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THE USE OF BIOLOGICALLY BASED CANCER RISK MODELS IN RADIATION EPIDEMIOLOGY

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INVITED PAPER

Abstract — Biologically based risk projection models for radiation carcinogenesis seek to describe the fundamental biological processes involved in neoplastic transformation of somatic cells into malignant cancer cells. A validated biologically based model, whose parameters have a direct biological interpretation, can also be used to extrapolate cancer risks to different exposure conditions with some confidence. In this article biologically based models for radiation carcinogenesis, including the two-stage clonal expansion (TSCE) model and its extensions, are reviewed. The biological and mathematical bases for such models are described, and the implications of key model parameters for cancer risk assessment examined. Specific applications of versions of the TSCE model to important epidemiological datasets are discussed, including the Colorado uranium miners' cohort; a cohort of Chinese tin miners; the lifespan cohort of atomic bomb survivors in Hiroshima and Nagasaki; and a cohort of over 200,000 workers included in the National Dose Registry (NDR) of Canada.

INTRODUCTION

Risk projection models for radiation carcinogenesis can be divided into two broad classes: empirical and biological. Unlike empirical models, which employ flexible statistical functions to describe key attributes of the available data, biologically based models seek to describe the fundamental biological processes involved in neoplastic transformation of somatic cells into malignant cancer cells, including mutation and cell kinetics. The application of biologically based models to epidemiological datasets can lead to a greater understanding of the mechanisms of radiation carcinogenesis, as well as elucidate complex inter-relationships between different exposure patterns and cancer risk. This article reviews biologically based models for radiation carcinogenesis, with emphasis on the two-stage clonal expansion (TSCE) model originally developed by Moolgavkar and Knudson[1], and its application to four important epidemiological datasets.

BIOLOGICALLY BASED MODELS OF CARCINOGENESIS

Hazard functions derived from the concept of multistage carcinogenesis have novel features that make them particularly suitable for use in the analysis of epidemiological datasets with complex time- and age-dependent patterns of exposure to putative carcinogens, providing an analytical method that is complementary to traditional statistical approaches. These models have several strengths, including the flexibility to explicitly consider time- and age-related patterns of exposure, and the joint analysis of intermediate and malignant lesions. The resultant estimates of the model parameters have a direct biological interpretation, and the models generate testable biological hypotheses. It should be recognised, however, that these models only provide a rough approximation to reality, as they balance biological detail against parameter identifiability and estimability.

Multistage carcinogenesis models are based on several assumptions. Firstly, it is assumed that cancer is brought about by the accumulation of critical mutations in a stem cell, resulting in the improper control of cell division, apoptosis and differentiation. Those mutations may occur either spontaneously or in response to an environmental exposure. Clonal expansion (promotion) of partially transformed cells can efficiently accelerate the process of malignant transformation. Promotion of a cell from an initiated state to a malignantly transformed cell may occur either spontaneously or in response to endogenous or exogenous promoters.

Armitage–Doll model

Cancer research in the first part of the twentieth century led to an observation that mortality and incidence rates for many forms of human cancer increased rapidly with age. It was unclear if this was a general effect of

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aging or an indication that carcinogenesis requires a lag time from exposure to tumour formation, involving several qualitatively different stages. In 1954, Armitage and Doll[2] observed that for many common human carcinomas the log–log plot of age-specific incidence rates against age is nearly linear up to moderately old ages.

In brief, Armitage and Doll's theory begins with a specific tissue with N cells that can experience carcinogenic transformation. The development of a malignant cancer is the result of the kth and last of a series of spontaneous and irreversible changes[3]. The derived distribution function for the time to appearance of the first cancer $G(t)$ can be described as

$$g(t) = G'(t) = at^{k-1} \exp\,[-(a/k)t^k],$$

with a resultant hazard function

$$h(t) = g(t)/[1 - G(t)] = at^{k-1}.$$

More comprehensive reviews of the mathematical theory have been given by Armitage and Doll[4], Whittemore[5] and Armitage[3].

These models have been fitted to age-specific incidence rates, leading to the conclusion that most cancers arise after the occurrence of five to seven stages[6]. Armitage and Doll[7] had earlier proposed a simpler two-stage model which would avoid a multiplicity of parameters that are not readily estimable from available data[8]. However, this two-stage model did not account for the proliferation of intermediate cells, which are likely to have different growth characteristics from normal somatic cells[7].

Two-stage clonal expansion models

Moolgavkar and Knudson[1] identified a deficiency of these early two-stage models: despite the well-known origin of cancers from dividing cells, none of the models accounted for the multiplication and death of normal cells, which does occur in tissues undergoing malignant change. The model they subsequently proposed differed in two major respects from earlier models: (1) it allowed for growth of normal tissue and (2) clonal expansion of intermediate cells was treated stochastically (which turns out to have important implications for the properties of the hazard functions generated by the model). They demonstrated that a two-stage model incorporating clonal expansion of initiated cells is consistent with many of the data on human cancers[1]. Numerous two-stage models have now been described in the literature[9–17].

