

# **Institut für Strahlenschutz**

der

Berufsgenossenschaft der Feinmechanik und Elektrotechnik

und der

Berufsgenossenschaft der chemischen Industrie

## **Epidemiological Investigations on the Health-Effects of Ionizing Radiation**

**Proceedings of the International Colloquium  
September 30, 1987**

in

**»berghof« Haus für Arbeitssicherheit  
Bad Münstereifel**

49/X 1.15

Institut für Strahlenschutz  
der Berufsgenossenschaft der Feinmechanik und Elektrotechnik  
Gustav-Heinemann-Ufer 130, 5000 Köln 51  
und der Berufsgenossenschaft der chemischen Industrie

Alle Rechte beim Herausgeber  
1. Auflage 1988

335  
M  
3

Univ. Bibl.  
Würzburg

8592686

# Table of Contents

	page
Wei Luxin: Cancer Mortality Study in High Background Radiation Areas of Yanjiang, China	7
Wang Zuoyuan: Exposure Dose of Beijing Residents to Diagnostic X-ray	26
A. Kellerer: New Developments in the Japanese Life Span Study	31
P. Fraser: The British Epidemiological Study on Nuclear Workers	42
C. Streffer: A Survey on Epidemiological Studies	50

# Cancer Mortality in Hiroshima and Nagasaki

## – Recent Implications for the Risk Estimates –

Albrecht M. Kellerer

Institut für Medizinische Strahlenkunde, University of Würzburg

### Introduction

To estimate the cancerogenic risks of small doses of ionizing radiations is an unavoidably formalistic procedure. It refers to increases of cancer rates which can not be observed, because they are far smaller than spontaneous incidences. There are, at least at present, no known DNA-markers which would permit a distinction between radiation induced neoplasms and those due to other factors. Radiation induced cancer can, therefore, be assessed only through epidemiologic studies, and such studies require substantial increments of cancer rates. Observed effects are, accordingly, always related to large exposures.

This uncertainty permits widely diverging opinions concerning the magnitude of the assumed risks. Inflated claims of radiation risks can not be falsified in most instances; they can merely be shown to be unlikely by judicious extrapolations from effects observed after large exposures. It is equally impossible to disprove extreme counterpositions, which range from general postulates of thresholds for radiation carcinogenesis to the broad assertion of beneficial effects of small doses.

The absence of hard evidence does not invalidate the basic principles of radiation protection. It is evident that detriments need to be kept at a level too low to be observed. But this alone is not sufficient. In view of the multiplicity of risk factors, due to environmental conditions and to life styles, one must take into account and must minimize even those risks which, by themselves, are certain to remain untraceable.

Risks estimates – even if they remain subject to large uncertainties – can serve as guidelines for control and limitation. They are required also to rectify distorted judgements which have survived, or even grown, in the public discussion – especially after the reactor catastrophe – and which have made it difficult to preserve a reasonably balanced perception of risks. The observations of the fate of the atomic-bomb survivors remain the most important source of knowledge of radiation risks, and it is, therefore, necessary to consider the implications of the dosimetry revision and of the continuation of the epidemiological study in Hiroshima and Nagasaki.

### Temporal Trends of Cancer Mortality in Hiroshima and Nagasaki

The revision of the dosimetry and the publication of the new dosimetry system DS-86 /1/ is an important division line in the work of the Radiation Effects Research Foundation (RERF) in Hiroshima. Essential earlier results on the time and age dependence of radiation induced tumors have, however, not lost their validity. They remain central for an understanding of risk estimates.

Temporal trends up to 1982 can be seen in Report-10 /2/ on cancer mortality in Hiroshima and Nagasaki. This report is still based on the former dosimetry (tentative 1965 dosimetry, TD-65). However it deals not primarily with dose dependences, and can thus bring out essential characteristics of the dependence of induced tumors on age at exposure and time after exposure. In this way it facilitates the appreciation of new risk estimates which are now being derived on the basis of the revised dosimetry.

The publication of Report-10 is an essential step in the work of RERF also in a further aspect. It is the first study which is accompanied by the release, in machine readable form, of the input data and of the algorithms utilized for the analyses. The data which are now available from RERF /3/ illustrate essential aspects of the epidemiological observations. Three main points will be briefly dealt with. The characteristic difference between the time distribution of leukemias and of solid tumors will be considered. Secondly, the substantially enhanced sensitivity of those exposed at young ages will be mentioned. Finally it will be seen that essential data are still to come, even though the epidemiological study has now covered more than 40 years.

The diagram in Fig. 1 indicates the difference between the **relative risk model**, which is currently assumed for solid tumors (except for osteosarcomas), and the **absolute risk model** which applies to leukemias and osteosarcomas. According to the relative risk model, tumor rates increase, after a latent period of approximately 5 to 10 years, by a certain dose dependent factor, so that the excess risk is always proportional to

