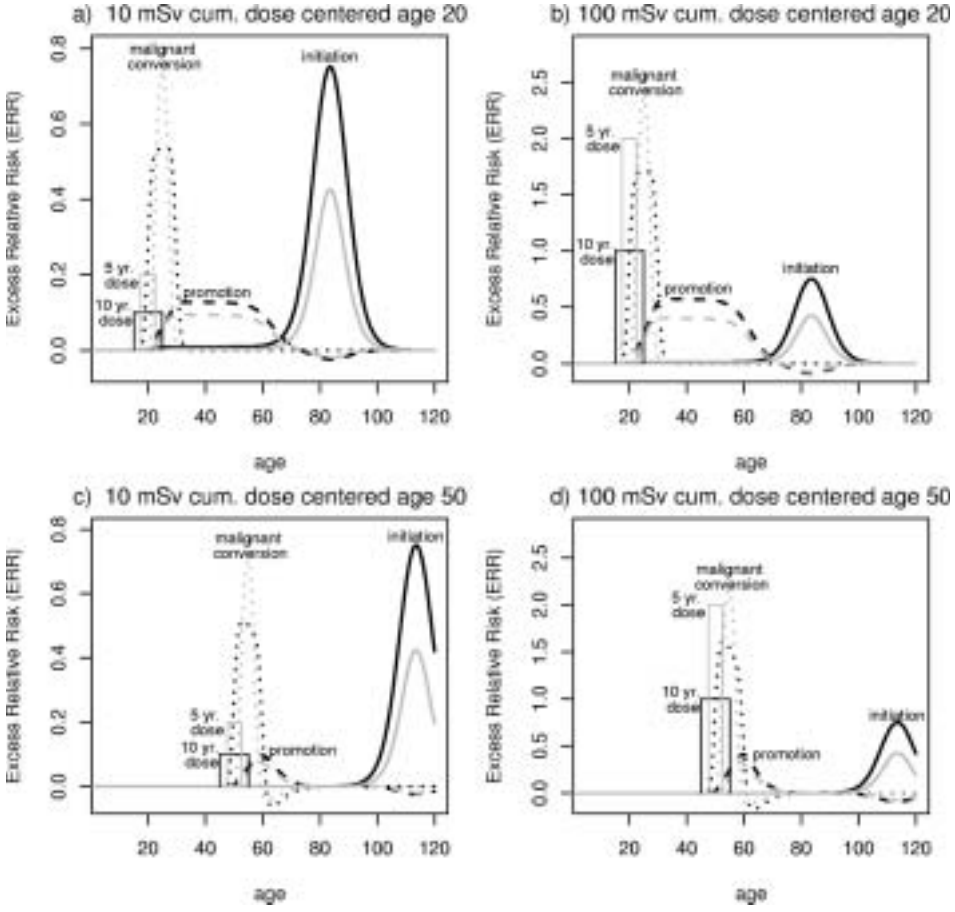

FIGURE 1. ERR estimates depend on exposure history and model assumptions. The four panels show the ERR for 10- or 100-mSv cumulative exposures centered at 20 or 50 yr of age. Each panel shows three separate TSCE model optimizations for Canadian males corresponding to dose response only on initiation (solid), promotion (dashed), or malignant conversion (dotted) for 5-yr (grey) and 10-yr (black) protractions.

in Figure 2 with dose response simultaneously affecting initiation, promotion, and malignant conversion steps in the TSCE model. The contributions from each step that are overlaid in Figure 1 are seen to contribute more or less separately to the temporal patterns of risk shown in Figure 2. With current follow-up, initiation appears highly uncertain, but if it is important, the model predicts a significant increase in ERR only at old age and only in association with early exposure.

The ERR generally increases with protraction of a given dose, often called an inverse dose-rate or protraction effect. However, in the first few years following end of exposure, there may be a direct dose-rate effect as shown in

