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CONTROVERSIAL ISSUE

W. F. Heidenreich · H. G. Paretzke · P. Jacob

No evidence for increased tumor rates below 200 mSv in the atomic bomb survivors data

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Abstract We investigated for which doses a significantly increased tumor rate can be seen in the RERF Life Span Study data sets on mortality or incidence of solid tumors. No significant increase was found below about 200 mSv.

Introduction

The Life Span Study (LSS) of the Radiation Effects Research Foundation (RERF) of the atomic bomb survivors of Hiroshima and Nagasaki [1, 2] is by far the most important source of epidemiological knowledge on radiation carcinogenesis. Radiation risk estimates are usually obtained by fitting functions to these data with a linear, nonthreshold dependence of excess risk on dose. As long as the applicability of this assumption of linearity and the absence of a threshold cannot be proven, it is of interest to analyze for which dose an increase of tumor rates due to irradiation can be directly found in these data sets. In a recent publication [1], it was claimed that the mortality data set shows a statistically significant increase of tumor mortality already for doses as low as 50 mSv. This important statement was tested in this paper with a method of analysis different from that in [1].

Materials and methods

The two data sets on mortality 1950–1990 resp. incidence 1958–1987 of solid tumors in the atomic bomb survivors' study – available from RERF [3, 4] – were used in this study.

In order to have a simple and direct means to estimate the possible minimal (i.e. due to statistics only) uncertainties, the number of expected cases was calculated for each dose class in the data sets under the assumption of no effect of radiation.

W. F. Heidenreich (✉) · H. G. Paretzke · P. Jacob
GSF – National Research Center for Environment and Health,
Institute of Radiation Protection,
D-85758 Neuherberg, Germany

Table 1 The parameter p and the values of the spontaneous hazard functions used in this paper. They were obtained by fitting Eq. (1) to the epidemiological data of the lowest dose groups (mortality 0–5 mSv, incidence 0–10 mSv) with both cities combined

Attained age (years)	Hazard $h/(10^4\ PY)^{-1}$				Exponent p		
	30	50	70	100	<50	50–70	>70
Male mortality	1.23	17.3	125	326	5.18	5.89	2.68
Female mortality	2.04	12.7	53.0	239	3.57	4.26	4.22
Male incidence	2.95	34.5	174	401	4.82	4.80	2.35
Female incidence	6.02	31.7	81.6	225	3.26	2.81	2.84

These expected numbers were then compared with the observed numbers. In order to get an impression of influences from sources of uncertainties other than purely statistical ones, the two cities and the two genders were treated separately, in addition to the combined analysis.

The expected number was calculated from an assumed cancer (mortality or incidence) hazard function of the form

$$h\,(t) = ct^{p} \qquad (1)$$

for three intervals of attained age t up to 50 years, from 50 to 70 years, and for those over 70. The three pieces were required to be continuous at the interval boundaries. They are completely determined by giving the hazard at age 50 and 70 years, and in addition the hazard at some lower and some higher age, e.g. 30 years and 100 years. As the logarithm of this hazard function depends linearly on the logarithm of age, the mathematics is straightforward. These four numbers were estimated from the lowest dose classes only (i.e. for mortality 0–5 mSv, and for incidence 0–10 mSv), with the two cities combined, separately for the two genders. The Poisson likelihood was maximized using the FORTRAN-code MINUIT from CERN [5]. Technical details can be found in [6]. Table 1 gives the obtained parameters p and the hazard values for the four attained ages. This technique provides an easy way to correct for the different age structures in the various dose classes.

Results and discussion

In Table 2, the observed numbers of solid tumor cases, the expected numbers based on the spontaneous hazard function given above, the ratio of observed to expected cases,

Table 2 The number of observed and expected solid tumor cases is given as well as their ratios and standard errors

Dose		Observed	Expected	O/E	$\sqrt{O}/E$
Class	Range (mSv)				
Tumor mortality					
1	0–5	3177	3177	1.000	0.018
2	5–20	1446	1398	1.034	0.027
3	20–50	864	826	1.047	0.036
4	50–100	624	609	1.024	0.041
5	100–200	531	506	1.050	0.046
6	200–500	671	580	1.157	0.045
7	500–750	222	176	1.259	0.085
8	750–1000	148	97	1.518	0.125
Tumor incidence					
1	0–10	4286	4286	1.000	0.015
2	10–100	2223	2204	1.009	0.021
3	100–200	599	577	1.038	0.042
4	200–500	759	627	1.211	0.044
5	500–1000	418	290	1.440	0.070

and the standard errors of these ratios based on the standard errors of the observed number of cases are given for the dose classes up to 1 Sv. In Fig. 1, the ratios of observed and expected cases and their error bars from the statistical standard errors of the observed cases are plotted for all dose classes. In Fig. 2, the same data for the low-dose classes, but also for the four combinations of city and gender are given. It should be noted that the dose classes in the incidence data set are wider than in the mortality data set.

If radiation does not affect the tumor rates, then the ratios of observed to expected cases would lie on a horizontal line in the figures, with fluctuations due to statistics and systematic uncertainties. This line would not necessarily be at a ratio $O/E = 1$, as the expected number is derived from the lowest dose class, which is also subject to statistical fluctuations.

A statistically significant increase of tumor rates in a dose class should be at least two standard deviations above such a horizontal line. According to this criteria, the lowest dose class for which we find a significant increase is no. 6 in the mortality data, and no. 4 in the incidence data, i.e. for both cases in the dose range of 200–500 mSv.