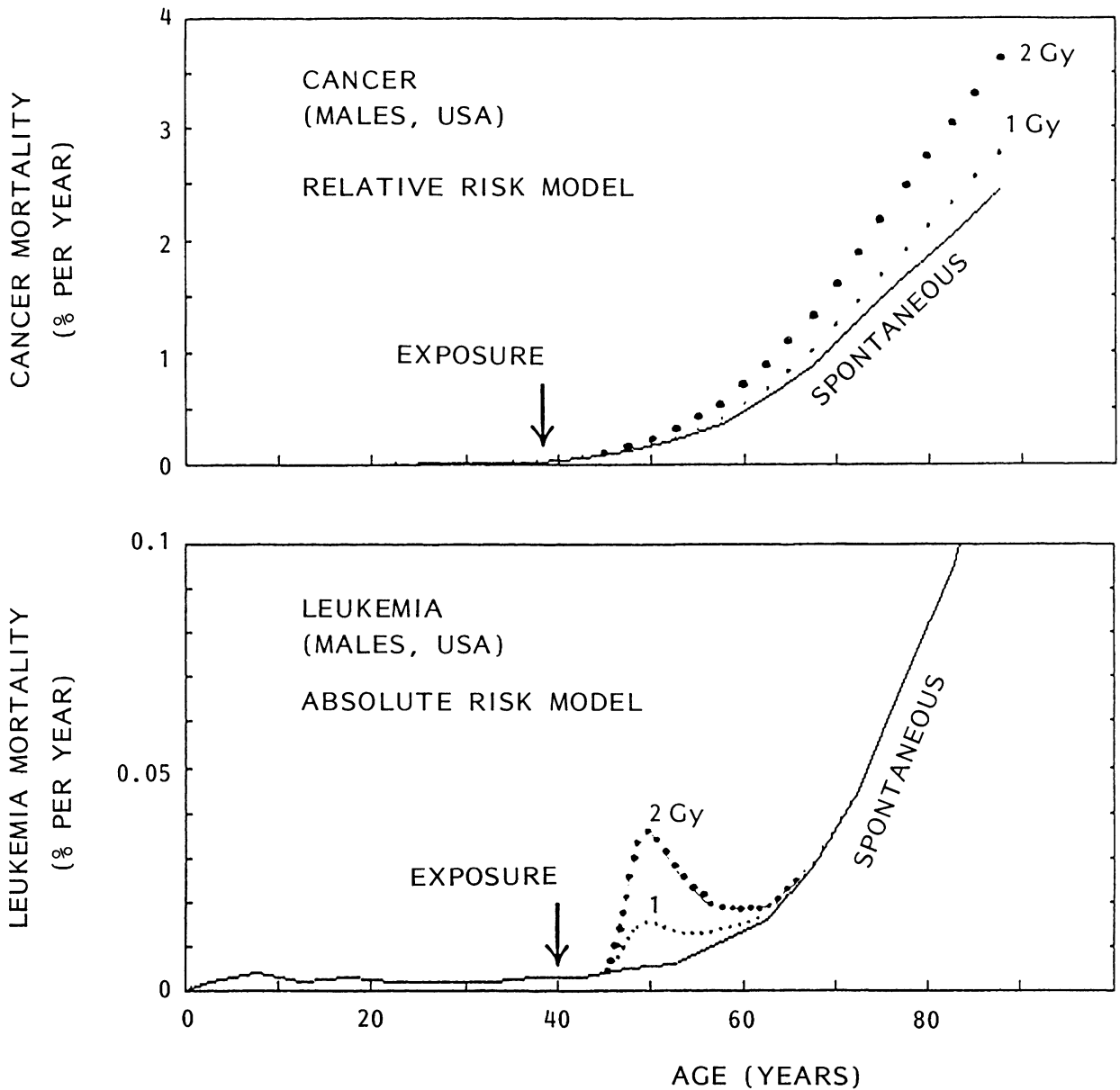


Fig. 1 Schematic diagram of cancer mortality according to the relative risk model and the absolute risk model.

The solid curves give the average rates for the male population of the United States (data from the SEER tables /4/). The relative risk model pertains to solid tumors, with the exception of osteosarcomas, and postulates a proportional increase of the age specific tumor rates five or ten years after a radiation exposure. The absolute risk model is applied to leukemias and osteosarcomas. It corresponds to a wave of increased tumor rates after exposure.

The examples are in line with the dose dependences utilized in the radioepidemiological tables of NIH /8/.

the spontaneous, age specific risk. The relative increase after a certain dose is assumed to depend on sex and on age at exposure. It may also depend on the type of tumor, although it is, at present, difficult to quantify such dependences. The observations on the survivors of Hiroshima and Nagasaki appear to be consistent – with the exception of leukemias – with the relative risk model. The model is, therefore, utilized in most, if not all, numerical analyses. It is, nevertheless, an open question, whether the radiation induced increments of tumor rates will persist in future decades, and this will largely determine whether those exposed at young ages are especially sensitive to the effects of ionizing radiation. In two other important epidemiological studies, namely the follow-up of the British ankylosing spondylitis patients /5/ and that of the uranium miners in Chechoslovakia /6/, there have been recent indications of declining relative risks, several decades after the exposures. Although the new BEIR-IV Report of the American Academy of



Science has not yet appeared, it is known /7/ that it, too, postulates a decline of the relative risk factors for lung cancer, some 40 years after the radon exposures.

The lower panel of the diagram indicates the absolute risk model, as it has been deduced from the leukemia frequencies in Hiroshima and Nagasaki. For leukemias, too, the spontaneous incidences increase steeply in old age. However, after a radiation exposure one observes a wave of additional leukemias, with a marked maximum after only a few years. In the formal analysis, for example in the radioepidemiological tables of NIH /8/, the wave has been approximated by a logarithmic normal distribution. The parameters of the distribution are taken to be dependent on the type of leukemia and also on age at exposure. Analogous relations have been obtained for the osteosarcomas induced in patients who were injected with radium-224 /9/.

Fig. 2 gives a synopsis of the cumulative cancer mortality in Hiroshima and Nagasaki for five cohorts of survivors with different ages at the time of the bombing. The diagrams are sum distributions plotted from the beginning of the epidemiological investigations 1950 up to 1982. Sum distributions are given, because they make for more readable diagrams and for more recognizable trends. Differential distributions would be too irregular, since one deals, at least partly, with small numbers of cases. The logarithmic ordinate is chosen to represent the trend of the time dependences over a wider range and, which is equally important, to make proportionality of the spontaneous rate and the rates in the highly exposed groups re-

