PRESENTATION OF U.S.A. NATIONAL ACADEMY OF SCIENCES REPORT ON THE EFFECTS ON POPULATIONS OF EXPOSURE TO LOW LEVELS OF IONIZING RADIATION. 3. SOMATIC EFFECTS

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Introduction

Consideration is given herein to effects of ionizing radiation that are manifest in exposed individuals themselves (i.e., somatic effects) as contrasted to effects that are manifest in subsequent generations (i.e., genetic, or inherited, effects). In general, moreover, acute effects of irradiation are not considered, since these occur only at dose levels well above protection standards.

With few exceptions, the somatic effects of interest manifest themselves only after an interval of years or decades following irradiation and are not detectable except in a statistical sense. In any given individual, a particular effect cannot be attributed conclusively to radiation, as opposed to some other cause, and the smaller the dose, the less the likelihood of radiation being the cause.

Because no somatic effects causing significant disease or mortality are known to be induced by ionizing radiation at dose rates approaching natural background, the risks of such effects at these dose rates can be estimated only by extrapolation from observations at higher radiation levels, based on assumptions about the relevant dose-effect relationships, the mechanisms through which the effects are produced, and the susceptibility of the populations at risk.

Principles Underlying Induction of Somatic Effects

For none of the effects of interest can the dose-response relation be defined over a wide range of dose and dose rate. For some effects, however, such as the induction of cataract of the lens and impairment of fertility, the relationship between effect and dose is nonlinear, these effects presumably depending on the killing of sufficient numbers of cells in the lens and gonads, respectively, so that there is little or no risk of the effects at dose rates approaching natural background radiation levels.

For induction of certain tumors, on the other hand, a linear non-threshold dose-effect relationship cannot be excluded, nor can the possibility that such effects might result from subtle injury in only one or a few cells of the body. The most important effect of radiation on the mortality of human populations, furthermore, apparently results from carcinogenic effects.

In assessing the induction of cancer, the following problems are noteworthy: (1) cancers induced by radiation are indistinguishable individually from those occurring naturally, their existence being demonstrable only in terms of an excess above the natural incidence; (2) the natural incidence of cancer varies by orders of magnitude, depending on the type of neoplasm, age and sex of population at risk, and other factors; (3) cancer of any one type occurs with sufficiently low incidence in man that few irradiated populations are large enough to provide relevant quantitative dose-incidence data; (4) the time elapsing between irradiation and the clinical appearance of a neoplasm is a matter of years or even decades, complicating the prospective follow-up of irradiated populations for tumor development and the retrospective evaluation of cancer patients for relevant radiation exposure history; (5) many of the data on radiation-induced tumors come from individuals exposed to internally deposited radionuclides, in whom the dose-incidence relation is obscured by

nonuniformities in temporal and spatial distribution of the dose; (6) other data come from studies of therapeutically irradiated patients, in whom effects of radiation may be confounded by effects of underlying disease processes or of treatments other than radiation; and (7) some of the available data concern cancer mortality, whereas others concern cancer incidence, hence radiation-induced malignancies that do not greatly alter the death rate (e.g., thyroid carcinoma) must be distinguished from those that are more generally fatal (e.g., leukemia).

Cancer Incidence and Radiation Dose

Despite the difficulties mentioned above, the incidence of several types of cancer in human populations has been shown unequivocally to increase with increasing dose. With few exceptions, however, the observed dose-incidence data pertain to relatively high doses and high dose rates. Nevertheless, the findings for any given neoplasm are reasonably consistent from one irradiated human population to another, suggesting that the observed relationship may be applicable within limits to the general population for purposes of risk evaluation.

In Japanese atomic-bomb survivors and in British patients treated with spinal irradiation for ankylosing spondylitis, the incidence of all leukemias except the chronic lymphocytic type has been increased, the relationship between incidence and dose at the relatively high doses and high dose rates in question, being compatible with a linear dose-incidence function with a slope corresponding to about 1 case of leukemia per 10^6 exposed persons, per year, per rem. Data for other irradiated populations, although far less quantitative, imply a comparable excess of leukemia per unit dose to the marrow, despite wide differences in the conditions of exposure; however, there is evidence that susceptibility may be several times higher *in utero*, during childhood, or late in adult life than at intermediate ages.

