Modelling late health effects of radiation exposure

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Increased risk of cancer is the most widely acknowledged late health effect of the explosion of a nuclear device. For the survivors of the atomic bombs on Japan, exposure to radiation increased their risk for many forms of cancer for the rest of their lives. This paper aims to give the reader an introduction to models developed in the Netherlands that can contribute to an assessment and understanding of late health effects of radiation after a nuclear attack.

The explosion of an improvised nuclear device during the Olympic Games that are currently taking place in Sochi must be a nightmare scenario for the organizers. In the event of a nuclear explosion, a large number of casualties, many of whom will not survive, will fall in the vicinity of the blast. Further away from ‘ground zero’, many people will be exposed to low or moderate doses of radiation. They will be confronted with a tremendous societal and economic disruption, as well as continued fear of cancer associated with the radiation doses received. This paper addresses the latter aspect, by giving an introduction to models developed at RIVM in the Netherlands that aim to improve estimates for long-term cancer risks in response to radiation exposure. Here, we focus on the long term risks related to nuclear detonation, but the models apply to other types of radiological attacks and to risk estimates in normal exposure situations such as to background radiation as well.

Compared to the effects of a high dose of radiation, health effects of exposure to a low or moderate dose remain ill understood. In fact, the uncertainties about the effects are so large that it is not even possible to accurately determine the global shape of the dose response curve: the figure below, taken from (HLEG, 2009) illustrates several possible relations between dose and risk.
To estimate the risk induced by exposure to radiation, assumptions have to be made about the relation between dose and effect. Central in current international radiation protection is the so-called Linear-No Threshold Hypothesis (LNT). In this hypothesis, it is assumed that any dose, no matter how small, is harmful, and that the effect of exposure to radiation is directly proportional to the dose. LNT is by no means an established scientific fact, but it is generally seen as a conservative model for first order risk assessment. Since LNT makes it possible to estimate the effect of low doses by simply extrapolating from high doses, it forms a pragmatic basis for radiation protection.

Implicit in the LNT hypothesis is the assumption that the mechanisms that are involved in radiation-induced carcinogenesis at high and low doses are the same. Recent scientific data challenge this assumption: there are indications that the mechanisms that determine the response of cells to radiation are different for high and low doses.

Biologically-based mathematical models can contribute to a better understanding of risks induced by exposure to a low dose of radiation. At the basis of such models are assumptions on the essential mechanisms that contribute to carcinogenesis, for example, assumptions on the stages in the process where radiation plays a role. These assumptions are translated into mathematical equations that can be solved either exactly or approximately. The resulting model still contains parameters for which values have to be determined from literature or by fitting the model to experimental data. An example of such a parameter is the rate at which mutations occur in the absence of radiation. The final model can be used to obtain risk estimates for different exposure scenarios - provided the underlying biological assumptions are correct - and can therefore contribute to accurate estimates of risks associated with radiation exposure.

Construction of such a model for radio-carcinogenesis requires a combined knowledge of the radiobiology underlying the process and the mathematics needed to develop the model. The National Institute for Public Health and the Environment (RIVM) in the Netherlands is one of very few institutes worldwide where these fields of expertise are combined. RIVM has a long tradition of modeling of radio-carcinogenesis, using a two stage model.

The figure below gives a schematic illustration of the model developed at RIVM, in close collaboration with international research groups:
Normal cells (N) can mutate, spontaneously or under the influence of radiation, into what are termed intermediate cells (I). These cells are not yet malignant, but they are assumed to divide faster than normal cells. After a second mutation, which can again be spontaneous or radiation induced, a malignant cell (M) is formed, which after a certain amount of time ($t_{lag}$) leads to cancer (T). This is a simplified description of carcinogenesis, which in reality usually involves more than just two mutations. Nevertheless, a reduction to two essential (or rate limiting) stages does often lead to a simple, but effective model. A special situation occurs for radiation induced leukemia in a genetically modified mouse, which has been shown to involve exactly two mutations (Suraweera et al, 2005). A model based on data for this mouse has been developed (Dekkers et al, 2011) as a preliminary step before applying the model to data for the atomic bomb survivors, which is work in progress.

Preliminary results indicate the model can be used to obtain estimates for the risk of leukemia after exposure to radiation from a nuclear device. For the survivors of the atomic bombs on Japan in 1945, preliminary results indicate that neutrons induced mutations circa 50 times more efficiently than gamma radiation, and that, when exposed to the same dose, men were roughly twice as likely as women to develop radiation-induced leukemia.

Recent estimates put the number of people who were in Hiroshima or Nagasaki when the atomic bombs fell at close to 600,000. Of these people, between 150,000 and 240,000 are estimated to have died within two to four months after the bombings (http://www.rerf.jp/general/qa_e/qa1.html, visited 6 feb 2014). Carcinogenesis is a process that takes years or even decades. Therefore, people who died in the first few months after the bombings died of causes other than radiation induced cancer. Based on epidemiological studies (Preston et al, 2007, Richardson et al, 2009), the number of cancer cases attributable to radiation in survivors of the atomic bombs is approximately 1% of the number of acute deaths, including those who passed away because of leukemia. The preliminary results from our studies are consistent with this number.

Leukemia is not the only form of radiation induced cancer that can be modeled. Illustrated is the agreement between model prediction and data for a model for radiation induced breast cancer and data from TB patients who were frequently exposed to radiation during treatment (Bijwaard et al, 2010).
The model developed was subsequently applied to estimate the risk that breast cancer will be caused by X-ray based screening for breast cancer. This is a general feature of mechanistic models such as those described here: once the model has been developed, it can be applied in a multitude of situations.

As a consequence, the Netherlands, specifically RIVM and its collaborators in the Low-dose Ionising Radiation Investigations ConSortium of the Netherlands (LIRICS), with many years of experience in modeling of radio-carcinogenesis, can contribute valuable expertise in assessing long term health effects of exposure to radiation after explosion of a nuclear device, as addressed at the second conference on the humanitarian impact of nuclear weapons.

References


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