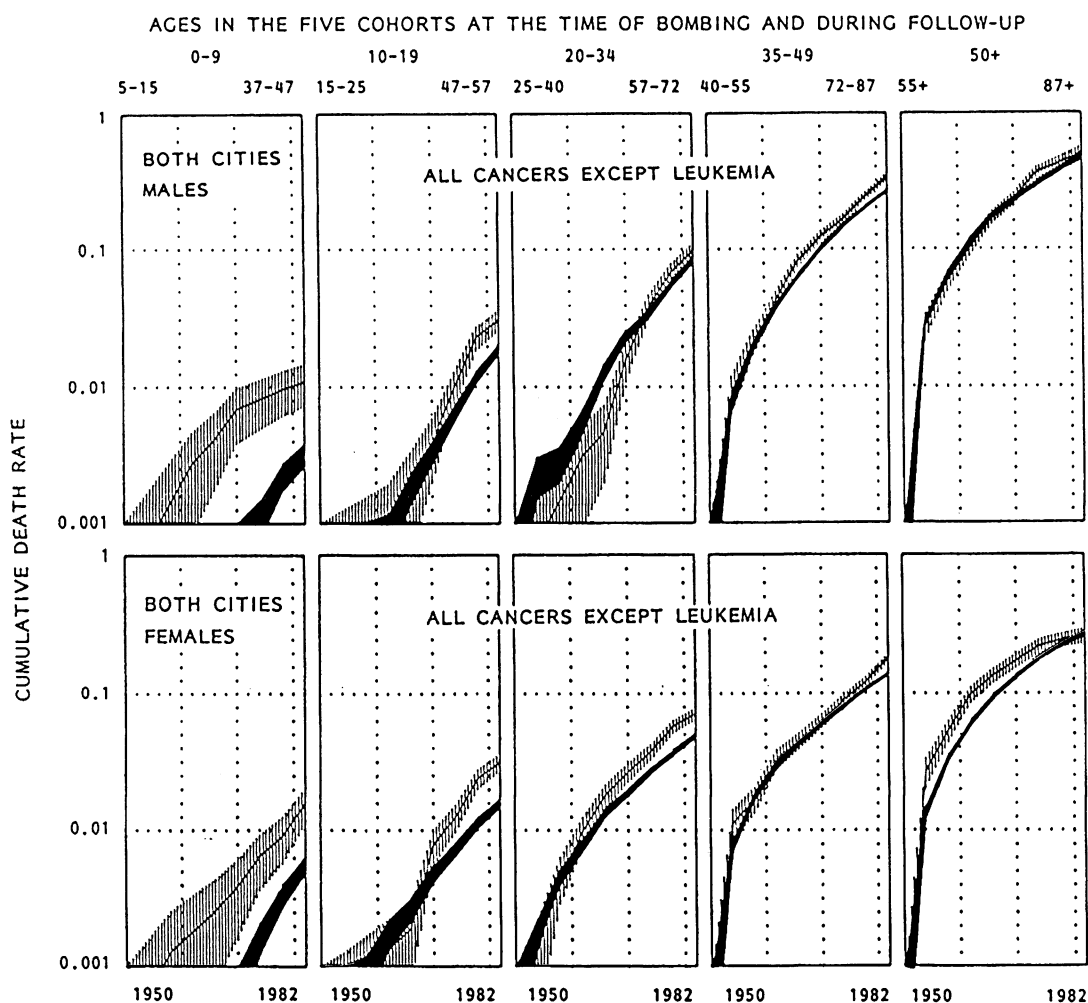


Fig. 2 Cumulative cancer mortality of the atomic bomb survivors. The solid bands refer to the collective of all persons assigned a TD 65 dose below 0.5 gray; the hatched bands correspond to those assigned a dose in excess of 0.5 gray. The width of the bands indicates the standard error.

The relations are given for males and females and for five cohorts which are separated according to the age at the time of the bombing. The abscissa represents the period of the epidemiological observations from 1950 to 1982. The computations utilize the data from RERF /3/ (for more detailed representations see /10/).

cognizable as parallel displacement of the curves. In view of the uncertainties of the old dosimetry which is still utilized in this data set, and also for more clarity of the results, a simple dissection is made between persons in the follow-up who had an estimated dose below 0.5 Gy and those who had higher exposures. All those with estimated doses below 0.5 Gy are pooled in the 'control' groups which are represented by the black bands. All those with higher doses are pooled in the 'exposed' groups which are represented by the hatched bands. The width of the bands gives the standard error of the cumulative rates.

It is often said that doses below 0.5 Gy can not lead to recognizably increased cancer rates, because no significant increases were found among the Japanese survivors with doses below 0.5 Gy. The latter part of the statement is true, but the inference is wrong or, at least, misleading. In fact, most doses in the group below 0.5 Gy are very small. The average TD-65 dose in the 'control' groups is only about 0.05 Gy. It is not surprising that one fails to see enhanced rates in these groups. It is equally evident that matters may be different in a group exposed to nearly equal doses close to 0.5 Gy. The late evacuees from the surrounding of Chernobyl are such a group (approximately 25,000 persons with an estimated mean dose of 0.45 Gy [see /11/, /12/]); one may, indeed, expect to see enhanced leukemia rates in the follow-up of this group.

The diagrams of Fig. 2 show the general enhancement of the cumulative rates in the more highly exposed groups. In these groups the mean dose is of the order of 1.5 Gy. The enhancements are substantial, although they may appear of minor magnitude in the logarithmic representation. The diagrams are given to facilitate a general understanding of the data and of the need to continue the observations. The exact statistical analysis must use sophisticated procedures which are designed to separate the influence of various confounding factors. The observations in the older cohorts are virtually terminated, since few in these cohorts are still alive. The youngest groups, on the other hand, are still nearly complete and have not yet reached the age of substantial spontaneous cancer incidences. For these cohorts the essential results are still to come. However, even in the summary diagrams, it is apparent that the radiation exposure has increased cancer mortality, and that the increases may be generally consistent with a parallel displacement, i.e., with a relative increase, of the rates. In spite of the statistical uncertainties the data are suggestive of a markedly higher sensitivity in the younger cohorts. It will remain a central topic of the epidemiological investigations whether the apparent enhancements will fully, or partly, persist up to old age.