In its simplest form, the TSCE model proposed by Moolgavkar and colleagues postulates that a normal stem cell is converted to a malignant cell after it has sustained two critical mutations. The TSCE model is a stochastic model of stem cell kinetics and mutation, relating to the initiation, promotion, malignant conversion and progression paradigm of carcinogenesis. The focus of the TSCE model is on the birth and death of stem cells that have departed slightly from homeostatic control through an initiation process, and on the chance that one of these cells will transform to a more active state of growth with progressive loss of regulation[8]. The biological assumptions of the model are that in any tissue there is a pool of cells susceptible to malignant transformation, usually associated with that tissue's stem cell population. Malignant tumours are clonal, as they arise from a single malignant, transformed progenitor cell. The transformation of a normal but susceptible stem cell into a malignant cell is the result of two specific, rate-limiting events. Furthermore, these transformational events are irreversible[18].

The first step of the two-step process is the initiation of the cell; this process involves the conversion of the normal cell into an intermediate cell. These intermediate cells are subject to clonal expansion, increasing the pool of cells available for malignant transformation. The second rate-limiting, irreversible and heritable event involves the conversion of the intermediate cell into a malignant cell, with the ability to proliferate into many malignant cells[19]. This process is shown in Figure 1.

In the most commonly used form, the model assumes a normal stem cell population of fixed size X and a rate of first mutation of $\nu(d)$, depending on dose d of the carcinogen. The number of initiated cells arising from the normal cell pool is described by a Poisson process with a rate of νX. The initiated cell can then divide either symmetrically or non-symmetrically. Symmetrical division results in two initiated cells while non-symmetrical division results in an initiated cell and a differentiated cell. The rate of symmetrical division is designated by $\alpha(t)$, and the death differentiation rate by $\beta(t)$. The rate of division into one initiated cell and one malignant cell is designated by $\mu(t)$. The difference, $\alpha - \beta$, is the net proliferation rate for initiated cells[8].

Let $X(t)$, $Y(t)$ and $Z(t)$ represent the number of susceptible stem cells, intermediate cells and malignant cells respectively, in the target tissue at some conversion time tu, and let Ψ denote the probability generating function:

$$\Psi(y,z;t) = \sum_{j,k} P_{j,k}(t) y^j z^k,$$

where $P_{j,k}(t) = \text{Prob}[Y(t) = j, Z(t) = k | Y(0) = 0, Z(0) = 0]$

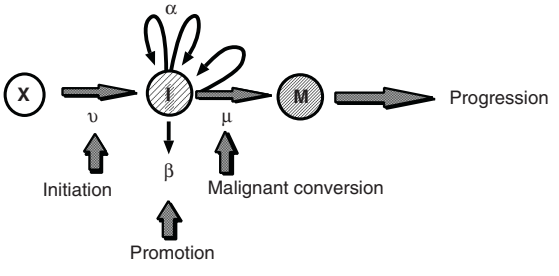

Figure 1. The two-stage clonal expansion model. (From: Luebeck *et al*[31]).

denotes the probability of having exactly j intermediate cells and k malignant cells at time t given that there are no intermediate and malignant cells at time t and $X(0) \geq 1$. Then the process $(Y(t),Z(t))$ is Markovian, and Ψ can be shown to satisfy the Kolmogorov forward differential equation[20,21] with the initial condition $\Psi(y,z;0) = 1$. The survival function is represented by $\Psi(1,0;t)$, the probability that there are no malignant cells at time t in the tissue of interest. $P(t) = 1 - \Psi(1,0;t)$ denotes the probability of at least one malignant cell in the tissue by time t[21]. The hazard funcation (disregarding the time lag and assuming the tumour is detectable) is given by $h(t) = \mu(t)E[Y(t)|Z(t) = 0]$, where E denotes the expectation. For simplicity, an approximate hazard has sometimes been used in practice[18].

As the mathematical modelling of the carcinogenic process continues to evolve, along with the understanding of the molecular mechanisms of the progression of a normal cell to a malignant cell, more and more complicated models have been developed. Although the TSCE model provides an excellent fit to many epidemiological datasets, and has generated important insights into cancer mechanisms, it has been criticised for being too restrictive in assuming only two rate-limiting events[22]. For example, prior to developing a colon cancer, the colonic stem cells appear to undergo a series of pre-initiation steps where they accumulate allelic losses and/or mutations[22].

Multistage clonal expansion model

In response to the criticism of the two-stage model, multistage models which take into account additional steps are now being considered. Zheng *et al*[23] have proposed a model describing mutational events at the DNA adduct level, so-called pre-initiation events. Their model requires four stages for a cell to become initiated. In the first stage the guanine (G) base of a G:C base pair is attacked by a chemical carcinogen and damaged by covalent bonding at a rate ρ_1. The modified cell then undergoes proliferation at a division rate ρ_2. Because of the adduct formation on the guanine base, it takes on some qualities of an adenine (A) base. Cell division then produces a normal cell and a mutated cell with a G* :T pairing. This cell may undergo one of two possible processes. The cell may undergo DNA repair (at rate σ_3) and the G* may be replaced with an adenine base. Second, if the division takes place before such a repair, the strand with the T bases will pair with an A base on the corresponding locus and the strand with the G* pairs again with a strand with a T base on the corresponding locus. As a result, one daughter cell resides in the G* :T compartment but the other moves to the A:T compartment (with rate μ). This is a complete G:C → A:T base-pair substitution process. The above process is significantly more complex than envisaged under the TSCE model, and may seem to conflict with the principle of parsimony. This complexity is, however, important, as each parameter quantifies an important biological component of the process of tumour formation. Data on these fundamental biological events are becoming gradually more available as the field of molecular epidemiology evolves[23]. However, other genetic and epigenetic mechanisms may also contribute to changes in gene expression that are important in carcinogenesis.

