

## Risk Projections in Time

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### Abstract

The nominal risk coefficients for radiation induced cancer are largely based on the follow-up of the mortality from solid cancers among the atomic bomb survivors. For those who have been exposed as adults, the observations are essentially complete, and the risk estimates are, therefore, firmly based on observations. Those who have been exposed as children, have still not reached the age of high cancer incidence. Their observation is, therefore, still incomplete, and the risk estimates are correspondingly uncertain.

The modelling of risk has predominantly been based on the postulate, that the relative risk (i.e. the actual cancer rate divided by the age specific normal rate) depend on dose and on age at exposure, and that it does not decline with time since exposure. The high relative risks observed at young ages lead, therefore, with this type of model, to high estimates of life time attributable risk. The ICRP recommendations contain these high risk estimates for young ages at exposure; the high sensitivity of children and juveniles has, indeed, become one of the basic tenets of radiation protection.

It is here shown that these conclusions are still hypothetical, because they are merely a matter of the choice of the model. An alternative model assumes a dependence of the excess relative risk on age attained, rather than age at exposure. This model fits the data equally well, and predicts no increased risk for young ages at exposure. A decision between the two models is not possible at present, it will have to await the continued follow-up of those who survived the atomic bombs as children.

The ICRP has been criticised for postulating a dose reduction factor (DDREF) in their nominal risk coefficients. If they abandoned this factor, and used the age attained model, rather than their present model, their numerical risk coefficients would remain unchanged.

### Introduction

Ionizing radiation is not one of the major cancer causing agents, such as smoking, solar UV light, or aflatoxins in countries without refrigeration. However, it is the factor that has been most extensively studied, and it is also the factor that causes in many countries the greatest apprehensions. The International Commission for Radiological Protection has used the extensive knowledge that has been accumulated in radiation research, to derive and to present numerical risk estimates for late stochastic effects and especially for radiation induced cancer (ICRP 26, 1977).

These risk estimates have become an important reference in discussions that were concerned with the magnitude of dose limits, especially for occupationally exposed persons. The ICRP has always emphasized, that the first principle of radiation protection is keeping the radiation exposures as low as reasonably achievable (ALARA), while the dose limits are merely a secondary tool. From this point of view, it is helpful to estimate the magnitude of radiation risks, but the precise numerical values are not critical for the correct performance of radiation protection.

Nevertheless, there have been heated debates in recent years about the risk estimates for ionizing radiation. The extension of the observations on the atomic bomb survivors has led to increased risk estimates, and the new recommendation of ICRP (ICRP 60, 1990) have, therefore, found especial interest. The new estimates are directly linked to the observations, mostly at high doses, of the atomic bomb survivors, and of some other major cohorts of exposed persons. In the extrapolation to low doses, ICRP has postulated a dose and dose rate reduction factor (DDREF) of 2. This factor is not directly based on epidemiological evidence, but is instead relat-

ed to radiobiological findings in cell cultures and in animal studies. There has been criticism, that the postulated dose reduction factor is hypothetical and that it may lead to an underestimate of radiation risks.

While there has been much discussion of the dose reduction factor, there has been little scrutiny of other assumptions that underlie the risk estimates. The present discussion is, therefore, concerned with another important aspect, namely the extrapolation in time. It will be seen, that in this aspect the risk estimates of ICRP may well be overestimates.

The consideration will require some mathematical formalism, but an attempt will be made to keep the formalism at a minimum and to bring out the main thoughts and results.

**The absolute and the relative risk model**

The simplest risk model is one, where one assumes an excess cancer rate that is caused by a radiation exposure and that begins after a latent period,  $T$ , and then remains constant. The total (incidence or mortality) rate at age  $a$  after a one-time radiation exposure with dose  $D$  is then:

$$r(a,D) = r_0(a) + \Delta r(e,D) \quad \text{for } a > e + T \quad (1)$$

where  $r(a,D)$  is the total rate, while  $r_0(a)$  is the spontaneous rate at age,  $a$ . The term  $\Delta r(e,D)$  represents the excess rate that is here taken to depend on dose  $D$  and on age,  $e$ , at exposure.

In this simple form, the above absolute risk model fits the data – for example those for the atomic bomb survivors – very poorly. In a modified form, where the excess risk depends on age at exposure and on time since exposure, it is adequate to represent the findings for the leukemia mortality among the atomic bomb survivors. This absolute risk model for the leukemias is exemplified in the upper panel of Fig.1.