Fig. 3 contains analogous diagrams for leukemias only. The absolute numbers of cases are smaller, however the number of radiation induced leukemias is, in the exposed groups, so strongly in excess of the spontaneous rates that the curves are well separated, in spite of the small numbers. The main difference to the observation for solid tumors is the earlier occurrence of the increases frequencies which are not in phase with the age dependent variations. The wave of radiation induced leukemias has been formally described in terms of a logarithmic normal distribution in time, and the distributions are found to be particularly narrow for those exposed at young age. On the other hand, one notes that the data do not exclude the possibility that there may be an added increase at old age, when the spontaneous rates are greatly enhanced. In the diagrams such a possibility would correspond to parallel dependences for the low dose and the high dose groups, and this may not be inconsistent with all the data observed up to now. Even for leukemias, the continued follow-up will, therefore, remain important. It would be wrong to discount this possibility, merely because there have been no significant excesses of leukemia rates in recent years.

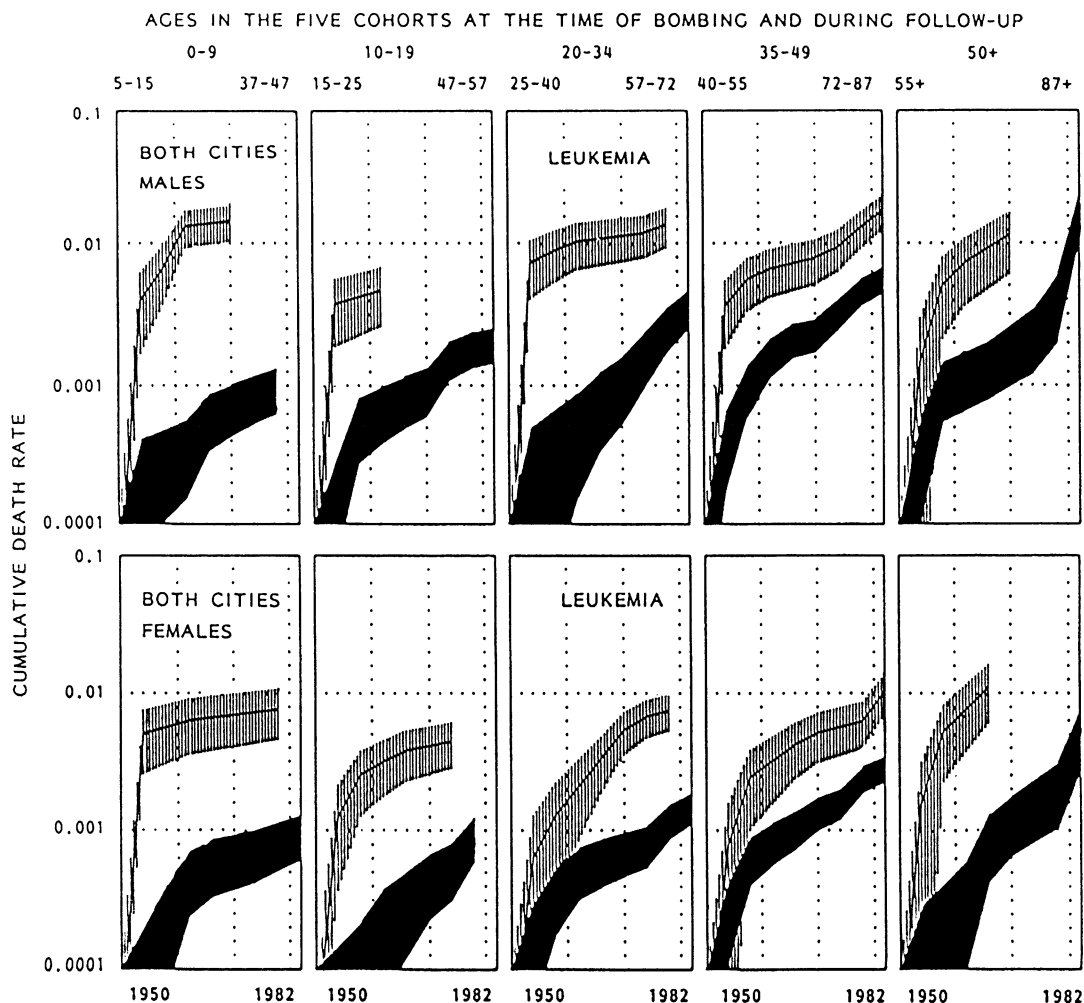


Fig. 3 Cumulative mortality of the atomic bomb survivors due to leukemias; the diagrams are analogous to Fig. 2.

Figs. 4 and 5 give examples for two selected sites. The results for lung cancer are instructive in view of the problem, whether the proportional increases of the spontaneous rates are additive or multiplicative with regard to the over-all rates. With the multiplicative assumption a certain exposure would produce more cancers in smokers than non-smokers, and more in men than women. However, the comparison of those exposed in the age interval 35 to 50 suggests additivity, since the separation of the curves is more marked for women. Another point of interest is the apparently larger separation for the younger cohorts. It shows the need for a continued follow-up, and alerts to the possibility of substantially higher sensitivities at younger ages. The data in Fig. 5 for mammary carcinomas support these conclusions; recent data on incidences are even stronger indications of the increased sensitivities at young age.



