RISK MODELS FOR ESTIMATING LIFETIME CANCER PROBABILITY: ALTERNATIVE TO RELATIVE RISK MODEL BY UNSCEAR/ICRP

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ABSTRACT

Based on the carcinogenesis model as proposed by Moolgavkar et al., time-dependent relative risk models were derived for projecting time variation in excess relative risk. If it is assumed that each process is described by time-independent linear dose-response relationship, the time variation in excess relative risk is influenced by the parameter related with the promotion process. Its parameter was discussed by analyzing spontaneous cancer incidence data. The model predicts larger variation in relative risk with time for younger ages at exposure.

INTRODUCTION

The ICRP adopted relative risk models for radiation-induced lifetime cancer probability in the 1990 recommendation(1). The application of the relative risk projection model mainly causes higher lifetime cancer probability than the ICRP 1977 recommendation(2). The main background why the ICRP adopted the relative risk model is based on the epidemiological data of A-bomb survivors in Japan. The atomic bomb data indicate that the variation of relative risk with time is constant for a given age-at-exposure, but the transfer of the constant relative risk to population other than the Japanese cannot be verified by the statistical models based only on the data fitting. However, there is no biological basis for projecting excess hazard rate of radiation. The carcinogenesis model as proposed by Moolgavkar et al.(3,4) can give a good fitting and interpretation for the age-dependent spontaneous cancer incidence rate of a specific population data. In this paper a risk projection model will be derived from the carcinogenesis model as biological basis. Moreover, the time variation in relative risk for age at exposure will be discussed.

CARCINOGENESIS MODELS

Moolgavkar et al.(2,3) proposed the two-stage carcinogenesis model, which will be referred to as MVK models below. The two-stage carcinogenesis model assumes that stem cells change to initiated cells by first mutation and furthermore tumor cells are induced by second mutation. In addition, the MVK model is a stochastic model which deals with a homogeneous filtered Poisson process of initiated cells. In the case of epidemiological data, the approximation of the hazard rate as an expected value is as follows:

$$r(t) = u_2(t) \int_0^t \{ u_1(s)X(s)\exp(\int_s^t [a(u)-b(u)]du) \}ds. \qquad \text{(Eq.1)}$$

DERIVATION OF MATHEMATICAL MODELS

It is assumed that each process is described by linear dose-response relationship which is time-independent. Furthermore, it can be assumed that a single exposure to radiation acts as an initiator. On these assumptions, if the stem cell population is constant, the hazard rate of spontaneous cancer (Rs(t)) and excess hazard rate (Rr(t)) due to a single exposure can be derived as:

$$Rs(t) = N_0\, ac/g\{\exp(gt)-1\} \qquad \text{(Eq.2)}$$

$$Rr(t) = N_0\, bcx\, \exp[g(t-t_0)], \qquad \text{(Eq.3)}$$

using the expressions as $u_1(t)=a+bx$, $u_2(t)=c$ and $a(t)-b(t)=g$.
In addition, N_0, x, t and t0 represent the number of normal cells, dose, attained age and age-at-exposure, respectively. The parameter g is the net rate of proliferating initiated cells and plays an important role in projecting the variation in relative risk. The above expressions are the most simple form with minimum unknown parameters.

If the growth of the normal stem cell population is modeled by an exponential function until t_1, the hazard rate of spontaneous cancer is then described by the summation of hazard rates that originate from the numbers of cells which are initiated until t_x and are initiated after t_x. The expression can be given by:

$$Rs(t) = \begin{cases} \{ack/(L-g)\}\{\exp[L-g)t_x+gt]-\exp(gt)\} \\ \quad + (acN_0/g)\{\exp[g(t-t_x)]-1\} & \text{if } t>t_x \quad \text{(Eq.4)} \\ \{ack/(L-g)\}\{\exp(Lt)-\exp(gt)\} & \text{if } t<t_x \quad \text{(Eq.5)} \end{cases}$$

where it is assumed that $X(t)=k\exp(Lt)$ $(t<t_x)$. The excess hazard rate due to a single exposure can be obtained as:

$$Rr(t) = \begin{cases} (kbcx)\exp[g(t-t_0)+Lt_0] & \text{if } t_0<t_x \quad \text{(Eq.6)} \\ (N_0bcx)\exp[g(t-t_0)] & \text{if } t_0>t_x \quad \text{(Eq.7)} \end{cases}$$

The expression of hazard rates involving time-dependent processes can be derived by dividing the age into two or more age groups in which the parameters are assumed to be time-independent. In the case of two age groups, the expression for the hazard rate of spontaneous cancer shown in Eq.2 must be rewritten into:

$$Rs(t) = (N_0a_1c/g_1)\{\exp[g_2(t-t_1)]\}\{\exp(g_1t_1)-1\} + (N_0a_2c/g_2)\{\exp[g_2(t-t_1)]-1\} \quad \text{if } t>t_1 \quad \text{(Eq.8)}$$

where the parameters of g_1 and g_2 are the net rates of proliferating initiated cells in each age group, and those of a_1 and a_2 are mutation rates per cell per year of one normal cell into one initiated cell. If $t_0<t_1$, the excess hazard rate due to a single exposure can be obtained as:

$$Rr(t) = \begin{cases} (N_0bcx)\exp[g_1(t-t_0)] & \text{if } t<t_1 \quad \text{(Eq.9)} \\ (N_0bcx)\exp[g_1(t_1-t_0)+g_2(t-t_1)] & \text{if } t>t_1 \quad \text{(Eq.10)} \end{cases}$$

MODEL FITTING TO SPONTANEOUS CANCER DATA

The cancer incidence data from 20 to 80 years of age in Japan in 1985(5) were used for the parameters by model fitting. By using Eq.2 and Eq.8, in which $t_1=60$, the results of data fitting to the incidence rates of lung cancer and stomach cancer of males were obtained as shown in Fig.1 and Fig.2, respectively. These organs have higher cancer probabilities in ICRP Pub.60. The MVK model agrees with the spontaneous cancer data.