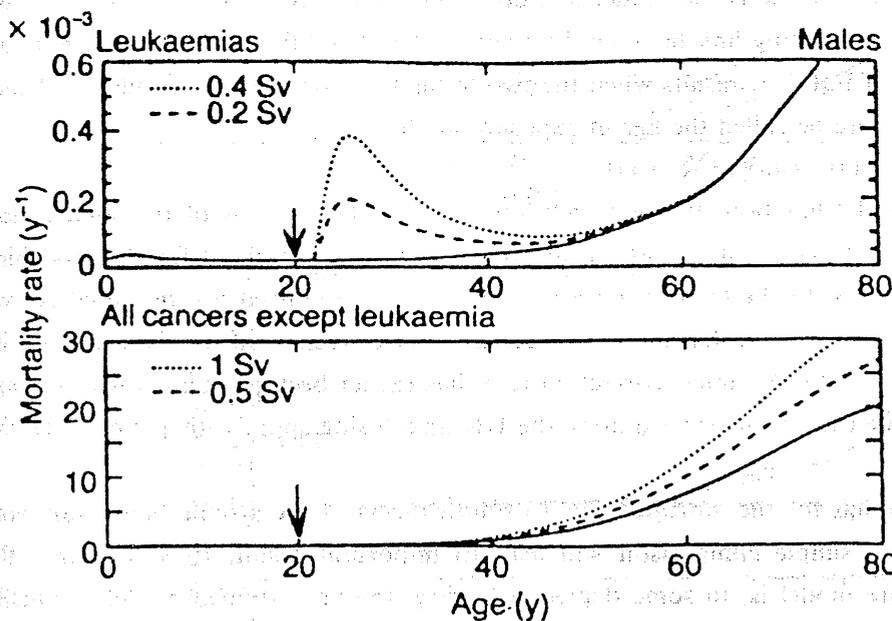


Figure 1. Age specific mortality rates (–) from leukemia (upper panel) and from other cancers (lower panel). The broken and dotted lines give the increased rates that result according to the estimates of ICRP 60, from exposures at age 20.

For solid cancers one utilises a somewhat different model which is termed the relative risk model. In analogy to Eq(1) one writes:

$$r(a,D) = r_0(a)[1 + \Delta r(e,D)] \quad \text{for } a > e + T \quad (2)$$

The individual terms have the same meaning as in Eq(1); however,  $\Delta r(e,D)$  is now an *excess relative risk*, not an absolute excess risk.

In the relative risk model one deals with a constant enhancement factor that appears after a latent period, of say  $T = 10$  years, after radiation exposure. In the most common formulation the excess risk is taken to be merely dependent on dose and on age,  $e$ , at exposure. The lower panel in Fig.1 exemplifies this dependence for the mortality from all solid cancers of the atomic bomb survivors. The ICRP risk estimates are largely based on

the two models that are indicated in Fig.1. There have been modified models, where the excess relative risk depends not only on dose and age at exposure, but also on time since exposure or on age attained. Such models were utilised for individual organs, for example in the detailed analyses in BEIR V (1990). There has, however, not been a systematic evaluation of the applicability of the different formulations.

#### A comparison of relative risk models

The relative risk model of Eq(2) provides a much better fit to the mortality from solid cancers than the absolute risk model of Eq(1). However, this comparison can not be seen as support for Eq(2); the simple absolute risk model is too poor a description of the observations to provide a meaningful comparison. A more realistic comparison of risk models is, therefore, required, and it will here be discussed.

#### A fairly general relative risk model:

A general risk model is of the form:

$$r(a,D) = r_0(a)[1 + \Delta r(e,a,D)] \quad (3)$$

Simplifying assumptions are, of course, required to make the model manageable. For the subsequent discussion it will be assumed, that the dependence in dose is linear. It will be further assumed, that the excess relative rate factorizes in the variables age at exposure,  $e$ , age attained,  $a$ , and time,  $t = a - e$ , since exposure. The dependence on sex is not written into the equation; similarly, confounders such as smoking are not listed among the variables. With these simplifications the equation reads:

$$r(a,D) = r_0(a)[1 + f(e) \cdot g(a) \cdot h(t) \cdot D], \text{ with } t = a - e \quad (4)$$

#### The two main special cases:

Even with its broadly simplifying assumptions the model of Eq(4) remains too complicated to be of much practical use. It serves here merely as a connecting link between different further simplifications that are in actual use. Eq(2) is, of course, a special case of Eq(4). It results when the two terms that contain age attained and time since exposure are omitted, and it will here be called the age at exposure model:

$$r(a,D) = r_0(a)[1 + f(e) \cdot D] \quad (5)$$

As stated, the age at exposure model has been the preferred approach to the analysis of the solid cancer mortality of the atomic bomb survivors. In contrast, the age attained model has been utilised for the modelling of lung cancer among underground miners. In the latter application one has seen the need for an added correction term that depends on time since exposure and that implies a decreasing effectiveness of the damage with increasing time since exposure (BEIR IV, 1988). A similar correction term has earlier been postulated with the age at exposure model, in the analysis of the cancer incidence among the UK ankylosing spondylitis patients (Darby and Doll, 1987).