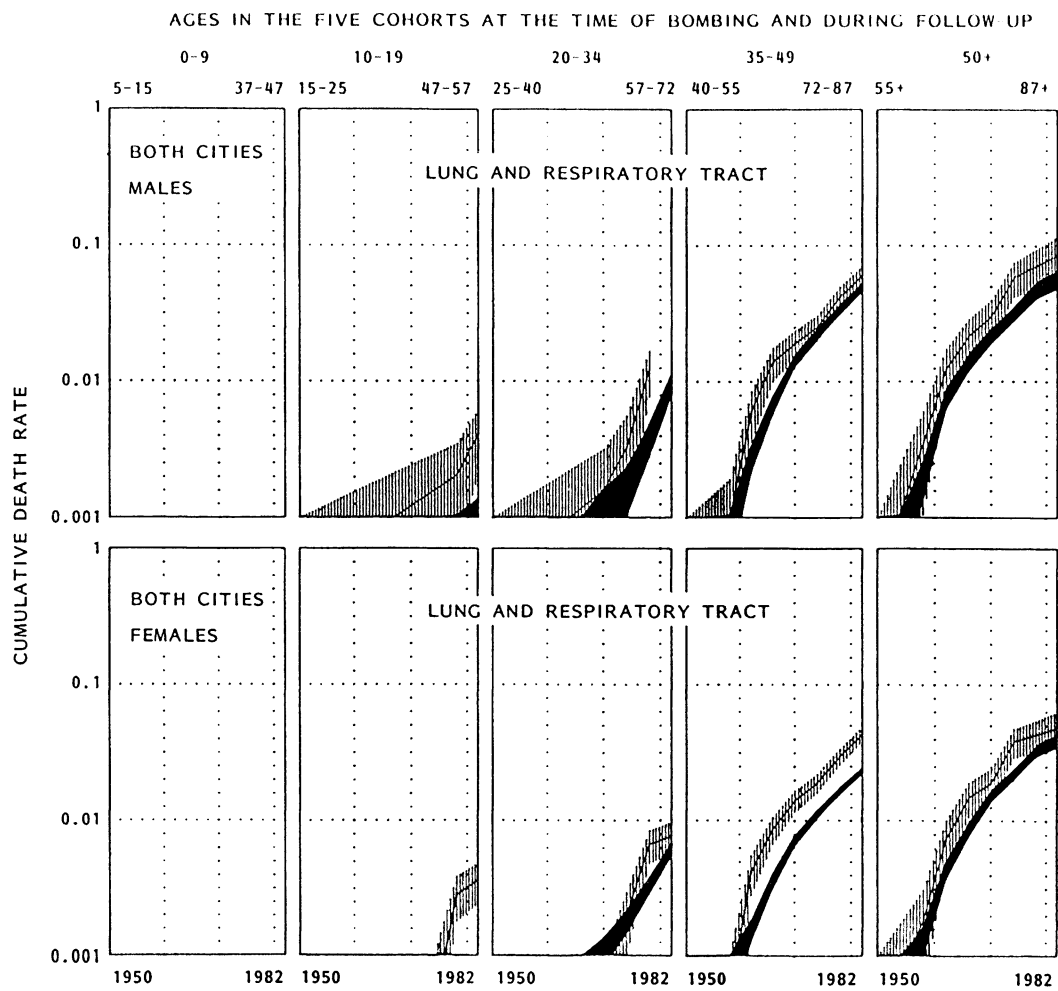


Fig. 4 Cumulative mortality of the atomic bomb survivors due to cancer of the lung and the respiratory tract; the diagrams are analogous to Figs. 2 and 3.

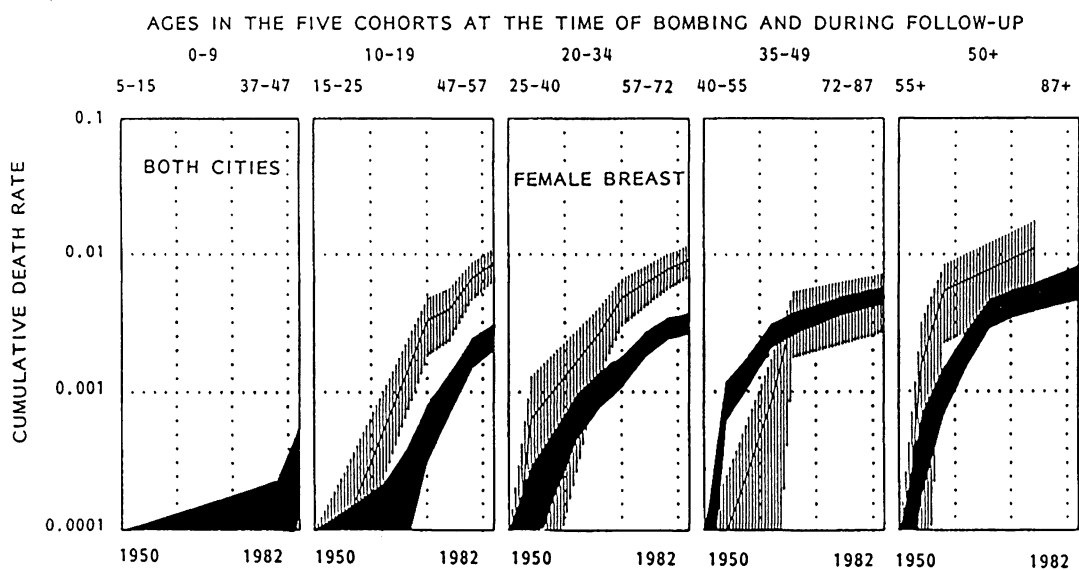


Fig. 5 Cumulative mortality of the female atomic bomb survivors due to mammary carcinoma; the diagrams are analogous to Figs. 2 to 4.

## New Risk Estimates for Cancer Mortality

A first analysis in terms of the new dosimetry has been published by Preston and Pierce /13/. This study is not yet based on definite computation of organ doses in all members of the life span study sample (LSS). However, new tentative dose determinations were used for 76.00 of the total of about 90.00 persons in the LSS.

The essential result of the revised dosimetry is the confirmation that neutron doses are far lower than earlier assumed /1/. A certain contribution of the neutrons to the effects observed in Hiroshima can not be excluded, especially at low doses where the relative biological effectiveness of neutrons may be very high. However, it appears unlikely that any neutron effects can be identified by the statistical analysis of the data. The study of Preston and Pierce is, therefore, confined to considerations which are based on certain postulates concerning the relative biological effectiveness of neutrons, and it is seen that these postulates have only minor implications for the resulting risk estimates for gamma rays. The influence of neutrons will, therefore, not be considered in the following.

With regard to the totality of all solid tumors, one finds that the influence of the dose revision is minor. If one applied the old dosimetry to the data up to 1985, one would obtain dose dependences for solid tumors which are not largely different from those obtained with the new dosimetry. That one obtains organ doses for gamma rays in the new dosimetry system which differ only modestly from the old estimates is the result of two nearly balancing changes. According to the new dosimetry the shielding by houses is considerably larger than earlier assumed; however the absorption in the body is less, and the doses to deeper organs are, therefore, larger for a given shielded kerma.

