A Two-Phase Poisson Process Model and Its Application to Analysis of Cancer Mortality among A-bomb Survivors

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Abstract

We consider a two-phase Poisson process model where only early successive transitions are assumed to be sensitive to exposure. In the case where intensity transitions are low, we derive analytically an approximate formula for the distribution of time to event for the excess hazard ratio (*EHR*) due to a single point exposure. The formula for *EHR* is a polynomial in exposure dose. Since the formula for *EHR* contains no unknown parameters except for the number of total stages, number of exposure-sensitive stages, and a coefficient of exposure effect, it is applicable easily under a variety of situations where there exists a possible latency time from a single point exposure to occurrence of event. Based on the multistage hypothesis of cancer, we formulate a radiation carcinogenesis model in which only some early consecutive stages of the process are sensitive to exposure, whereas later stages are not affected. An illustrative analysis using the proposed model is given for cancer mortality among A-bomb survivors.

Key words: Excess hazard ratio, Latency of cancer, Multistage model, Poisson process, Radiation carcinogenesis, Single point exposure

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1. Introduction

Many chronic diseases can be characterized by stages and may be expressed mathematically by an irreversible point process. As for human cancer, Muller (1951) and Nordling (1953) proposed the idea of a multistage model to explain the observation that mortality rates increase proportionately to the fifth or sixth power of age. The quantitative consequences of this theory were derived by Stocks (1953). Armitage and Doll (1954) considered that cancer was the end result of the accumulation in a normal cell of a critical number (k) of independent transitions through a series of intermediate states, assuming that the cancer was caused by exposure to carcinogens at a fairly constant rate throughout life, and that age is the same as the duration of carcinogenic exposure. For most cases of cancer 5 to 7 stages are indicated for the value of k (Doll, 1971). The multistage model has been incredibly useful as a conceptual tool to understand the role of time in carcinogenesis (Day, 1983). From the aspect of biological science, Vogelstein et al. (1988) revealed that the process of colorectal cancer, for example, consists of several carcinogenic mutations of specific genes. Molecular biologists have reinterpreted the theory as the “Hallmarks of Cancer” (Hanahan and Weinberg, 2000, 2011). Chiang (1979) proposed a multistage model based on a non-stationary Poisson process to describe a chronic disease process, and derived explicit formulas for the density and distribution functions of time to event. Ohtaki and his colleagues (Ohtaki, 1981; Ohtaki et al., 1985; Ohtaki and Niwa, 2001) developed a generalized Armitage-Doll model based on an approximation to Chiang’s result. Applying this model, Doi et al. (2011) analyzed cohort data on former workers in a poisonous gas factory and clarified that lung cancer incidence decreased with age at exposure to sulfur mustard. Pierce and Vaeth (2003) showed that the effects of exposure shift the age scale instead of acting multiplicatively on cancer rates, and that those effects can be specified by age and dose. As for analyses of the effects of the radiation exposure, Pierce et al. (1996), Preston et al. (2004), Izumi and Ohtaki (2004, 2007), and Ozasa et al. (2012) performed detailed analyses of the data from the Life Span Study (LSS) cohort of A-bomb survivors using a model for a single point radiation exposure. These traditional multistage carcinogenesis models, however, do not explain the evidence that the incidence of many solid tumors among the A-bomb survivors requires more than 20 years of latency from the radiation exposure due to the Atomic bomb (Shimizu et al. 1991). Whittemore (1977) considered time and age dependence of cancer incidence resulting from various types of carcinogenic exposures, assuming that the exposure affects one of several changes necessary for malignant cell transformation. Based on these studies, we extend the generalized Armitage-Doll model with non-stationary transitions to cope with the problem of long latency.

In Section 2, we present the mathematical formulation of the point process model. In Section 3, the hazard ratio of time to event due to a single point exposure is considered. In

Section 4, we show an application to the analysis of mortality risk from solid cancer among A-bomb Survivors. In Section 5, some discussions on mathematical modeling of carcinogenesis and speculations on the results of our data analysis are given.

2. Two phase Poisson process

In this section, we modify the multistage model due to Chiang (1979) such that only some early consecutive stages of the process are sensitive to the exposure of interest, whereas later stages are not affected by that exposure. In other words, we assume that there exists a stage u at which the transition becomes irreversibly insensitive to the exposure of interest (Figure 1).