Tumors of the thyroid gland also have been found to be increased in incidence in irradiated populations. The dose-effect relationship at relatively high doses and high dose rates, like that for leukemia, can be represented by a linear, non-threshold function, corresponding to a risk of roughly 2-9 cases of cancer per 10^6 exposed children, per year, per rem to the thyroid gland, averaged over the fifth to twenty-fifth years after exposure. In those irradiated during childhood, susceptibility appears several times higher than in those irradiated as adults.

For tumors of other types and sites, dose-response data are more limited, and estimates of risk correspondingly cruder. For cancer of the lung, mortality at high doses has been estimated to approximate one death per 10^6 exposed persons per year, per rem. For cancer of the breast, mortality at high doses has been estimated to approximate two deaths per 10^7 exposed persons per year, per rem. For cancer of the GI tract, including the stomach, mortality at high doses has been estimated to approximate one death per 10^6 persons per year, per rem. For cancer at all other sites combined, mortality has been estimated to approximate one death per 10^6 persons per year, per rem, which implies that either susceptibility to such malignancies is low, by comparison with susceptibility to the types mentioned earlier, or that the latent periods for such malignancies extend well beyond 25 years of follow-up.

Some studies suggest that after prenatal irradiation the overall juvenile cancer mortality may be increased by about 50 cases/10^6/rem/year, averaged over the first 10 years of life; however, there is also evidence that the observed excess may be dependent on factors other than radiation.

The variations in rate of induction of different types of cancer by irradiation are apparently unrelated to variations in the natural incidence of the respective types. Hence it is clear that the doubling dose of radiation is not uniform for all types of cancer.

Probability of Cancer Induction at Low Doses and Low Dose Rates

The dose-mortality figures cited above, which pertain chiefly to populations exposed at high doses and high dose rates, may be used to estimate the probability of cancer at lower doses and lower dose rates, if it is assumed that the relationship between mortality and dose remains the same irrespective of changes in dose, dose rate, and population at risk. However, there are cogent radiobiological reasons for doubting that the dose-incidence relationship remains constant in the face of such changes. One reason is the widespread occurrence of repair of most types of injury induced at low doses and low dose rates by low-LET radiations. The dose rate characteristic of background radiation (approximately 0.1 rem/year) is 10^8-10^9 times lower than the dose rate at which effects have been observed in most irradiated populations, and at background levels ionizing events in individual mammalian cell nuclei occur at a frequency of less than one per day, whereas at the higher dose rates mentioned, thousands of such events occur every second. Because of this difference, and its implications for the production and repair of radiation damage at the molecular level, the risk of cancer induction at low doses and low dose rates may be appreciably smaller per unit dose than at high doses and high dose rates (as has been observed to be the case in certain radiation-induced tumors of experimental animals). The possibility of zero risk at low dose rates is not excluded by the data.

Relative Biological Effectiveness

Another source of uncertainty complicating extrapolation from available data is the variation in relative biological effectiveness among different types of radiations. This problem pertains to the interpretation of data from atomic bomb survivors of Hiroshima, underground miners exposed to radon gas and its radioactive decay products, and populations with high body burdens of alpha-emitting radionuclides.

In Hiroshima, the numbers of survivors are larger (and the statistics correspondingly better) than in Nagasaki; but the radiations at Hiroshima included an appreciable component of fast neutrons. Hence it is necessary to estimate the relative biological effectiveness (RBE) of this component in order that the dose-effect data for the two cities can be compared. The best estimate of the RBE, derived from intercomparison of the Hiroshima and Nagasaki data for leukemia, is between 1 and 5; however, for many radiobiological effects the risk-per-rad of low-LET radiations, such as x-rays and gamma rays, decreases to a greater degree with decrease in the dose and dose rate than does the effectiveness of high-LET radiations, which may decrease little if at all. Hence the RBE value of 1-5 for leukemia induction may be considerably smaller than the RBE value applicable to low doses and dose rates. Nevertheless, since RBE values of 1 and 5 have been assigned in this report to the Hiroshima neutrons for the purpose of calculating the risk per rem, the resulting estimates of risk may err on the conservative side.

