

## AGE DEPENDENCES IN THE MODELLING OF RADIATION CARCINOGENESIS

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### INVITED PAPER

**Abstract** — Models for the dose and age dependence of radiation induced cancer have been based primarily on the follow-up of the atomic bomb survivors. Two different concepts have been deduced for leukaemias and for other cancers. The excess leukaemias appear in a distinct temporal wave with a maximum 5 to 10 years after radiation exposure; the distribution is more narrow for younger ages, but there is little dependence of the total attributable risk on age at exposure. For other cancers the latent periods are longer and, according to the current interpretation, the excess rates are then proportional to the age specific spontaneous rates, so that most excess cases would arise at old age. The factors of proportionality, and thus the attributable risks, are assumed to be markedly higher for young ages at exposure. It is argued here, that there is no firm support for this interpretation. The present analysis compares the current model for cancers other than leukaemia to a more meaningful alternative than the so-called additive model which is usually invoked as a standard of comparison. The analysis is performed in terms of analytical expressions, to make the characteristics of the different concepts more transparent. It is seen that the Japanese data are equally well fitted by a model that assumes no dependence of sensitivity on age at exposure but merely accounts for a dependence of the excess risks on dose and on age attained. This 'age attained model' corresponds, in essence, to formulations that have been used earlier for the analysis of lung cancers in uranium miners. The data up to 1985 for the atomic bomb survivors do not yet permit a decision between the different models. But the acceptability of the age attained model shows the age dependences for leukaemias and other cancers to be less fundamentally different than commonly assumed. The age attained model leads to risk projections for young ages at exposure that are substantially lower than present estimates. In fact it predicts essentially the same lifetime attributable risks for exposures at young and intermediate ages; decreased risks result only for exposures at advanced ages where the expression periods are already substantially reduced.

### INTRODUCTION

Doll and Peto<sup>(1)</sup> conclude in their analysis of the causes of cancer, that about 90% of all cancers appear to be avoidable in principle, i.e. that they are due to diet, other aspects of lifestyle, and to environmental factors. Some of the major causes are known, such as smoking, solar UV light, or, in countries without refrigeration, aflatoxins. Ionising radiation is not one of the major causes of cancer, but it is the one that has been most thoroughly analysed and the one for which detailed quantitative models have been constructed to account for dependences on dose, age, and on time since exposure. The models are descriptive approximations subject to considerable uncertainty. They are, nevertheless, a necessary element of any attempt to quantify radiation risks. As molecular biology advances, the models may lose their merely descriptive character. The present discussion, however, is of restricted scope; it is intended to explain the formal relations that are used to model radiation induced cancer.

### CURRENT MODELS AND EQUATIONS

There are at present — in spite of considerable interest in the matter and some important pre-

liminary findings<sup>(2)</sup> — no established clinical traits or molecular markers that are specific to radiation induced leukaemias or solid tumours. Radiation induced cancer can, therefore, be recognised only indirectly in epidemiological studies that assess increased tumour rates in collectives of exposed persons. This type of investigation requires complex mathematical methods that account for various confounding factors. It requires also models on dose, age, and time dependences that are often difficult to judge, and the essential features of such models will therefore be considered.

The basic quantity is the tumour incidence (or mortality) rate. The subsequent discussion will deal with mortality rates, but it will be recognised that it relates equally to incidence rates, i.e. to the frequencies of newly diagnosed tumours rather than the resulting deaths. The rate is a statistical concept, it is the average number of cases per person and per unit time. It can be only roughly estimated in small collectives of persons; to obtain good estimates one needs observations in cohorts that are large enough for a considerable number of cases to occur. While it is usual to express the rates per 100,000 persons per year, the choice of the unit is, of course, irrelevant to the subsequent discussion.

To determine increases of the cancer rate due to radiation exposures, one needs first to know the rates in unexposed collectives of persons; we will in the following speak of spontaneous rates, although most of the 'spontaneous' cases are also, as stated at the outset, due to extraneous causes. Population statistics provide the spontaneous mortality rate for different tumours and for different sexes, for specified ages, and for different ethnic groups or geographic regions; the solid curves in Figure 1 give the age specific rates for males and females in the US<sup>(3)</sup>. In certain studies, and the follow-up of the atomic bomb survivors is an example, it is also possible to obtain the age specific rates directly from an internal control group. In the subsequent discussion merely the age attained,  $a$ , will be noted in the argument of the age specific rate, i.e. it will be designated by  $r_0(a)$ ; other variables, such as sex, are omitted in the notation, although they need to be taken into account.