Figure 1. Schematic diagram of the two-phase irreversible k -stage point process $M(u, k-u)$

Definition 1. Suppose that there are k stages in a process, $S_0, S_1, \dots, S_{k-1}$ and a final stage S_k and that the only possible transition in this process is $S_{j-1} \rightarrow S_j$ for $j=1, 2, \dots, k$. Given an element in stage S_j at time t , the intensity of the transition $S_{j-1} \rightarrow S_j$ during the interval $(t, t+dt)$ is $\lambda_j \theta(t)$ if $j \leq u$ and λ_j if $j \geq u+1$, $u=1, \dots, k-1$ for all $0 \leq t < +\infty$, where λ_j denotes a transition intensity at $S_{j-1} \rightarrow S_j$ in the case of non-exposure and $\theta(t)$ is the effect of exposure on the transition intensity at t . Let T be the time at which an element that is initially in stage S_0 at time 0 enters the final stage S_k . We call this process *the two-phase irreversible k -stage point process*, and denote it by $M(u, k-u)$ (see Figure 1).

As for the process $M(k-1, 1)$, explicit formulas for the density and distribution functions of T were given by Chiang (1979) and simple approximations with the gamma distribution were provided by Ohtaki (1981). We present them without

detailed proof in the following proposition.

Proposition 1. Let $f_k(t|\lambda, \theta)$ and $F_{(k-1,1)}(t|\lambda, \theta)$ be the density and distribution functions of T in $M(k-1,1)$, respectively. Let $\Theta(t) = \int_0^t \theta(z)dz$, $t \geq 0$. If $\lambda_i \neq \lambda_j$, then for $i \neq j$,

$$f_{(k-1,1)}(t|\lambda, \theta) = \lambda_1 \cdots \lambda_k \theta(t) \sum_{i=1}^k \frac{1}{\prod_{\substack{j=1 \\ j \neq i}}^k (\lambda_j - \lambda_i)} \exp(-\lambda_i \Theta(t)), \quad (1)$$

$$F_{(k-1,1)}(t|\lambda, \theta) = \lambda_1 \cdots \lambda_k \sum_{i=1}^k \frac{1}{\prod_{\substack{j=1 \\ j \neq i}}^k (\lambda_j - \lambda_i) \lambda_i} \{1 - \exp(-\lambda_i \Theta(t))\}, \quad t \geq 0, \quad (2)$$

and these are approximated by the following gamma-type density and distribution functions:

$$g_k(t|\mu, \theta) = \frac{\mu^k}{(k-1)!} \theta(t) \{\Theta(t)\}^{k-1} \exp(-\mu \Theta(t)), \quad (3)$$

$$G_k(t|\mu, \theta) = 1 - \exp(-\mu \Theta(t)) \cdot \sum_{j=1}^k \frac{\mu^{j-1}}{(j-1)!} \{\Theta(t)\}^{j-1},$$

respectively, where $\mu = \sqrt[k]{\lambda_1 \cdots \lambda_k}$. More precisely, we have

$$\begin{aligned} \sup_{0 \leq \tau \leq t} \frac{|f_{(k-1,1)}(\tau|\lambda, \theta) - g_k(\tau|\mu, \theta)|}{g_k(\tau|\mu, \theta)} &\leq \sup_{0 \leq \tau \leq t} \frac{|F_{(k-1,1)}(\tau|\lambda, \theta) - G_k(\tau|\mu, \theta)|}{G_k(\tau|\mu, \theta)} \\ &\leq \frac{1}{2} \left\{ \exp((\bar{\lambda} + \mu) \Theta(t)) - \exp(2\mu \Theta(t)) + 1 - \exp(-(\bar{\lambda} - \mu) \Theta(t)) \right\}, \quad t \geq 0, \quad (4) \end{aligned}$$

where $\bar{\lambda} = \max_{j=1, \dots, k} \lambda_j$.

Proof of Proposition 1:

Formulas (1) and (2) were derived by Chiang (1979; Theorem 2); the approximating formula and related inequalities were given in the theorem of Ohtaki (1981).