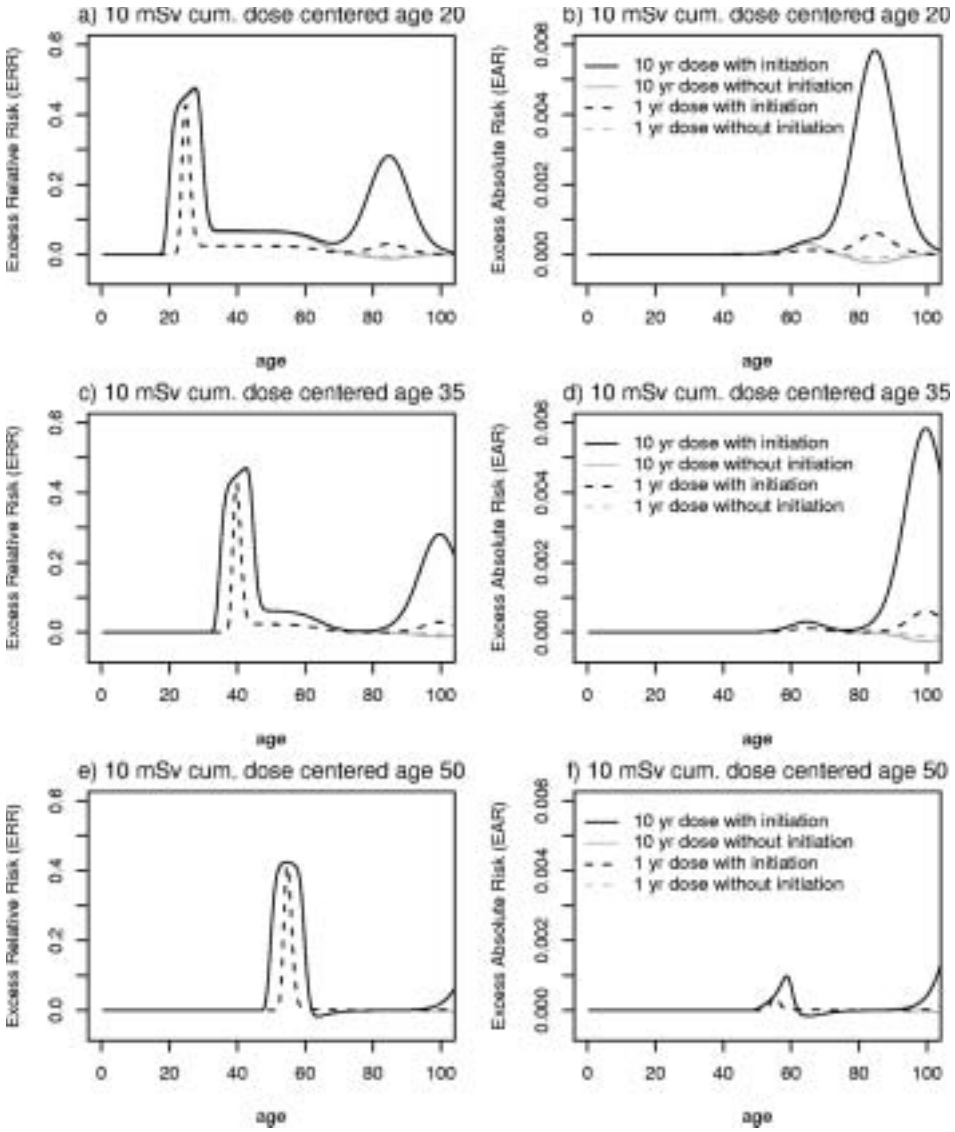

FIGURE 2. Comparison of excess relative risk (ERR) and excess absolute risk (EAR) based on the full male TSCE model (black), or the full model with dose response on initiation turned off (gray); 10-mSv exposures are protracted for 1 yr (dashed lines) or 10 yr (solid lines), centered at ages 20, 35, or 50 yr.

Figure 3a. Promotion and malignant conversion are both significant, but dose response on initiation makes an insignificant improvement in likelihood. ERRs for the full model, with or without dose-response on initiation, and for the reduced model are shown in Figure 3b. The full and reduced models shown in Table 1 lead to differences in ERR centered around age 85 yr, primarily