The major basis for the quantification of radiation carcinogenesis is the follow-up of the atomic bomb survivors. In a cohort of 78,000 survivors in Hiroshima and Nagasaki about 14,000 received a dose (shielded kerma) in excess of 200 mGy and about 3100 received a dose in excess of 1 Gy. More than 7000 cancer deaths have been observed up to 1985. Of nearly 200 leukaemia deaths, roughly 70 are seen as the excess due to the radiation exposure, while among the solid tumours about 5%, i.e. about 350 deaths, are ascribed to the radiation exposure<sup>(4,5)</sup>.

A characteristic difference was seen between the radiation induced excess of leukaemias and the excess of solid tumours. The excess leukaemias began to occur only a few years after the radiation exposure, and after several decades the excess is

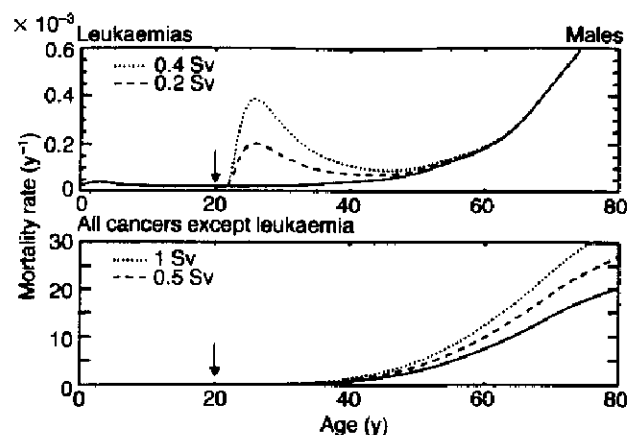


Figure 1. Age specific mortality rates from leukaemia and from other cancers (—) and the increased rates that result according to the estimates of ICRP 60, but without dose reduction factor, from exposures at age 20. Figures 2 and 3 give analogous diagrams for cancers except leukaemia on the basis of other model calculations.

now much less marked. With the solid tumours the time sequence was entirely different; no statistical significant excesses were observed up to about 15 years after exposure, but then the relative excess in the more highly exposed groups became apparent and, in a given age at exposure cohort, it appears to be roughly constant and it may continue to persist into the future. Figure 1 illustrates these characteristic dependences in terms of an acute exposure at age 20 and with numerical values that correspond to the risk estimates of ICRP 60<sup>(6)</sup>, but without the reduction factor of 2 that ICRP proposes for low doses. In a description of the appearance of excess leukaemias, on the one hand, and excess solid cancer, on the other hand, one speaks of the absolute and the relative risk model. These concepts are often used in somewhat different interpretations, but the subsequent paragraphs explain the essentials.

### The absolute risk model

In the most simplified model one assumes that, after a certain latent period, one has a constant excess rate,  $r_E(e,D)$ , that depends only on radiation dose,  $D$ , and on age,  $e$ , at exposure:

$$r(a,D) = r_0(a) + r_E(e,D) \quad a > e + t_0 \quad (1)$$

$r_0(a)$  is the spontaneous rate at age  $a$ , and  $r(a,D)$  corresponds to the observed rate. The assumption of an excess rate that remains constant after exposure, once the latent period has passed, disagrees with the results of all major epidemiological studies of exposed populations, both with regard to leukaemias and solid tumours. Nevertheless, there have been computations of this simplified nature, where one compares the observed cases in a cohort during an extended observation period with those that would be expected on the basis of population statistics. Dividing the excess by the number of person-years, one then estimates the excess rate. Not infrequently the computations have been performed without specification of the ages at risk in a cohort; the results expressed in terms of excess cases per person-year can then be highly misleading.

A more realistic treatment that is in good agreement with observations of leukaemias among the atomic bomb survivors — but also of bone tumours in patients injected with the short-lived  $\alpha$  emitter  $^{224}\text{Ra}$ <sup>(7)</sup> — specifies a wavelike temporal distribution of excess cases after radiation exposure. In an adequate approximation this dependence can be represented by a skew distribution, e.g. a log-normal distribution, in time after exposure. The diagram in the upper panel of Figure 1 corresponds to this description.