The subsequent comparison of models for the mortality due to solid cancers of the atomic bomb survivors will refer to Eqs(5) and (6). Even this simple comparison will lead to important result. It is seen that the conventional use of the age at exposure model is, to some degree, arbitrary; the age attained model is equally good. This finding would be unimportant, if the results of the two models were equal. However, there are substantial differences in time projection between the two models.

#### Results of the two models:

Maximum likelihood computations in terms of the age at exposure model and the age attained model have been performed for the mortality from solid cancers among the atomic bomb survivors up to 1985 (Kellerer and Barclary, 1992). In the present context it is sufficient to point out, that the two fits are of very nearly the same quality, either in terms of the maximum likelihood or the deviance. Figs.2 and 3 illustrate the results in terms of an exposure with 1 Gy, either at age 5 or at age 40.

The results are quite different. Fig.2 gives what one may call the current dogma: the relative risk due to exposures at young ages is much higher. This leads in an integration over the entire life time to substantially higher attributable risks for radiation exposures at young age. However, one must note, that the broken curve for

the exposure at age 40 has been derived from actual observations, while the dotted curve has been checked against observed data only up to an attained age of 45. The curve for the young age at exposure is, thus, in its significant part a mere extrapolation.

An alternative is the age attained model. It results if one omits in Eq(4) the terms that depends on age,  $e$ , at exposure and time,  $t$ , since exposure:

$$r(a,D) = r_0(a)[1+g(a) \cdot D] \quad (6)$$

Fig.3 gives the results for the age attained model. In this model there is only one general dependence which is independent of age at exposure. One notes that the dependence is in close agreement with the dependence for exposure at age 40 as it has been obtained in the age at exposure model. The model does not predict the much larger relative risk for early exposures.

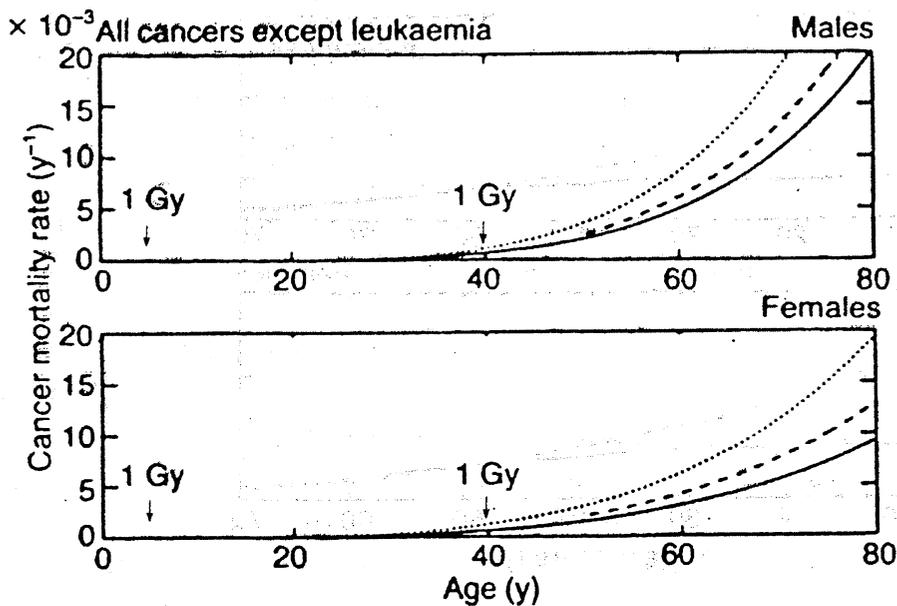


Figure 2 Age specific cancer mortality rates (solid lines) and the increased rates after an assumed exposure at ages 5 (dotted lines) or 40 (broken lines). The data result from maximum likelihood fits obtained on the basis of Eq(5) to the observations on the atomic bomb survivors up to 1985.

