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Reflections Article

Genome-based, mechanism-driven computational modeling of risks of ionizing radiation: The next frontier in genetic risk estimation?☆,☆☆

K. Sankaranarayanan, H. Nikjoo *

Radiation Biophysics Group, Department of Oncology-Pathology, Karolinska Institutet, Box 260, P9-02, Stockholm SE 17176, Sweden

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ABSTRACT

Research activity in the field of estimation of genetic risks of ionizing radiation to human populations started in the late 1940s and now appears to be passing through a plateau phase. This paper provides a background to the concepts, findings and methods of risk estimation that guided the field through the period of its growth to the beginning of the 21st century. It draws attention to several key facts: (a) thus far, genetic risk estimates have been made indirectly using mutation data collected in mouse radiation studies; (b) important uncertainties and unsolved problems remain, one notable example being that we still do not know the sensitivity of human female germ cells to radiation-induced mutations; and (c) the concept that dominated the field thus far, namely, that radiation exposures to germ cells can result in single gene diseases in the descendants of those exposed has been replaced by the concept that radiation exposure can cause DNA deletions, often involving more than one gene. Genetic risk estimation now encompasses work devoted to studies on DNA deletions induced in human germ cells, their expected frequencies, and phenotypes and associated clinical consequences in the progeny. We argue that the time is ripe to embark on a human genome-based, mechanism-driven, computational modeling of genetic risks of ionizing radiation, and we present a provisional framework for catalyzing research in the field in the 21st century.

1. Historical background

The estimation of genetic risks of exposure of human populations to ionizing radiation has been a major area of radiobiology since the early 1950s. Genetic risk estimates together with those on cancers provide the scientific basis for radiological protection recommendations [2,3]. From the very beginning of these efforts, the paucity of directly usable human data on adverse genetic effects in the progeny of those exposed to radiation necessitated the *indirect* estimation of risks using mouse germ cell data on radiation-induced mutations. This is in contrast to cancers for which risk estimates have always been made from human epidemiological data, initially on mortality and later on incidence; see [2]. The notion that radiation-induced mutations would cause genetic diseases similar to those that occur naturally as a result of spontaneous single-gene mutations in germ cells dominated the thinking of scientific committees involved in risk estimation from the mid-1950s onwards. Consequently, efforts at risk estimation were focused on finding a suitable method that would allow the prediction of risks in terms of the number of additional "cases" of genetic diseases in the progeny of those exposed, over and above their baseline frequencies in the population. The method chosen, namely, the 'doubling dose method', enabled the conversion of mutation rate estimates derived from mouse data into estimates of the 'risk of genetic disease' in humans, albeit with a number of assumptions (reviewed in [4]).

While scientific committees pursued the mouse-data-based approach for estimating genetic risks, genetic epidemiological studies initiated in Japan in the late 1940s in the aftermath of the A-bombings were focused on ascertaining directly whether any adverse genetic effects could be demonstrated in the children of A-bomb survivors using indicators that were practicable at the time these studies were initiated. The indicators were: untoward

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☆☆ This article is also paper XVIII in a series entitled 'Ionizing radiation and genetic risks' authored by K. Sankaranarayanan and colleagues between 1991 and 2013 and published in Mutation Research (except paper XVI which was published in Int. J. Radiat. Biol. in 2011 [1]).

* Corresponding author. Tel.: +46 8 517 724 90; mobile: +46 7 2300 8252.
E-mail address: hooshang.nikjoo@ki.se (H. Nikjoo).

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pregnancy outcomes (including stillbirths, neonatal deaths and congenital malformations in live births in phase I (1948–1954); sex-ratio shifts and survival of live-born infants in phase II (1955–1968); and cancers in F_1 children, sex-chromosomal aneuploids, balanced structural rearrangements and mutations affecting protein charge or function in phase III (1969–1990) (reviewed in [5]). Of note is that these studies were *not* aimed at detecting possible increases in the frequencies of children affected by radiation-induced genetic diseases. Reports of progress in these studies published from time to time until 1998 [6] provided no evidence of any detectable increase in adverse effects (as measured by the indicators mentioned above) in children attributable to radiation exposure of the parents. In retrospect, two factors relegated the Japanese data to the sidelines of genetic risk estimation efforts until the 1990s: (1) most of these indicators were not sensitive enough to induced mutations at the low average doses sustained by the survivors, and (2) the adverse effects measured could not be readily compared with or fitted into the framework of the 'risk of genetic diseases' envisioned by the scientific committees. The principal message from the Japanese studies, namely, low genetic risk at the low average doses sustained by the survivors, however, was finally reconciled with the risk estimates arrived at by the committees [7,9].

