GENETIC RISKS OF IONIZING RADIATION: 1988 UNSCEAR ESTIMATES AND FUTURE PERSPECTIVES

K. Sankaranarayanan
MGC Department of Radiation Genetics & Chemical Mutagenesis, Sylvius Laboratories, State University of Leiden, Wassenaarseweg 72, 2333 AL Leiden, The Netherlands

Introduction. The estimation of genetic risks of exposure of human populations to ionizing radiation has been an on-going scientific activity since the mid-1950s. UNSCEAR has published a number of reports on this subject, the most recent one being that published in 1988.

In the context of radiation genetic risk estimation, what is of interest is the risk of genetic disease in man at low doses and low dose-rates of radiation. The data used for this purpose are those on induced mutations and chromosomal aberrations collected predominantly in mouse studies carried out using high doses of radiation delivered at high dose rates. The gap between species and between mutation data in animals and risk of genetic disease in man is bridged using a number of assumptions and correction factors. Extrapolation inevitably involves a number of uncertainties and their nature and magnitude are dependent on the strengths and weaknesses of the data used and the assumptions made.

Methods. Quantitative genetic risk estimation is made using two methods, namely, the direct method and the doubling dose method. With the first, the rates of induction of mutations and of chromosomal aberrations are "directly" converted into risk of genetic disease in the first generation progeny of an irradiated population. The data for this come from experiments on the induction of dominant skeletal and dominant cataract mutations in mice and of reciprocal translocations in primate species. The doubling dose method is used to estimate risks to a population under continuous irradiation. The doubling dose (DD) is the amount of radiation necessary to produce as many mutations as those that occur naturally in a generation and is obtained as a ratio of spontaneous rate and rate of induction by unit dose. The reciprocal of the DD is the relative mutation risk (RMR).

The DD method is used to estimate risk to a population under continuous irradiation and is based on the following equation:

Risk per unit dose = Natural prevalence of genetic diseases in the human population x RMR

The quantity so estimated is the risk at equilibrium; the risk to the first generation progeny is estimated from that at equlibrium using certain assumptions.

The DD that is currently used is 1 Gy, for low LET, low dose, low dose-rate irradiation and is based on mouse data. The prevalence data are from human epidemiological studies. Estimates of risk obtained using the two methods are given in Tables 1 and 2. As can be seen, the estimate for the first generation, obtained using the direct method is nearly the same as that obtained using the DD method. Also note that, with the DD method, no risk estimate is provided for multifactorial

diseases. The risk estimates of BEIR V, obtained using the DD method (and a DD of 1 Gy) are nearly the same except that this Committee has also presented estimates of risk for one sub-class of multifactorial diseases, namely, congenital abnormalities.

Table 1. 1988 UNSCEAR estimates of genetic risk: direct method

Risk associated with	Risk per 10^6 progeny/10^{-2} Gy following irradiation of	
	Males	Females
Induced mutations with dominant effects	10-20	0-9
Unbalanced products of induced translocations	1-15	0-15

Table 2. 1988 UNSCEAR estimates of genetic risk: doubling dose method

Disease classification	Prevalence per 10^6	Effect of 0.01 Gy/generation	
		1st generation	Equilibrium
Autosomal dominant & X-linked	10000	15	100
Autosomal recessive	2500	No increase	15
Chr. diseases due to struc. anomalies	400	2.4	4

Perspectives. Biochemical and molecular studies of gene mutations that lead to disease in man and of analysis of radiation-induced mutations in mammalian experimental systems permit some conclusions which are relevant in the context of risk estimation. The main conclusions from these studies are the following: 1. The phenotypic effects of a gene mutation (dominant or recessive) depend on the gene and its function. 2. For mutations in genes that lead to recessives, a wide array of molecular changes is possible; for dominants, this array is limited. 3. At the molecular level, approximately 50% of spontaneous mutations in genes that lead to diseases are due to DNA deletions, the remainder due to point mutations (PMs). 4. The mutational sites in genes may not be randomly distributed and this is true of deletions as well. 5. A significant proportion of spontaneous point mutations and deletions can be explained on the basis of known mechanisms. 6. Most radiation-induced mutations in mouse in vivo systems and in mammalian somatic cells in vitro are DNA deletions and 7. At gene loci in which only PMs will be compatible with survival, radiation is "ineffective" in inducing mutations.

If most of the radiation-induced mutations are deletions (and only about one-half of those arising spontaneously in man are of this type), the prevalence figure used in the risk equation (doubling dose method; see above) may need to be revised downwards which means that the risk will be lower. Further, the DD of 1 Gy used in risk estimation is based on mouse data, predominantly those for recessive specific locus mutations at non-essential loci. Considering the wide variety of molecular changes that can lead to recessive mutations, the restricted array of changes that lead to dominant phenotypes, it would seem that the use of the DD of 1 Gy may overestimate the risk of dominant genetic disease in man.