3. Excess hazard ratio due to single point exposure

In this section we consider the excess relative hazard for arrival at the k^{th} stage when a single point exposure exists. In the case of a single point exposure of dose D at time a , the effect of the exposure on transition can be specified as

$$\theta(t) \equiv \theta(t | D, a) = 1 + \beta_a D \cdot \delta(t - a), \quad (5)$$

where β_a is a function of a and $\delta(t - a)$ is the Dirac delta function with support a . Then the intensity of the transition $S_{j-1} \rightarrow S_j$ during the interval $(t, t + dt)$ is

$\lambda_j \{1 + \beta_a D \delta(t - a)\}$ if $j \leq u$ and λ_j if $j \geq u + 1$. As for the probabilities of

occupying the various stages, we have the following lemma.

Lemma 1. Assume that $M(u, k - u)$ with a single point exposure of dose D at time a is given. Let X_t be the stage number at time t defined by $X_t = j$ if the stage is $j \in \{1, 2, \dots, k\}$. Denote $\lim_{\varepsilon \downarrow 0} \Pr(X_{a-\varepsilon} = j)$ and $\lim_{\varepsilon \downarrow 0} \Pr(X_{a+\varepsilon} = j)$ by $\Pr(X_{a-0} = j)$ and $\Pr(X_{a+0} = j)$, respectively. Then

$$\Pr(X_{a-0} = j) = \frac{\lambda_1 \cdots \lambda_j}{j!} a^j \cdot \left\{ 1 + o\left(\max_{m=1, \dots, j} \lambda_m\right) \right\}, \quad (6)$$

$$\Pr(X_{a+0} = j + \ell | X_{a-0} = j) = \frac{\lambda_{j+1} \cdots \lambda_{j+\ell} (\beta_a D)^\ell}{\ell!} \cdot \left\{ 1 + o\left(\max_{m=j+1, \dots, j+\ell} \lambda_m\right) \right\}, \quad (7)$$

and

$$\Pr(X_t = k - 1 | X_{a+0} = j + \ell) = \frac{\lambda_{j+\ell+1} \cdots \lambda_{k-1}}{(k - 1 - j - \ell)!} (t - a)^{k-1-j-\ell} \cdot \left\{ 1 + o\left(\max_{m=j+\ell+1, \dots, k-1} \lambda_m\right) \right\}, \quad (8)$$

for $\ell = 1, \dots, u - j$, $j = 1, \dots, u$.

Proof of Lemma 1: Let $\mu_{j+1} = \sqrt[j+1]{\lambda_1 \cdots \lambda_{j+1}}$, and

$$f_{j+1}(t | \lambda) = \lambda_1 \cdots \lambda_{j+1} \sum_{i=1}^{j+1} \frac{1}{\prod_{\substack{m=1 \\ m \neq i}}^{j+1} (\lambda_m - \lambda_i)} \exp(-\lambda_i t),$$

$$g_{j+1}(t | \mu_{j+1}) = \frac{(\mu_{j+1})^{j+1}}{j!} t^j \exp(-\mu_{j+1} t), \quad t \geq 0,$$

for $j = 1, \dots, k - 1$. Then, from (4) in Proposition 1,

$$\left| f_{j+1}(t | \lambda) - g_{j+1}(t | \mu_{j+1}) \right| < \frac{1}{2} \cdot \frac{(\mu_{j+1})^{j+1}}{j!} t^j \left\{ e^{(\bar{\lambda}_{j+1} + \mu_{j+1})t} - e^{2\mu_{j+1}t} + 1 - e^{-(\bar{\lambda}_{j+1} - \mu_{j+1})t} \right\},$$

where $\bar{\lambda}_{j+1} = \max_{i=1, \dots, j+1} \lambda_i$. Therefore, we have

$$f_{j+1}(t | \lambda) = g(t | \mu_{j+1}) \cdot \{1 + o(\bar{\lambda}_{j+1})\} = \frac{\lambda_1 \cdots \lambda_{j+1}}{j!} t^j \cdot \{1 + o(\bar{\lambda}_{j+1})\}.$$

Since $f_{j+1}(t | \lambda) = \lambda_{j+1} \cdot \Pr(X_t = j)$, for $0 \leq t < a$, Equation (6) follows from

$$\Pr(X_{a-0} = j) = \lim_{t \uparrow a} \Pr(X_t = j) = \lim_{t \uparrow a} \frac{f_{j+1}(t | \lambda)}{\lambda_{j+1}} = \lim_{t \uparrow a} \frac{\lambda_1 \cdots \lambda_j}{j!} t^j \cdot \{1 + o(\bar{\lambda}_j)\}.$$

Using similar arguments, we obtain (7) and (8).

