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Review

Current trends in estimating risk of cancer from exposure to low doses of ionising radiation

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Although ionising radiation has proven beneficial in the diagnosis and therapy of a number of diseases, one should keep in mind that irradiating healthy tissue may increase the risk of cancer. In order to justify an exposure to radiation, both the benefits and the risks must be evaluated and compared. The deleterious effects of medium and high doses are well known, but it is much less clear what effects arise from low doses (below 0.1 Gy), which is why such risk estimates are extremely important. This review presents the current state, important assumptions and steps being made in deriving cancer risk estimates for low dose exposures.

KEY WORDS: *Dose and Dose-Rate Effectiveness Factor; epidemiology; Life Span Study; low-LET radiation; Linear No Threshold model; radiation risk*

Its great benefits aside, any use of ionising radiation in the diagnosis and treatment of disease is also a potential threat for the occurrence of unwanted, harmful effects. Ionising radiation can damage DNA, either directly due to an ejected electron or indirectly through the production of free radicals. Among the many types of DNA damage, double strand breaks (DSBs) are considered to be the most dangerous, as they can lead to cell death or carcinogenesis and heritable effects if their reparation fails (1).

It is very important to know what kind of health risks arise from specific radiation doses. Sufficiently high doses of radiation (above 0.5 Gy) will kill a sufficient number of cells to cause tissue reactions ("deterministic effects") (2). Deterministic effects are characterised by threshold doses below which effects do not occur and the severity of effects increases as the dose increases. Radiosurgery and radiotherapy use very high doses for killing off (or disabling) cancer cells. Non-lethal cell damage can cause cancer and heritable effects ("stochastic effects") and the probability (but not severity) of stochastic effects depends on the dose (2).

During diagnostic radiology all organs, and during radiotherapy and radiosurgery out-of-field organs, are exposed to low doses (below 0.1 Gy). That is why knowledge on cancer risk estimates for low doses is very important. Lately, this topic has attracted increased interest due to three main reasons. First, developments in photon therapy techniques such as Intensity Modulated Radiotherapy (IMRT) and tomotherapy have yielded a more conformal target dose distribution but, compared to previous conventional radiotherapy techniques, whole body exposure to low doses from scattered and leakage radiation has increased. The increasing use of these new techniques has raised interest regarding second cancer risk for patients undergoing radiotherapy. Second, the prognosis for many cancers, including some that largely rely on radiotherapy (e.g., prostate, breast, etc.), is steadily improving; an increasing number of patients are surviving periods comparable to or larger than the latent period for the incidence of

a cancer induced by radiation. Third, the use of Computed Tomography (CT) constantly and significantly increases. CT has established itself as an essential tool, not only for diagnosis but also for the follow-up of diseases, as an aid in intervention and for radiotherapy imaging. It is associated with low doses (organ doses within the scanned volume are typically a few tens of mGy), but doses considerably larger in comparison to corresponding conventional radiographs (3). Many medical procedures require more than one CT scan, which increases the cumulative patient dose. Finally, it should be emphasized that children are of particular interest because cancer risks generally increase strongly as age lowers and children are expected to survive for periods much longer than the latent period of irradiation-induced cancer incidence.

This paper describes the current state and important assumptions and steps being made in deriving cancer risk estimates after exposures to low doses of X and gamma rays. The upper limit for the low dose region is not strictly defined, but this article assumes them to be below 0.1 Gy (4).

Cancer risk estimate for low doses

The statistical models describing the dose-cancer risk relationship used here have been derived from data gathered in epidemiological studies taking into account experimental results from radiobiology (2, 13-15). Epidemiology is used to quantify risk from past exposures by following and comparing irradiated and non-irradiated populations.

The most important epidemiological study for cancer risk modelling is the study on Japanese atomic bomb survivors from Hiroshima and Nagasaki (the so-called Life Span Study, LSS). The LSS cohort of approximately 120,000 survivors (but for the most recent analysis, it was restricted to under 100,000) of the atomic bombings in Hiroshima and Nagasaki is the largest cohort selected for other reasons than disease or occupation. It includes both genders and all ages at exposure, whole-body exposure (mainly to external gamma rays, but a non-negligible ratio of neutrons was also present) with a wide range of doses (ranging from low doses relevant to diagnostic radiology to much higher, even lethal doses) and has a long follow-up period (more than 50 years), which makes it a very important and unique source of data for cancer risk assessment (5-8). The first cancer associated with radiation in the LSS population was leukaemia and it has had the highest relative risk (ratio of the cancer rate in the irradiated group and cancer rate among the non-irradiated group) of any other cancer.

Statistical modelling cannot begin before cancer data assembled during the follow-up period has been assigned to dose data. Doses for the LSS population were reconstructed using DS86 and DS02 dosimetry (9, 10).