**The relative risk model**

For solid cancers among the atomic bomb survivors an excess rate of solid cancers is seen much later after irradiation than for leukaemias, but the excess rates are more persistent than those of the leukaemias. The most familiar model, largely based on the observations among the atomic bomb survivors, is that after a certain latent period,  $t_0$ , the rates are increased proportionally to the age specific spontaneous rates. The 'proportional hazards factor', i.e. the observed rate divided by the spontaneous rate, is taken to depend on dose and on age at exposure,  $e$ , but not on time since exposure:

$$r(a,D) = r_0(a) (1 + f(e,D)) \quad a > e + t_0 \quad (2)$$

In the analysis of the follow-up of the atomic bomb survivors a linear dependence on absorbed dose is found to be an adequate approximation:

$$r(a,D) = r_0(a) (1 + f(e) D) \quad a > e + t_0 \quad (3)$$

The most characteristic implication of this relative risk model — we will in the following speak of the age at exposure model — is the fact, that most of the radiation induced tumours appear a long time after exposure and, in fact, at old age. This explains the fact that low risk estimates were obtained by ICRP in 1975, when it based its first quantitative risk estimates only on the cases up to the year 1972. In the meantime the relative excesses of the rates of solid cancers have largely continued, and many additional tumours have appeared in the aging collective of the atomic bomb survivors. The risk estimates, in terms of the absolute number of fatalities per Gy, have gone up accordingly.

While the proportional hazard factors appear to be roughly independent of time after exposure, they depend markedly on age at exposure, with the highest values for exposures at young age. However, it must be noted that the spontaneous rates at young ages are low. A high proportional hazard factor at young ages implies, therefore, merely a small absolute risk. For the same reason the number of cases is so low that there is considerable statistical uncertainty about the excess rates at young and intermediate ages. The problem of the projection of risk in age is, therefore, still unsolved for exposures at young ages. It is possible that the proportional hazard factors do not indefinitely remain constant after an exposure at young age. In fact a slight trend of the data among the atomic bomb survivors indicates a decrease of the proportional hazard factors for the youngest cohorts<sup>(5)</sup>, and this would be in agreement with findings for the second most important collective of exposed persons, the UK ankylosing spondylitis patients<sup>(8)</sup>.

**A COMPARISON OF RELATIVE RISK MODELS**

For the leukaemias there is no particular need to reconsider the problem of risk projection in age. The simple model in Equation 1 provides inadequate fits, but a log-normal distribution of excess rates in time after exposure fits the data adequately. One finds no marked dependence of the absolute excess risk on age at exposure, but one observes broader distributions in time after exposure for exposures at older ages. The quantitative dependences are well summarised in existing reports<sup>(9,10)</sup>. For the solid tumours the situation is different. There is still considerable uncertainty concerning the proper models and much of this uncertainty is related to the question of the age dependence.

In its recent (1991) re-evaluation the ICRP<sup>(6)</sup> has emphasised a comparison that is perhaps too simple, but that has, nevertheless, been taken as firm support for the relative risk model in the form of Equation 3. In the following a more meaningful comparison of models will be given.

One may consider first the general form of a relative risk model, as it has also been considered in the BEIR V report<sup>(10)</sup>. This formulation has no practical applicability, but it can serve as an ordering principle, to bring out the interrelation between the models that are used in practice and that are then recognised as special cases of the general relation. The general relative risk model — one can also speak of a multiplicative model — is:

$$r(a,D) = r_0(a) (1 + f(e,a,D)) \quad (4)$$

A somewhat more specific relation, which is still of fairly general nature, results if one factorises the dependences on age at exposure,  $e$ , age at diagnosis,  $a$ , and time since exposure,  $t$ . To simplify the discussion, and in view of the seemingly linear dependences in Hiroshima and Nagasaki, proportionality of the excess rate to dose will be assumed in the subsequent considerations:

$$r(a,D) = r_0(a) (1 + f(e)g(a)h(t)D) \quad (5)$$

It will be noted that the three parameters  $e$ ,  $a$ , and  $t = a - e$ , are interrelated, and some of the implications of this interrelation will be considered subsequently.

While earlier calculations have been performed in terms of step functions, with comparatively few bins in age at exposure and in time after exposure, we will in the following utilise analytical functions. Numerically the two approaches can be largely equivalent, but a comparison of models is made more transparent by the use of continuous functions.

### The age at exposure model

The BEIR V report utilises various special cases of Equation 5, but the most widely used model for the mortality from solid cancers among the atomic bomb survivors is the relative risk model in the form of the age at exposure model (see Equation 3). In this model excess rates begin to occur after a latent period,  $t_0$ , of about 10 years, and — as has been stated in the previous section — it is postulated that the relative rate, i.e. the observed rate divided by the age specific cancer rate, does not subsequently change with time after exposure. The observations in Hiroshima and Nagasaki show that at the same calendar years the absolute excess was, up to now, smaller for those exposed at young ages, while the relative rate was substantially larger than that for the older cohorts. The age at exposure model is, therefore, represented by Equation 3 with a dependence  $f(e)$  that decreases with increasing age,  $e$ , at exposure.

