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Radiation Risk Estimation Models

by David G. Hoel*

Cancer risk models and their relationship to ionizing radiation are discussed. There are many model assumptions and risk factors that have a large quantitative impact on the cancer risk estimates. Other health end points such as mental retardation may be an even more serious risk than cancer for those with *in utero* exposures.

Introduction

Besides cigarette smoking, ionizing radiation is probably the most intensively studied environmental agent with regard to adverse effects on human health. The large body of information from the prospective study of A-bomb survivors in Hiroshima and Nagasaki and data from several studies of the medical diagnostic and therapeutic use of ionizing radiation provide us with a great deal of human exposure data. The A-bomb survivor group represents the largest single study, with well over 120,000 individuals who have been followed prospectively since 1950. Much of our collective knowledge of radiation health effects in man has been based on this study. This particular effort in turn serves as a model for other environmental agents and suggests important issues that we must address.

Carcinogenesis and genetic effects are believed to be the primary effects of radiation. In the A-bomb survivors, carcinogenesis has certainly been established. However, genetic effects have not been observed in this population (*1*). This apparent genetic soundness is a surprise to many, since our understanding of mechanisms and results of experimental studies imply that radiation should indeed be a mutagen. The lack of genetic aberrations in the A-bomb survivors indicates that man may be more resistant to ionizing radiation than are laboratory animals. This is indeed welcome news. On the other hand, carcinogenesis is present in the same population and demonstrates that radiation affects a large number of various cancers and cancer sites.

Radiation Cancer Models

Radiation-induced cancers follow one of two fairly distinct patterns. We observe the first pattern with the leukemias. These cancers begin to occur after a short latency period, sometimes as short as 2 years since exposure. The leukemia incidence rate approaches a maximum after 5 to 10 years. About 20 years postexposure the rates decline to little or no effect. The rates are quite high compared to spontaneous rates and are therefore easily detectable. The other primary cancers that have produced sufficient data for modeling purposes are those of the lung, breast, stomach, and thyroid. These particular cancers are not observed until much of the leukemia has already begun to decline. In particular, it appears that there is at least a 10-year latency period, and that the cancers follow the pattern of a constant, increased relative risk. This in turn implies that the number of excess cancers at any site due to radiation increases with increasing time since exposure. Spontaneous cancer rates also follow this pattern (*2*).

The relative risk effect is not constant for a given amount of radiation in relation to the spontaneous rate. Instead, it tends to behave in an additive manner for a given cancer site. The evidence for this is based primarily upon the results observed in breast cancer. The spontaneous rate of breast cancer in the Japanese is

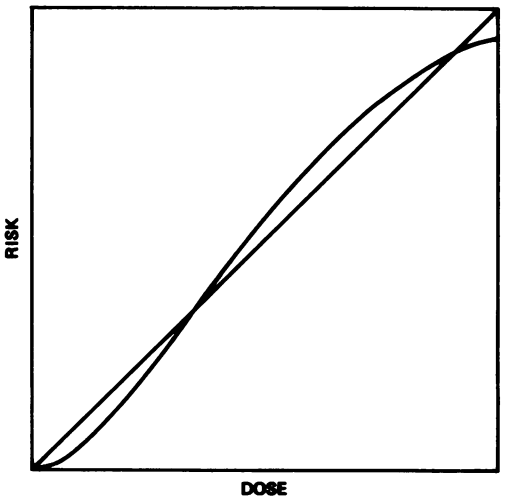

FIGURE 1. Comparison of linear dose-response curve and a quadratic curve with exponential cell killing.

* Division of Biometry and Risk Assessment, National Institute of Environmental Health Sciences, Research Triangle Park, NC 27709.

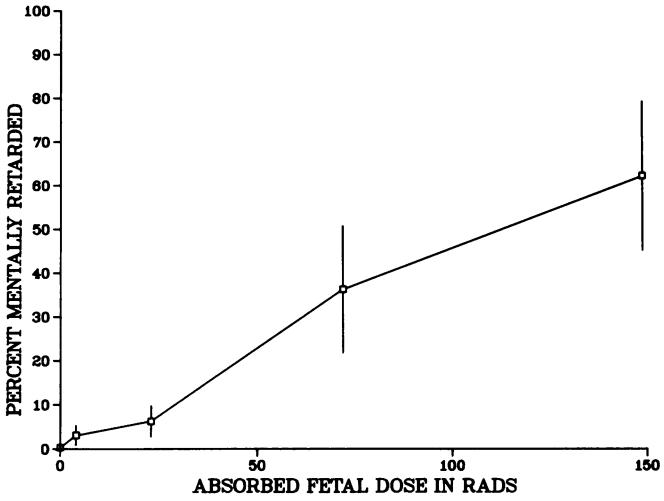

FIGURE 2. Incidence of mental retardation among *in utero* exposed (8–15 weeks gestational age) A-bomb survivors. Data from Otake and Schull (*7*).

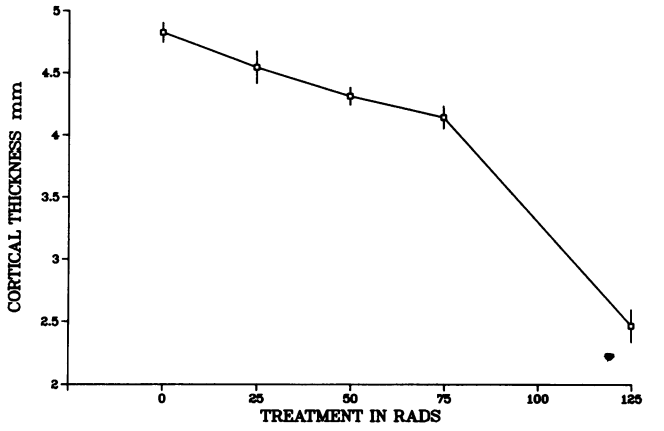

FIGURE 3. Cortical thickness of rats 4 months of age after prenatal X-irradiation. Data from Norton and Donoso (*8*).

much lower than in the U.S., yet the amount of breast cancer induced per unit of radiation tends to be approximately the same between the two populations. This implies that we are dealing with constant relative risk within a population, with an additive risk situation existing between populations for a given cancer site. This finding is an important tool for extrapolating data between human population groups (*3*).