What we know from current data

For medium doses (approx. 0.1-2.5 Gy), LSS data suggest an approximately linear relationship between dose and solid cancer induction. Leukaemia is a major exception for which a linear-quadratic model is the accepted standard, because it fits the data significantly better than the linear model (7, 11). Above and below the medium dose range, the situation is much less clear. Although epidemiological data for doses below 0.1 Gy exist, statistical limitations, i.e. uncertainties, are large. The size of an exposed cohort that would be required to detect a statistically significant increase in cancer risk from doses of interest approximately increase as the inverse square of the dose (12). For low doses, extremely large epidemiological studies would be required to maintain the statistical significance of cancer risk results. Therefore, linear extrapolation from higher doses, suggested by different standard bodies (2, 13-15), is a reasonable solution for low doses.

However, we have to be aware that some known effects and phenomena suggest scenarios where linear extrapolation could underestimate (e.g., bystander effect) or overestimate risk (e.g., adaptive response). On the other side of the dose-risk curve, for doses above 2.5 Gy, the deviation from linearity and reduction of risk due to cell killing and repopulation effects are expected.

The Linear No Threshold model

Several risk models have been developed by standard bodies to estimate cancer incidence and mortality for low doses: Committee on the Biological Effects of Ionizing Radiation [BEIR (13)], National Council on Radiation Protection and Measurements [NCRP (14)], International Commission on Radiological Protection [ICRP (2)], and United Nations Scientific Committee on the Effects of Atomic Radiation [UNSCEAR (15)]. They all have in common the assumption of the Linear No Threshold (LNT) dose-risk relationship. In other words, risk is directly

proportional to the received dose and exists for each dose. The uncertainties associated with each model are close to, or exceed, variations between the models. Using LNT models for a dozen or so different types of cancers, as a function of important parameters such as gender, age at exposure and time since exposure, have been developed. It has also been established and used in the field of radiation protection that the average risk of developing cancer induced by whole body low dose exposures during a lifetime is approximately 5 % per Sv (2).

Dose and Dose-Rate Effectiveness Factor (DDREF) value

Because the LSS population was exposed to a high dose rate and risk estimates for low doses had to be based on data for higher doses, which following linear extrapolation overestimates the risk for low doses, the reduction factor called Dose and Dose-Rate Effectiveness Factor (DDREF) was introduced. In another words, DDREF implies that the radiobiological effectiveness of low dose and/or low dose rate exposures differs from the effectiveness of high dose and/or high dose rate exposures. Values for DDREF have been mainly deduced from experiments with laboratory animals, radiobiological measurements, and statistical methods (Bayesian analysis) on epidemiological data.

In order to be able to rely on the developed models, one should be aware of their uncertainty. There are two important sources of uncertainty: the very procedure to determine the DDREF value and the "transport" of cancer risk estimations based on a Japanese population to non-Japanese populations, particularly those predominantly Caucasian.

BEIR VII and ICRP reduced cancer risk values in atomic bomb survivors by a DDREF of 1.5 and 2.0, respectively (2, 13). However, a recent review article on cancer risk in radiation workers after low dose rate and moderate dose exposures reported higher cancer risks than BEIR VII and ICRP, implying that their DDREF values were overestimated (16).

To clarify the DDREF, we should use knowledge from radiobiology. For doses of up to a few Gy, an effect $E(D)$ (e.g., chromosomal aberrations, mutations, animal carcinogenesis) induced by an acute dose of low-LET (Linear Energy Transfer) radiation (such as X and gamma rays) delivered over a few minutes can be described by a linear-quadratic function (17):

$$E(D)=\alpha D+\beta D^2 \qquad \text{(I)}$$

Theoretically, the linear and quadratic term can be associated with "single-track action" (cell damages (e.g. DSBs) are caused by a single track) and "double-track action" (two or more tracks increase damage of the cell), respectively (18). Although, equation (I) is most suited for medium doses (0.1-2.5 Gy), it is better to use a more simpler linear function ($E_{Medium}(D)=\alpha_M D$) for fitting data because the corresponding error for risk estimates is much smaller than the one caused by the uncertainties of the data.

As already mentioned, equation (I) should be used only for leukaemia. For low doses, the probability for "double-track action" is negligible, so the quadratic term in (I) can be neglected and only the linear term is important ($E_{Low}(D)=\alpha D$). $E_{Medium}(D)$ and $E_{Low}(D)$ are different linear functions. If applied for low doses, $E_{Medium}(D)$ overestimates the risk and therefore reduction factor DDREF is used.

The second important source of uncertainty is the "transport" of data and the conclusions that arise from it from the studied Japanese population to other populations that may have different genetic and life-style characteristics leading to different baseline risks.