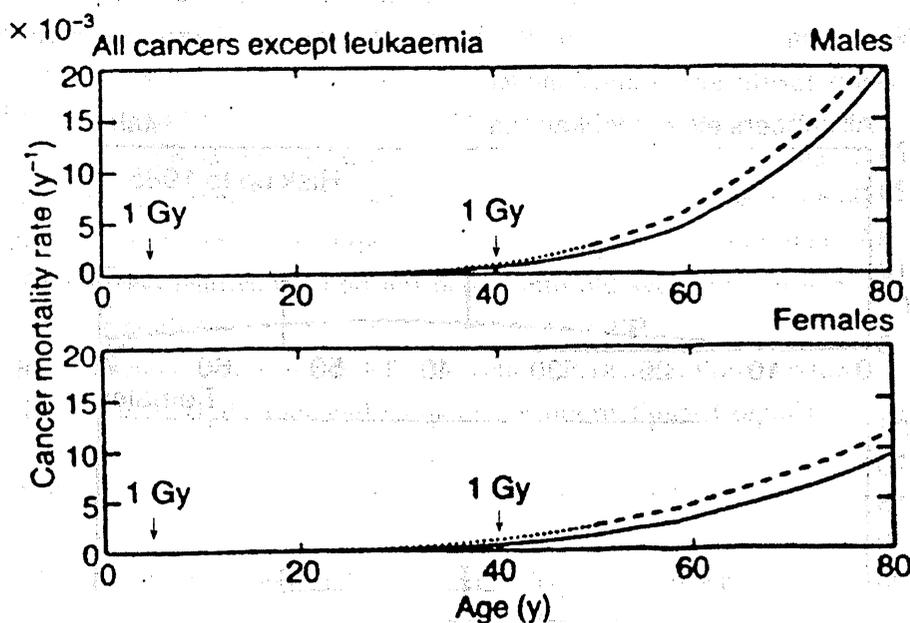


Figure 3 Age specific mortality rates (solid lines) and the increased rates after an assumed exposure at ages 5 and 40. The data result from maximum likelihood fits in terms of Eq(6) to the observations on the atomic bomb survivors up to 1985.

Life time attributable risk according to the two relative risk models:

Fig.4 gives — in dependence on age at exposure — the life time attributable risk according to the age

at exposure model and the age attained model. The results for the age at exposure model are essentially in line with the calculations that have been used as basis for the ICRP risk estimates. They agree with the common conception, that radiation exposures at young age carry a substantially higher life time attributable risk than exposures at later age. The dependencies for the age attained model are quite different. They do not show the enhanced life time attributable risk for young age at exposure, thus, they cast into doubt one of the basic tenets in risk modelling. It is striking, that two substantially different models should fit equally well the extensive data set of the cancer mortality among the atomic bomb survivors. One feels uncomfortable about the conclusion, that even this thoroughly studied data set should nevertheless lead to uncertain results. However, the seeming contradiction can be resolved, as will be seen in the next section.

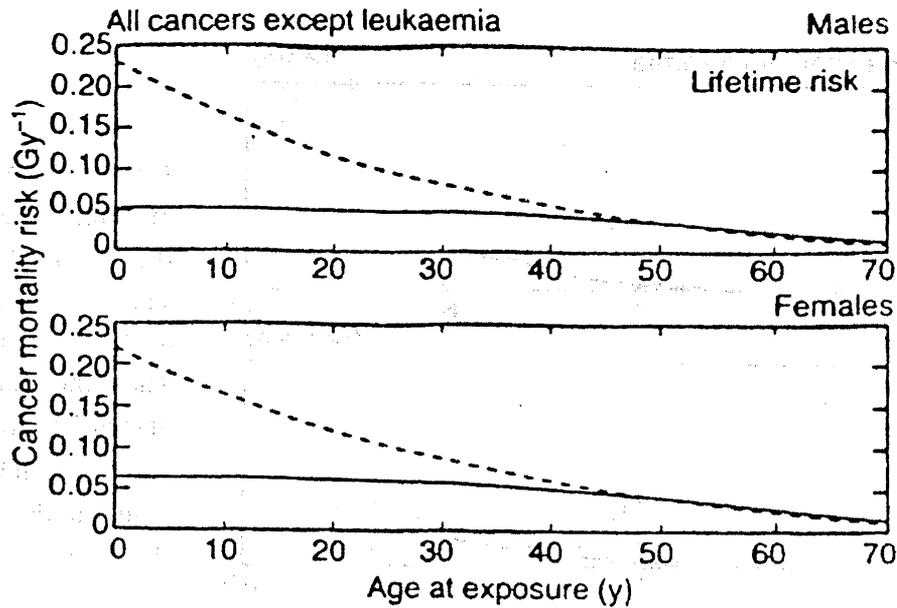


Figure 4 Lifetime attributable risks for mortality from cancer (except leukemia) in dependence on age at exposure. The broken lines give the dependences for the age at exposure model, the solid lines the dependences for the age attained model.