Multistage carcinogenesis models are beginning to find application in several contexts, including colorectal cancer[22,24], lung cancer in association with radiation exposure[25], and lung cancer in rats[26]. Luebeck and Hazelton[22] provided a recent review of multistage carcinogenesis models and radiation exposure.

Interactive effects

The effects of joint exposure to carcinogens are an important facet of risk epidemiology, as there is a potential for interaction between the agents[27]. Interaction occurs when the effects of joint exposure to two agents are, in some sense, greater (synergism) or less (antagonism) than the expected sum of the effects of the two agents alone[28]. The combined effects of radiation and other agents were comprehensively reviewed by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) in 2000[29]. Other studies have explored joint carcinogenic action specifically within the context of the two-stage clonal expansion model[8,28,30,31].

The relative risk (RR) can be defined in terms of the age-specific hazard

$$\mathrm{RR}(t;d_1,d_2) = h(t;d_1,d_2)/h(t;0,0),$$

where d_1 is the dose from carcinogen 1 and d_2 the dose from carcinogen 2.

There are two special case of particular interest, the additive relative risk model,

$$\mathrm{RR}^{+}(t;d_1,d_2) = \mathrm{RR}(t;d_1,0) + \mathrm{RR}(t;0,d_2) - 1,$$

and the multiplicative relative risk model,

$$\mathrm{RR}^{*}(t;d_1,d_2) = \mathrm{RR}(t;d_1,0) \times \mathrm{RR}(t;0,d_2),$$

It is important to note that while $\mathrm{RR}(t; d_1,d_2)$ is estimated from the observed data, both $\mathrm{RR}^*(t;d_1,d_2)$ and $\mathrm{RR}^+(t; d_1,d_2)$ are predicted from relative risks for each of the two agents to which the exposure may occur. Thus, we can compare the observed value of the $\mathrm{RR}(t; d_1,d_2)$, $\mathrm{RR}^*(t; d_1,d_2)$ and $\mathrm{RR}^+(t; d_1,d_2)$ and infer if an effect is more likely to be additive, multiplicative or otherwise using Thomas' index of synergy (S)[28], defined by

$$S = [\mathrm{RR}(t;d_1,d_2) - \mathrm{RR}^{+}(t;d_1,d_2)]/ [\mathrm{RR}^{*}(t;d_1,d_2) - \mathrm{RR}^{+}(t;d_1,d_2)].$$

An S value of 0 indicates that the risk is additive, while $S < 0$ reflects sub-additivity or antagonism; $S > 0$ corresponds to a synergistic interaction, and values approach-

ing 1 suggest a multiplicative interaction. Finally, an S value exceeding 1 may indicate that the agents may interact with supra-multiplicative effects.

Figure 2 gives an example of four different interactions based on age-specific hazards. These results were generated using plausible values of the parameters in the TSCE fit to data on lung cancer in Colorado uranium miners exposed to radon and tobacco smoke[28]. The interaction between two initiators has an additive effect at all ages. Exposure to an initiator and a completer (conversion from an initiated to a malignant cell) increases risk multiplicatively at young ages; this risk becomes supra-multiplicative with increasing age. The negative values of S that occur at older ages for exposure to two promoters warrants comment. This is a result of the joint effect of two promoters leading to the formation of large numbers of intermediate cells at early ages. The antagonism observed at older ages is mediated by the high probability that the first malignant cell arises from this large pool of intermediate cells at an early age. Finally, the interaction of an initiator and a promoter results in a synergistic interaction at young ages which quickly progresses to supra-multiplicative at moderate ages. It is important for the purposes of risk assessment to identify how carcinogens interact, and whether the effects are additive, synergistic or even antagonistic.

APPLICATIONS

This section describes several datasets to which versions of the TSCE model have been applied. These include the Colorado uranium miners' cohort in which miners exposed to radon and tobacco smoke are at increased risk of lung cancer; a cohort of Chinese tin miners at increased risk of lung cancer due to exposure to radon, arsenic and tobacco smoke; the lifespan cohort of 100,000 atomic bomb survivors in Hiroshima and Nagasaki who are at increased risk of a number of different types of cancer; and a cohort of over 500,000 workers included in the National Dose Registry (NDR) of Canada, which includes monitored radiation exposures dating back to 1950.

