

Uncertainty, low-dose extrapolation and the threshold hypothesis

Charles E Land

Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA

Received 11 March 2002

Published 4 September 2002

Online at stacks.iop.org/JRP/22/A129

Abstract

Risk-based radiation protection policy is influenced by estimated risk and by the uncertainty of that estimate. Thus, if the upper limit, at (say) 95% probability, of risk associated with a given radiation dose is at an 'acceptable' level, it is unlikely (or not credible) that the true level of risk associated with the dose is at an unacceptable level. Central estimates presented alone, in the absence of probability limits, lack this safety factor. Estimating cancer risks from low doses of ionising radiation involves extrapolation of risk estimates based on high-dose data to the much lower dose levels that characterize the vast majority of exposures of regulatory concern. Proof of a universal low-dose threshold, below which there is no radiation-related risk, would revolutionise radiation protection. Available data fail to provide such proof and, in fact, leave considerable room for the possibility that DNA damage from a single photon can contribute to the carcinogenic process. Allowing for the *possibility* of a threshold would, however, remove very little of the regulatory burden associated with the so-called linear, no-threshold hypothesis, unless that possibility were a virtual certainty.

1. Introduction

Ionising radiation exposure is a known, and well quantified, cancer risk factor. Nevertheless, estimation of cancer risk following radiation exposure is a very uncertain process for most cases of regulatory and/or popular concern. One reason is that risk estimates are usually applied to populations different from those on which the estimates are based. Another is that public and regulatory concern is usually with exposures at radiation doses far lower than those at which useful information about risk can be obtained.

We have reasonably good information on cancer risk following acute exposures in the range 0.5–5 Sv and above. There have been numerous epidemiological studies of populations containing 'high-dose' subsets with radiation doses in this range. These populations include patients treated with radiation for benign and malignant disease, patients who received

extensive diagnostic radiography over a lengthy illness, such as tuberculosis patients treated by lung collapse therapy monitored by frequent fluoroscopy examinations, persons who received substantial exposures because of their occupations, such as uranium miners exposed to radon decay products in mine atmospheres and instrument dial painters who ingested radium contained in luminescent paint, and survivors of the atomic bombings of Hiroshima and Nagasaki, Japan. These studies, and in particular inferences based on the high-dose component of the populations under study, form the epidemiological basis for estimation of radiation-related risk.

Except for radiation therapy, where there is a perceived benefit from the radiation dose itself, very few people are exposed to radiation doses of 0.5 Sv and above. Most public concern is with exposures to less than 50 mSv, the historical annual limit for radiation workers, and extends to doses well below 1 mSv, a typical annual dose from natural background radiation for most tissues other than the lung. A chest x-ray, for example, delivers about 0.1 mSv to bone marrow; the dose to breast tissue from a two-view mammography examination is about 3 mSv; an astronaut may get about 2.4 mSv on a typical 3 day space shuttle mission, and would get about 48 mSv on a 60 day tour in the space station now under construction (NCRP Report 138, 2001b).

Although such low-dose exposures (except for the astronaut's) are very common, it is extremely difficult to estimate their health effects by studying populations with exposures limited to the low-dose range. This is because, at doses below 50 mSv or so, the radiation-related excess risk, which is thought to be proportional to dose or perhaps somewhat less, tends to be dwarfed by statistical and other variation in the normal risk level in the absence of exposure. Because of this, truly enormous sample sizes (e.g. millions) would theoretically be required to obtain a statistically stable estimate of radiation-related risk, and even then the estimate would be untrustworthy because we do not understand, and therefore cannot control or adjust for, all of the sources of variation in baseline levels of risk (Land 1980). At higher dose levels there are fewer such problems because the excess risk tends to be greater than most statistical variation in baseline risk, and we are more likely to understand the causes of any substantial variation that might be confounded with radiation dose.

Arguably the most important single problem in radiation risk protection is how to extrapolate from statistically stable, and relatively unbiased, risk estimates that pertain to higher-dose exposures, down to the lower dose levels that are of greater concern in everyday life. Clear and accurate information is needed for the following reasons:

- (1) as guidance for radiation protection efforts;
- (2) as a basis for informed consent by persons who may be asked to accept a certain level of exposure in the interests of medical research, economic progress or some other social good;
- (3) for adjudication of claims and disputes concerning cases of disease possibly related to past radiation exposure and
- (4) for risk-benefit analyses of public policy initiatives related to radiation.