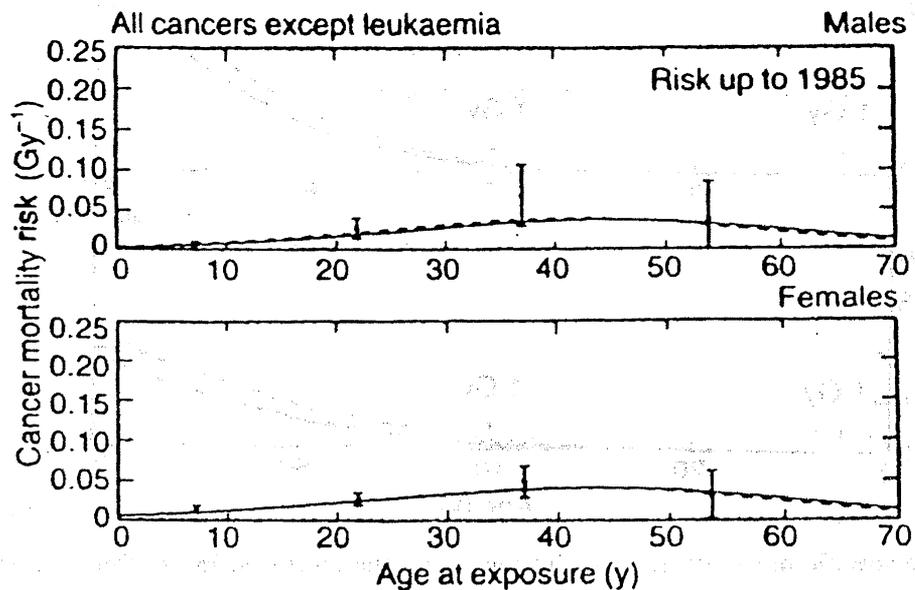


Figure 5 Mortality risks for cancers except leukemia for an observation period of 40 years after exposure. The curves correspond, except for the reduced period at risk, to those in Fig.4. The points and standard deviations are the results of a model-free computation of the cumulative cancer mortality among the atomic bomb survivors up to 1985.

**Certainty of past observations and uncertainty of projected risks:**

The results in Fig.4 give the impression that the two models describe the cancer mortality among the atomic bomb survivors very differently way. In reality, however, Fig.4 describes not so much the past observations than the projected risks. To clarify this, one may plot the attributable risks not for the entire projected life time, but for the follow-up time to the year 1985, i.e. for the period of the actual data. One finds then a substantially changed dependence. For the exposures at higher ages the curves remain substantially unchanged; this must be so, because these cohorts have actually lived out their lives during the follow-up. For the young ages at exposure, however, only a small part of the period at risk has been lived out, and the higher ages, with larger cancer rates, have not yet been reached. The observed excess is, therefore, still small. The important point is, that the results of the two different models agree for the actual observation time. The points and standard errors are model free calculations of excess risks for this observation period; they confirm, that the two models are in agreement with the observations.

The disagreement between the two models is, thus, merely a matter of the projection beyond the period where observations are available. The age at exposure model postulates constant relative risks. Since the relative risks are high at young ages for those who have been exposed early in life, the projection must lead to high life time risks. The age attained model does not postulate a constant relative risks; it admits the possibility, that the relative risk declines with attained age. There are some indications of such a decline among the atomic bomb survivors who have been exposed at young age. However, the decision between the two models will have to be based on future observations in the study.

**Conclusion**

The conventional comparison of the age at exposure model with a simple additive model has, in the past, been seen as support for this model. However, a comparison between two relative risk models is more meaningful. Such a comparison has, therefore, been performed between the age at exposure and the age attained model. It is found that the two models fit equally well the overall cancer mortality, without leukemias, among the atomic bomb survivors. The life time attributable risk, averaged over the entire population, is about two times larger for the conventional age at exposure model. The current risk estimates of ICRP for solid cancers are based on the age at exposure model for solid cancers. They are, therefore, somewhat conservative in character. If the age attained model is correct – and there are some indications of decreasing relative risks with time since exposure – the projected risks will be lower by about a factor of 2 than the present estimates.

One concludes that the nominal risk coefficients of ICRP may, on the one hand, be underestimates, if there is no dose reduction factor in the extrapolation to low doses, but that they may, on the other hand, be overestimates, if the excess relative risks do not persist into old age. The two uncertainties go in opposite direction, which adds to the confidence into the risk estimates of ICRP.

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