Most of the recent evaluations on the mortality from cancers except leukaemia among the atomic bomb survivors have been based on this age at exposure model. The model is in good agreement with the observations. Because of this good agreement it is also used for risk projections, i.e. its validity is postulated even for periods after irradiation that exceed the observation period for the atomic bomb survivors.

The confidence in the age at exposure model has been derived from a comparison<sup>(6)</sup> with the additive model in its simple form:

$$r(a,D) = r_0(a) + b(e)D \quad a \geq e + t_0 \quad (6)$$

The equation postulates constant absolute excess rates that apply after the latent period,  $t_0$ , and are then dependent only on age at exposure and on dose. In all calculations with the Japanese data on solid cancers the additive model is seen to fit the data much less well than the multiplicative age at exposure model. The superior fit is then taken as support for the age at exposure model. The recent recommendations of ICRP follow this line of argument.

However, the comparison between the two models is virtually pointless. The simple additive model (Equation 6) is too clearly at variance with the observations to serve as standard of comparison. For the age at exposure model (Equation 3) to be superior to the additive model means little; it does not make it the best relative risk model nor one that can be trusted to give correct extrapolations beyond the period that is supported by actual observations. More sophisticated comparisons are, therefore, required, and they have been performed by a number of authors, notably Pierce *et al.*<sup>(11)</sup>, Vaeth and Pierce<sup>(12)</sup>, Little and Charles<sup>(13)</sup>, and

Little *et al.*<sup>(14)</sup>. The subsequent considerations are of more summary form than these detailed investigations, and they attempt to make the comparison and its implications more illustrative by the use of analytical models.

### The age attained model

The studies of lung cancer in uranium miners are largely analogous to those on the atomic bomb survivors<sup>(15)</sup>, and the same numerical techniques have been utilised. However, it is not generally appreciated that the preferred model in the studies of uranium miners differs markedly from the age at exposure model. The choice of a different model may have been a matter of numerical convenience in dealing with protracted exposures, but there are more than technical differences between the two formulations, and it is important to consider the implications.

Simplifying matters somewhat, one can state that the analysis of the lung cancer mortality of uranium miners is based on the equation:

$$r(a,D) = r_0(a) (1 + g(a)D) \quad (7)$$

where  $D$  is the cumulated exposure 'lagged' by the assumed latency period  $t_0$ . The similarity to the age at exposure model is evident, but the relative excess rate depends not on age at exposure,  $e$ , but on age attained,  $a$ . One can therefore speak of the age attained model. Although the equation is here written as a 'relative risk model', it could equally be given in the form of an 'absolute risk model' (see Equation 1):

$$r(a,D) = r_0(a) + r_E(a,D), \text{ with: } r_E(a,D) = r_0(a)g(a)D \quad (8)$$

The difference between the two models of Equations 6 and 7 has implications that can be understood without mathematical formalism. Consider a short time exposure either at age 20 or 40. This will cause a subsequent excess in cancer rate, and the excess at age 60 will be taken as an example. According to the age at exposure model (Equation 3) the excess, at age 60, will be larger for the exposure at age 20. According to the age attained model (Equation 7) the excess at age 60 will be the same, regardless whether the exposure occurred at age 20 or 40.

Assume, on the other hand, an exposure at age 30, and consider as example the excess cancer rates at ages 50 and 70. According to the age at exposure model the relative excess will be the same at ages 50 and 70. According to the age attained model the relative excess at age 70 will be less than the relative excess at age 50.

In the study of lung cancer in uranium miners<sup>(15)</sup> an added term,  $h(t)$ , (see Equation 5) is employed

that corresponds to a decrease of the excess risk with time after exposure,  $t$ . To return to the numerical example, this added term implies that at age 60 it is actually less detrimental to have received an exposure at age 20 than at age 40, and this is just the opposite of what the age at exposure would predict. This specific feature of the radon daughter studies can be disregarded at present. Instead the age at exposure model and the age attained model will be compared in their simple form. It will be seen that they fit the observations for cancer, except leukaemia, among the atomic bomb survivors equally well, but that they lead to substantially different risk projections.