The 'current' genetic risk estimates were first published more than a decade ago [8], and they are summarized in the reports of the BEIR VII Committee of the U.S. National Academy of Sciences [7] and the United Nations Scientific Committee on the Effects of Atomic Radiation [9]. These are presented in Table 1. The estimates show that the total risk to the first post-radiation generation is of the order of 3000–4700 cases per 10^6 progeny per Gy, which represents 0.41–0.64% of the baseline risk. With the exception of congenital abnormalities, the risk estimates for genetic disease have been obtained using the doubling dose method. The risk of congenital abnormalities has been estimated using mouse data on induced developmental abnormalities (i.e., congenital anomalies ascertained in utero, skeletal abnormalities and cataracts) without recourse to the doubling dose method. This is an important point and will be returned to later.

Table 1
Estimates of genetic risks from exposure to low LET, low dose chronic irradiation (based on [7–9]) and an assumed doubling dose of 1 Gy.

Disease class	Baseline frequency (per 10^6 live births)	Risk per Gy per 10^6 first-generation progeny
Mendelian		
Autosomal dominant	16,500	~750–1500
X-linked		
Autosomal recessive	7500	0
Chromosomal	4000	[a]
Multifactorial		
Chronic	650,000[b]	~250–1200
Congenital abnormalities	60,000	~2000[c]
Total	738,000	~3000–4700
Total expressed as percentage of baseline		~0.41–0.64

[a] Assumed to be subsumed in part under the risk of autosomal dominant and X-linked diseases and in part under that of congenital abnormalities.
[b] Frequency in the population.
[c] Estimate obtained using mouse data on developmental abnormalities, not with the doubling dose method. This estimate overlaps with that shown as risk under the heading of 'autosomal dominant and X-linked diseases'; see text for details.

2. Uncertainties and unsolved problems

Although the estimates presented in Table 1 reflect the state of the art in the field at the end of the 20th century, several uncertainties and unsolved problems remain. These have been discussed in detail elsewhere [7–9]. In what follows, we briefly address three of the most obvious ones, namely, (a) the doubling dose method of risk estimation itself; (b) inability to define the genetic radiosensitivity of human females and (c) lack of evidence for radiation-induced genetic disease in humans. Radiation risk assessment, genomics and DNA repair all involve specialized terminology. Table 2 explains the acronyms, abbreviations and technical terms that are used in this paper.

2.1. The doubling dose (DD) method of risk estimation

The conceptual foundations for the doubling dose (DD) and the method that bears its name were laid by Muller in the 1950s [10–12]. The DD method permits the use of mutation data from mouse radiation studies for estimating the risk of genetic disease in humans. The DD is the amount of radiation required to produce as many mutations as those occurring spontaneously in a generation. Ideally, it is calculated by dividing the average spontaneous mutation rate of a set of genes by the average induced rate for the same set of genes, although this has not always been possible.[1] The quantity [1/DD] is called the relative mutation risk (RMR) per unit dose. The DD estimate in current use for low dose, chronic, low LET irradiation (the radiation conditions used for risk estimation) is 1 Gy.

The DD method is based on the theory of equilibrium between mutation and natural selection, which population geneticists use to describe the dynamics of mutant genes in populations. It assumes that the stability of mutant gene frequencies (and hence of disease frequencies) in a population is a reflection of the existence of a balance or equilibrium between spontaneous mutations that enter its gene pool at a finite rate every generation and natural selection that eliminates these same mutations through failure of survival or reproduction. This assumption implies that the baseline frequencies of genetic diseases one measures in a population represent those of a population in 'mutation-selection equilibrium'. When such a population sustains radiation exposure in every generation, induced mutations enter its gene pool and are also subject to natural selection. Eventually, the population reaches a new equilibrium between mutation and selection at a higher mutant frequency, and thus of disease frequency.

In the early years of genetic risk estimation, the focus was on ascertaining the 'total added risk of genetic disease' at the new equilibrium under conditions when the population sustains radiation exposure at a finite rate in every generation. The DD method allows one to estimate this total risk as a product of two quantities, namely, the baseline frequencies [P] and [1/DD]:

$$\text{Total risk per unit dose} = P \times \left[\frac{1}{\text{DD}}\right] \quad (1)$$

Estimates of risk for the first, second, and later post-radiation generations were derived from the total risk at the new equilibrium making assumptions about the magnitude of selection. Two new

[1] The DD method has evolved over the years along with revisions of the data used for estimating DD [4] and of the data on baseline frequencies of genetic diseases [3]. In the 'recent' UNSCEAR [9] (2001) and BEIR VII [7] (2006) reports, the DD was calculated using a spontaneous mutation rate of human genes ($n = 135$) and an induced mutation rate of mouse genes ($n = 34$).

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