Preliminary report

Mathematical Implication for Radiation Carcinogenesis based on Hypothesis of Induction of Genomic Instability

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We developed a mathematical model of carcinogenesis with the genomic instability hypothesis, a feature characterized by destabilization of the genome is induced in irradiated cells permanently or semipermanently, leading to an increase of cancer risk at cancer age of the exposed individuals. This model also takes into consideration the “induction of cell death,” which is another important effect of radiation on cells. It is assumed in this model that the effect of radiation exposure on “cell killing” may occur in all stages of carcinogenic process. Using the resulting model, we can explain not only paradoxical relationship between low mutation rate and high cancer incidence but also the well known empirical evidence from the cohort study on atomic-bomb survivors in Hiroshima–Nagasaki that the excess relative risk of solid cancer incidence for exposed individuals has been almost constant irrespective of the number of years after exposure.

Key words: Armitage-Doll model; Genomic Instability hypothesis; Mathematical model; Multistage model; Radiation carcinogenesis; Single point exposure.

1. Introduction

It has been demonstrated at the molecular level that solid cancer develops following a multi-step process. Radiation is known to be a risk factor of cancer, the dose-response curve of which is almost linear in many instances. How does radiation work in the process of development of cancer? A number of interesting epidemiological research and animal-experiment studies which seem to provide clues to this question have been reported. A cohort study by researchers of RERF concerning A-bomb survivors in Hiroshima and Nagasaki shows that the relative mortality risk of solid tumors has been constant irrespective of the number of years after A-bomb exposure, except for those who were as young as 10 years old or under at the time of bombing (Shimizu *et al.*, 1990; Matsuura *et al.*, 1997; Pierce and Mendelsohn, 1999). This indicates that radiation has increased only the risk level of cancer, and has not brought about essential shortening of the latent period of cancer. Kamiya *et al.* (1995) analyzed the frequency of cancer using mammary epithelial stem cells of irradiated rats transplanted to the host and re-

ported that cancer initiation occurred at a high frequency of 1/100 cells in the irradiated cells. Nomura (1982) reported an increase in the rate of lung cancer by 10% in F1 mice born to parent mice exposed to 1 or 2 Gy. It has been shown by the in vitro tissue culture assay that the frequencies of somatic as well as germ line mutations at this dose range are usually of the order of 1/10000. This means that the frequencies of initiation are 100 to 1000-fold higher than those of mutations. Is it paradoxical that high cancer incidence comes from such a very low mutation rate? Moreover, most of transgenerational carcinogenesis in successive generations is manifested when the hosts reach the so-called cancer age. A hypothesis was postulated in which the so-called “genomic instability,” a feature characterized by destabilization of the genome is induced in irradiated cells permanently or semipermanently, leading to an increase of cancer risk at cancer age of the exposed individuals. With this hypothesis, we developed a mathematical model of carcinogenic process. This model also takes into consideration the “induction of cell death,” which is another important effect of radiation on cells. It is assumed in this model that the effect of radiation exposure on “cell killing” may occur in all stages of carcinogenic process.

2. Modeling based on Genomic Instability Hypothesis

In this section, we introduce a mathematical formula for carcinogenesis with genomic instability in a target cell. The formula is described by a Poisson process, and is regarded as one of the modified versions of Armitage-Doll model (Armitage and Doll, 1954). In the modeling, we propose the following assumptions.

- A1. Carcinogenic transformation of one normal target cell requires that it undergo a change m times and that the change at each stage is irreversible.
- A2. The state of “genomic instability”, a feature characterized by destabilization of the genome occurs stochastically in target cells, leading to an increase of carcinogenic mutation risk permanently or semipermanently.
- A3. The occurrence of genomic instability and carcinogenic transformations in cells are mutually independent.

Besides the carcinogenic stage of cells, we assume that there are two phases as stated in A2. The status of cells in a genetically stable condition is designated S -Phase, otherwise U -Phase. Based on the assumption of A1 and A2, there exist $2m - 1$ distinct stages for a target cell. We name each state of cell as follows.