### APPLICATION OF THE TWO MODELS

Applying the two models to observed data one needs to specify the general form of the functions  $f(a)$  and  $g(e)$ . As mentioned earlier, it is not uncommon to utilise for this purpose simple step functions, usually with a very limited number of bins. While the step functions will be adequate approximations, their discontinuities can evidently not be correct and, more importantly, they make it difficult to discern the common features of the models and their differences. We will therefore employ continuous functions, and a plausible choice is exponential dependences. This analytical form will still be only an approximation, but it may make it easier to grasp the essentials. The analogue of Equation 5 is then:

$$r(a,D) = r_0(a) (1 + k \exp(-c_1 e) \exp(-c_2 e) \exp(-c_3 e)) \quad (9)$$

Due to the interrelation  $t = a - e$  one can, of course, eliminate any one of the three variables  $e$ ,  $a$ , or  $t$ . For example one can write:

$$r(a,D) = r_0(ca) (1 + k \exp(-k_1 e) \exp(-k_2 a) D) \quad (10)$$

with  $k_1 = c_1 - c_3$  and  $k_2 = c_2 + c_3$ .

The age at exposure model is:

$$r(a,D) = r_0(a) (1 + k \exp(-ce) D) \quad (11)$$

and the age attained model is:

$$r(a,D) = r_0(a) (1 + k \exp(-ca) D) \quad (12)$$

With regard to this age attained model one may note a certain connection to the analysis by Darby *et al*<sup>(8)</sup> of cancer mortality among the British ankylosing spondylitis patients. They saw in these data a decrease of the proportional hazards factors with time,  $t$ , after exposure and this corresponds, in effect, to a modified age at exposure model:

$$r(a,D) = r_0(a) (1 + g(e)h(t) g D) \quad (13)$$

Among the variety of formulations utilised in the BEIR V report for different sites of cancer one can

find instances of the same approach.

Using exponential functions for the dependences  $f(e)$  and  $h(t)$  one recognises that the age attained model is a special case of the modified age at exposure model:

$$\begin{aligned} r(a,D) &= r_0(a) (1 + k \exp(-ce) \exp(-ct) D) \\ &= r_0(a) (1 + k \exp(g-ca) D) \end{aligned} \quad (14)$$

but these interconnections will not be further explored in the present context.

A maximum likelihood fit to the cancer mortality data without leukaemias of the atomic bomb survivors<sup>(16)</sup> was obtained for Equations 11 and 12, in terms of the computer algorithm AMFIT<sup>(17)</sup>; the same software package has also been used by the RERF statisticians and by the authors of the BEIR IV and BEIR V reports. Table 1 gives the resulting parameters. Figures 2 and 3 represent the cancer mortality rates that result according to the two models for males and females exposed at 5 years and at 40 years of age. For the higher age at exposure one obtains nearly the same excess rates with the two models. This has to be so, because the observation period from 1945 to 1985 covers almost all the lifetime of those who were 35 years or older at the time of the atomic bombings. The observation being complete, the fits in terms of both models must, therefore, each conform to the observed data — i.e. 40 years follow-up after the exposure — and must, thus, roughly agree. However the two models differ greatly for those who were exposed at young ages and whose observation is not yet completed. For them one obtains markedly higher lifetime estimates with the age at exposure model. That the two models should in this case fit the observed data equally well but give substantially different projections into the future, is understandable. When the observation covers only young and intermediate ages, where the cancer rates are still low, the extrapolation into the higher ages where most of the cancers occur must remain uncertain.

The essential result of the comparison is that the two models fit the overall cancer mortality among the atomic bomb survivors about equally well. Neither of the two models can, at this point, be rejected. But the two models differ considerably. As illustrated in Figure 4, the age attained model indicates a substantial decrease of the proportional hazards factors, i.e. the relative rates, with increasing age. With regard to this relative scale one could say that the 'harm' of an exposure decreases with increasing age or increasing time after exposure. But, as seen in Figure 5, this statement could be quite misleading, since the absolute excess rate, probably a better measure of the 'harm', increases with age or time after

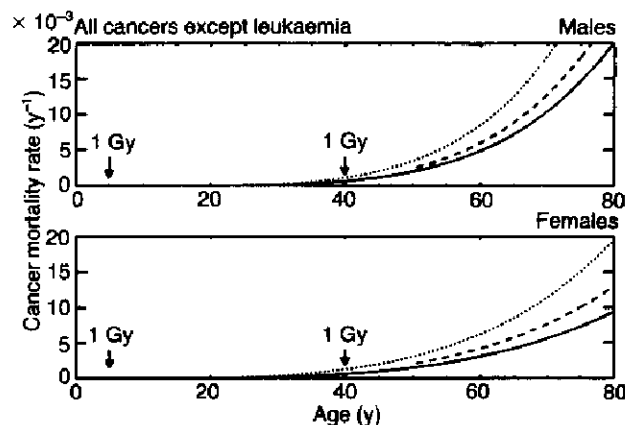


Figure 2. Age specific mortality rates and the increased rates after an assumed exposure at ages 5 or 40. The data result from maximum likelihood fits obtained on the basis of Equation 3 to the observations on the atomic bomb survivors up to 1985 (see Table 1).