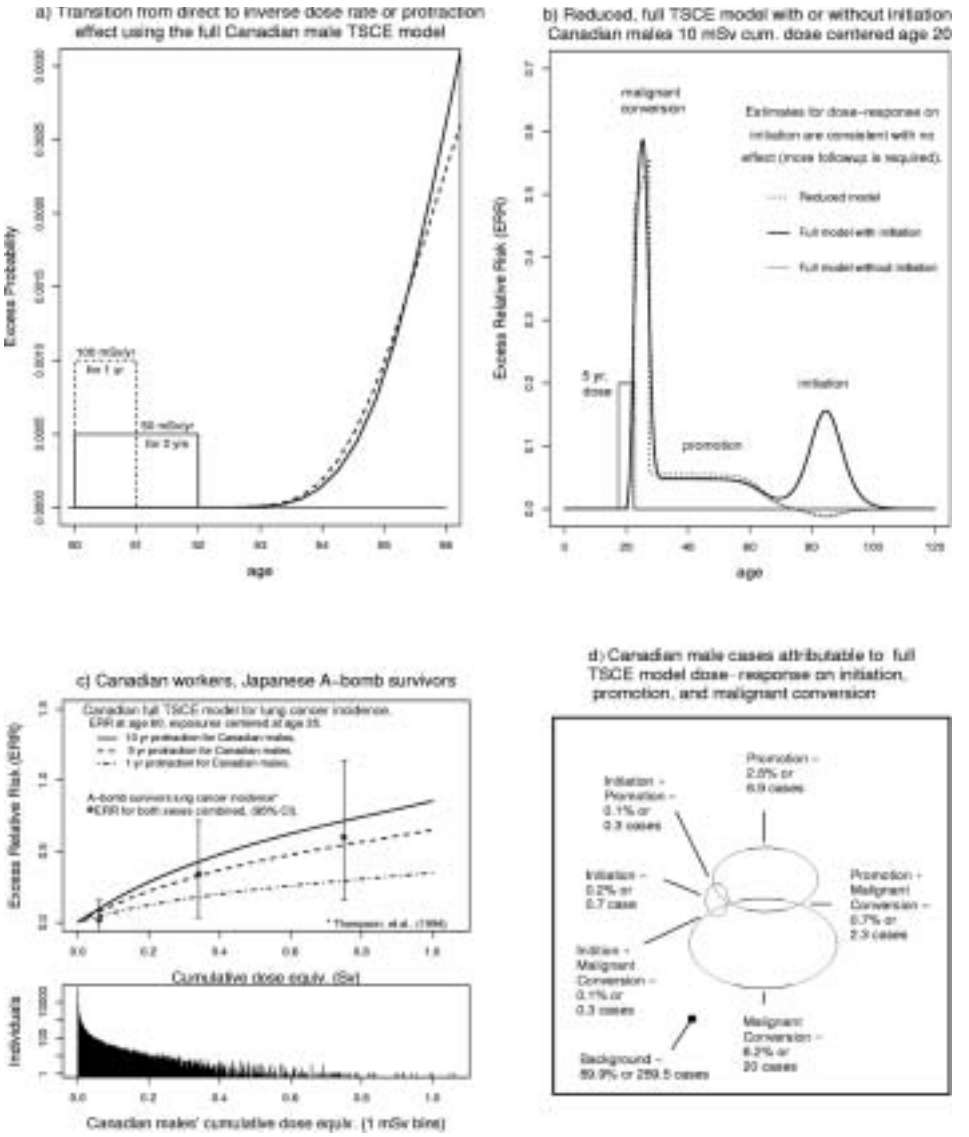

FIGURE 3. (a) The excess probability using the full male TSCE model shows a transition from direct to inverse dose-rate effect for 100-mSv total exposure protracted either 1 or 2 yr. b) Comparison of ERR for full male model, with or without dose response on initiation, with reduced model. (c) ERR for Canadian males as a function of cumulative exposure for 1-, 5-, and 10-yr protractions centered at age 35, compared with ERR for incidence among atomic bomb survivors. Most Canadian workers received low doses (see lower frame). The calculated ERR per sievert for the average Canadian worker is high compared with that of the Japanese atomic-bomb survivors because the slope of the ERR curves for Canadian males at low doses is relatively steep compared with the slope at higher doses. (d) Radiation-related initiation, promotion, and malignant conversion, and combinations of these, account for approximately 10% of the total number of cases. Malignant conversion appears most important, given current follow-up.

because of the uncertainty in dose-response effects for initiation. Figure 3c shows that the ERR for males is concave downward with increasing radiation exposure centered at age 35. The attributable risk associated with initiation, promotion, and malignant conversions are shown in Figure 3d. Background processes appear to account for approximately 90% or 288 cases, radiation-dependent promotion for 9 cases, radiation-dependent malignant conversion for 20 cases, radiation-dependent initiation for about 1 case, and the combination of promotion and malignant conversion appear responsible for about 2 cases. Approximately 31 cases are attributable to gamma exposure and 2 cases to tritium exposure.

Table 2 shows tabulated values for observed versus expected number of incident lung cancer cases for the reduced male TSCE model for gamma versus tritium, cumulative dose versus duration, and birth year versus dose and duration. These factors are categorized into bins of no exposure or exposure quartiles.

We are concerned about potential confounding of results by work environments that may allow exposure to low levels of neutrons for some individuals in the cohort. We analyze a restricted cohort of 69,826 males not flagged for possible neutron exposure. Background and dose-response parameter estimates for this subcohort do not differ significantly from estimates for the full male cohort. The tritium exposure response is not significant in this restricted cohort.

DISCUSSION

Why utilize several multistage clonal expansion models to analyze lung cancer incidence in the CNDR cohort of individuals exposed to low-dose external ionizing radiation? The motivation is not only to identify biological rate-limiting steps associated with lung cancer incidence, but also to improve risk estimation for the cohort and test the robustness of mathematical models (Little, 1995) that naturally predict changing risk throughout each individual's lifetime, depending on factors such as age at exposure, dose, duration, and age at follow-up.

Analyses based on the incidence cohort of atomic-bomb survivors are thought to provide quite reliable risk estimates for acute exposure to low-LET radiation for humans. As discussed later, analyses of occupational exposure cohorts with protracted exposure to low-LET radiation have been difficult to interpret, with wide confidence intervals and results that sometimes appear contradictory.

Animal studies have quite consistently indicated a direct dose-rate effect (increased risk with an increase in dose rate for the same cumulative dose) for low-LET radiation, although the effects of protraction appear to differ depending on animal species and strain. Based primarily on animal data exposed at medium to high dose rates, a direct dose rate effect with low-LET radiation has been assumed to apply to humans (National Council on Radiation Protection and Measurement, 2001). This is in contrast to evidence indicating there is an

TABLE 2. Observed Versus Expected Number of Lung Cancer Cases for the Reduced Male TSCE Model for Gamma Versus Tritium, Cumulative Dose Versus Duration, and Birth Year Versus Dose and Duration, with Each Factor Categorized Into Bins of No Exposure or Exposure Quartiles

	Observed vs. calculated Canadian male lung cancer cases by cumulative gamma and tritium dose quartiles, cumulative tritium (mSv)									
Cum. gamma (mSv)	None		0.01–0.54		0.54–3.10		3.10–14.95		14.95–237.45	
None	72/34762	71.07	2/257	1.02	3/159	0.96	1/39	0.35	0/3	0.05
0.01–0.50	46/14879	41.95	0/231	0.40	0/91	0.18	0/15	0.07	0/7	0.05
0.50–1.80	47/14320	46.57	2/408	0.89	1/226	0.51	0/47	0.20	0/7	0.01
1.80–9.44	44/13137	57.27	2/629	1.05	1/738	1.33	3/367	0.83	0/60	0.11
9.44–1059.14	72/9319	69.25	4/733	5.20	6/1043	5.07	9/1777	8.17	7/2176	9.41
Units	Cases/N	TSCE model	Cases/N	TSCE model	Cases/N	TSCE model	Cases/N	TSCE model	Cases/N	TSCE model
	Observed vs. calculated Canadian male lung cancer cases by cumulative low-LET dose and duration quartiles, exposure duration (yr)									
Cum. low-LET (mSv)	None		1		2–3		4–7		8–38	
None	72/34762	71.07	0/0	0.00	0/0	0.00	0/0	0.00	0	0.00
0.01–0.50	0/0	0.00	31/11551	27.50	15/3456	14.21	2/243	1.43	0/31	0.09
0.50–1.84	0/0	0.00	10/4398	8.00	20/7092	18.85	20/3224	19.64	1/358	2.19
1.84–9.90	0/0	0.00	4/1726	3.52	9/4041	9.19	22/5918	23.40	19/3466	26.20
9.90–1062.72	0/0	0.00	1/324	0.70	1/1295	2.77	10/3819	9.35	85/9726	83.84
Units	Cases/N	TSCE model	Cases/N	TSCE model	Cases/N	TSCE model	Cases/N	TSCE model	Cases/N	TSCE model