The Linear Hypothesis

Although there is experimental evidence that the dose-effect relationship for x-rays and gamma rays may not be invariant with dose and dose rate, the use of a non-linear hypothesis in estimating risks for purposes of radiation

protection would be impractical in the present state of knowledge, since it would require allowance for individual variations in temporal and spatial distribution of tissue dose, as well as for other variables which cannot be analyzed at this time.

Furthermore, it is the whole population from birth to death that is to be protected, and no body of human observations provides risk estimates for longer than about 25 years. Moreover, the human fetus may be especially susceptible to radiation carcinogenesis. Thus, in a situation that calls for a careful weighing of costs and benefits it has seemed prudent to present risk estimates on the basis of human data exclusively, with the use of a linear interpolation into the region of low dose.

Risk Estimation

In the Japanese atomic-bomb survivors, the excess mortality from all forms of cancer, including leukemia, corresponds to roughly 50-78 deaths per 10^6 exposed persons per rem over the 20-year period from 1950-1970; i.e., from the fifth to the twenty-fifth year after exposure. In the irradiated spondylitics, the excess mortality corresponds to a cumulative total of roughly 92-165 deaths from cancer per 10^6 persons per rem during the first 27 years after irradiation. If such rates, extrapolated to low-dose levels without allowance for the possible dependence of the effect on dose and dose rate, are assumed to apply generally, than exposure of the U.S. population of about 200 million persons to an additional 0.1 rem during one year (approximately equivalent to a doubling of irradiation from background sources) could be expected to cause 1350-3300 deaths from cancer during the 25 years following irradiation, or about 50 to 130 deaths per year. Continual exposure of the population to the additional 0.1 rem per year could be expected ultimately to cause 1350 to 3300 deaths annually, provided that the effect of a given increment of dose did not persist beyond 25 years after exposure. However, use of a factor to allow for the influence of dose and dose rate on the dose-effect relationship might reduce these estimates appreciably.

In assessing the cumulative effects of low-level irradiation on an entire population, attention must be paid to differences in age at exposure, duration of the latency for carcinogenesis, and size and duration of the carcinogenic effects; however, only tentative allowances can as yet be made for these variables. Nevertheless, a range of values can be assumed for each parameter (Table 1), enabling the effects of chronic low-level exposure of the U.S. population to be estimated, at least for illustrative purposes. These estimates (Table 2) imply that exposure of the entire population continuously throughout life at a dose rate of 0.1 rem per year could cause up to 1,700-9,000 cancer deaths per year, corresponding to 0.6-2.9% of the natural cancer death rate. For individuals exposed continuously from age 20 to age 65 years at a dose rate of 5 rems per year, the same approach yields an estimate of 380-930 excess cancer deaths per 10^6 persons per year (Table 3), corresponding to 1-2% of the natural cancer death rate at age 60-64 years.

Because the extrapolation model used in the above calculations made no allowance for the influence of repair at low doses and low dose rates, the derived estimates may be too high. For other reasons also, the estimates may be too high or too low: (1) insofar as high dose data have provided the primary basis for the estimates, the risks may have been overestimated, owing to side effects at the high dose levels which may have enhanced the carcinogenic action of radiation; (2) longer periods of follow-up may lead to estimates of risk that differ in magnitude from those above; (3) the data on most radiation-induced tumors are too scanty to allow construction of dose-incidence curves adequate for extrapolation; (4) uncertainty attaches to the RBE values used for alpha and neutron radiations; (5) uncertainty attaches to the relevant tissue dose, owing to nonuniformity in the distribution of the dose throughout

the body; and (6) the carcinogenic effects per unit dose might, under certain conditions, conceivably be even higher at low doses and low dose rates, owing to less killing of the cells that are most susceptible to cancer induction.

Comment

The figures presented in the foregoing are not to be taken as precise estimates of risk, since they are derived from evidence that is now incomplete. Moreover, the values are based largely on mortality data; and if expressed in terms of cancer incidence, the estimates could be higher by a factor of 2. Despite the limitations indicated, the current estimates suffice to indicate that the mean dose to the individual, as well as the mean dose to the population, should be kept as low as practicable.