The status of normal cells (cells which have never undergone carcinogenic mutation) is designated 0-Stage if the cell is in S -Phase, 0'-stage if the cell is in U -Phase. The status from the first carcinogenic mutation to the status just prior to the second carcinogenic mutation, is designated 1-Stage and 1'-Stage for S -Phase cell and U -Phase cell, respectively. In general, the status of cells from the j^{th} carcinogenic mutation to the status just prior to $(j+1)^{th}$ carcinogenic mutation is generally designated j -Stage or j' -Stage. It is assumed that the cells do not have the characteristics of cancer cells up to $(m-1)$ -Stage or $(m-1)'$ -Stage, but they undergo carcino-

Fig. 1. Schema of Carcinogenic Transition of Stages of Cell with Relation to Gene Instability.

genic mutation in m -Stage and begin to proliferate chaotically. We assume that the risk of occurrence of carcinogenic mutation for a cell is magnified ρ_j ($\gg 1$) times by changing the cell status from S -Phase to U -Phase. (see Fig. 1.)

Suppose that ξ denotes the hazard rate of the occurrence of genomic instability in one target cell, and that the carcinogenic transition rate to the next stage is expressed as ε_j and $\rho_j\varepsilon_j$ for the $(j-1)$ -Stage and $(j-1)'$ -Stage cell, respectively. Here, let h_B be the hazard function of occurrence of the phenomenon where one specific target cell for a host in back ground population undergoes m carcinogenic mutations. If it is assumed that ξ and $\rho_j\varepsilon_j$ $j=1, \dots, m$ are sufficiently small, then, the hazard function at attained age y of the host can be expressed approximately as

$$h_B(y) = \frac{\xi(\bar{\rho}\bar{\varepsilon})^m}{m!} y^m \{1 + \rho_1^{-1} + (\rho_1\rho_2)^{-1} \dots + (\rho_1 \dots \rho_{m-1})^{-1}\} + \frac{\bar{\varepsilon}^m}{(m-1)!} y^{m-1}, \quad (1)$$

where $\bar{\rho} = (\prod_{j=1}^m \rho_j)^{1/m}$ and $\bar{\varepsilon} = (\prod_{j=1}^m \varepsilon_j)^{1/m}$. Since it follows from (1) that the ratio of terms to the first one are about $1 : \rho_1^{-1} : (\rho_1\rho_2)^{-1} : \dots : (\rho_1\rho_2 \dots \rho_{m-1})^{-1} : m\xi^{-1}y^{-1}\bar{\rho}^{-m}$, the second or latter terms can be neglected if ρ_1 is large enough. Then $h_B(y)$ can be approximated as follows,

$$h_B(y) = \frac{\xi(\bar{\rho}\bar{\varepsilon})^m}{m!} y^m. \quad (2)$$

Hence, it can be regarded that almost all the carcinogenic processes in a cell progress via the pathway 0 -Stage $\rightarrow 0'$ -Stage $\rightarrow 1'$ -Stage $\rightarrow \dots \rightarrow (m-1)'$ -Stage $\rightarrow m$ -Stage. It means that genomic instability has occurred in the cell prior to the accumulation of carcinogenic mutations in almost all cases. In other words, the cells in S -Phase seldom or never attain m -Stage. Therefore we can assume that accumulation of carcinogenic mutations follows the occurrence of genomic instability in carcinogenesis.

3. Effects of Single Point Exposure of Radiation

In this section, based on the hypothesis of induction of genomic instability by radiation,

Fig. 2. Schema of Transitions of Cell Stage due to Single Point Radiation Exposure.

we give a mathematical formulation of the cancer risk due to a single point radiation exposure. With respect to radiation effects on cells, we assume the following

- A5. Radiation induces genomic instability in exposed cells stochastically, the excess risk of which is proportional to the dose.
- A6. Radiation induces carcinogenic mutation in exposed cells or cell-death stochastically, the excess risks of which are proportional to the dose.