Continued

TABLE 2. *(Continued)*

	Observed vs. calculated Canadian male lung cancer cases by birth year and cumulative low-LET dose quartiles, cumulative low-LET (mSv)									
Birth year quintile	None		0.01–0.50		0.50–1.84		1.84–9.90		9.90–1062.72	
1891–1936	60/4851	56.98	39/2867	35.88	41/3123	41.40	49/3547	54.70	91/4423	87.26
1936–1945	9/6218	8.61	6/3467	5.03	8/3271	5.08	4/3148	5.34	4/2950	6.79
1945–1950	1/7068	3.29	2/3099	1.54	2/2707	1.39	0/2618	1.43	0/2364	1.70
1950–1955	2/8245	1.65	0/2774	0.57	0/2777	0.60	0/2649	0.61	1/2317	0.66
1955–1969	0/8380	0.54	1/3074	0.20	0/3194	0.23	1/3189	0.24	1/3110	0.26
Units	Cases/N	TSCE model	Cases/N	TSCE model	Cases/N	TSCE model	Cases/N	TSCE model	Cases/N	TSCE model

	Observed vs. calculated Canadian male lung cancer cases by birth year and low-LET duration quartiles, low-LET duration (yr)									
Birth year (mSv)	None		1		2–3		4–7		8–38	
1891–1936	60/4851	56.98	35/2640	32.14	41/2861	37.29	44/3162	47.17	100/5297	102.64
1936–1945	9/6218	8.61	6/3296	4.77	4/3427	5.24	8/2835	4.72	4/3278	7.50
1945–1950	1/7068	3.29	4/3500	1.71	0/3067	1.58	0/2186	1.22	0/2035	1.55
1950–1955	2/8245	1.65	0/3820	0.78	0/3027	0.66	0/2148	0.51	1/1522	0.49
1955–1969	0/8380	0.54	1/4743	0.32	0/3502	0.25	2/2873	0.21	0/1449	0.15
Units	Cases/N	TSCE model	Cases/N	TSCE model	Cases/N	TSCE model	Cases/N	TSCE model	Cases/N	TSCE model

inverse dose-rate effect for high-linear-energy-transfer (high-LET) radiation such as from radon exposure among humans. Studies with the TSCE model (Hazelton et al., 2001; Lubeck et al., 1999; Moolgavkar et al., 1993) indicate that the inverse dose-rate effect of high-LET radiation may be explained by an increase in promotion that appears to saturate with increasing dose rate. The promotion may be a response to growth signals regulating homeostasis.

A number of recent studies have shown inverse dose-rate effects for x-ray and gamma radiation in inducing somatic and germ-line mutations in mammalian cells at very low dose rates (Amundson & Chen, 1996; Colussi & Lohman, 1997; Vilenchik & Knudson, 2000; Furre et al., 1999; Koufen et al., 2000), with several models postulated to describe this phenomenon (Brenner et al., 1996). However, the very low dose rates in these studies appear to exceed the mean exposure rates for most individuals in the Canadian cohort.

Temporal Patterns of Risk

Exploration using the TSCE and extended models indicates that models with dose response affecting individual identifiable parameters associated with initiation, promotion, and malignant conversion contribute characteristic and distinct features of temporal risk that persist in the pattern of lifetime risk when all of these transition rates are allowed to vary with dose. Figure 1 shows the predicted ERR associated with several cumulative radiation doses, ages at exposure, and durations of exposure based on three different optimizations for the male cohort with dose response only on initiation, promotion, or malignant conversion. Of these three optimizations, the TSCE model with dose response only on initiation provides a small (insignificant) improvement in likelihood, whereas the likelihood is improved significantly for dose response on either promotion or malignant conversion. Likelihood ratio tests indicate that models with dose response on both promotion and malignant conversion steps are significantly better than on only one step.

An increase in malignant conversion due to occupational exposure acts on existing initiated and promoted intermediate cells, leading to a relatively prompt increase in ERR. The ERR with dose-response on promotion, as seen in Figure 1, rises a few years after first exposure, forming a plateau that continues until around age 60. A dose response on initiation that occur after childhood will cause a peak in risk approximately 60 yr after center age of exposure, as shown in Figure 1. Early childhood exposures that affect initiation may cause an elevated ERR throughout life, but the later occupational exposure of this cohort produces a significant rise only late in life.

The features just discussed, where only one of the identifiable parameters is assumed to be responsive to dose, are evident in the optimized full TSCE model analysis for males with combined dose-responses on initiation, promotion, and malignant conversion. Plots of lifetime ERR and excess absolute risk (EAR) based on the full model for several dose protractions centered at several ages are shown in Figure 2.

Perhaps the most striking feature is the inverse dose-rate or protraction effect. There is clearly a diminishing of response when the same dose is given at higher dose rates for correspondingly shorter durations, consistent with an inverse dose rate effect in the cohort. On the ERR scale, effects of malignant conversion appear large but actually represent few cases for early occupational exposures as indicated in the EAR plots, since the baseline risk is small. However, malignant conversion may hasten the date of incidence, especially with exposure at older age, and these features contribute significantly to the likelihood for the cohort. Effects of promotion tend to follow the response from malignant conversion, and also appear highly significant in this cohort. As the effects of promotion apparently diminish by ages 60–70, effects from initiation, to the extent it exists, may begin to rise for individuals with early occupational exposure. Although initiation estimates for the cohort are not statistically significant, they may become so with additional follow-up.