Information useful for radiation risk protection and informed consent includes central estimates of dose-specific risk, but also lower and (especially) upper probability bounds on risk. A lower probability bound (e.g. a 95% confidence limit) greater than zero is evidence that there really is an excess risk. An upper probability bound, if less than some 'tolerable' level of risk, can be used to help justify a favourable risk-benefit assessment for a particular exposure. It can also provide a margin of safety in decision making, e.g. regarding risk protection or informed consent related to possible hazards of radiation exposure. Probability bounds can

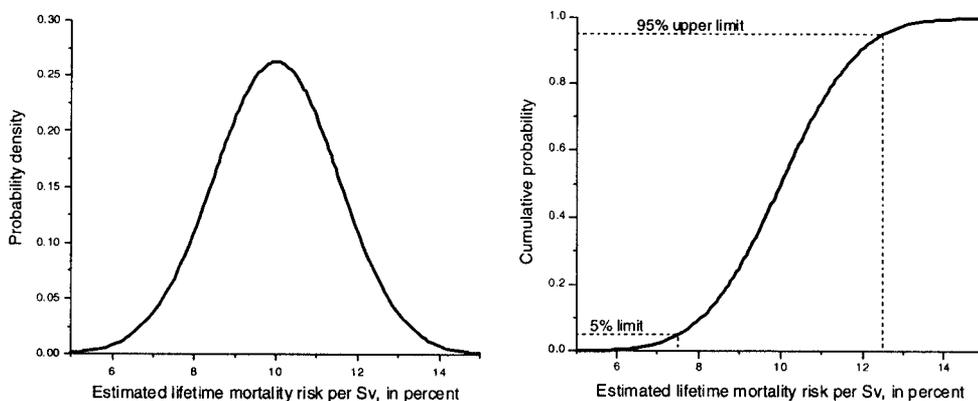


Figure 1. Nominal statistical uncertainty distribution for estimated excess lifetime risk of solid cancer mortality among atomic-bomb survivors associated with a whole-body dose of 1 Sv from low-LET radiation. Probability density function (left-hand panel) and cumulative probability distribution (right-hand panel).

reflect both statistical uncertainty, estimated by fitting a mathematical model to observational data, and subjective uncertainty about model assumptions.

General acceptance of a universal, low-dose threshold, below which there is no radiation-related risk, would substantially simplify radiation protection. At present, the threshold concept is not generally accepted, nor is there a consensus about the quantitative value of any such threshold. The purpose of the present paper is to explore the implications for radiation protection of a possible, but uncertain, threshold.

2. Example

In NCRP Report 126 (1997) a statistical uncertainty distribution was postulated for lifetime excess mortality risk of solid cancer following exposure of Japanese atomic-bomb survivors to a whole-body, neutron-weighted dose of about 1 Sv (figure 1). The plotted distribution, shown in probability density form in the left-hand panel and cumulative form in the right-hand panel, is normal with mean $10\% \text{ Sv}^{-1}$ and 90% confidence limits $7.5\text{--}12.5\% \text{ Sv}^{-1}$. Note that the uncertainty limits are obtained from the cumulative distribution function by drawing horizontal lines from the 5 and 95% values on the ordinate of the graph and dropping vertical lines to the abscissa from the intersection points with the cumulative distribution curve. In order to apply the uncertain estimate of figure 1 to an American population similarly distributed by age and sex, uncertain correction factors must be applied for biases and errors in atomic-bomb survivor dosimetry and possible interaction between radiation dose and the different baseline cancer rates in the two populations (NCRP 1996, 1997). For extrapolation to low doses and low dose rates, an uncertain dose and dose rate effectiveness factor (DDREF) was applied (see figure 6.2 of NCRP Report 126 (NCRP 1997)). When all these adjustments were factored into the risk estimate, the resulting uncertainty distribution for excess risk per Sv was as shown in figure 2. The uncertainty distribution is approximately log-normal with 90% probability limits $1.2\text{--}8.8\% \text{ Sv}^{-1}$.

