

# Cancer Risk Models for Ionizing Radiation

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Risk estimation in radiation carcinogenesis depends primarily on epidemiological data and hazard rate models. The A-bomb survivors follow-up provides information on the complexity of this process. Several hazard rate models are briefly discussed and illustrated using the A-bomb experience.

## Introduction

Carcinogenic risk estimation is an especially complex problem, and its complexity is best illustrated by considering data on the effects of ionizing radiation. These data are possibly the most extensive example of a human health outcome in large numbers of individuals exposed to a wide range of doses of both gamma and X-ray radiation. The data allow one to consider the adequacy of various statistical models for carcinogenic risk in human populations.

The data have shown that there are many complex factors involved in trying to predict a cancer risk from a single agent. Table 1 presents several of the major radiation issues. The assumptions underlying any one of these factors can have a profound effect on subsequent quantitative estimation and, hence, on any exposure standard or regulation that is derived from such estimates. This paper briefly discusses some of these factors using the data from the Japanese A-bomb survivors. This study involves the follow-up of over 100,000 individuals for over 30 years. The data have been considered the primary data for most analyses of carcinogenic risk from low linear energy transformation (LET) radiation (1,2).

## Japanese A-Bomb Survivors

The most recent analysis of cancer mortality among the bomb survivors is given in Preston et al. (3). Those cancer sites that are related to radiation dose are given in Table 2. Over 6000 cancer deaths have been recorded in this population, and they are basically divided into leukemia and nonleukemia deaths. Deaths are separated into these two categories because leukemias occur early and tend to peak in terms of excess incidence after about 5 to 10 years postexposure. The nonleukemias, on the other hand, seem to have a 10 to 20 year latency period, after which the risk is increased and remains at

Table 1. Factors in radiation cancer risk estimation.

Structure of relative risk functions
Dependence on age-at-exposure
Dependence on spontaneous rates
Dose-response relationships
Dose-rate effects
Biological effectiveness of radiation type
Interaction with other risk factors

Table 2. Cancer mortality among A-bomb survivors (1950-1982): Cancer sites that have a statistically significant increasing trend in radiation.<sup>a,b</sup>

Site	Radiation risk, 100 rads	Excess, 10 <sup>6</sup> PYR <sup>c</sup>
Leukemia*	3.95	1.51
Nonleukemia*	1.17	3.88
Esophagus	1.23	0.17
Stomach*	1.11	0.96
Colon*	1.38	0.30
Liver	1.35	0.08
Lung*	1.33	0.82
Breast*	1.69	0.65
Ovary	1.52	0.27
Bladder-kidney*	1.55	0.24
Multiple myeloma	1.51	0.06

<sup>a</sup> From Preston et al. (3).

<sup>b</sup> Note: 6270 total cancer deaths, ( $p \leq 0.05$ ).

<sup>c</sup> Person-year-rads.

\*  $p < 0.01$ .

an increased rate approximately proportional to the background or spontaneous rate.

The leukemias are the most noticeable site because the relative risk is the greatest for them: 3.95 compared with 1.17 for nonleukemic cancers. On the other hand, the nonleukemic cancers are well ahead of the leukemias in terms of total excess cancers: 3.88 versus 1.51 per 10<sup>6</sup> person-year-rads. Those individual cancer sites that have the greatest excess in the Japanese survivors are leukemia, followed by stomach, lung, and breast.

The Japanese A-bomb survivor population presents some specific problems for extrapolating the effects to other population groups. The amount of excess at a given cancer site may or may not depend upon the spontaneous rate of that cancer site. For example, breast

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cancer in Japan is much lower than in the U.S., whereas stomach cancer is much higher. Therefore, the question is how best to extrapolate those effects from Japan to the U.S. population where the spontaneous rates differ. Based on other radiation studies in primarily medically exposed groups in the U.S. and Europe, it has been concluded [at least for breast cancer (4)] that the excess risk that is not particularly dependent on the spontaneous rate should remain approximately constant between population groups. This is difficult, however, because of the complexity of comparing the various studies and their limitations (5).

Stewart and Kneale (6) raised the issue of possible survival of the fittest among the A-bomb survivors: those that received the higher doses and survived are somehow more resistant to disease than those who did not. This is borne out somewhat when one analyzes both cancer and noncancer deaths due to radiation (Table 3). For example, one observes an excess of cancer deaths in males, namely 122 over the period of 1950 to 1982, using a linear-quadratic dose-response model. On the other hand, mortality due to other diseases is at a deficit. The quadratic term in the dose response is positive, so for individuals with midlevel radiation doses there appears to be a protective effect. The protective effect may be due simply to survival of the fittest or there may be some other bias related to exposure that has yet to be identified. This then yields a total mortality deficit of 74 for the male population. How or whether one takes this into account when estimating the dose-response relationship between cancer mortality and exposure is not clear at this point.