Based on Lemma 1, we deduce the following theorem.

Theorem 1. Assume that $M(u, k-u)$ with single point exposure of dose D at time a is given. If $\lambda_1, \lambda_2, \dots, \lambda_{k-1}$ are sufficiently small, then the excess hazard ratio at time t can be expressed approximately as

$$\begin{aligned} & EHR_{(u, k-u)}(t | D, a) \\ &= \left(1 - \frac{a}{t}\right)^{k-1-u} \sum_{\ell=1}^u \frac{(k-1)!}{\ell!(k-1-\ell)!} \left\{ \sum_{j=0}^{u-\ell} \frac{(k-1-\ell)!}{j!(k-1-\ell-j)!} \left(\frac{a}{t}\right)^j \left(1 - \frac{a}{t}\right)^{u-\ell-j} \right\} \left(\frac{\beta_a D}{t}\right)^\ell, \end{aligned} \quad (9)$$

for $u = 1, \dots, k-1$.

Proof of Theorem 1:

Since

$$\lim_{\Delta t \rightarrow 0} \frac{\Pr(X_{t+\Delta t} = k | X_t = k-1)}{\Delta t} = \lambda_k,$$

the hazard of the arrival to the k^{th} stage at time t can be expressed as

$$h_{(u, k-u)}(t | D, a) = \lambda_k \cdot \Pr(X_t = k-1) \cdot \left\{1 + o\left(\max_{j=1, \dots, k-1} \lambda_j\right)\right\}. \quad (10)$$

Note that there are the following two cases of processes:

- 1) the stage at time (at exposure) a is earlier than u , and
- 2) the stage at time a is between u and $k-1$,

which are disjoint. Then, it follows from (6), (7) and (8) in Lemma 1 that

$$\begin{aligned}
& \Pr(X_t = k-1) \\
&= \sum_{j=0}^{u-1} \sum_{\ell=0}^{u-j} \Pr(X_{a-0} = j) \cdot \Pr(X_{a+0} = j+\ell \mid X_{a-0} = j) \cdot \Pr(X_t = k-1 \mid X_{a+0} = j+\ell) \\
&\quad + \sum_{j=u}^{k-1} \Pr(X_{a-0} = j) \cdot \Pr(X_{a+0} = j \mid X_{a-0} = j) \cdot \Pr(X_t = k-1 \mid X_{a+0} = j) \\
&= \left\{ \sum_{j=0}^{u-1} \sum_{\ell=0}^{u-j} \frac{\lambda_1 \cdots \lambda_j}{j!} a^j \cdot \frac{\lambda_{j+1} \cdots \lambda_{j+\ell}}{\ell!} (\beta_a D)^\ell \cdot \frac{\lambda_{j+\ell+1} \cdots \lambda_{k-1}}{(k-1-j-\ell)!} (t-a)^{k-1-j-\ell} \right. \\
&\quad \left. + \sum_{j=u}^{k-1} \frac{\lambda_1 \cdots \lambda_j}{j!} a^j \cdot \frac{\lambda_{j+1} \cdots \lambda_{k-1}}{(k-1-j)!} (t-a)^{k-1-j} \right\} \cdot \left\{ 1 + o\left(\max_{j=1, \dots, k-1} \lambda_j\right) \right\} \\
&= \frac{\lambda_1 \cdots \lambda_{k-1}}{(k-1)!} t^{k-1} \cdot \left\{ \sum_{j=0}^{u-1} \frac{(k-1)!}{j!(k-j-1)!} \left(\frac{a}{t}\right)^j \sum_{\ell=1}^{u-j} \frac{(k-1-j)!}{\ell!(k-1-j-\ell)!} \left(1-\frac{a}{t}\right)^{k-1-j-\ell} \left(\frac{\beta_a D}{t}\right)^\ell \right\} \\
&\quad \cdot \left\{ 1 + o\left(\max_{j=1, \dots, k-1} \lambda_j\right) \right\}. \tag{11}
\end{aligned}$$