3. Implications of an uncertainty distribution for estimated risk

The overall uncertainty distribution in figure 2 expresses essentially all the usable information, in the form of statistical data and informed opinion, that we have about the risk we wish to

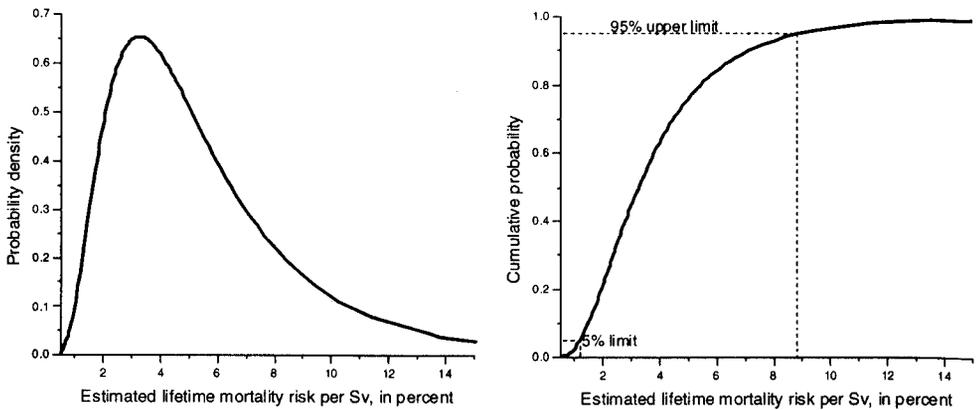


Figure 2. Uncertainty distribution for excess lifetime risk per Sv associated with exposure to low-LET radiation at low doses and dose rates: general United States population. Adapted from NCRP Report 126.

estimate. The mean of the distribution expresses only one characteristic of that information (it is the point on the abscissa at which the probability density distribution would balance, if a fulcrum were placed there). The mean (or other central value such as the median or mode) tells us little about how large, or how small, the risk might credibly be, a matter of some interest if one were contemplating action that would result in exposure to a population or oneself. A demonstration that the 95% upper probability limit on risk is small provides more assurance that the risk from a particular exposure is acceptable, in view of any associated benefits, than a demonstration that the expected risk is small. Radiation protection should offer a demonstrable margin of safety.

4. The linear, no-threshold (LNT) and threshold hypotheses

The so-called linear, no-threshold (LNT) hypothesis (see, e.g., Brenner and Raabe (2001)) is part of the current basis for risk-based radiation protection. The model assumes proportionality between radiation dose and subsequent cancer risk, usually with allowance for a DDREF to reduce risk per unit dose of low-LET radiation at dose levels below 200 mSv (ICRP 1990). However, at doses below that at which the DDREF applies fully, excess risk is assumed to be proportional to dose. A consequence of the LNT model is that exposures resulting in very small average doses to very large populations are assumed to be associated with excess numbers of cancers that, although undetectable by epidemiological study, are real enough to those affected.

A competing model, which if accepted would revolutionise radiation protection philosophy, is the threshold hypothesis. According to this model, there is some 'threshold' dose below which there is either no radiation-related health detriment or a radiation-related health benefit that outweighs any detriment. A consequence of the model is that, at some point, a very low dose to any number of people has no associated risk and can be ignored.

One argument made against the LNT hypothesis is that there is little or no direct epidemiological evidence of excess cancer risk in populations exposed to less than 50 mSv or so. That is not quite true: one example is cancer risk among children exposed *in utero* to radiation from x-ray pelvimetry (Stewart *et al* 1956, MacMahon 1962, Monson and MacMahon 1984, Harvey *et al* 1985, Bithell and Stiller 1988); another is breast cancer risk among women exposed to high cumulative doses from multiple chest fluoroscopy examinations, delivered in fractions on the order of 10 mSv (Boice *et al* 1991). But this is a matter of degree; it is true that

there is no direct, credible epidemiological evidence of a radiation-related risk associated with exposures on the order of 1 mSv, for example. However, if we assume the LNT hypothesis to be true, the chances of detecting a small excess risk associated with a dose of 1 mSv is very small for any achievable study. Thus, failure to observe a statistically significant excess risk from a low-dose study is predicted by the LNT hypothesis; such a finding is not strong evidence for the LNT hypothesis, but neither is it evidence of any kind against it.