Another important observation that has been made in the A-bomb survivors is that of age and sex susceptibility in relation to carcinogenic effects. For the nonleukemia cancers, one observes that the risk increases with decreasing age-at-exposure. By increasing risk, we mean the cancer risk at a given age of the individual. Of course, the older individual is at higher risk (measured in duration since exposure) because the effect is based on a relative risk. However, the total lifetime carcinogenic effect may be an order of magnitude higher for a child than for a 50-year-old adult.

The *in utero*-exposed may possibly be the most susceptible group of all. It has only been 40 years since the Hiroshima-Nagasaki *in utero* group was exposed, and the excess cancers are just beginning to appear. It will be another 20 years or so before this issue of *in utero* susceptibility is clarified. The question of age-at-exposure has obvious implications to risk analyses where one uses occupational-exposed groups of limited duration to estimate environmental lifetime cancer risk for the general population and vice versa. There are similar implications regarding the analyses of animal carcinogenicity studies and their comparison to epidemiological data. The chemical carcinogens data are most often derived from occupational exposures.

Dose-Response Relationships

Dose and dose rate present a particularly problematical issue for risk estimation of ionizing radiation. The data from Hiroshima and Nagasaki are such that we do not observe statistically significant cancer effects for individuals in the dose groups exposed to less than 50 rads. This is primarily due to sample size and random variability. As such, we cannot determine the shape of the dose-response curve at the lower doses based on epidemiological data. Ideally, we would like to consider risks at the 0.1 to 1 rad range. To do this, however, we must depend upon experimental studies and hypothetical models for the shape of the dose-response curve for the particular cancer sites of interest. In studying the shape of the dose-response relationships in animal studies, we see that at higher doses cell killing takes place, and there is in fact a reversal in the dose-response relationship. This is due to the increased likelihood of death of cancerous cells at increased dose levels. This has been clearly demonstrated by Upton in the RF mouse (*4*). The same effect has also been observed in some human studies. For example, analyses conducted by Land on A-bomb survivors have included a cell-killing term that has an effect on the highest dose groups (*5*). In studies of therapeutic radiation at extremely high exposure levels, we do not observe subsequent cancers that we would have predicted from an ordinary linear dose-response relationship. Thus it has been fairly well-established that cell killing lowers the cancer risk at the higher dose levels.

At the low dose levels, there is considerable debate about the shape of the dose-response curve. Possibilities are linear, nonlinear, threshold, and hormesis, which gives a protective effect. At the 1 rad level, whether one uses a linear dose-response function or a purely quadratic dose-response function with an exponential cell-killing term, the risk differs by two orders of magnitude (*6*). The problem is that based upon observed cancer data we cannot differentiate between these two possible curves, since a purely quadratic dose response with exponential cell killing can be mathematically

shown to closely approach a simple linear relationship. This phenomenon is illustrated in Figure 1. Even with the large sets of epidemiological data and rodent carcinogenicity studies, the issue of low-dose radiation effects is not resolved. Hence, there is little prospect that the risk estimation for particular chemical carcinogens would be any more precise.

A biological marker that can be measured, either in individuals or in biological systems, is needed to better represent the possible linearity or nonlinearity of dose-response relationships. The issue of cell killing also raises the possibility that for some of the chemicals that have been tested, the highest dose studied may produce less cancer than an intermediate level, even after appropriate adjustments are made for competing mortality. While the initial reaction to these chemical studies that produce nonmonotonic responses may be to regard the data as potentially unreliable, experience for the field of radiation suggests instead that the lack of monotonicity may well be due to cell killing.

Noncancer End Points

Environmental studies have focused primarily on carcinogenic effects. Other issues such as reproduction, neurological, and immunological effects have received less attention, but may in some instances be of equal or greater importance in assessing the impact of health hazards. Again, ionizing radiation provides us with an important example. In Figure 2, data on the incidence of severe mental retardation are shown for individuals who received exposure at approximately 8 to 15 weeks of gestational age. The limited available data indicate a high risk and do not suggest the presence of a threshold level. Animal studies have also been carried out, and in Figure 3, data are given that indicate the possible lack of a threshold level. The data presented by Otake and Schull (*7*) for mental retardation in the A-bomb survivors indicate fetal dose, which is approximately 40% of the external dose. For comparative purposes, the doses shown in Figure 2 should then be increased by a factor of 2.5. Assuming linearity, an external dose of 1 rad to the fetus would result in approximately 200 cases per 10^5 (based upon 36% incidence at 72 rad fetal dose). This is compared with an estimated 20 to 100 cases per 10^5 for total cancers for an age-at-exposure of 0 to 9 years (*6*). By equating severe retardation with cancer mortality we see a greater risk of retardation per unit of exposure.

In summary, we have shown, albeit superficially, the complexity of human health effects with regard to a single agent that has been examined extensively both in human populations and in laboratory animals. This review also shows the complexity of human risk estimation and suggests some particular issues that should be addressed when considering studies of other environmental agents; in particular, questions of dose response, age and sex susceptibility, and end points other than the traditional one of carcinogenesis.

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