Since the density function for the background hazard can be described as

$$h_{(u, k-u)}(t \mid 0, a) = \frac{\lambda_1 \cdots \lambda_k}{(k-1)!} t^{k-1} \cdot \left\{ 1 + o\left(\max_{j=1, \dots, k-1} \lambda_j\right) \right\},$$

it follows from (10) and (11) that the hazard ratio at time t can be expressed as

$$\begin{aligned}
HR_{(u, k-u)}(t \mid D, a) &= \frac{h_{(u, k-u)}(t \mid D, a)}{h_{(u, k-u)}(t \mid 0, a)} \cdot \left\{ 1 + o\left(\max_{j=1, \dots, k-1} \lambda_j\right) \right\} \\
&= \frac{\lambda_k \cdot \Pr(X_t = k-1 \mid D, a)}{\lambda_1 \cdots \lambda_k t^{k-1} / (k-1)!} \cdot \left\{ 1 + o\left(\max_{j=1, \dots, k-1} \lambda_j\right) \right\} \\
&= 1 + \sum_{j=0}^{u-1} \frac{(k-1)!}{j!(k-j-1)!} \left(\frac{a}{t}\right)^j \sum_{\ell=1}^{u-j} \frac{(k-1-j)!}{\ell!(k-1-j-\ell)!} \left(1-\frac{a}{t}\right)^{k-1-j-\ell} \left(\frac{\beta_a D}{t}\right)^\ell \cdot \left\{ 1 + o\left(\max_{j=1, \dots, k-1} \lambda_j\right) \right\},
\end{aligned}$$

for $u=1, \dots, k-1$. Hence, it follows from $\max_{j=1, \dots, k-1} \lambda_j \doteq 0$ that

$$\begin{aligned}
EHR_{(u, k-u)}(t \mid D, a) &\equiv HR_{(u, k-u)}(t \mid D, a) - 1 \\
&\doteq \sum_{j=0}^{u-1} \frac{(k-1)!}{j!(k-j-1)!} \left(\frac{a}{t}\right)^j \sum_{\ell=1}^{u-j} \frac{(k-1-j)!}{\ell!(k-1-j-\ell)!} \left(1-\frac{a}{t}\right)^{k-1-j-\ell} \left(\frac{\beta_a D}{t}\right)^\ell \\
&= \left(1-\frac{a}{t}\right)^{k-1-u} \sum_{\ell=1}^u \sum_{j=0}^{u-\ell} \frac{(k-1-\ell)!}{j!\ell!(k-1-\ell-j)!} \left(\frac{a}{t}\right)^j \left(1-\frac{a}{t}\right)^{u-\ell-j} \left(\frac{\beta_a D}{t}\right)^\ell,
\end{aligned}$$

for $u=1, \dots, k-1$. Thus, Theorem 1 is established.

It is noteworthy that Formula (9) for $EHR_{(u, k-u)}$ shows that the excess hazard

ratio can be described by a u^{th} order polynomial in dose D which does not depend on the values of the transition parameters $\lambda_1, \dots, \lambda_k$. When the exposure time a is known, it contains no unknown parameters except for the number of total stages k , number of exposure-sensitive stages u , and coefficient of exposure effect β_a .

We then have the following obvious results:

$$\begin{aligned} EHR_{(1,k-1)}(t | D, a) &= (k-1) \left(1 - \frac{a}{t}\right)^{k-2} \frac{\beta_a D}{t}, \\ EHR_{(k-1,1)}(t | D, a) &= \left(1 + \frac{\beta_a D}{t}\right)^{k-1} - 1, \end{aligned} \quad (12)$$

for $k = 2, 3, \dots$. Formula (12) was also obtained by Pierce and Vaeth (2003).

Neglecting the quadratic and higher-order terms with respect to $\beta_a D/t$ in Formula (9) in Theorem 1, we obtain a “linear” approximation formula for $EHR_{(u,k-u)}$ as follows:

$$EHR_{(u,k-u)}^{(1)}(t | D, a) = (k-1) \left(1 - \frac{a}{t}\right)^{k-1-u} \left\{ \sum_{j=0}^{u-1} \frac{(k-2)!}{j!(k-2-j)!} \left(\frac{a}{t}\right)^j \left(1 - \frac{a}{t}\right)^{u-1-j} \right\} \frac{\beta_a D}{t}, \quad (13)$$

for $u = 1, \dots, k-1$, when $\beta_a D/t$ is sufficiently small.