Dose-Rate Effects

The dose responses for malignant conversion, promotion, and initiation in the full model all increase as dose to a power, with a power of dose less than 1, as shown in Table 1. Malignant conversion can be modeled as a step function without harming the likelihood significantly, as shown in the reduced model in Table 1. The concave downward trends for dose response for initiation, promotion, and malignant conversion appear linked to the concave-downward trend for ERR when plotted against dose rate, as seen in Figure 3c. These results appear generally consistent with the ERR for lung cancer incidence for combined sexes seen among the atomic-bomb survivors (Thompson et al., 1994).

The inverse dose-rate or protraction effect found in association with low-dose exposure to gamma and tritium radiation using the TSCE model for the male cohort runs counter to accepted beliefs about the effects of protraction of exposure with low-LET radiation.

Mouse, rat, and dog experiments provide the strongest evidence indicating a direct dose rate effect for low-LET radiation risk for lung tumors in the animal models (National Council on Radiation Protection and Measurement, 2001). Clearly there are differences between animal lung tumor models and human lung cancer incidence, but there are also differences inherent in the temporal patterns of exposure, risk, and follow-up. The endpoint in animal studies generally occurs at most a few years after exposure. Figure 3a shows that the TSCE model predicts, in some scenarios, a transition from direct dose-rate effect for a few years after exposure to an inverse dose-rate or protraction effect thereafter. The plot shows the excess probability of male lung cancer incidence, with 100 mSv cumulative dose protracted for either 1 or 2 yr beginning at age 50, making a transition from direct to inverse dose-rate effect sometime after age 55, more than 3 yr after the end of the longest dose protraction interval.

Comparison of TSCE Model With Extended Multistage Models

As the dose response we found for promotion and malignant conversion appears to generally lead to an inverse dose-rate or protraction effect, the question arises: How model-dependent are these results? To address this question, we developed code that incorporates exact multistage initiation (with any number of stages) ahead of a clonal expansion stage, with rates for all stages based on piecewise constant individual radiation exposures.

Analysis using one initiation stage ahead of clonal expansion in the extended model gives parameter estimates for mutation and clonal expansion consistent with the TSCE model estimates, and almost identical likelihood values. (However, the TSCE model is more economical in use of parameters, requiring two fewer to represent the process because of identifiability considerations.) Adding a second initiation stage in the extended model improves the likelihood significantly, but the best estimates indicate a background promotion rate that is increased slightly, rather than decreased. Extended models with 1 to 10 initiation stages were tested, with the best likelihood found for 3 stages. Above 3 stages the likelihood gradually becomes worse. Promotion is highly significant in all these models, as determined by likelihood-ratio tests. Best estimates for the background promotion rate approach 0.3 excess divisions per intermediate cell per year for models with 3 or more initiation steps, an increase of about 15% above the TSCE model prediction. Thus the background promotion rate does not appear to be an artifact of the TSCE model. Exact Armitage–Doll models are nested within the extended models in the limit that cell birth and cell death approach zero. Based on the poor likelihoods for the extended models with cell birth and cell death set to zero, we find that pure Armitage–Doll models do not provide good fits to this cohort data.

Comparison With Japanese Atomic-Bomb Survivors' Incidence

A previous analysis of lung cancer incidence in the Canadian Dose Registry data, with some differences in exclusions, by Sont et al. (2001) found significant effects of low-LET radiation, with an ERR of 3.1/Sv. In an invited commentary on this study, Gilbert (2001) makes the point that these estimates are apparently not in agreement with accepted risk estimates based on Japanese atomic bomb survivors. There are two features common to the TSCE and extended models that appear to reconcile the apparent high ERR seen by Sont et al. with estimates from the atomic bomb survivors cohort. First is the concave-downward trend in ERR with dose in the Canadian male data, as seen in Figure 3c, leading to a smaller value for ERR per Sv at the higher cumulative doses typical of the atomic bomb survivors. Second is the apparent protraction effect predicted by the model that suggests there may be lower risks for acute exposures.

Comparisons of ERR per Sievert between different cohorts can be difficult due to nonlinear dose-response and protraction effects, and further complicated if background risks differ between cohorts. Figure 3c illustrates this,

where ERR curves are plotted for Canadian males with several exposure durations compared with the ERR for incidence among atomic bomb survivors (Thompson et al., 1994), including both genders. The slope of the ERR curves at low doses for 1-, 5-, and 10-yr protractions is quite steep, indicating a high ERR per Sievert for exposures typical of most Canadian workers (see lower frame). However, the nonlinearity in the curves lowers the estimates for ERR per Sievert at higher doses to values in the range of estimates for the Japanese atomic bomb survivors at comparable doses. The second point illustrated by Figure 3c is how comparison of ERRs between cohorts may be misleading when background cancer rates differ. Extrapolating the ERR for Canadian workers to short duration exposures appears to underpredict (rather than overpredict) the risk for equivalent doses among atomic-bomb survivors. However, this is due to the higher background lung cancer risk among Canadians compared with the Japanese. As discussed later and shown in Table 3, if the Canadian dose-response model is extrapolated to short-duration exposures, it makes quite good predictions of risk among atomic-bomb survivors when background rates are adjusted to fit the Japanese population.