Colorado uranium miners

The Colorado Plateau uranium miners' study contains information on 3347 white male underground miners. The data were assembled by the US Public Health Service for uranium miners working in the Colorado

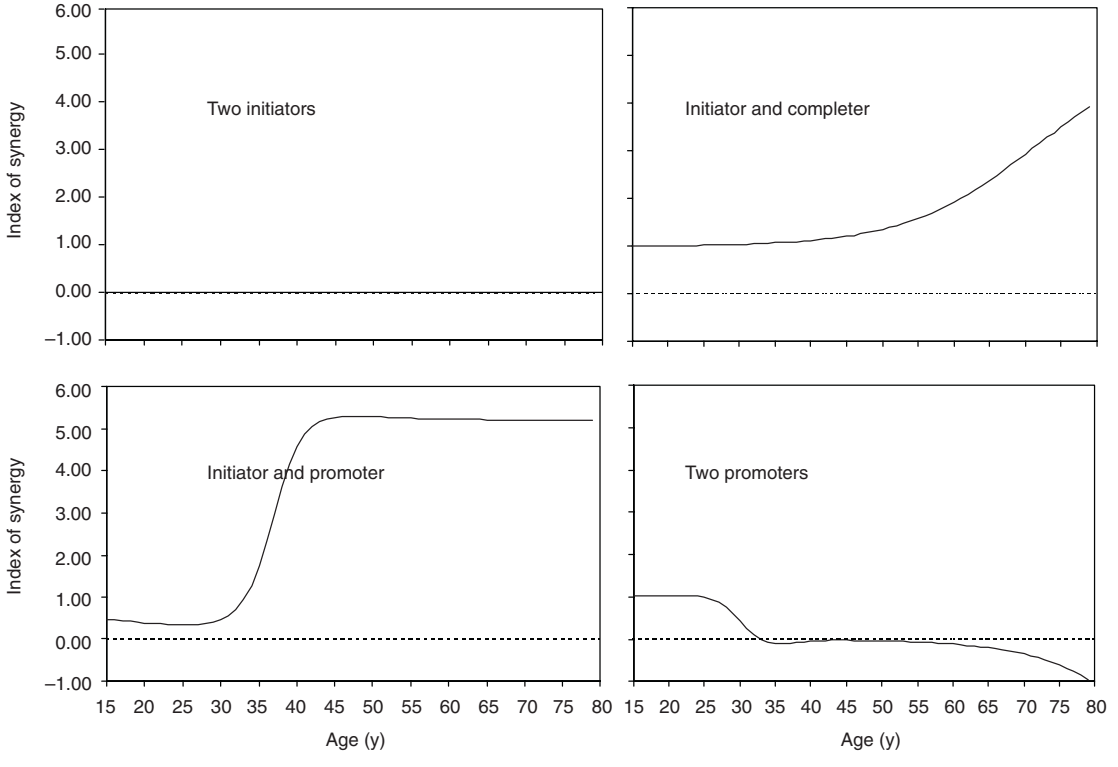

Figure 2. Temporal patterns of interaction between two carcinogens using the two-stage clonal expansion model, based on an age-specific hazard. (From: Zielinski *et al*[28]).

Plateau between the years 1950 and 1964[32], and are available from the National Institute for Occupational Safety and Health. The vital status on each of the cohort members was followed up to 31 December 1990; during the 40 years of follow-up there have been 294 lung cancer deaths[31]. The dataset provides individual covariate information on smoking patterns, and on radon exposure from hard rock and uranium mining[31].

An analysis of the Colorado miners' cohort used the following equations to model the effects of exposure to radon and tobacco smoke on the first- and second-stage mutation rates ν and μ[32]:

$$\nu(d_s,d_r) = a_0 + a_s d_s + a_r d_r$$

and

$$\mu(d_s,d_r) = b_0 + b_s d_s + b_r d_r.$$

Here, a_0 is the background mutation rate for conversion of a normal cell to an initiated cell and b_0 is the background mutation rate for conversion of an initiated cell to a malignant cell. The terms a_s and a_r represent the initiation rate associated with tobacco smoke and radon exposure, while d_s and d_r represent the doses of tobacco smoke and radon, respectively. The terms b_s and b_r, represent the rate of conversion of initiated cells to a malignant cells associated with tobacco smoke and radon, respectively.

The promotion of the intermediate cell was described as

$$(\alpha - \beta)\,(d_s,d_r) = c_0 + c_{s1}\,[1 - \exp(c_{s2}d_s)] + c_{r1}[1 - \exp(-\,c_{r2}d_r)],$$

with β/α held constant. The term c_0 is the background promotion rate of intermediate cells. The terms c_{s1} and c_{s2} represent the promotional effects of tobacco smoke, while c_{r1} and c_{r2} represent the promotional effects of radon. The relative risks of lung cancer associated with radon, tobacco smoke and a combined risk are presented in Table 1.