For leukemias the situation is somewhat different, because the dose in bone marrow had in the old dosimetry not been much affected by shielding due to the body. The reduction of the neutron doses and the enhanced shielding in houses leads, therefore, to substantially reduced organ doses and, accordingly, to risk estimates which are, by about a factor 2, in excess of earlier estimates. It is still uncertain whether different computational methods in the recent study may also be partly responsible for the increased risk estimates for leukemias.

The new risk estimates of cancer mortality, apart from leukemia, differ from the earlier values mostly because of the continued observations. The changes are substantial, because younger cohorts have entered the age of spontaneously increased tumor rates, and the corresponding increases of radiation induced tumor rates have become apparent.

For the first time in the work of RERF one has now introduced mathematical models /3/ which correspond generally to the so-called proportional hazard models and to the algorithm introduced by Cox. The essential postulate is that of the relative risk, as indicated in the diagram of Fig. 1. It is assumed that the proportional increases of the spontaneous rates will persist throughout life. On the basis of this assumption Preston and Pierce have obtained the central result which is shown in Fig. 6. In the figure the excess relative risk is given as a function of the estimated dose to the deeper organs. The diagram relates to the total life-span study sample, i.e., to the entirety of all age cohorts. In Table 1 scaling factors for the different age cohorts are given, in a rough subdivision, for men and women. The values relate to the relative increases, and the factors are, therefore, higher for women. However, age specific over-all cancer mortality is lower by a factor of about 2 for women than for men, and the frequency of induced cancers is, therefore, not higher in women for a given period at risk. On the other hand, women have added life expectancy and, therefore, also a correspondingly larger integrated cancer risk from a given dose.

According to the dependence in Fig. 6, Preston and Pierce infer from linear regression of the data an increase of cancer mortality by 70 % after a gamma-ray dose of 1 Gy. With an assumed chance of 0.18 for an individual to die of cancer, the increase would correspond to an added risk of about 0.14 per Gy. This differs markedly from the much more shallow dependence which corresponds to the risk estimates given by ICRP for cancer mortality, except leukemia /14/. However, a direct comparison of the two dependences is misleading, because the risk estimates of ICRP were derived with reference to a time at risk of only 30 years after exposure, and furthermore because these risk estimates incorporated an assumed reduction factor for low doses and low dose rates of 2 to 3. If one accepts the reduction factor of 3 which is suggested by UNSCEAR /15/ one obtains the straight line which is higher by a factor of 4 than the ICRP risk estimates.

What are the reasons for this remaining difference? One reason is the projection of the relative risk model throughout life. A second reason is, that the new estimates relate to a population including young ages at exposure, while the ICRP estimates are given for a working age population. If one applies the scale factors from Tab. 1 for males of age 20 to 35, one finds a ratio of the new to the old risk estimates of

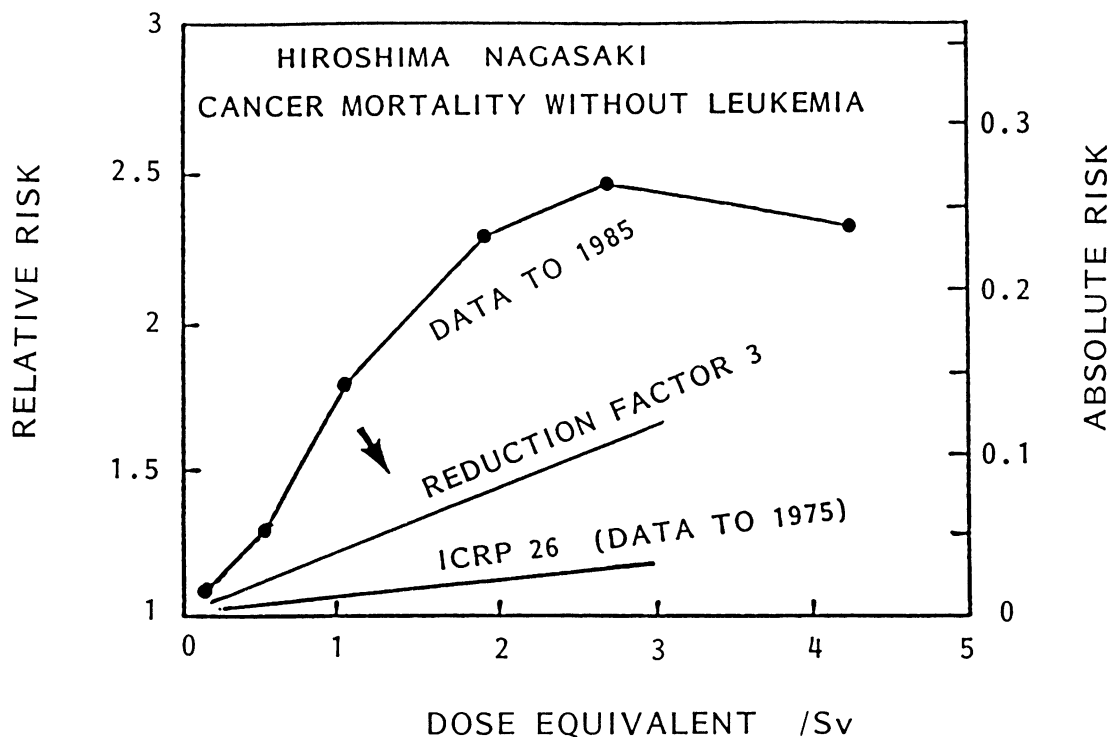


Fig. 6 Dose dependence of the relative and the absolute risk of cancer mortality (without leukemias) according to the results of Preston and Pierce /13/, and comparison with the risk estimates of ICRP 26 /14/. The intermediate dependence corresponds to the results of Preston and Pierce when they are reduced by a factor 3 to account for low doses and low dose rates (see /15/).

The results of the new analysis refer to the collective of all atomic bomb survivors. Table 1 contains the adjustment factors for different age groups. The ICRP estimates were based on data up to 1975 and relate to an adult working-age population.