Comparison of the models for Canadian workers with Japanese atomic-bomb survivors requires rather uncertain extrapolation from the annual dosimetry for the CNDR cohort to acute exposures. We represented acute exposures of the incidence data for male survivors from Hiroshima and Nagasaki with DS86

TABLE 3. Observed Male Incident Lung Cancer Cases and Person-Years at Risk Among Japanese Atomic-Bomb Survivors From Hiroshima and Nagasaki with DS86 Dosimetry and Follow-Up From 1958 to 1987, and Expected Cases With the Reduced Male TSCE Model Using Dose-Response Parameters as Optimized for the Canadian Males, but With Reoptimized Background Parameters

	Age, ATB	Attained age (yr)								
		10–19	20–29	30–39	40–49	50–59	60–69	70–79	80–89	90–99
Obs/Exp	0–9	0/0.0	0/0.2	0/1.9	8/3.7					
Per Yrs	0–9	24197	72733	60374	31964					
Obs/Exp	10–19		0/0.1	2/1.5	10/8.0	16/16.6				
Per Yrs	10–19		16612	67437	56980	32918				
Obs/Exp	20–29			0/0.2	2/2.3	10/10.7	19/24.6			
Per Yrs	20–29			5969	19168	19113	13092			
Obs/Exp	30–39				2/1.9	20/20.4	51/61.7	38/36.9		
Per Yrs	30–39				11844	35443	27236	8428		
Obs/Exp	40–49					10/11.2	93/80.8	94/84.3	20/19.9	
Per Yrs	40–49					16529	44956	20722	3982	
Obs/Exp	50–59						27/23.7	51/57.5	18/17.3	0/1.2
Per Yrs	50–59						12550	18795	4081	256
Obs/Exp	60–69							1/7.7	16/13.3	0/0.4
Per Yrs	60–69							2932	4242	114

Note. Values are observed vs. expected cases among male Japanese atomic-bomb survivors using fixed CNDR model dose response, reoptimized background parameters. Obs, observed; Exp, experimental; Per yrs, person-years.

dosimetry and follow-up from 1958 to 1987 as 2-wk protracted exposures (perhaps reflecting an interval of tissue repair following radiation damage) using the reduced male TSCE model. Table 3 shows the observed male incident lung cancer cases and person-years at risk among the Japanese atomic-bomb survivors, and expected cases with the reduced male TSCE model using dose-response parameters as optimized for the Canadian males, but with reoptimized background parameters. The fits appear fairly good, similar to fits by Kai et al. (1997) using a TSCE model with dose response only on initiation.

Kai et al. assumed in their analysis that only initiation was affected by acute exposure to ionizing radiation in the atomic-bomb cohort. Our model here indicates that promotion is far more important than initiation. How can we reconcile these two model descriptions? With short exposure durations, effects on initiation and promotion are difficult to distinguish because the TSCE model effectively sees only the number of new initiated cells created, either by de novo initiation of normal cells or the division of already initiated cells.

Low-level exposure to ionizing radiation is not the only cause of lung cancer. Tobacco consumption may differ significantly between the Canadian and Japanese cohorts, and preexisting health status can also be a factor in the development of cancer. We assume that the separately estimated background parameters for the Canadian and Japanese cohorts should adjust for these effects.

Analyses of incidence (Thompson et al., 1994; Pierce & Preston, 2000; Ron et al., 1994) and mortality (Ron et al., 1994; Pierce et al., 1996; Shimizu et al., 1996) for lung (and other) cancers among Japanese atomic bomb survivors find small but significant increases in ERR in association with acute low to high dose gamma radiation. In the most recent follow-up, from 1950 to 1990, of mortality in the Life Span Study (LSS) of individuals exposed at Hiroshima and Nagasaki, Pierce et al. (1996) and Preston et al. (2000) found childhood exposure associated with a large ERR that tends to decrease with age, but exposures at older ages associated with a nearly constant ERR. The LSS study began 5 yr after dropping of the bombs, so early deaths may be missed (Stewart & Kneale, 1993) (as may occur preferentially for older individuals in association with malignant conversion). There may be some evidence of selection bias (Stewart & Kneale, 1993; Stewart, 2000) in the atomic-bomb cohort, with a deficit of in utero children less than 8 wk of fetal age when exposed, and a significant deficit in the high-dose group of individuals under age 10 or over age 50 at time of bomb. Prenatal exposure to x-rays (Jablon & Kato, 1980) may be associated with larger risk than seen from the atomic bomb data. Enhanced risks for early exposure are consistent with TSCE and extended model projections.

Pierce et al. (1996) point out that there is an apparent concave-downward trend in ERR at low doses for all cancers, and for lung cancer incidence (Thompson, 1994) as shown in Figure 3c. Pierce suggests this apparent concave-downward nonlinear trend is of marginal significance (Pierce et al., 1996). This general trend is similar to the concave-downward dose-response for ERR found here with the low-dose exposures in the Canadian cohort.

Risk Patterns in Other Cohorts Exposed to Ionizing Radiation

There have been a number of lung cancer mortality studies but fewer analyses of lung cancer incidence in association with low-LET ionizing radiation in cohorts of nuclear workers, medical workers, medically treated individuals, atomic bomb survivors, individuals exposed by accidental release of radiation, and combined cohorts. (Thompson et al., 1994; Sont et al., 2001; Pierce & Preston, 2000; Ron et al.,1994; Pierce et al., 1996; Shimizu et al., 1996; Stewart, 2000; Cardis et al., 1995; Gribbin et al., 1993; Muirhead et al., 1999; Darby et al., 1993; Checkoway et al., 1988; Howe, 1995; Weiss et al., 1994; Gilbert et al., 1993; Wing et al., 1991; Beral et al., 1988; Ritz et al., 1999; Ritz, 1999; Kneale et al., 1981; Wing, 2000; Richardson & Wing, 1999; Kneale & Stewart, 1993).