A re-analysis of the data, performed in 1999, applied an updated version TSCE model allowing for the inclusion of detailed patterns of exposure for both radon and cigarette smoke[31]. The model employed four parameters: the net proliferation of intermediate cells; the rate of initiation among normal cells times the background rate of malignant conversion; the asymptote of the hazard function; and the second mutation rate. These parameters were converted to dose–response functions for exposure to tobacco smoke and radon progeny; the final model contained nine parameters. The model demonstrated a birth cohort effect, despite the explicit modelling of the effect of smoking on lung cancer risk. The model also suggested that exposure to radon affects both the rate of initiation of intermediate cells and the rate of proliferation for intermediate cells.

Figure 3 shows the predicted lifetime excess absolute risk (LEAR) per working level month (WLM) for various total exposures and exposure durations. These results demonstrate that for varying levels of total radon exposure the LEAR/WLM first increases with duration, reaches a maximum, and then declines. In cases of low total exposure the inverse dose rate is weaker and the direct dose rate is apparent earlier. Furthermore, Figure 3 exhibits that non-smoking miners exposed to radon for 10 y have approximately the same risk per WLM as a non-smoking individual who spends 10–20 y in a residence with very low levels of radon. One conclusion reached in this study was that it was not necessary to assume a biological interaction of radon and cigarette smoke affecting the initiation and promotion parameters to achieve a good fit to the data.

Chinese tin miners

In 1976, the Yunnan Tin Corporation surveyed a cohort of 12,011 male miners and has followed them until 1998[8]. The cohort dataset contains information on lifetime records for arsenic, radon, cigarette smoke and pipe smoke exposure. It has been observed that lung cancer mortality among the miners increased from a few cases per year in the 1950s to 80–100 cases per year in the 1980s, with a total of 842 incident cases of lung cancer in the cohort[8]. The TSCE model has been applied to this cohort in an attempt to model the risk of

Table 1. Relative risks (RR) associated with single and joint exposures to radon and cigarette smoke from the Colorado uranium miners' cohort.

Radon[a] (WLM month^{-1})	Tobacco[b] (cigarette d^{-1})	RR radon	RR tobacco	RR combined at age 60
1.0	10	1.3	5.3	6.4
1.0	30	1.3	10.0	12.0
1.0	40	1.3	11.6	14.1
50.0	10	12.3	5.3	26.6
50.0	30	12.3	10.0	44.1
50.0	40	12.3	11.6	52.0

[a]Exposure to radon between 30 and 40 years of age.
[b]Cigarette smoking between 15 and 60 years of age.

lung cancer attributable to arsenic, radon, cigarette smoke and pipe smoke[8]. The final model from this analysis had 14 parameters and used a two-parameter gamma distribution for lag time for tumour growth, rather than a fixed lag. This model was used to estimate mortality attributable to radon, arsenic and tobacco exposures, individually and in all combinations. The attributable risk was calculated for all exposure combinations as the sum of the integrated hazard with different exposures set to zero. The background risk was calculated with all exposures set to zero. The results of this analysis are shown in Figure 4.

Background proliferation was very high in this cohort, possibility a result of arsenic contamination in the water supply, dietary deficiencies or genetic susceptibility[8]. Exposure to arsenic appears to increase the promotion of initiated cells and their malignant conversion. This may be a result of the slow clearance rate for particles containing arsenic from the lung tissue. However, tobacco use appears to be the most important risk factor in this cohort. Tobacco use appeared to cause malignant conversion and to increase cell turnover in a non-linear (roughly cubic) dose-related manner. Radon appeared to be a less important risk factor than tobacco and arsenic exposure; however, the net cell proliferation and malignant conversion rates increased significantly with radon exposure[8].

The application of the TSCE model to the Chinese tin miners' cohort demonstrates the usefulness of the TSCE model in evaluating the impact of three separate exposures and their interactions (Figure 4). From this analysis, it was possible to identify the importance of arsenic exposure in the cohort and to recognise the significant interaction between arsenic and tobacco smoke. Finally, the analysis suggests that while the progression from initiated cells to a malignancy may be due to multiple sequential mutations, the second stage may be a good approximation to this multistep process[8].

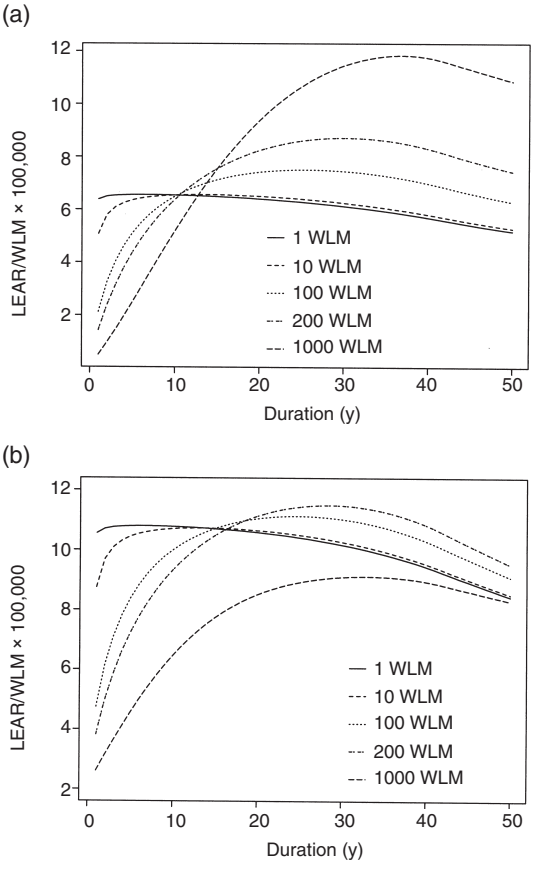

Figure 3. Lifetime excess absolute risk (LEAR) per working level month (WLM) at age 70 as a function of duration of exposure in the Colorado uranium miners cohort. (a) Exposure centred at age 40 (non-smokers). (b) Exposure centred at 40 (smokers). (From: Luebeck *et al*[31]).