PREDICTED TIME VARIATION IN EXCESS RELATIVE RISK

The reduction in excess relative risk can be predicted by the g parameter which is obtained by data fitting to spontaneous cancer incidence rates. Figure 3 illustrates the excess relative risk in stomach for a single exposure at adult age or young age. The excess relative risk for the young age decreases more rapidly with time than that for the adult age. This is

influenced by the age-dependence of the growth of radiation-induced initiated cells and spontaneously induced initiated cells.

CONCLUSION

It was suggested that the MVK model is a useful tool as a carcinogenesis model for projecting the time variation in excess relative risk. The reduction rate in excess relative risk can be obtained by the data fitting to spontaneous cancer incidence data. For adult exposure, the excess relative risks are approximately constant for some cancers such as lung, colon and stomach. However, for breast cancer, the excess relative risk decreases with attained age. In applying the above risk model to epidemiological data for estimating lifetime cancer probability, the parameters related with the time variation in relative risk can be estimated by analyzing the spontaneous cancer incidence data.

REFERENCES

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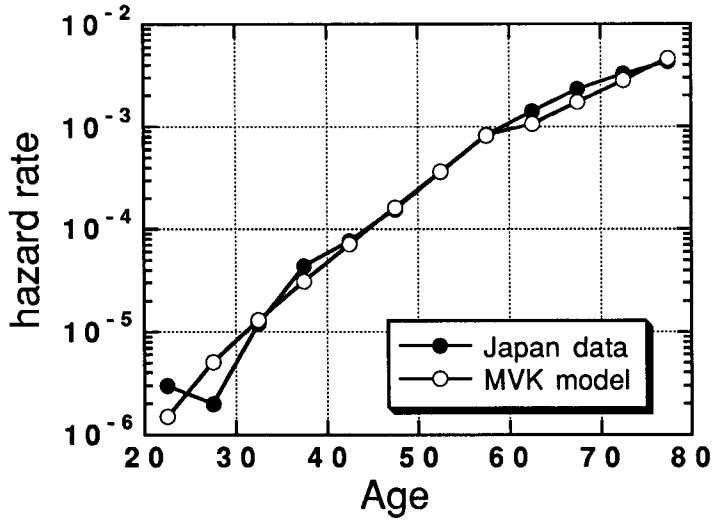


Fig. 1 Lung cancer incidence in Japan and the data fitting by MVK model.

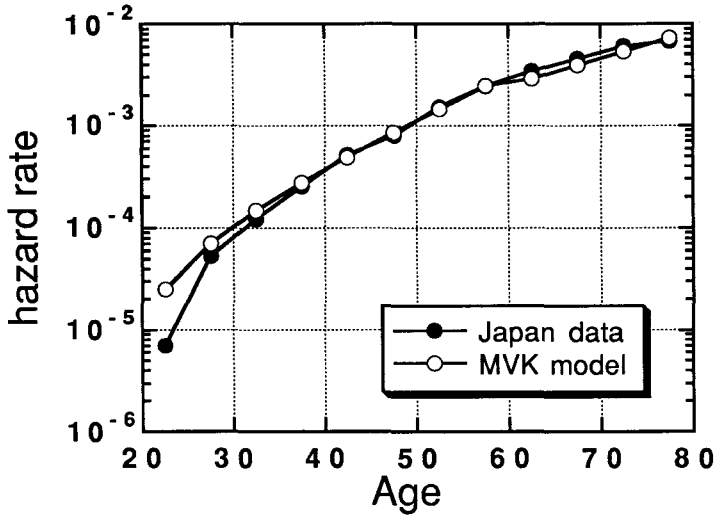
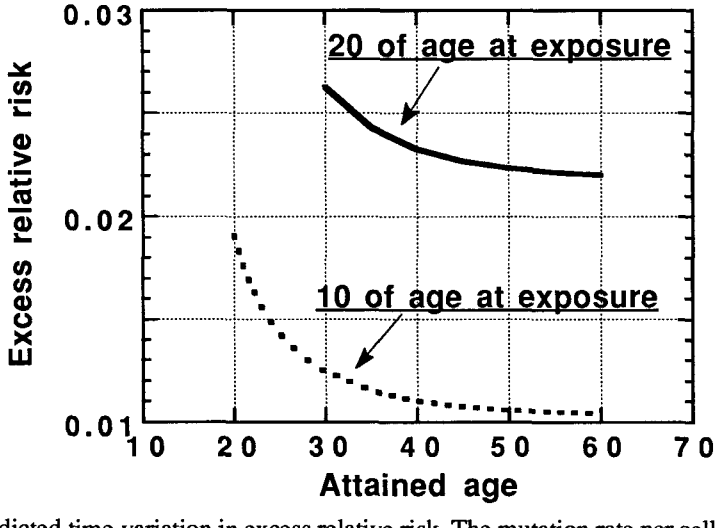


Fig. 2 Stomach cancer incidence in Japan and the data fitting by MVK model.



Fi.g 3 Predicted time variation in excess relative risk. The mutation rate per cell per year of one normal cell into one initiated cell is assumed to be independent of age-at-exposure.