Basic terms used for risk estimate

The most recent statistical analyses of epidemiological data made for the purpose of cancer risk estimates are based on either Excess Absolute Risk (EAR) models or Excess Relative Risk (ERR) models (2, 13-15). EAR models express excess risk as the difference in the total risk and the background risk, while ERR models express excess risk relative to the background risk. Several measures of lifetime risk have been introduced, but our focus is primarily on Lifetime Attributable Risk (LAR). LAR is defined as the probability that an irradiated person during his life could develop cancer induced by radiation. The LAR for a person exposed to dose D at age e is calculated as follows (13):

$$\mathbf{LAR}(D,e)=\sum_{a=e+L}^{a_{max}} M(D,e,a)\frac{S(a)}{S(e)} \qquad \text{(II)}$$

where

a = attained age

e = age at exposure

L = latent period i.e. the period during cancer incidences caused by radiation are not expected (BEIR VII has adopted L = 2 for leukaemia and L = 5 for solid cancers)

$S(a)$ = probability of surviving until age a

$S(e)$ = probability of surviving until age e

$M(D, e, a)$ is a linear combination of EAR(D, e, a) and ERR(D, e, a) that depends on how transport from one studied population to another is made.

Two approaches that have been used are multiplicative or relative risk transport and additive or absolute risk transport (2, 13-15). The first approach assumes that the cancer risk induced by radiation exposure is proportional to the baseline risk, whereas the second presumes the opposite. Results from these two approaches can be very different. For example, the baseline risk for stomach cancer is much higher in Japan than in the United States (13) and there is almost an order-of-magnitude difference in the estimates of stomach cancer risks based on absolute and relative risk transport. For cancer sites other than breast, thyroid and lung, BEIR VII (13) recommends a weight of 0.7 for the estimates obtained using relative risk transport and a weight of 0.3 for the estimates obtained using absolute risk transport with the weighting done on a logarithmic scale. For example, if lifetime attributable risks for the aforementioned stomach cancer based on relative and absolute risk transport are LARr and LARa, respectively, the final result for LAR, combined and adjusted by DDREF is:

$$\mathbf{LAR} = \frac{\exp(\mathbf{0.7}\ln(\mathbf{LARr}) + \mathbf{0.3}\ln(\mathbf{LARa})}{\mathbf{DDREF}} \quad \text{(III)}$$

Diagrams on Figure 1 illustrate LAR data estimated by BEIR VII (13). The BEIR VII table 12D-1 provides LAR data for leukaemia and cancer for several radiosensitive organs of persons exposed to a single dose of 0.1 Gy. Both sexes and eleven discrete ages at exposure are covered and LARs for the measured organ doses in other studies can be estimated by using linear extrapolation and/or interpolation. According to these results, the risks are highest for children and decrease with age at exposure. For most radiosensitive organs, women endure higher risks than men. They also have the highest LAR for breast, lung, and thyroid cancer, while the highest male LAR is for colon and lung cancer.

Other studies

There have been many studies on medically, occupationally, and environmentally exposed populations whose results have been compared against those from the LSS. The results of comparisons are always expressed within certain statistical limits.

A few years ago, the largest study of nuclear workers found radiation-induced cancer risk consistent with the LNT cancer risk models based on LSS data (19). Medical studies include patients irradiated for the treatment of disease or diagnosis and provide valuable information for understanding radiation risk, especially for some specific cancers (e.g., thyroid and breast) (20). Analysis of childhood cancer risks after prenatal X-ray exposures found increased cancer risk for the dose of 10 mSv (21). Due to increased interest for cancer risk estimate after CT, currently more than ten studies concerning risk of cancer after CT for different national cohorts are in progress (22). Recently, results for the British (23) and Australian (24) cohort of children and young adults have been published and both assessed the excess cancer risk after CT scans. Environmental radiation studies comparing medical and occupational data are mostly limited and uncertain. The most valuable information can be derived from studies after the Chernobyl accident (mostly regarding increased risk of radiation-induced thyroid cancer among children due to exposure to radioactive iodine); a recent study (28) reports statistically significant increased risk for children and adolescents but not for older people.

The validity of the LNT model and concluding remarks

Between 50 and 100 mGy, cancer risk estimates based on LSS data lose their conventional statistical significance, but for the low dose region they remain consistent with the LNT model as well as with some nonlinearities (7). Although there is evidence that doses of approximately 10 mGy increase the risk of certain cancers (21), according to present epidemiological data the lowest dose of photon radiation for which reasonably reliable evidence of increased cancer risk exists is about 10-50 mGy for single and 50-100 mGy for protracted exposure (25). There is no doubt that present cancer risk models can be used for doses above the mentioned limit, but one should always be careful with extrapolation to lower doses (especially below 10 mGy).