Atomic bomb survivors

Five years after the atomic bombs were dropped on Hiroshima and Nagasaki, the first nationwide survey of atomic bomb survivors was conducted[33]. This survey identified 284,000 individuals who were still alive who had been exposed to radiation from the bomb. These individuals continue to be followed up by the Radiation Effects Research Foundation. Numerous analyses have been performed on these data; however, this article will focus on a recent study with follow up from 1958–1987 to illustrate the usage of the TSCE model in radiation epidemiology[19]. This study examined three types of cancer: lung, colon and stomach. The hazard function is specified as

$$h(t,t_0,d) = h_0(t) + h_{ex}(t,t_0,d),$$

where $h_{ex}(t,t_0,d)$ denotes the excess hazard and $h_{ex}(t,t_0,d)/h_0(t)$ denotes the excess relative risk. Here, t and t_0 denote the attained age and age at exposure, respectively.

Figure 5 shows the excess relative risk for males and females aged 5 y, 15 y and 30 y at the time of the bomb (ATB). The excess relative risk appears to be higher for females than males. It would also appear that younger males ATB are at a higher risk than males who were older ATB, whereas within the female subgroup, younger women are at similar or decreased excess relative risk as compared with older women. Other important findings stemming from the application of the TSCE model to the cohort include: high excess risks among children are not necessarily explained by enhanced tissue sensitivity to radiation exposure; the temporal patterns in cancer risk were explained by radiation-induced increase in the pool of initiated cells; and radiation-induced initiation leads to a direct dose-rate effect[19].

Recently, exact solutions of the TSCE model[34] and

multistage models[35] have been applied to the atomic bomb survivors' data. The different models predict different temporal patterns of risk after radiation exposure. Under the TSCE model, the high excess risks among children are not explained by enhanced tissue sensitivity to radiation exposure; rather, temporal patterns in cancer risk are explained by radiation-induced increase in the pool of initiated cells, which in turn leads to a direct dose-rate effect.

National Dose Registry of Canada

The National Dose Registry of Canada (NDR) is maintained by the Radiation Protection Bureau of Health Canada. This database contains personal dosimetry records for Canadian workers exposed to ionising radiation dating back to 1951, with current records for over 500,000 individuals, from about 24,000 organisations[36]. The work histories for the cohort members are described in terms of an 80-category job classification code and a 14-category code describing to which organisation the individual is associated, such as industry or hospital. The NDR contains information on several types of exposures including external exposures to gamma rays, beta rays, X rays, and neutrons, as well as internal exposures to tritium and radon progeny[37].

A recent study constructed a cohort from the NDR consisting of 191,042 individuals with complete records for radiation exposure between 1951 and 1988. This cohort was linked to cancer incidence data between 1969 and 1998 from the Canadian Cancer Database to obtain 322 male and 78 female cases of lung cancer[25]. A TSCE model examining exposure to gamma rays and tritium radiation was applied to the data. The results indicate a significant dose–response relationship for promotion and malignant conversion, but not initiation, for lung cancer in males.