Many of the previous studies with individuals receiving different patterns of exposure have been inconclusive. This is perhaps not surprising if ERR depends on detailed exposure patterns throughout life and age at follow-up, as suggested by this study. Many parameters are required for multifactorial analysis in statistical models that may lead to loss of power. In contrast, the models utilized here naturally predict time-dependent absolute individual risk that depends on exposure rate, duration, and age at first and last exposure, as well as more complicated exposure patterns, age at follow-up, and a birth cohort effect.

A large, combined analysis of cancer mortality among nuclear workers monitored at Hanford, WA, Oak Ridge National Laboratory (ORNL), TN, and Rocky Flats Weapons Plant, CO, in the United States by Gilbert et al. (1993) found a weak positive trend for lung cancer at Hanford and ORNL, a negative trend at Rocky Flats, and a combined trend statistic of 0.07 with wide confidence bounds indicating no significant correlation with radiation dose when assuming a constant ERR for all ages. A weak negative trend in ERR with dose was seen for all cancers combined. However, Gilbert et al. found a significant correlation at Hanford and ORNL of all cancers with radiation dose among individuals 75 yr and older ($p < .005$), although there was a weak negative trend in ERR with dose when analyzed for all ages. The correlation with the 75 + yr age group at Hanford was primarily due to lung cancer. Exposures at Hanford tended to occur at older ages than exposures for the ORNL cohort. The apparent trends for all cancer risk at Hanford and ORNL in the Gilbert et al. Table IX may share some features roughly consistent with TSCE model predictions shown in Figure 2. The Hanford ERR is weakly positive for <65 yr ages, dropping to negative values around ages 65–74, followed by strongly positive values for ERR at ages 75+, qualitatively consistent with TSCE model calculations shown (for male lung cancer in the Canadian cohort) in Figure 2, whereas the ORNL cohort ERR is positive for the 65–74 yr range, increasing to large values for ages 75+, again apparently consistent with TSCE model predictions for effects of promotion and perhaps initiation with exposure at earlier ages. Gilbert et al. (1993) suggest the age 75+ increase in Hanford and ORNL cohorts may

be questionable because in the atomic bomb survivors cohort, Pierce et al. (1991) found at most a small increase in all cancer risk at old ages. If there is a dose-response for initiation in the TSCE model, it would predict a much smaller increase in ERR at old age for equivalent doses given acutely.

Combining cohorts in studies without explicit modeling of individual exposure patterns may make it more difficult to reach significant conclusions about the effects of radiation exposure. Studies by Cardis et al. (1995) of 95,673 nuclear workers in three countries, including the U.S. cohorts studied by Gilbert et al., found a nonsignificant negative trend for lung cancer of –0.28 per Sievert (simulated *P* value of 0.61), but did not present an analysis of trends at older ages. A second analysis of mortality in an enlarged cohort of 124,743 workers in the National registry for Radiation Workers (NRRW) in the United Kingdom (Muirhead et al., 1999) assuming constant ERR following a lag period of 10 yr found a nonsignificant negative trend of –0.11 per Sievert, with 90% CI –0.72, 0.72 for the ERR of malignant neoplasms of the trachea, bronchus, and lung. A faster rise following first employment in the standard mortality ratio (SMR) for lung and esophageal cancer compared with the all-cause SMR may suggest excess respiratory malignancies occurring early in association with a malignant conversion process

Uncertainties

Various sources of bias and confounding may influence the apparent dose-response and age effects that are seen in this study. These include measurement and reporting error, including use of a threshold in reporting badge doses, no adjustment for background radiation exposures, possible low-level exposure to neutrons for some individuals, incorrect and incomplete linkage between the dose registry and incidence databases, misclassification of dose, and confounding associated with smoking, socioeconomic status, or other factors.

Smoking is a primary determinant of lung cancer incidence, and is thought to be a complete carcinogen, affecting initiation, promotion, and malignant conversion. Smoking patterns have changed markedly over time, but smoking information is not available for individuals in the cohort. We attempted to control for this and other secular trends by optimizing with a birth cohort effect in the models, finding a quite stable dose response to radiation with or without the birth cohort effect. As described in the Methods section, we utilized surrogate dose information based on annual apparent per-capita cigarette consumption among U.S. males between 1900 and 1990 (Psoter & Morse, 2001) to built a dose-response model, and found this factor could explain about two-thirds of the log-likelihood improvement compared with the birth cohort effect. The model has the best likelihood with the surrogate smoking dose beginning between ages 13 and 15. The radiation-related dose-response parameters using the surrogate smoking data were generally consistent with estimates using the birth cohort effect.

Separate optimizations were done for the TSCE and some of the extended models restricted to the 69,826 males without a flag indicating possible neutron

exposure. The apparent dose-response relations for exposure to gamma radiation in this subcohort were very similar to those of the whole male cohort.

The data did not contain sufficient information to control for socioeconomic class. However, separate optimizations were performed for each of the four job categories: medical, dental, industrial, and nuclear. Similar dose responses were found within each subcohort.

False linkage rates were estimated by manual review of over 1700 potential links, and linkage weights were adjusted so that false negative links and false positive links were equal. Tax records were utilized for confirmation of vital status of 169,791 out of 206,620 members of the full cohort (Ashmore et al., 1998).