Reducing the dose and approaching the level of background radiation, things become even more unclear and it has to be borne in mind that values for estimated risk of radiation-induced cancer will be very small and comparable with variations in baseline risk (e.g., smoking). It would be impossible to make an adequate epidemiological LNT test for doses below approx.10 mGy and controversies (26, 27) will always exist.

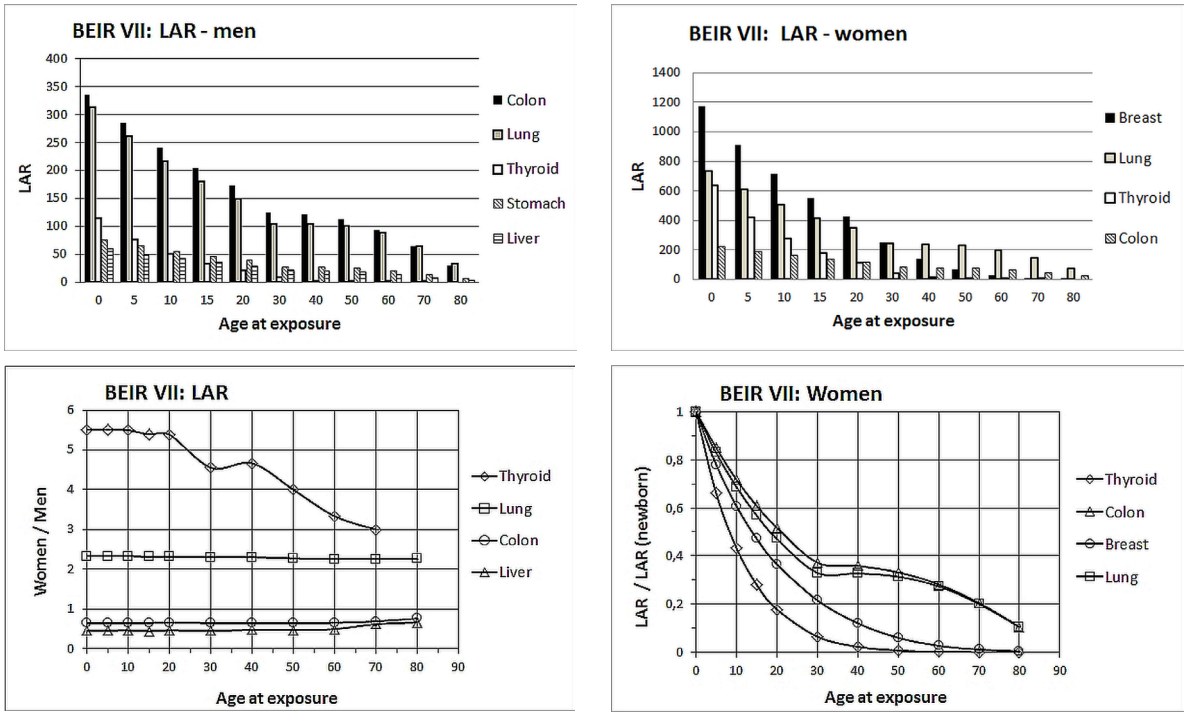

Figure 1 *Diagrams illustrate LAR data for cancer incidences presented in BEIR VII table 12D-1 (13). LAR is expressed as a number of cancer cases among 100,000 irradiated persons exposed to a single dose of 0.1 Gy. Only organs with the highest cancer risk values are presented*

However, evidence for cancer risk after low dose exposure exists and that risk can be predicted by current LNT models. The LNT model is still the most robust and most frequently used model for making cost-benefit decisions in medical exposures, but improvements to existing models as well as new findings for the low dose region are eagerly awaited.

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Sažetak

Procjena rizika za nastanak karcinoma zbog izloženosti malim dozama ionizirajućeg zračenja

Unatoč velikoj važnosti i koristi ionizirajućeg zračenja u dijagnosticiranju i liječenju mnogih bolesti, treba imati na umu da se ozračivanjem zdravog tkiva može povećati rizik od karcinoma. Stoga je vrlo važno znati kakve rizike možemo očekivati ovisno o primljenoj dozi zračenja. Za razliku od područja srednjih i velikih doza za koje su štetni učinci dobro poznati, područje malih doza (ispod 0,1 Gy) puno je nejasnoća, a procjena rizika vrlo je važna. U ovom radu prikazane su osnovne pretpostavke i koraci u procjeni rizika od karcinoma uzrokovanih zračenjem u području malih doza.

KLJUČNE RIJEČI: *faktor DDREF; epidemiologija; LSS; model LNT; radijacijski rizik; zračenje niskog LET-a*

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