Suppose that the hazards of the occurrence of genomic instability, that of the occurrence of carcinogenic mutation and that of cell-death for a $(j-1)$ -Stage cell of an individual who was exposed at age a with single point radiation of dose D are expressed as $\xi[1 + \beta D\delta(y-a)]$, $\varepsilon_j[1 + \gamma_j D\delta(y-a)]$ and $\mu_{j-1} D\delta(y-a)$, respectively, where $\delta(\cdot)$ denotes the Dirac function. Also suppose that the hazards of the occurrence of carcinogenic mutation and of cell-death for a $(j-1)'$ -Stage cell (in U -Phase) are expressed as $\rho_j \varepsilon_j[1 + \gamma_j D\delta(y-a)]$ and $\mu_{j-1} D\delta(y-a)$, $j=1, \dots, m (=k-1)$. (See Fig. 2.)

Let h be the hazard function of the appearance of one cancer cell in an individual who was exposed to radiation of dose D at age a . Then the approximate risk can be expressed as,

$$h(y|a, D) = \omega \left[\sum_{j=0}^k S_j(y|a, D) + D \sum_{j=1}^k A_j(y|a, D) \right], \quad (3)$$

$$S_j(y|a, D) = \begin{cases} e^{-\mu_j D} \frac{a^j}{j!} \frac{(y-a)^{k-j-1}}{(k-j-1)!} I_{(a, \infty)}(y), & j=0, \dots, k-1, \\ \frac{y^{k-1}}{(k-1)!} I_{(0, a)}(y), & j=k, \end{cases}$$

$$A_j(y | a, D) = \begin{cases} \beta e^{-\mu_0 D} \frac{(y-a)^{k-1}}{(k-1)!} I_{(a, \infty)}(y), & j=1, \\ \gamma_{j-1} e^{-\mu_{j-1} D} \frac{a^{j-1}}{(j-1)!} \frac{(y-a)^{k-j-1}}{(k-j-1)!} I_{(a, \infty)}(y), & j=2, \dots, k-1, \\ \gamma_{k-1} e^{-\mu_{k-1} D} \frac{a^{k-2}}{(k-2)!} \delta(y-a), & j=k, \end{cases}$$

where $\omega = N\xi(\bar{\rho}\bar{\epsilon})^{k-1}$, and $I_{(c,d)}$ denotes the indicator function of an interval (c, d) . Then the incidence for an individual of age y who was exposed to radiation of dose D at age a is expressed approximately as

$$g(y | a, D) = \int_0^y h(t | a, D) w(y-t | a, D) dt, \quad (4)$$

where w is the density function for the waiting time from the appearance of one cancer cell (m -Stage cell) to the clinical diagnosis of the tumor after chaotic proliferation.

Since Formula (3), containing $2k+1$ unknown parameters, has too many parameters to overview the risk through itself, a reduction of the model is made by introducing constrains in the parameters for the dose effect coefficients of radiation on the occurrence of carcinogenic mutation and cell-death such as

$$\gamma_1 = \gamma_2 = \dots = \gamma_{k-1} = \gamma,$$

$$\mu_0 = \mu_1 = \dots = \mu_{k-1} = \mu.$$

Then, we have

$$h(y | a, D) = \frac{\omega}{(k-1)!} y^{k-1} e^{-\mu D} \left[1 + \gamma D \frac{k-1}{y} \left\{ 1 + \left(\frac{\beta}{\gamma} - 1 \right) \left(1 - \frac{a}{y} \right)^{k-2} + \left(\frac{a}{y} \right)^{k-2} \delta(y-a) \right\} \right], \quad (5)$$

It should be noted that Formula (5) coincides with the one proposed by Pierce and Mendelsohn (1999) as a special case when the conditions $\mu=0$ and $\beta=\gamma$ hold.