Whether other somatic effects deserve to be considered in the same category with cancer in evaluating the risks of low-level irradiation remains to be determined. For those effects that may be conceived to fall into this category, however -- induction of cataracts, disturbances in the growth and development of the embryo, life-shortening from causes other than cancer, and impairment of fertility -- existing dose-effect data suggest that these are not likely to occur at dose levels compatible with present radiation protection guides. Hence, it seems reasonable to limit consideration to cancer alone for this evaluation.

Table I

Assumed values used in calculating estimates of risk shown in Tables 2 and 3.

Age at Irradiation	Type of Cancer	Duration of Latent Period (years)	Duration of Plateau Region (years)[a]	Risk Estimate: Absolute Risk[b] (deaths/10^6/yr/rem)	Risk Estimate: Relative Risk (% incr. in deaths/rem)
In Utero	Leukemia	0	10	25	50
	All other cancer	0	10	25	50
0-9 Years	Leukemia	2	25	2.0	5.0
	All other cancer	15	(a)30 (b)Life	1.0	2.0
10 + Years	Leukemia	2	25	1.0	2.0
	All other cancer	15	(a)30 (b)Life	5.0	0.2

[a] Plateau region = interval following latent period during which risk remains elevated.

[b] The absolute risk in those aged 10 or more at the time of irradiation, for all cancer excluding leukemia, can be broken down into respective sites as follows:

Type of Cancer	Deaths/10^6/year/rem
Breast	1.5*
Lung	1.3
GI incl. Stomach	1.0
Bone	0.2
All other cancer	1.0
Total	5.0

* This is derived from a value of 6.0, corrected for a 50% cure rate and the inclusion of males as well as females in the population.

(From Report of U.S.A. National Academy of Sciences Committee on the Biological Effects of Ionizing Radiation, 1972)

Table 2

Estimated numbers of deaths per year in the U.S. population attributable to continual exposure at a rate of 0.1 rem per year, based on mortality from leukemia and from all other malignancies combined.

Age at Irradiation	ABSOLUTE RISK MODEL[a]		RELATIVE RISK MODEL[a]	
	Excess Deaths Due to:		Excess Deaths Due to:	
	Leukemia	All other Cancer	Leukemia	All other Cancer
In Utero	75	75	56	56
0-9 years	164	(a) 73 (b) 122	93	(a) 715 (b)5,869
10 + years	277	(a)1,062 (b)1,288	589	(a)1,665 (b)2,415
Subtotal	516	(a)1,210 (b)1,485	738	(a)2,436 (b)8,340
TOTAL	(a) 1,726 = 0.6% increase		(a) 3,174 - 1.0% increase	
	(b) 2,001 = 0.6% increase		(b) 9,078 - 2.9% increase	

[a]The figures shown are based on the following assumptions:

(1) 1967 U.S. vital statistics can be used for age specific death rates from leukemia and all other cancer, and for total U.S. population.

(2) Values for the duration (a or b) of the latent period (the length of time after irradiation before any excess of cancer deaths occur), duration of risk ("plateau region"), and magnitude of average increase in annual mortality for each group are as shown in Table 1.

(From Report of U.S.A. National Academy of Sciences Committee on the Biological Effects of Ionizing Radiation, 1972)

Table 3

Estimated excess annual numbers of cancer deaths for individuals exposed from 20 to 65 years of age.

Population Exposed and dose rate	ABSOLUTE RISK MODEL Excess Deaths Due to:		RELATIVE RISK MODEL Excess Deaths Due to:	
	Leukemia	All other Cancer	Leukemia	All other Cancer
U.S. Pop'n 0.1 rem/yr	195	(a) 721	436	(a) 1,444
		(b) 808		(b) 1,793
10^6 people: 5 rem/yr.	81	(a) 300	181	(a) 601
		(b) 336		(b) 746

(From Report of U.S.A. National Academy of Sciences Committee on the Effects of Ionizing Radiation, 1972)