4. Application to analysis of cancer mortality among A-bomb Survivors

In this section we apply the model to the analysis of cancer mortality among A-bomb Survivors. We assume that carcinogenesis is an irreversible multistage point process. The Radiation Effects Research Foundation (RERF) and its predecessor, the Atomic Bomb Casualty Commission (ABCC), have conducted a cohort study, called the Life Span Study (LSS), on A-bomb survivors in Hiroshima and Nagasaki since 1950. Ozasa et al. (2012) recently published the 14th report on cancer mortality as well as non-cancer mortality in the LSS, covering the period 1950-2003. The number of subjects analyzed was 86,611 (58,494 in Hiroshima and 28,117 in Nagasaki). The LSS data are available for public use on the RERF website (<http://rerf.jp/>).

We analyzed the data on solid cancer mortality using the two-phase multistage models $M(u, 6-u)$, $u = 1, \dots, 5$, where the number of stages of carcinogenesis k was assumed to be 6 based on Doll (1971). We then compared our results with those of Ozasa et al. (2012). The dose-response relationship for solid cancer incidence/mortality among A-bomb survivors in the LSS was considered to be

linear rather than a higher order polynomial such as quadratic or cubic (e.g. Pierce et al., 1996, Ozasa et al., 2012). In keeping with their analysis, Poisson regression methods for grouped survival data with the linear approximation to the excess relative risk were used to describe the dependence of risk on radiation dose and to evaluate the variation of the dose response with respect to city, sex, age at exposure, and attained age. Analyses of all solid cancers were based on colon dose as representative of doses to all organs. The models we used are as follows.

For the excess relative risk (ERR), which is equivalent to the excess hazard ratio (EHR), a model of solid cancer death for an individual at age t who was exposed to dose D at age a was assumed to be

$$h(t | D, a, sex, c) = h_0(t | a, sex, c) \cdot [1 + ERR(t | D, a, sex)],$$

where h_0 is the baseline or background mortality rate at zero (initial) dose, depending on city (c), sex, birth year ($b \equiv 1945 - a$), and attained age (t). The baseline mortality rate h_0 was modeled using stratification on city and birth year for the ERR model. The ERR model utilized at RERF is

$$ERR(t | D, a, sex) = (1 + \sigma_{sex}) \cdot t^v e^{\tau a} \beta D,$$

where the parameters τ , v and σ are coefficients for effect modification by ATE (age at exposure), attained age, and sex, respectively. The term that includes sex ($sex = 1$ for female and $sex = -1$ for male) as a modifier allows the parameter β to represent a sex-averaged dose effect.

We obtain from (13) that the linear approximation to the excess relative risk of cancer mortality using the model $M(u, 6 - u)$ can be specified as

$$ERR_{(u, 6-u)}^{(1)}(t | D, a, sex) = (1 + \sigma_{sex}) \cdot \left(1 - \frac{a}{t}\right)^{5-u} \left\{ \sum_{j=0}^{u-1} \frac{120}{j!(4-j)!} \left(\frac{a}{t}\right)^j \left(1 - \frac{a}{t}\right)^{u-1-j} \right\} \left(\frac{e^{\tau a} \beta D}{t}\right), \quad u = 1, \dots, 5.$$

To implement these models, we used the generalized nonlinear model (gnm) package (Turner and Firth, 2007) in R (version 2.15.1). The resultant AIC, a measure of goodness of fit of the model (Akaike, 1973, 1992), is shown in Table 1. The minimum value of AIC was attained when the model of $ERR_{(4,2)}^{(1)}$ based on $M(4, 2)$ was used, which implies that some latency time is required from the time of exposure (due to the A-bomb radiation) to the actualization of the excess risk of death from cancer among subjects in the LSS; we call this our “optimal model”. Figure 2 shows the estimated excess relative risk by

age at exposure for a subject who was exposed to 1 Gy, where the shaded curve indicates the projected *ERR* for the period without direct follow-up in the LSS. Tables 2.1 and 2.2 show the estimated regression coefficients based on RERF's *ERR* model and our optimal model $ERR_{(4,2)}^{(1)}$ based on $M(4,2)$, respectively. The results of Table 2.1 coincide with those of Table 6 in Ozasa et al. (2012).