The excess relative risk of cancer incidence can be expressed, under the assumption that the length of tumor growth period is zero for simplifying the argument, as

$$ERR(y | a, D) = e^{-\mu D} \left[1 + \gamma D \frac{k-1}{y} \left\{ 1 + \left(\frac{\beta}{\gamma} - 1 \right) \left(1 - \frac{a}{y} \right)^{k-2} \right\} \right] - 1, \quad (6)$$

which is obtained by calculating the ratio (5) to the background risk $(\omega/(k-1)!))y^{k-1}$. Furthermore, for a very low dose-range, Formula (6) can be rewritten approximately to

$$ERR(y|a,D)=\gamma D \frac{k-1}{y} \left\{ 1 + \left(\frac{\beta}{\gamma} - 1 \right) \left(1 - \frac{a}{y} \right)^{k-2} \right\}, \quad (7)$$

indicating that the excess relative risk increases linearly with the exposure dose D , that is, the so-called linear dose-response relation is derived.

On the other hand, the feature of time trend of the ERR may vary with the value of the ratio of β to γ . In case of $\beta/\gamma=1$, the ERR attains the maximum value just after exposure, then decreases uninterruptedly in proportion to the reciprocal age of the individual. As the value of β/γ increases, the time trend of ERR shows a more complicated behavior, with local minimum and maximum values. Figure 3 shows the theoretical time trend of ERR based on (7) in the case where $k=6$ and $\gamma D=10$.

It can be seen from Fig. 3 that the ERR becomes almost constant irrespective of the number of years after exposure if $\beta/\gamma \geq 5$ except for those who are as young as 5 years old at the time of exposure ($a=5$).

4. Discussion

It has been reported that among A-bomb survivors in Hiroshima and Nagasaki, the relative mortality risk due to solid tumors has been constant irrespective of the number of years after A-bomb exposure, except for those who were as young as 10 years old or under at the time of bombing (Shimizu *et al.*, 1990). Applying the classical multistage model for carcinogenesis developed by Armitage-Doll to this data, Little *et al.* (1992) found that the model with two inconsecutive sensitive stages to radiation exposure, the second and fifth stages fits the data best, for which no simple biological mechanism seems to be provided. On the other hand, we can give a simpler and more plausible explanation based on the hypothesis of genomic instability. That is, it is considered that radiation exposure induces not only the genomic instability of cells but carcinogenic mutation in any stage of carcinogenesis. The effect on induction of carcinogenic mutation is limited within only one. We assume that target cells have the characteristics of being sensitive to radiation in any stage, but that the change of stage due to one-time exposure is restricted to one step. In that sense, our assumption complies with Mendelsohn's hypothesis (Mendelsohn, 1996). However, there is one serious question in this hypothesis. It is "Assuming that radiation exposure contributes to the stage changes of cells, why is the change limited to only one stage? What is the mechanism behind it?" So far no explanation has been given to this question. Actually, the model we developed has a clue to the solution of this question. The clue is based on the fact that "radiation exposure induces not only genomic instability and mutation but also cell killing," which is expressed in our model as the coefficients of radiation dose effects on cell killing $\mu_0, \mu_1, \dots$. It is known that the frequency of cell killing after radiation exposure is higher than that of carcinogenic mutations by several orders of magnitude. Thus the probability of one-time radiation exposure inducing several carcinogenic mutations without

Fig. 3. Expected Change of Excess Relative Risk of Cancer Incidence by Age at Exposure. These curves represent the output from Formula (7) with $k=6$ and $\gamma D=10$.

killing the cell is very small. In these circumstances, the carcinogenic effects of radiation on cells would work only as a one-stage change. Exceptions may be hematopoietic cancer including leukemia and childhood cancer. We would like to review these diseases in a separate analysis. Finally, we note that some latent period should be existed for clinical diagnosis of cancer

due to tumor growth time (Ohtaki *et al.*, 1985; Ohtaki, 1993). Therefore, we have to modify the above models using Formula (4) when actual data of cancer incidence or mortality are analyzed.

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