Long-terms Effects of Ionizing Radiation

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Introduction

The fact that X-rays can induce mutation was established first in 1927. In the years following the mutagenic effects of β-and γ-rays, α-rays and neutrons were described. When DNA was identified as the universal genetic material, it soon became obvious, and was confirmed by genetic evidence that the genetic material of all living beings is susceptible to radiation induced damage When DNA is damaged by radiation enzymes within the cell nucleus attempt to repair that damage If repair does not succeed or not correctly, the cell may die or may suffer changes in genetic information. It is thought that killing of cells is the basis for deterministic effects and that subtlechanges in information are important in the development of radiation-induced cancer, or of genetic effects if these changes are induced in germ cells.

Biological effects of ionizing radiation

Deterministic radiation effects

A radiation effect is called deterministic when it is directly perceptible in the irradiated individual within a short time after exposure and when it is sure to occur if the dose is large enough. At high doses (more than 0.5 Sv) cells might be killed to impair the function of an irradiated tissue or organ. In extreme cases, the human organism itself may die, if the dose received is higher than 2 to 4 Sv The probability of causing a deterministic effect like erythema or depression of the blood forming system will be zero at low doses, but increases steeply to 100% above a given threshold.

If a pregnant woman is irradiated, deterministic effects might be most expressed at the time when the relevant tissue is being formed in utero. The killing of a few, but essential cells may result in malformations An important effect of exposure in utero is a dose-related increase in mental retardation. This is explained by the impaired proliferation, differentiation, migration and connection of neural cells when the relevant brain cortex is being structured 8 to 15 weeks after conception.

The mentioned deterministic radiation effects, with the probable exemption of the in utero exposure of the conceptus at the one cell stadium, occur only after a threshold dose of more than 0 2 Gy is exceeded Therefore, deterministic effects are of less concern after low dose exposure In the low dose range (below 0.2 Gy), only stochastic effects are important

Stochastic radiation effects and quantification of risk

If irradiated cells are modified rather than killed, stochastic effects like cancer of genetic effects might result This kind of effect is called stochastic because of its random or statistical nature.

Somatic effects

The process of carcinogenesis is supposed to be a multistep process. Single changes in the DNA like the activation of a recessive oncogene or, more importantly, the inactivation of a recessive tumor suppressor gene is usually insufficient to result in a fully transformed cell capable of progressing to cancer. After the initiation step, at least of two or more additional mutations are required to provide the modified cell with some proliferative advantage, which is expressed after adequate promotion

At present, no established clinical traits or molecular markers are specific to radiation induced tumors. Therefore, any radiation induced tumor can only be recognized by statistical methods, e g when an irradiated population develops more cancer cases than an unirradiated control population

Estimated of stochastic radiation risk predominantly depend upon the kind of model used for the extrapolation from high to low doses, assumed duration of the induced radiation effect and from transfer of data from the Japanese bomb survivors to populations with perhaps different baseline cancer rates.

The most important study for the estimation of stochastic radiation risks is the follow-up of the survivors of the atomic bombing in Hiroshima and Nagasaki, because the study comprises a large population of all ages and both sex exposed to a range of doses. Studies of other radiation-exposed populations such as cervical cancer patients, ankylosing spondylitis patients, and uranium miners, for example, serve to clarify, confirm, extend and even correct findings from the atomic bomb survivors For some cancer sites like breast, leukaemia, bone liver, and thyroid, there are risk estimates from studies other than the atomic bomb survivors. The results do not suggest great disparities between the studies.

The risk estimate of additional radiation induced leukaemias and solid tumors averaged for all ages and both sex is given by UNSCEAR (1994) as 12% per Sv The corresponding years of life lost per case is 12 years for solid tumors and 26 years for leukaemia UNSCEAR (1993) indicates that the risk estimates derived at high doses and high dose rates should be divided by a small factor to obtain the risk at low doses. If a factor of 2 is used the risk is about 5 - 6% per Sv for a constant relative risk projection

Therefore, based mostly on the epidemiological studies of the atomic bomb survivors, the lifetime probability of a fatal radiation-induced cancer in the world-wide population of all ages and both sexes has been estimated by ICRP (1991) as 5% per Sv for exposure to low doses or at low dose rates from low LET radiation This value is twice as high as 40 years of observation indicate. If the relative risk of most cancer types were not to remain constant during the whole life, but to decrease beyond the period of follow-up for the atomic bomb survivors, then the risk could turn out to be lower than predicted. The use of a relative risk model instead of an absolute model has contributed significantly to in creased risk estimates and shows the importance of

the proper choice in modeling. The relative values for the different organs are quite similar to those for fatal cancer except that the contribution of leukaemia is much greater by about the factor of two, due to the shorter latency period

Genetic effects

Changes in the DNA of germ cells may result in hereditary disorders in the progeny of the irradiated persons. Any non-lethal damage to DNA can, in principal, be transmitted to subsequent generations. The induced hereditary disorders vary widely in their severity Like cancer, the severity is determined more by the location and nature of the radiation damage on DNA than by the dose.

As it is known from experimental animals physical factors and biological factors as well, were found to influence the mutation rate per unit dose High LET radiation (fission neutrons) induces about 20 times more mutations than low LET radiation at high dose rate is 3 times higher than after irradiation at low dose rate The stem cells in spermatogenesis are not as sensitive to radiation as the differentiated spermatocytes (factor of about 2). The above mentioned factors derived from mouse experiments are used for radiation protection purposes

The most important and homogeneous data sets for the evaluation of genetic risk in men are again those from the atomic bomb survivors. Different genetic endpoints in the progeny of exposed parents were investigated e g congenital effects, survival through the first 2 weeks of life, sex ratio, pre-reproductive death, chromosomal abnormalities, mutations affecting certain characteristics of proteins, cancer incidence No indication of an increased level of risk was observed.

Whether radiation increases the mutation rate in man is no longer a question. However, between the initially induced DNA lesions and the ultimate recovery of an induced mutation in the succeeding generation there are a number of intervening steps that will influence the frequency of genetic effects observed. They include DNA repair, mutation fixation, transmission of mutant bearing germ cells, as well as zygotic, embryonic, and postnatal survival of mutations

For risk estimation data from experimental mouse are used The question whether mouse and men posses similar mutation sensitivity is not yet answered There are two methods of risk estimation:

1 The doubling dose method (indirect method) Estimation of expected risk to a population under conditions of continuous irradiation, expressed in terms of the natural prevalence of genetic disease. It is based on the concept that with stable population structure and living conditions, there is a balance between mutations that arise spontaneously and those that are eliminated by selection in every generation.

When an additional mutation source is introduced, the population will (over a number of generations) reach a new equilibrium between mutation and selection. If it is the additional risk at this new equilibrium that is estimated with this method

2 The direct method Estimation has its basis as a measure of the extent of induced phenotypic damage found in the offspring of mice exposed to radiation Damage in the first generation would be expected to result almost entirely from induced dominant mutations

Independent of the method used for risk estimation, the estimated risk for the first generation is in good agreement. After 0 01 Gy of parental irradiation, 17 out of 106 progeny will be expected to carry mutations that cause one or another kind of dominant genetic disease in the first generation