Compared with RERF's *ERR* model, although the estimated values of dose effect parameters (β) and modifying effect of age at exposure on the dose effects (τ) were quit similar, there existed a large difference in the estimated trends of *ERR* in relation to attained age after the bombing. Our proposed model suggested that no (or very low) *ERR* was expected during some period just after the bombing irrespective of age at exposure, and attained a peak with a slower rise to peak *ERR* particularly at older ages at exposure. On the other hand, the expected *ERR* in RERF's *ERR* model attained a peak just after exposure and decreased monotonically thereafter. It should be noted that crude values of dose effect parameters in the two models have different meanings, because the way in which the dose effect is varying with attained age in our proposed model differs from that of RERF's model. Therefore, the comparison of dose effects between the two models should be modified by the aging effect, which corresponds to the aging trend of excess relative risks given in Figure 2.

As a theoretical aspect of our proposed model, the aging trend of excess cancer risk in $M(5,1)$ becomes a maximum at the time of ATE and decreases in inverse proportion to attained age. The aging trend of RERF's *ERR* is similar to that of $M(5,1)$, except for including the additional parameter ν , in the RERF's model the estimate of ν for LSS data was -0.86. In the proposed model with no latency time $M(5,1)$, the value of ν is specified automatically as -1. We consider that this shrinkage is a consequence of the effect of latency time in radiation carcinogenesis. Therefore, the *ERR* model without a latency time is not suitable to describe the ageing trend in the dose effect. Although there is no latency time in $M(5,1)$ and RERF's model, $M(6-u,u)$, $u=2,\dots,5$, models reflect the effect of latency time based on the number of sensitive stage u . Table 1 shows AIC of candidate models for the LSS data, which provides basic information on the numerical comparison of performance between RERF's model and $M(6-u,u)$, $u=1,2,\dots,5$. The improved performance of our optimal model using fewer free parameters compared with that of the traditional model, which is indicated by a reduction of 2.39 in AIC, may not be astounding (see Table 1, Table 2.1 and Table 2.2). The minor difference in their performance may be due to lack of information about cancer mortality among survivors in the early years just after the bombing. it was also noted that about 10% higher value was estimated

for the coefficient of dose effect, and that about 23% smaller value was estimated for the modifying effect of age at exposure on the dose effect in our model. Note that the main differences of aging trends of ERR in RERF's model and $M(6-u, u)$, $u=1,2,\dots,5$ appear in the initial period after the bombing.

Table 1. Goodness of fit (AIC) of candidate models for the LSS data: the numerical comparison of performance between RERF's model and $M(6-u, u)$, $u=1,2,\dots,5$

Model	AIC
RERF's ERR model	33838.36
$ERR_{(5,1)}^{(1)}$ model based on $M(5,1)$	33836.50
$ERR_{(4,2)}^{(1)}$ model based on $M(4,2)$	33835.97
$ERR_{(3,3)}^{(1)}$ model based on $M(3,3)$	33838.43
$ERR_{(2,4)}^{(1)}$ model based on $M(2,4)$	33846.92
$ERR_{(1,5)}^{(1)}$ model based on $M(1,5)$	33859.61

Table2.1 Estimated regression parameters for RERF's ERR model

Parameter	Coef.	s.e	z-value	p-value
β : dose effect	0.4226	0.0503	8.397	< 0.001
σ : sex (female =1, male =-1)	0.3441	0.0878	3.918	< 0.001
τ : age at exposure (per 10-year increment)	-0.3462	0.0814	-4.254	< 0.001
ν : attained age (log(age/70))	-0.8576	0.4232	-2.026	0.0427

Table 2.2 Estimated regression parameters based on our optimal model $ERR_{(4,2)}^{(1)}$

Parameter	Coef.	s.e	z-value	p-value
β : dose effect	0.4609	0.0532	8.664	< 0.001
σ : sex (female =1, male =-1)	0.3375	0.0878	3.846	< 0.001
τ : age at exposure (per 10-year increment)	-0.2824	0.0752	-3.758	< 0.001