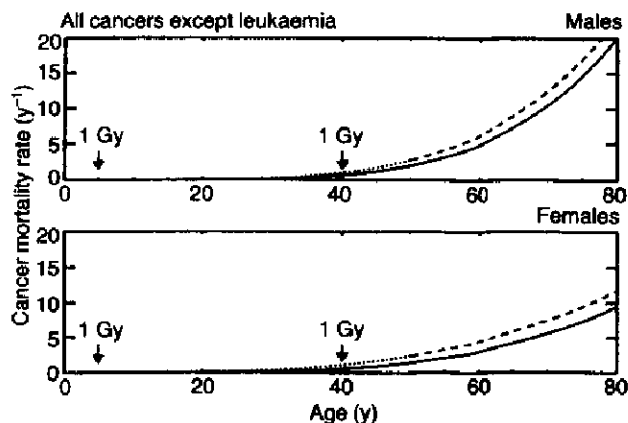


Figure 3. Age specific mortality rates and the increased rates after an assumed exposure at ages 5 or 40. The data result from maximum likelihood fits (see Table 1) in terms of Equation 7 to the observations on the atomic bomb survivors up to 1985 (see Table 1).

exposure even for the age attained model; its increase is merely much less pronounced than with the age at exposure model.

It is furthermore of interest to note in Figures 3 to 5 that, once the latent period has passed, the excess rates according to the age attained model do not depend on the age at exposure. One needs only one curve to represent the result of the fit, rather than a series of curves.

The results of the maximum likelihood fits can be utilised to obtain lifetime attributable risks. For this purpose we have, in line with the procedure in ICRP 60, utilised Swedish life expectancies. The transfer of risk estimates between populations

involves, of course, uncertainties. But in the present context absolute numbers are of less interest than characteristic differences between the models. Figure 6 gives the lifetime attributable risks, on the basis of the two models, as a function of age at exposure. The diagrams bring out the large difference in risk projections that exists between these two models that are equally in agreement with the data obtained up to 1985. It underlines the point that the risk projections are uncertain for young ages at exposure. It suggests, furthermore, that the estimates of BEIR V or of ICRP 60 which are based on the age at exposure model, may be substantially over-conservative.

Table 1. Maximum likelihood solutions for cancer mortality except leukaemia among the atomic bomb survivors, obtained by the computer algorithm AMFIT. A latency period of 10 y is assumed. Doses are set equal to shielded kerma and all data in excess of 4 Gy were disregarded. The parenthesised numbers show the standard errors. For computational convenience, the equations corresponding to the age at exposure model (Equation 11) and age attained model (Equation 12) have been rewritten with rescaled variables as follows:

$$r(a,e,D) = c_0(a/50)^{p_0} \{ 1 + k \exp[-p(e-60)]D \} \quad (11')$$

$$r(a,e,D) = c_0(a/50)^{p_0} \{ 1 + k \exp[-p(a-60)]D \} \quad (12')$$

	$c_0$ (SE)	$p_0$ (SE)	$k$ (SE)	$p$ (SE)	Deviance chi squared	(df)
<b>Age attained model</b>						
M	0.001972 (0.000104)	4.958 (0.111)	0.2725 (0.0755)	0.3435 (0.0194)	1096.4 1583.8	(1311)
F	0.001432 (0.000103)	4.027 (0.100)	0.4805 (0.0833)	0.0344 (0.0119)	1119.0 1423.8	(1308)
<b>Age at exposure model</b>						
M	0.001969 (0.000104)	4.957 (0.108)	0.1183 (0.0659)	0.0335 (0.0159)	1094.6 1646.4	(1311)
F	0.001447 (0.000103)	3.988 (0.095)	0.2113 (0.0858)	0.0294 (0.0117)	1120.5 1530.5	(1308)

Abbreviations: SE, standard error; df, degrees of freedom; M, males; F, females.

Recent discussions have emphasised that the assumption of a dose reduction factor in the new recommendations of ICRP might underestimate the risk, but they have not usually noted that an overestimation inherent in the risk protection may offset any such underestimation.

IMPOSSIBILITY OF DECIDING BETWEEN THE TWO MODELS

It is hardly surprising that the risk projections are uncertain when they go beyond the periods for which observations exist. Nevertheless, it is startling to see that two equally acceptable models differ so substantially when applied to the largest and most important data set on radiation induced

cancer. One must, therefore, examine this point in somewhat more detail.