Age and sex effects play an important role in radiation carcinogenesis. As shown in Table 3, the excess cancer deaths were higher in females than males with similar background numbers. In particular, there is an estimated 206 excess deaths in females compared with 122 in males. Table 4 shows age-sex effects with respect to leukemia and nonleukemia cancers. The relative risk for leukemias is about the same in both males and females, but the background rate is about one-half for females compared to males. On the other hand, the relative risk of nonleukemias for females is significantly higher than for males. What this yields is that the excess of leukemia deaths is significantly greater in the males than in the females: 1.95 versus 1.2 per  $10^6$  person-year-rads. The nonleukemias, however, are higher in the females than in the males (4.42 versus 3.29), although this latter difference is not statistically significant. Finally, for the

susceptibility of age-at-exposure, one sees from Table 4 that individuals exposed before the age of 20 had a higher relative risk for both leukemias and nonleukemias, with a significant difference for nonleukemias. The statistics above illustrate the complexity of attempting to quantify risks for human populations where sizable differences exist simply with age-at-exposure and sex of the individual.

## Hazard Rate Risk Models

Human mortality data are typically described through a hazard rate  $\lambda(a)$ , which is the instantaneous probability of an effect (e.g., death due to lung cancer) at age  $a$ . This function then can be constructed in order to describe the changing disease rates as a function of an individual's age. For many human cancers, we find that approximately  $\lambda(a) = c \cdot a^k$ , where  $c$  is a constant and  $k$  is a number in the range of 4 to 6 depending upon the cancer site and type. For an exposed group with dose  $d$ , we model the hazard function as

$$\lambda(a,d) = \lambda_0(a) + AR(d) \quad [1]$$

where  $\lambda_0(a)$  is the spontaneous (unexposed) hazard rate. This additive risk model assumes that the increased disease incidence is constant over time.

The second common model is the relative risk model:

$$\lambda(a,d) = \lambda_0(a)RR(d) \quad [2]$$

If either  $AR(d)$  or  $RR(d)$  is also dependent on age or time of exposure, then one does not have an additive or relative risk model, but a more complex situation. The simple additive risk and relative risk models were considered (1), and the relative risk model appeared to describe the data in a much more adequate manner. The risk estimates for extrapolating in time using either the additive risk or relative risk model will produce significant differences. This problem has been recently discussed by Cohen (7).

To have a more general model, we can define the relative risk to depend upon age and age-at-exposure in the following manner:

$$RR(d) = 1 + f(d)g(a,e,t) \quad [3]$$

where  $a$  = age,  $e$  = age-at-exposure, and  $t = a - e$ , time-since-exposure. This is for a single exposure, as in the A-bomb situation. This more complex relative risk model relates to the multistage mutational model for carcinogenesis, which has been described by Armitage and Doll (8) and Peto (9). The multistage model assumes that the carcinogenic process is described by a finite number of mutational stages and has been used to explain cancer data in both animal and human populations. If we assume that the  $j^{\text{th}}$  stage of the  $k$  stages is affected

Table 3. Estimated deaths due to radiation (1950-1982).\*

Cause of death	Male		Female	
	Excess	Background	Excess	Background
Cancer	122	3106	206	3148
Blood disease	10	49	17	86
Other diseases	-166	10921	-49	11881
Other deaths	-45	1072	15	655
Total	-74	15147	190	15769

\*Hiroshima and Nagasaki, life-span sample.

Table 4. Cancer mortality among A-bomb survivors (1950–1982): age-sex effects.<sup>a</sup>

	RR <sup>b</sup> at 100 rads		Excess at 10 <sup>6</sup> PYR <sup>c</sup>		Background rate Female/male	RR at 100 rads, age-at-exposure	
	Male	Female	Male	Female		0–19	20+
Leukemia	3.84	4.08	1.95	1.20*	0.54	6.2	3.3
Nonleukemia	1.11	1.25†	3.29	4.42	0.57	1.6	1.1†

<sup>a</sup> From Preston et al. (3).

<sup>b</sup> Relative risk.

<sup>c</sup> Person-year-rads.

\*  $p < 0.05$ , 1.95 versus 1.20.