Figure 2. Theoretical curves of ERR/Gy of solid cancer mortality among subjects in the LSS by age at exposure and attained age obtained from the candidate models

5. Discussion:

Our proposed multistage model of carcinogenesis accommodates fundamentally only single events such as cellular mutations. However, the last event in the process should be related more closely to tumor growth than to cellular transformation. A more explicit model for the carcinogenesis process may require that a mechanism of clonal expansion be incorporated in the model, such as with the two-stage clonal expansion (TSCE) model of Moolgavkar and Venzon (1979), which assumes clonal expansion as a stochastic process after two exposure-sensitive stages of cellular change in the earliest part of carcinogenesis. The TSCE model consists of not only transition parameters related to cellular stage as in the ordinary multistage model but also parameters concerning the clonal expansion (birth and death) process. To analyze the dose-response relationship, it is necessary to use a model having a structure for describing the dose effect. In the case of a single point exposure like radiation exposure due to the atomic bomb, a structure common to that of the ordinary multistage model for the cellular transition parameter may be assumed in the TSCE model (Kai et al., 1997). However, it is difficult to formulate the effect on the birth and death process, in that it is not easy to formulate the exposure effect on ERR in relation to attained age after exposure; therefore, we have not compared its performance with our model in actual data analysis. As for quantification of carcinogenesis, there are more recent models that do not fall within the Armitage-Doll or TSCE frameworks, which are regarded as extensions of the TSCE model having more complex structures with many additional parameters (Little, 1995; Aalen and Tretli, 1999; Luebeck and Moolgavkar, 2002; Nowak et al., 2007; Little and Wright, 2003; Beerenwinkel et al., 2007; Meza et al., 2008).

For illustrative application of the proposed model, we think that use of incidence data rather than mortality data is more reasonable, and would clearly provide a better test of the fit of our proposed model. However, the downloadable incidence data is limited to only observations taken from the period 1958 to 1998, while the latest version of mortality data which is available for us covered the wider period from 1950 to 2003. Use of the data of the early period around 1950 (just after the A-bomb exposure) is very important to clarify the performance of our proposed model. Therefore, we chose the mortality data rather than incidence data. We know the demerit of the use of mortality data for the test of the fit of our model. Actually, the length of clinical period of cancer (the period from cancer diagnosis to death, which has been assumed about several years) is ignored in our model. The last transition to the final stage may mean the clinical period, with some lack of accuracy, in our carcinogenesis model based on the Poisson process.

The result of our analysis of cancer mortality data among A-bomb survivors

suggests a perspective “ionizing radiation works mainly as initiation” so that radio-therapy has been commonly applied to cancer patients. If ionizing radiation operates positively at late stages in carcinogenesis, cancer risk among exposed people would begin to increase soon after exposure, which was not observed in epidemiological studies (e.g., Shimuzi, et al., 1991; Travis, 2006). It was shown that a model with later stages of carcinogenesis insensitive to radiation fit the LSS solid cancer mortality data quite well, which provides a mathematical explanation for the latency time of appearance of the excess cancer risk among A-bomb survivors after radiation exposure. We think that the reason why the later stages of carcinogenesis are insensitive to radiation can be explained by the difference of target size for carcinogenic change among stages and the effect of radiation-induced apoptosis (Dewey et al., 1995). In the earlier stages, not only exons including oncogenes or suppressor genes but also introns are supposed to be the target (Nomura, 1982; Ohtaki and Niwa, 2001). On the other hand, in the later stages a few specific genes such as *src*, *ras*, and *myc* can be the target, where carcinogenic transitions should be rate-limiting events. Thus, the earlier stages have a relatively large target whereas the later stages have a small one. It is also well known that most irradiated cells are more susceptible to apoptosis than to carcinogenic transformation, which must reduce the sensitivity to radiation-induced carcinogenic transition in cells at later stages. With other kinds of exposure, such as chemicals, no latency time may exist in the carcinogenic process where all stages of cell transformation must be sensitive to exposure. For example, no latency time was expected between mustard gas exposure and excess risk of lung cancer morbidity among workers in the Ohkunojima Poisonous-gas factory in Japan (Doi et al., 2011).

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