Table 1: Factors for adjusting the data in Fig. 6 to specified age groups.

#### Age at Radiation Exposure

	< 20	20-35	> 35
Females	2.16	1.29	0.71
Males	0,97	0.58	0.32

about a factor of two. A minor part of this remaining difference is due to the revision of the dosimetry. The major change is due to the reference to the entire life time, rather than to the 30 years of observation which had passed when ICRP published its earlier values. Apart from the increased estimates for leukemia which result from the changed dosimetry, the projection to longer times at risk is, therefore, the essential change which necessitates the renewed discussion of the risk factors. Accordingly it is of interest to quantify these considerations somewhat.

Fig. 7 is based on life-table data for total mortality and for cancer mortality which apply to the U.S. but are probably fairly valid for the Japanese atomic bomb survivors. It gives the fraction of cancer mortality expressed up to certain ages. Under the assumption of a complete relative risk model the fractions of radiation induced cancer mortality have then been computed up to specified calendar years for those exposed to the bomb radiation at different age. The results are given in Fig. 8. One concludes that a substantial part of the total expected cancer mortality in the intermediate age cohorts has occurred between 1975 and 1985. One notes also that most of the information is still to come for those exposed at young ages. If the relative risk model applies, and enhanced rates persist throughout life in proportion to the age specific increases, one will still encounter the major part of the effects, and this contribution will not be exhausted before the first decades of next millennium. The observations on the fate of the survivors of the atomic bombings will, therefore, remain a lasting obligation for a long time to come.

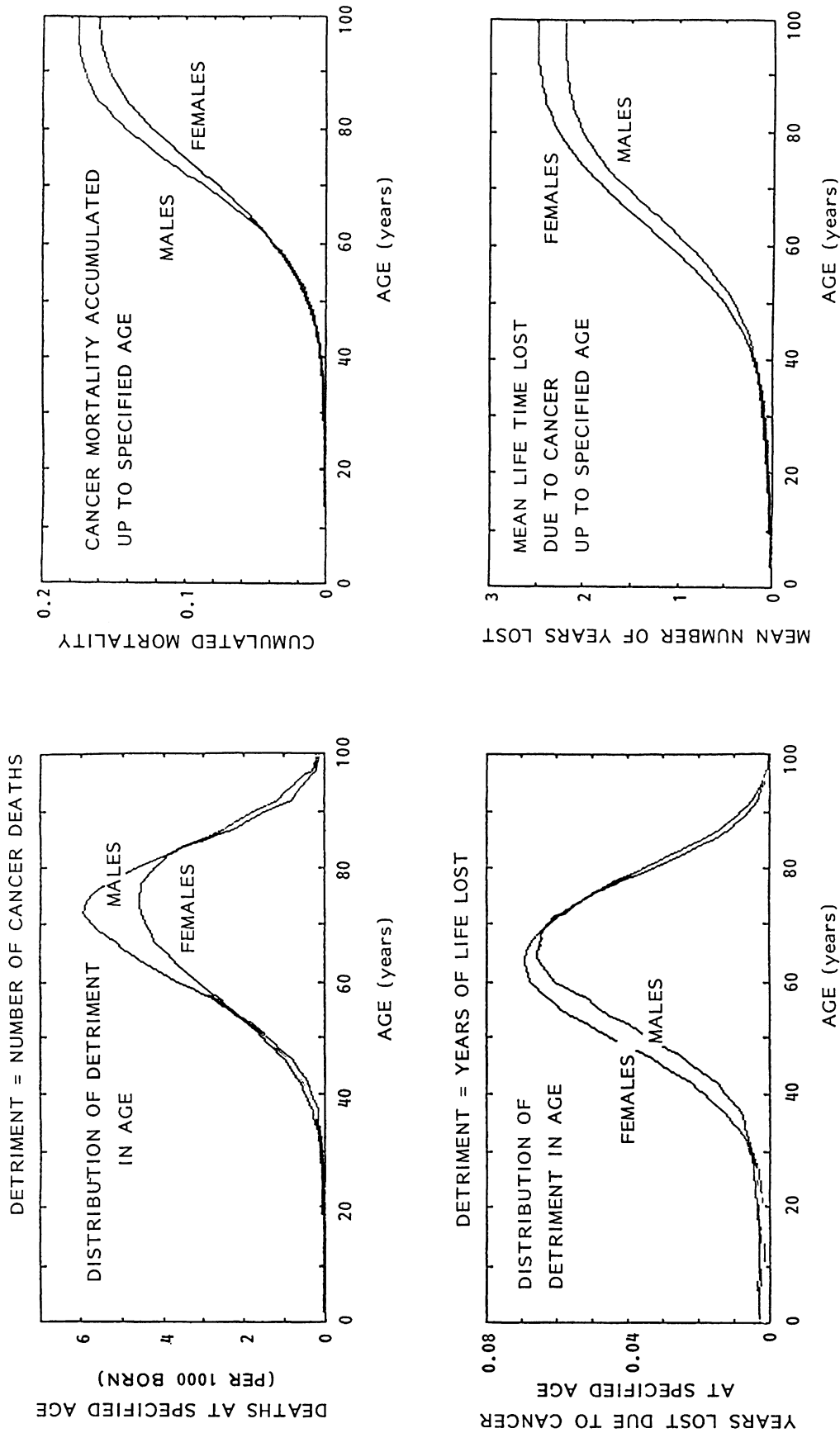


Fig. 7 The upper panels give the distribution of cancer mortality in age and the corresponding sum distribution. The lower panels give the distributions weighted by the loss of life time. According to the relative risk model for solid tumors, the dependences are the same for radiation induced cancer.