†  $p < 0.01$ , 1.11 versus 1.25 and 1.6 versus 1.1.

by an acute exposure of radiation, then, as Whittemore (10) has shown, the generalized relative risk model is in the form

$$g(a, e, t) = \exp\{(k - j - 1)\log(t) - (k - 1)\log(a) + (j - 1)\log(e)\} \quad [4]$$

A few observations should be made with regard to Equation 4. If the first stage of the  $k$  stages is affected, i.e.,  $j = 1$ , then the relative risk term is simply a factorable function of the individual's current age and time since exposure and does not involve age-at-exposure *per se*. If, however, the affected stage is the penultimate stage, i.e.,  $j = k - 1$ , then we see that the excess risk is constant for any specified age-at-exposure. In other words, we have an additive risk model. For the multistage model, however, we cannot have a constant excess relative risk, although there are situations where one can come reasonably close numerically. Suppose, for example, that an individual is exposed at the age of 20 and that there are five stages ( $k = 5$ ) in the multistage model. The ratio of the relative risk term as a function of age varies over the range of ages in this case, with the degree of the variability depending upon which stage is affected by the radiation. In this example, if the third stage is affected, then the ratio of the great-

est value of the relative risk term to the smallest value after a 10-year latency (i.e., consider only the range of ages 30–80) has a value of approximately 2. If, on the other hand, the first stage is affected, then this ratio is approximately 100. So, with actual epidemiological data, one could possibly accept that the data are consistent with a constant relative risk model, yet the data may actually be consistent with a multistage model where the third of five stages is the affected stage.

In an examination of the A-bomb cancer mortality data, Hoel and Preston (11) considered the category of epithelial tumors, which was defined as those tumors that were neither hemopoietic nor hormonally related. They showed that the more complex relative risk models provided the best description of the data. Also, the choice of model made a considerable difference in actual risk estimates, especially for the younger exposed individuals where lifetime risk estimates could differ by more than an order of magnitude. Table 5 shows fits to the various relative risk and additive risk models for the group of nonleukemia deaths. Looking at the relative risk fit, the data were well described by a model that had both an age term and a time-since-exposure term, but no term for age-at-exposure. A purely relative risk model without a term for age-at-exposure did not describe the data nearly as well as a model that either incorporated age-at-exposure or time-since-exposure and attained age. These data suggest that one cannot determine whether the cancer effect is dependent upon age-at-exposure or time-since-exposure and attained age. Therefore, it may not be correct to conclude that there is age susceptibility. This is a result of the collinearity of age, age-at-exposure, and time-since-exposure; however, one can safely conclude that a purely constant relative risk or purely additive excess risk does not describe the epithelial or nonleukemia tumor groups in the A-bomb survivors nearly as well as a more complex model. Insofar as being consistent with the multistage model, the data are reasonably close, but are not of sufficient precision to allow more careful discrimination between models.

These issues are currently being discussed in the area of radiation carcinogenic risk estimation and have a significant bearing on the quantification of risk. Such issues indicate the complexity one faces when dealing with other carcinogens, such as occupational exposures to industrial chemicals and environmental agents. The issues beyond simple dose response are important, and

Table 5. Nonleukemia cancer mortality among A-bomb survivors (1950–1982).<sup>a</sup>

	Dose, 10 <sup>2</sup>	Log time	Log age	ATB20	City	Sex	Deviance <sup>b</sup>
Relative risk	0.42	NS <sup>c</sup>	NS	-1.61	-0.79	1.25	1167
	0.15	1.23	-3.13	NS	-0.72	1.11	1164
	0.13	S	-2.38	S*	-1.00	1.40	1174
	0.24	0.66	-1.96	-0.69	-0.78	1.19	1163
Additive risk	0.55	NS	3.16	-0.86	-0.82	0.81	1162
	0.34	0.84	1.85	NS	-0.73	0.61	1161
	0.31	S	2.24	S	-0.91	0.85	1168
	0.46	0.54	2.52	-0.46	-0.76	0.67	1160

<sup>a</sup>  $g(e, a, t) = \exp a_1 \log(\text{time}/20) + a_2 \log(\text{age}/50) + a_3 \text{ATB20} + a_4 \text{city} + a_5 \text{sex}$ , where the tabled values are the coefficients  $a_1 \dots a_5$ . ATB20 = 1 if age at exposure is > 20 years, city = 1 if Nagasaki, and sex = 1 if male.

<sup>b</sup> Measure of model fit to data. A smaller value indicates a better fit.

<sup>c</sup> Nonsignificant.

\* Statistically significant,  $p < 0.05$ .

the lessons from ionizing radiation in human epidemiology must be remembered in attempts to quantitate human risk from situations where the data are considerably limited, as contrasted with the radiation experience.

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