5. Some radiobiological reasons to question the universal existence of a low-dose threshold

The most important mechanism by which ionising radiation exposure contributes to radiation carcinogenesis has long been thought to be the induction of double-strand DNA breaks and more complex clustered DNA damage. Such events have been demonstrated by calculation (Brenner and Ward 1992, Goodhead 1994) and by experiment (Boudaiffa *et al* 2000a, 2000b) to result from a single low-energy electron track produced by an x-ray or photon interaction. At low doses and low dose rates, the occurrence of such events is proportional to radiation dose and to the number of cells irradiated (Kellerer 1985).

Complete efficiency of repair of double-strand breaks (DSB) and complex lesions at low doses and low dose rates would provide a strong argument for the existence of thresholds. However, in mammals, the predominant mechanism for repair of such lesions is non-homologous end joining, which is known to be inefficient (Jeggo 1998, Jeggo and Concannon 2001). Somatic mutations resulting from mis-repaired DSB and complex lesions are thought to be contributors to the carcinogenic process (NCRP Report 136, 2001a).

Thus, while we cannot now rule out the possible existence of a threshold dose, below which radiation exposure does not contribute to carcinogenesis (and indeed we may never be able to do so), the threshold hypothesis is at most a possibility, and not a particularly strong one, on the basis of current knowledge.

6. Implications of a low-dose threshold as an uncertain possibility

The considerations just cited do not prove that there could *not* be a universal radiation dose threshold, but they do indicate that there is much room for doubt. It is useful to consider the possible existence of a threshold as another uncertain factor that must be taken into account when estimating cancer risk associated with low-dose radiation exposure. The simplest uncertainty model is to assume that, at or above a radiation dose of interest, a universal low-dose threshold exists with some probability $p = 20\%$ (say), and that it does not with probability $1 - p = 80\%$. The resulting uncertainty distribution for low-dose risk places 20% probability on zero risk and the remaining 80% on the low-dose uncertainty distribution shown in figure 2. The exercise can be repeated for other assumed threshold probabilities, such as 50 and 80%. In their cumulative forms, these distributions have jumps of 20, 50 or 80% at zero, corresponding to the probability placed on zero risk (figure 3). Upper probability limits are obtained as in the right-hand panels of figures 1 and 2.

Means and upper 95% probability limits on risk per Sv are plotted in figure 4 as analytical functions of the assumed threshold probability. Analytical representations are as follows:

$$\text{Mean}(p) = (1 - p) \times 3.8\% \text{ Sv}^{-1};$$

$$95\% \text{ upper limit} = F^{-1}((0.95 - p)/(1 - p)),$$

where p is the assumed threshold probability and F^{-1} is the inverse cumulative log-normal distribution function with 90% probability limits 1.2–8.8% Sv⁻¹.

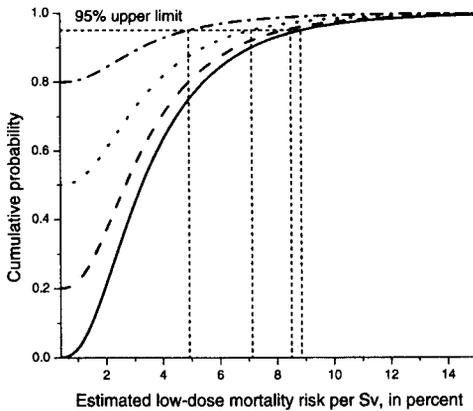


Figure 3. Effect on the probability distribution of figure 2 of assuming the possible existence of a low-dose threshold, with probability $p = 0.2, 0.5$ or 0.8 .

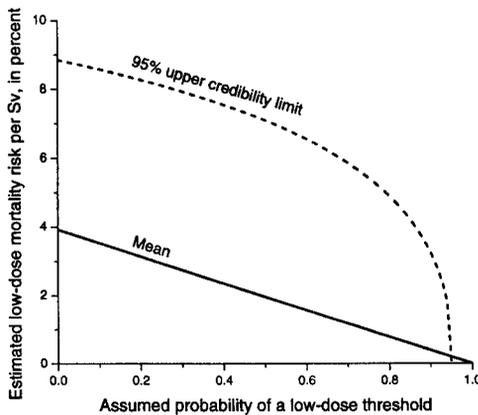


Figure 4. Mean and upper 95% probability limit, as functions of the assumed threshold probability p , of distributions like those illustrated in figure 3.