Gilbert (2001), in a commentary on a previous analysis of incidence in the National Dose Registry of Canada by Sont et al. (2001), suggests that bias may be more severe in the Canadian cohort than in other worker studies because of the low doses and apparent high values of ERR per Sievert. The concave downward trend in ERR and inverse dose-rate effect appear to reconcile the ERR estimates for the Canadian cohort with the atomic-bomb survivors, as discussed earlier. Gilbert also states that the apparently strong dose response in the Canadian cohort for noncancer diseases, which is similar to the ERR per Sievert for cancer alone, could suggest bias in the Canadian data. However, Shimizu et al. (Preston et al., 2000; Shimizu et al., 1999) found strong evidence for long-term increases (by about 10% for a 1-Sv dose) in noncancer disease mortality in the recent follow-up in the LSS cohort of atomic bomb survivors that cannot be explained by diagnostic misclassification, confounding, or selection effects. Preston et al. (2000) state that "The most appropriate comparisons of excess non-cancer and solid cancer risks in the LSS are made in terms of age-dependent EARs. These comparisons suggest that after a 1-Sv exposure prior to age 50 the excess non-cancer and solid cancer rates are roughly comparable for attained ages of 60 to 80."

In summary, it appears difficult to make a compelling case for bias based on these arguments because of population differences, and, perhaps more importantly, because of how risks for cancer and noncancer outcomes may be influenced by magnitude and protraction of dose. However, multiple potential sources of bias that might influence the results discussed in this article cannot be ruled out.

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APPENDIX

The extended model assumes n sequential initiation steps. Let v_{ij} be the transition rate from stage j to $j + 1$ in time interval i, and $p_j(s)$ be the probability that a single cell is in stage j at time s ($t_{i-1} \le s \le t_i$). A normal cell is labeled by $j = 0$ and an initiated cell by $j = n$.

The $p_j(s)$ probabilities satisfy the system of ordinary differential equations (ODE)s,

$$\frac{dp_j(s)}{ds} = v_{i(j-1)}p_{j-1}(s) - v_{ij}p_j(s) \quad \text{for} \quad 0 \le j \le n, \quad (v_{i-1} = 0,\ p_{-1}(s) = 0, v_{i,n} = 0) \tag{4}$$

The boundary conditions are $p_0(t_0) = 1$, and $p_j(t_0) = 0$ for $1 \le j \le n$. Let $p_{i\uparrow|j}(t_{i-1},s)$ represent the conditional probability that a cell in stage j at time t_{i-1} has mutated to stage 1 or beyond at time s. This is the probability that it is not in any previous stage k, for $j \le k \le l - 1$. We consider two cases. If all mutation rates are different, the conditional probability is

$$P_{l\uparrow|j}(t_{i-1},s) = 1 - \sum_{k=j}^{l-1}\left(e^{-v_{ik}(s-t_{i-1})} \prod_{m=j}^{l-1} \begin{Bmatrix} 1 & \text{for } m = k \\ \dfrac{v_{im}}{(v_{im} - v_{ik})} & \text{for } m \ne k \end{Bmatrix} \right) \tag{5}$$

If all mutation rates are identical, for example, $v_{ik} = v_{im}$ for all m, the conditional probability is

$$P_{l\uparrow|j}(t_{i-1},s) = 1 - \sum_{k=j}^{l-1} e^{-v_{ik}(s-t_{l-1})} \frac{(v_{ik}(s - t_{i-1}))^{(k-j)}}{(k-j)!} \tag{5b}$$

Other expressions may be derived if two out of three or more mutation rates are identical, and so on, but good numerical results are achieved using Eq. (5) by symmetrical spreading of nearly identical mutation rates by numerical epsilons about their mean value. The probabilities in each stage $l \le n$ are calculated by iterating over time intervals,

$$p_l(s) = \sum_{j=0}^{l} p_j(t_{i-1})\left[p_{l\uparrow|j}(t_{i-1},s) - p_{i+1\uparrow|j}(t_{i-1},s) \right] \quad \text{with } p_{n+1\uparrow|j}(t_{i-1},s) = 0 \tag{6}$$

The density in stage n is

$$\frac{d}{ds}p_n(s) = \sum\nolimits_{j=0}^{n} p_j(t_{i-1})\ \frac{d}{ds}p_{n\uparrow|j}(t_{i-1},s)$$

Using Eq. (5) for all mutation rates different,

$$\frac{d}{ds} p_{n\uparrow|j}(t_{i-1}, s) = \sum_{k=j}^{n-1} \left(\nu_{ik} e^{-\nu_{ik}(s-t_{i-1})} \prod_{m=j}^{n-1} \begin{cases} 1 & \text{for } m = k \\ \dfrac{\nu_{im}}{(\nu_{im} - \nu_{ik})} & \text{for } m \neq k \end{cases} \right)$$

The probability that a single cell becomes malignant is calculated by convolving the initiation density $(d/ds)\ p_n(s)$ with the probability for malignancy following clonal expansion, $1 - y(s,t)$. [Piecewise constant recursion formulae for $y(s,t)$ and $(d/dt)\ y(s,t)$ are given by Heidenreich et al. (1997).] Thus for X cells, the survival probability that no cell is malignant at time t is

$$S(t) = \left(1 - \int_0^t \frac{d}{ds} p_n(s)(1 - y(s,t))\, ds \right)^X \tag{7}$$

and the hazard at time t [using the clonal expansion boundary condition that $y(t,t) = 1$] is

$$h(t) = X \frac{-\int_0^t \dfrac{d}{ds} p_n(s)\ \dfrac{d}{dt} y(s,t)}{1 - \int_0^t \dfrac{d}{ds} p_n(s)\ (1 - y(s,t))\, ds} \tag{8}$$

Log likelihoods based on individual exposure patterns were calculated as just shown, using the log of survival for survivors and the log of density, the product of hazard and survival, for cases.