## DETRIMENT FROM 1950 TO EXTINCTION OF COHORT

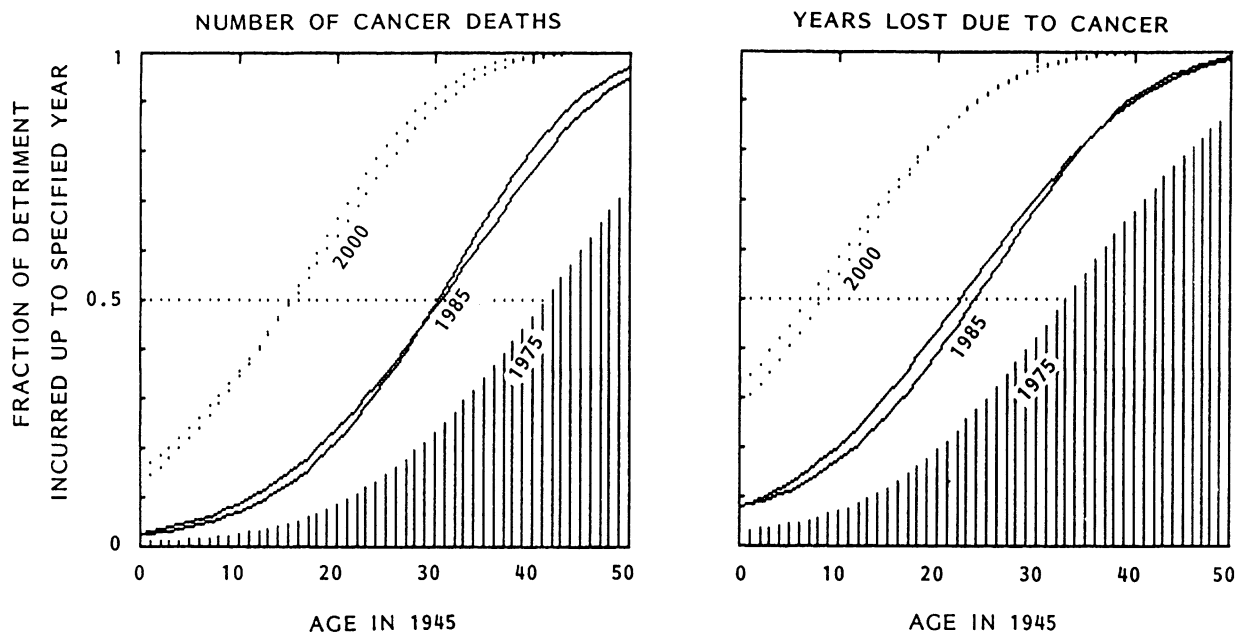


Fig. 8 Fraction of detriment expressed – according to the relative risk model – among the atomic bomb survivors up to specified years in the follow-up. The domains above the curves correspond to the effects not yet observed. The projected effects may be substantially smaller, if the increased relative risks do not persist throughout life.

## References

- /1/ DS 86, US-Japan Joint Reassessment of Atomic Bomb Radiation Dosimetry in Hiroshima and Nagasaki, Final Report, Vol. 1, 2 W. E. Roesch, (Ed.), Radiation Effects Research Foundation, Hiroshima, 1987.
- /2/ Preston, D. L., Kato, H., Kopeccky, K. J., Fujita, S. Life Span Study Report 10, Part 1, Cancer Mortality Among A-Bomb Survivors in Hiroshima and Nagasaki, 1950–82, Technical Report RERF TR 1–86. Radiation Effects Research Foundation, Hiroshima, 1987.
- /3/ RERF LSS-E 85, Report 10 data file R10CANCER. DAT, available from Editorial Office, RERF (1986).
- /4/ Horm, J. W., Asire, A. J., Young, Jr., J. L. and Pollack, E. S. SEER Programm: Cancer Incidence and Mortality in the United States 1973–81. NIH Publication No. 85–1837. U.S. Department of Health and Human Services, 1984.
- /5/ Darby, S.C., Doll, R., Gill, K., Smith, P. G. Long Term Mortality After a Single Treatment Course with X-Rays in Patients Treated for Ankylosing Spondylitis. *Br. J. Cancer* 55 179–190, (1987).
- /6/ Ševc, J., Kunz, Tomášek, L., Plaček, V. and Horáček, J. Cancer in Man After Exposure to Rn Daughters. *Health Physics* 54, 27–46 (1988).
- /7/ Fabrikant, J. I. BEIR IV The Effects on Populations of Exposure to Internally Deposited Alpha-Emitting Radionuclides: 1987. LBL-24173 UC-48, Lawrence Berkely Laboratory, University of California, 1987.
- /8/ National Institutes of Health, Report of the NIH Ad Hoc Working Group to Develop Radioepidemiological Tables. NIH Publication No. 85-2748. U.S. Department of Health and Human Services, 1985.
- /9/ Chmelevsky, D., Kellerer, A. M., Land, C. E., Mays, C. W. and Spiess, H. Time and Dose Dependency of Bone-Sarcomas in Patients Injected with Radium-224. *Rad. and Environm. Biophys.* 27, in press, 1988.
- /10/ Kellerer, A. M. Cancer Mortality in Hiroshima and Nagasaki 1950–1982 – Cumulative Hazard Functions –. Internal Report, IMSK 86/109/2, 1986.
- /11/ Interlaboratory Task Group on Health and Environmental Aspects of the Soviet Nuclear Accident, Health and Environmental Consequences of the Chernobyl Nuclear Power Plant Accident. Report to the U.S. Department of Energy, DOE/ER-0332, Battelle, Washington, 1987.

- /12/ World Health Organization, Nuclear Accidents and Epidemiology. Environmental Report, 25, Copenhagen, 1987.
- /13/ Preston, D. L., Pierce, D. A., The Effect of Changes in Dosimetry on Cancer Mortality Risk Estimates in the Atomic Bomb Survivors. RERF TR 9-87, Radiation Effects Research Foundation, Hiroshima, 1987.
- /14/ ICRP. Annals of the ICRP, Publication 26. Recommendations of the International Commission on Radiological Protection. Pergamon Press, 1977.
- /15/ United Nations Scientific Committee on the Effects of Ionizing Radiation: Genetic and Somatic Effects of Ionizing Radiation. United Nations Sales Publication Number E.86.IX.9, New York, 1986.