7. Conclusions

While certain, or nearly certain, existence of a universal low-dose threshold at some non-negligible value would greatly simplify radiation protection, the uncertain *possibility* of a threshold does not. The mean value of the uncertainty distribution for risk decreases in direct proportion to $1 - p$, where p is the assumed threshold probability, and is therefore very small only if p is near one. The upper 95% uncertainty limit disappears for $p = 95\%$ or greater, but for p less than 80% the relative decrease is slight. Given present knowledge, the possibility of a low-dose threshold should not influence radiation protection policy.

References

- Bithell J F and Stiller C A 1988 A new calculation of the carcinogenic risk of obstetric x-raying *Stat. Med.* **7** 857-64
 Boice J D Jr, Preston D, Davis F G and Monson R R 1991 Frequent chest x-ray fluoroscopy and breast cancer incidence among tuberculosis patients in Massachusetts *Radiat. Res.* **125** 214-22

- Boudaiffa B, Cloutier P, Hunting D, Huels M A and Sanche L 2000a Resonant formation of DNA strand breaks by low energy (3–20 eV) electrons *Science* **287** 1658–60
- Boudaiffa B, Hunting D, Cloutier P, Huels M A and Sanche L 2000b Induction of single- and double-strand breaks in plasmid DNA by 100–1500 eV electrons *Int. J. Radiat. Biol.* **76** 1209–21
- Brenner D J and Raabe O A 2001 Is the linear-no-threshold hypothesis appropriate for use in radiation protection? *Radiat. Prot. Dosim.* **97** 279–85
- Brenner D J and Ward J F 1992 Constraints on energy deposition and target size of multipli-damaged sites associated with DNA double-strand breaks *Int. J. Radiat. Biol.* **61** 737–48
- Goodhead D T 1994 Initial events in the cellular effects of ionizing radiations: clustered damage in DNA *Int. J. Radiat. Biol.* **65** 7–17
- Harvey E B, Boice J D Jr, Honeyman M and Flannery J T 1985 Prenatal x-ray exposure and childhood cancer in twins *New Engl. J. Med.* **312** 541–5
- ICRP (International Commission on Radiological Protection) 1990 Recommendations of the ICRP *ICRP Publication* 60 (*Ann. ICRP* **21**(201))
- Jeggo P A 1998 Identification of genes involved in repair of DNA doublestrand breaks in mammalian cells *Radiat. Res.* **150** S80–91 (Suppl.)
- Jeggo P A and Concannon P 2001 Immune diversity and genomic stability: opposite goals but similar paths *J. Photochem. Photobiol.* **B 65** 88–96
- Kellerer A M 1985 Fundamentals of microdosimetry *The Dosimetry of Ionizing Radiation* ed K R Kase, B E Bjarngard and F H Attix (New York: Academic) pp 77–162
- Land C E 1980 Cancer risks from low doses of ionizing radiation *Science* **209** 1197–203
- MacMahon B 1962 Prenatal x-ray exposure and childhood cancer *J. Natl Cancer Inst.* **28** 1173–91
- Monson R R and MacMahon B 1984 Prenatal x-ray exposure and cancer in children *Radiation Carcinogenesis: Epidemiology and Biological Significance* ed J D Boice Jr and J F Fraumeni Jr (New York: Raven) pp 97–105
- National Council on Radiation Protection and Measurements (NCRP) 1996 A guide for uncertainty analysis in dose and risk assessments related to environmental contamination *NCRP Commentary* 14 (Bethesda, MD: NCRP)
- National Council on Radiation Protection and Measurements (NCRP) 1997 Uncertainties in fatal cancer risk estimates used in radiation protection *NCRP Report* 126 (Bethesda, MD: NCRP)
- National Council on Radiation Protection and Measurements (NCRP) 2001a Evaluation of the linear-nonthreshold dose–response model for ionizing radiation *NCRP Report* 136 (Bethesda, MD: NCRP)
- National Council on Radiation Protection and Measurements (NCRP) 2001b Radiation protection guidance for activities in low-Earth orbit *NCRP Report* 138 (Bethesda, MD: NCRP)
- Stewart A, Webb J, Giles D and Hewitt D 1956 Malignant disease in childhood and diagnostic irradiation in utero *Lancet* **2** 447