For a direct comparison of the two models with the observations up to 1985 one needs to restrict the integration of the computed excess rates to 40 years after the exposure. With this restriction one obtains instead of Figure 6 the curves in Figure 7. Instead of the lifetime attributable risk of an exposure, these curves give the risks attributable to a period of 40 years after exposure. For exposures at higher ages the results are, of course, the same. For exposure at younger ages the values in Figures 6 and 7 differ considerably. The points and standard deviations which are superimposed on the curves are based on a direct, i.e. model free,

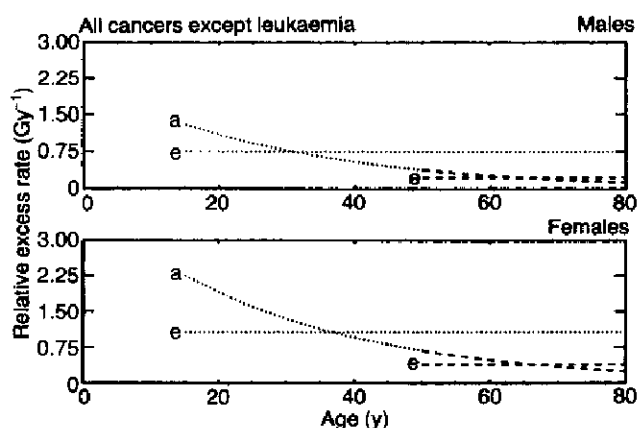


Figure 4. Relative excess rates of mortality from cancers except leukaemia among the atomic bomb survivors on the basis of the age at exposure model (e) and the age attained model (a). The dependences correspond to the maximum likelihood fits in Table 1 and to the curves in Figures 2 and 3. (.....), exposure at age 5; (---), exposure at age 40.

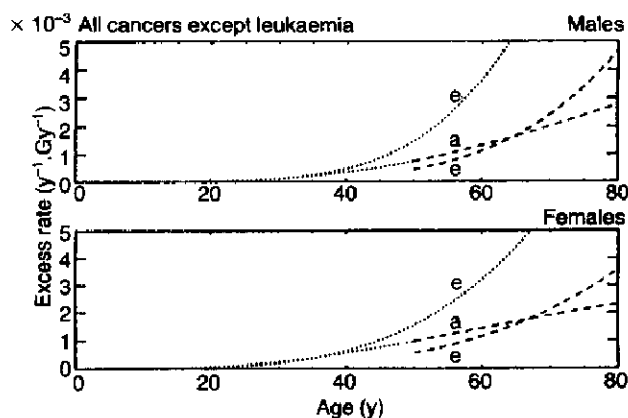


Figure 5. Excess rates of mortality from cancers except leukaemia among the atomic bomb survivors on the basis of the age at exposure model (e) and the age attained model (a). The dependences correspond to the maximum likelihood fits in Table 1 and to the curves in Figures 2 and 4. Key as Figure 4.

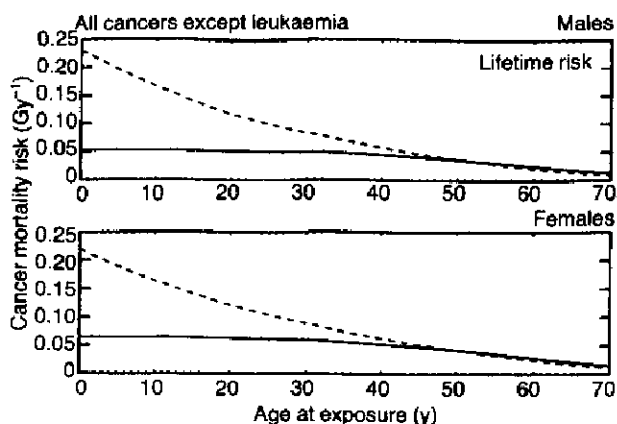


Figure 6. Lifetime attributable risks for mortality from cancer except leukaemia in dependence on age at exposure. The (---) give the dependences for the age at exposure model, the (—) for the age attained model. The dependences result from the maximum likelihood solutions in Table 1 by integration over the same life expectancies that have been used in ICRP 60.