Figure 6 shows the plots of lifetime excess relative

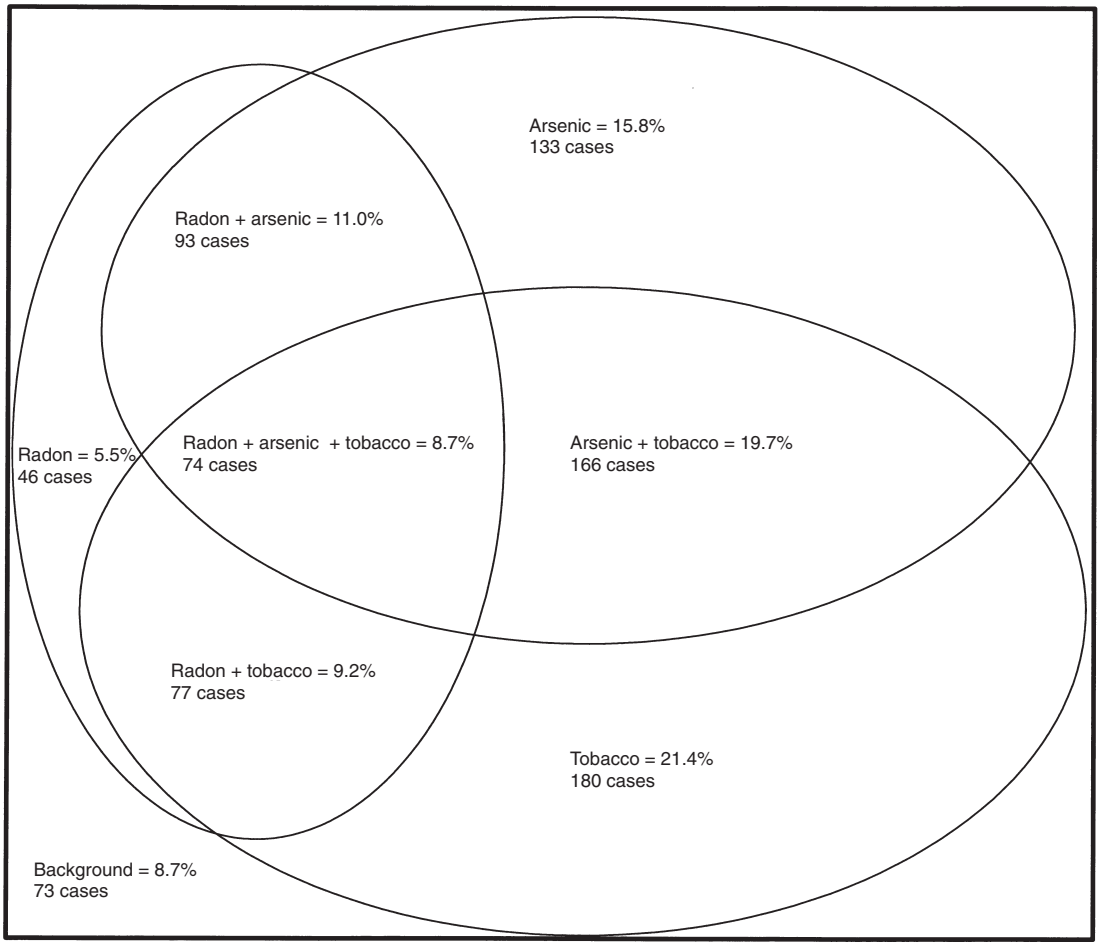

Figure 4. Attributable lung cancer mortality in the Chinese tin miners' cohort due to arsenic, radon, tobacco exposure and the background risk. (From: Hazelton *et al*[8]).

risk (ERR) and excess absolute risk (EAR) for several dose protractions centred at several ages. The most striking feature of this analysis is the inverse dose rate or protraction enhancement effect, in which a diminished response is observed when the same dose is given at a higher dose rate at correspondingly shorter durations. This is consistent with an inverse dose rate effect in the cohort. The effects of malignant conversion are apparent at young ages on the ERR scale, but not on the EAR scale, because of the small number of early onset lung cancer cases[25].

Prior analyses of the cohort[36] have been subject to criticism that the estimates are not in agreement with risk estimates based on the Japanese atomic bomb survivors' data. A recent analysis addresses whether or not risk can be reliably extrapolated from the high-dose acute exposures of the Japanese atomic bomb survivors to the low-dose, often protracted exposures, seen among some Western working populations[25]. The TSCE model suggests an explanation of the apparently high ERR seen by Sont and colleagues[36]; the model reveals that the dose–response for the NDR cohort is consistent with the lung cancer incidence in the atomic bomb survivors' cohort, provided that proper adjustments are made for duration of exposure and differences in the background rate parameters.

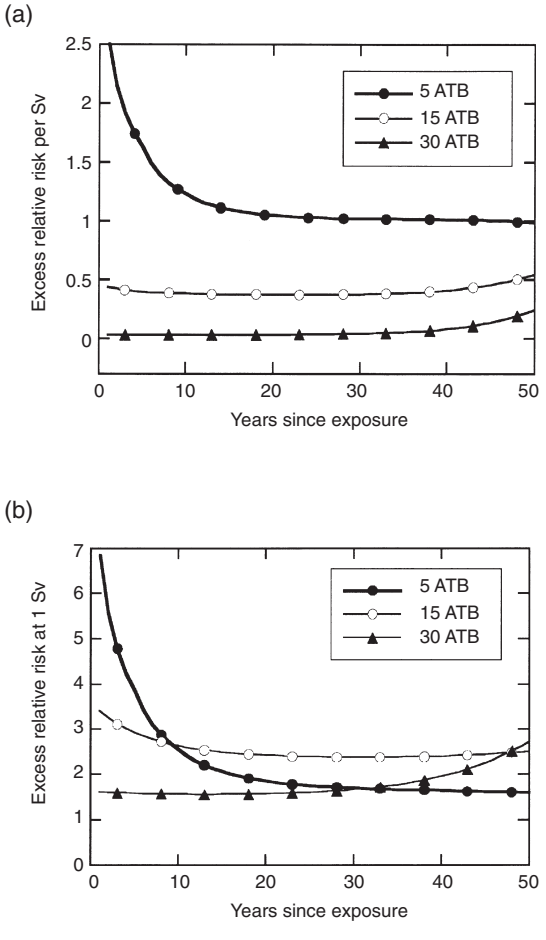

Figure 5. Excess relative risk as a function of years since exposure stratified by various ages in the atomic bomb survivors cohort: (a) male lung; (b) female lung. 5 ATB etc. Indicate age (in years) at the time of the bomb (ATB). (From: Kai *et al*[19]).

DISCUSSION

Biologically based models for radiation carcinogenesis have now been successfully applied to a number of important datasets, including the atomic bomb survivors and occupational groups such as nuclear power plant workers and underground miners. Unlike empirical approaches to risk modelling which rely on statistical models to describe the available data, biologically based models are based on fundamental assumptions regarding the mechanisms of radiation carcinogenesis. Biologically based models, whose parameters have a direct biological interpretation, can afford considerable insight into cancer mechanisms and invite substantive questions about the pathways by which exposure to ionising radiation can increase cancer risk. Biologically based models also provide a natural way of describing temporal patterns of exposure and risk, first by making use of individual time-dependent exposure profiles at the model-fitting stage and then by providing predictions of risk under arbitrary time-dependent exposure scenarios, thereby permitting an assessment of direct and indirect dose-rate effects. A validated biologically based model, which acknowledges the effects of tissue growth, cell kinetics and mutation, and whose parameters fall within plausible biological limits, may permit projections of risk outside the conditions under which the original data were gathered to be made with greater confidence.

Biologically based models also have a number of limitations. These models provide only an approximation to biological reality, and require an understanding of the underlying mechanisms of radiation carcinogens. Further, it can be difficult to distinguish between alternative models that yield similar dose–response curves without direct information on the fundamental biological processes represented by the model, including mutation and cell proliferation. For example, some studies have found the strongest effects at the initiation stages, whereas other studies have found the main effect of the radiation to be on the proliferation of intermediate cells. Nonetheless, the TSCE model has found many applications to important epidemiological datasets, and has proved to be a useful tool in furthering our understanding of radiation carcinogenesis.

Biologically based models are generally more complex than empirical models and may require richer databases to develop properly. The successes achieved to date with biologically based risk models for radiation

carcinogenesis afford considerable encouragement to explore the utility of such models in future analyses of important epidemiological datasets that directly inform the association between radiation exposure and human cancer risk. The authors' team is currently continuing to apply models of the type discussed in this article in further analyses of data from the National Dose Registry of Canada and the atomic bomb survivors' lifespan cohort. The results of this research will be reported in future publications.

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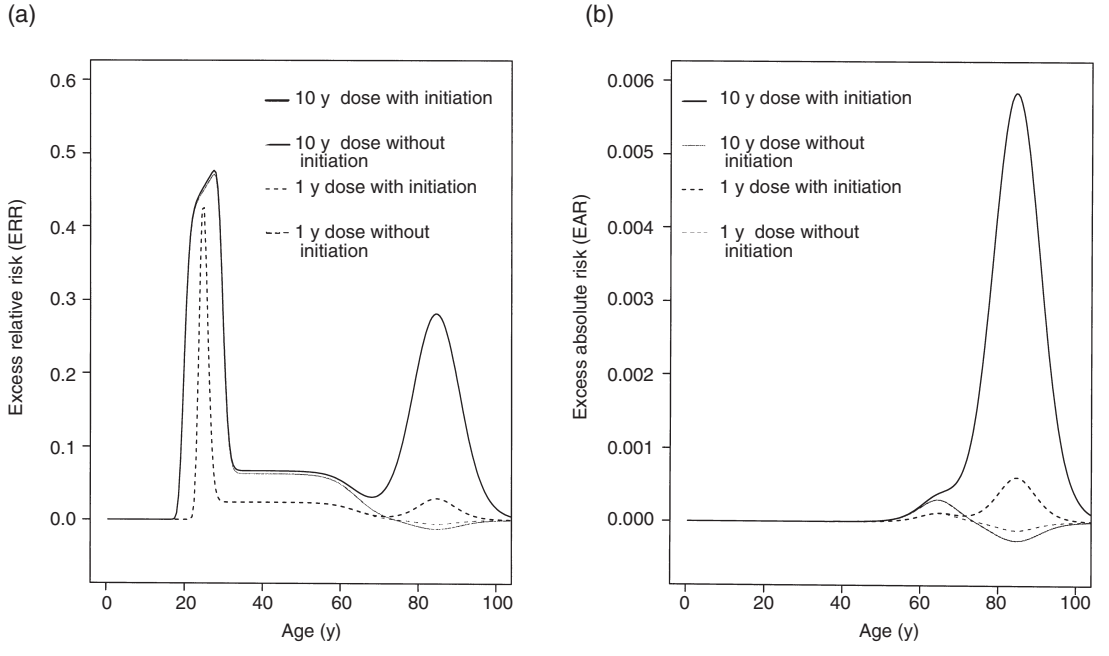

Figure 6. Comparison of (a) excess relative risk (ERR) and (b) excess absolute risk (EAR) for varied exposures with and without initiation based on the National Dose Registry of Canada. Both parts are for a 10 mSv cumulative dose centred at age 20. (From: Hazelton *et al*[25]).

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