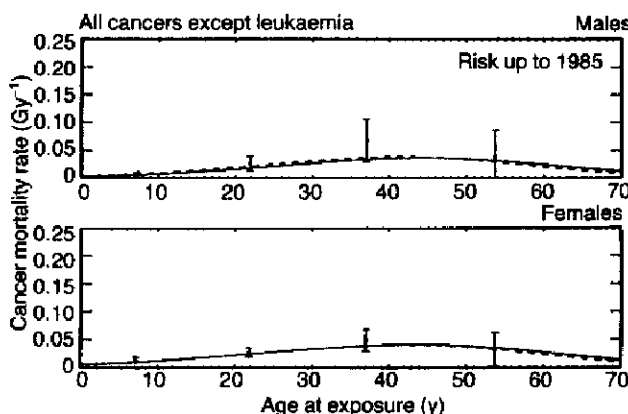


Figure 7. Mortality risks for cancers except leukaemia for an observation period of 40 years after radiation exposure. The curves correspond, except for the reduced period at risk, to those in Figure 6. The points and standard deviations are the results of a model-free computation of the cumulative cancer mortality among the atomic bomb survivors up to 1985.

computation of excess cases among the atomic bomb survivors. They represent the roughly 350 excess cases that are attributed to the radiation exposure up to 1985. A comparison with Figure 6 shows that the age at exposure model predicts an ultimate number of excess cases that may be about four times larger, while the age attained model predicts only roughly a doubling of excess cases.

## CONCLUSION

Past studies, and especially the treatment in the most recent ICRP recommendations, have emphasised the comparison of the familiar multiplicative model (Equation 3) with the so-called additive model (Equation 6). The mortality from cancer other than leukaemias among the atomic bomb survivors fits the multiplicative model far better than the simple additive model. The comparison makes the multiplicative age at exposure model appear sufficiently reliable to be used for risk projection. In fact the new risk coefficients recommended by ICRP are based on this model.

However, the simple additive model is too poor an approximation to serve as a standard of comparison. A more meaningful comparison is achieved in terms of an alternative model; the familiar age at exposure model is compared to an age attained model, similar to the one used in the analysis of lung cancer among uranium miners. The application of the two models to the cancer mortality data without leukaemias among the atomic bomb survivors provides fits to the observations up to 1985 of about equal quality. No decision between the two models is, therefore, possible at present. The high and the low risk projections are, at this point, equally acceptable and equally uncertain. The follow-up of the atomic bomb survivors will have to be continued for a considerable time to narrow down the estimates of lifetime attributable risk for exposures at young age.

The age at exposure model has been favoured in the past. It postulates an inherently higher sensitivity to radiation exposure at younger ages; earlier exposures are not only associated with longer periods at risk, they are also associated with higher relative excess cancer rates. According to the somewhat simpler age attained model there is no inherent dependence of the excess rates on age at exposure. An age dependence arises merely because exposures at higher ages are associated

with reduced periods at risk. The reduction, however, plays a role only when it pertains to advanced ages, where the spontaneous cancer rates are substantial; whether an exposure occurs at age 10 or 30 is at least for most, late occurring cancers — and mammary tumours are an exception — irrelevant to the lifetime attributable risk.

The present analysis does not exclude the current interpretation and the current risk estimates, it merely makes them appear as the conservative choice among an alternative of equally possible outcomes. The age attained model yields the lower estimates. The real dependence may well lie somewhere in between. While lifetime attributable risks are reliably known for exposures beyond age 30, they are quite uncertain for young ages at exposure. The present study shows that the familiar multiplicative model, the age at exposure model, provides far higher risk projections than an equally good alternative model, the age attained model. The present risk estimates, being based on the age at exposure model, may be highly conservative for exposures at young age. Averaged over all ages, the risk estimate exceeds the one for the age attained model by about a factor of 2. Thus one could abandon the controversial dose reduction factor of 2 which has been postulated by ICRP, and choosing the age attained model rather than the age at exposure model, one would still obtain the same risk coefficients that have been proposed by ICRP. While the present analysis underscores the uncertainty of risk projections in age, it actually gives added support to the current nominal risk coefficients for solid cancer.

The different age dependences in the two models may suggest different mechanisms, and one may note in this context that the postulate of exponential functions for the dependence,  $f(e)$ , on age at exposure (see Equation 3) or for the dependence,  $h(a)$ , on age attained provides better fits than the choice of power functions in an earlier analysis<sup>(13)</sup>. Considering the familiar multistep models of carcinogenesis one might have expected that power functions are a better approximation not only for the spontaneous age dependent rates but also for the radiation induced excess rates. While the exploration of such implications is outside the scope of the present investigation, they will nevertheless be of interest in any attempt to develop risk assessment beyond the present stage of empirical, descriptive models.

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AGE DEPENDENCES IN MODELLING RADIATION CARCINOGENESIS

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