This purely statistical condition requires that all samples be taken from the same population. However, this is not the case as the various doses depend approximately on the distance from the explosion. This may lead e.g. to slightly different baseline risks or to inhomogeneities in the diagnosis [1]. A rough idea of possible additional uncertainties can be obtained by comparing the data sets for

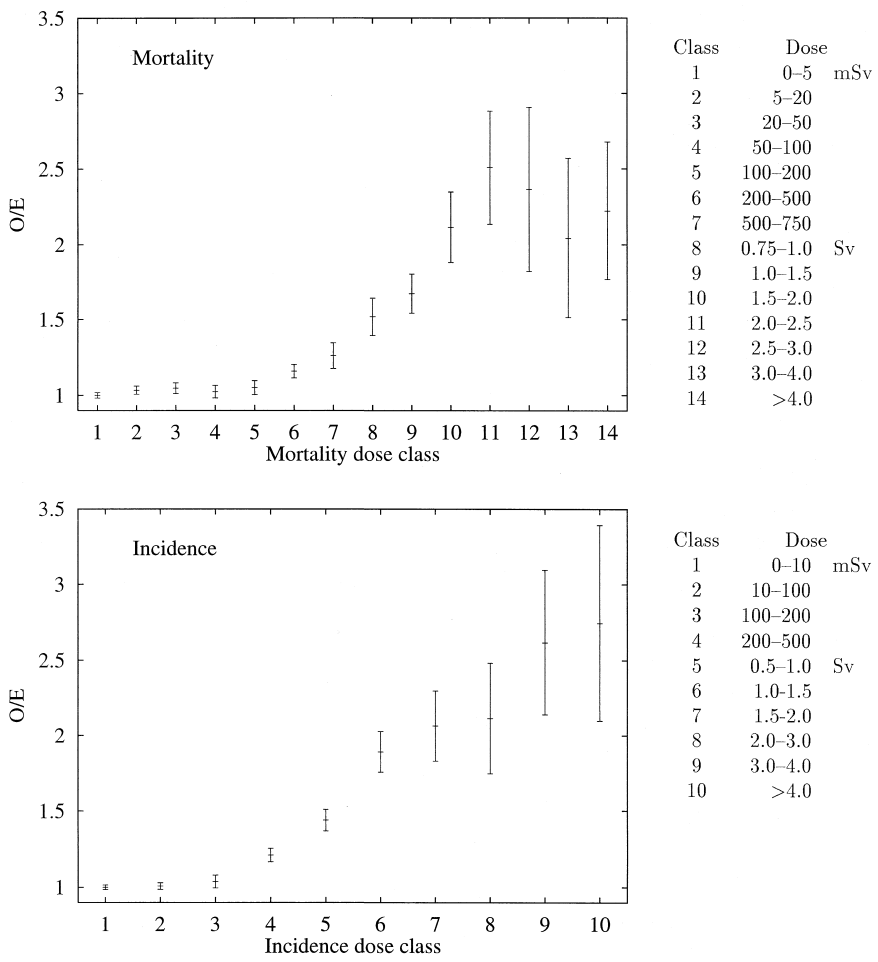

Fig. 1 Ratios of observed to expected numbers of solid tumor cases in various dose classes. The errors indicated represent one standard deviation, using the observed cases

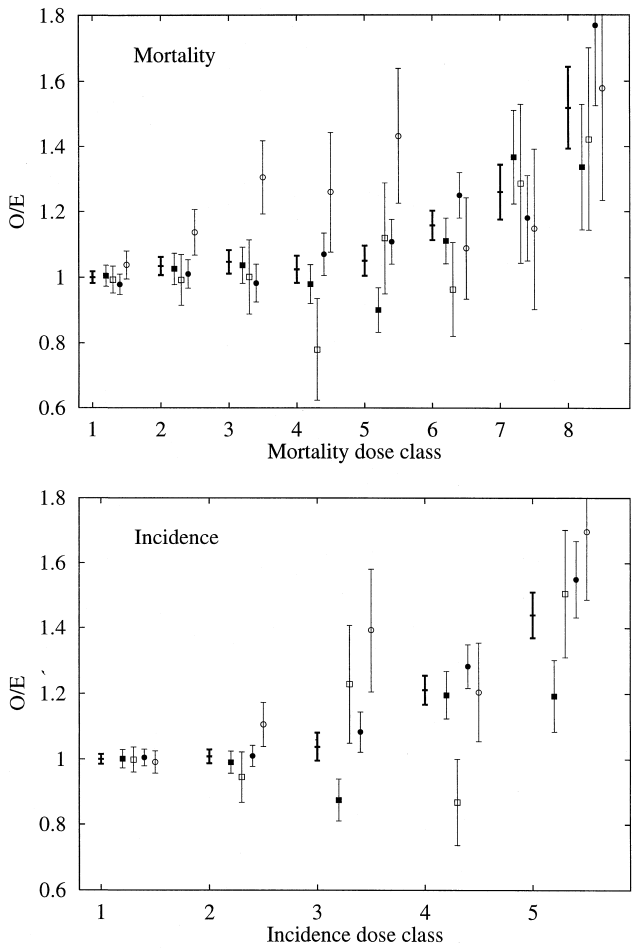

Fig. 2 Ratios of observed and expected numbers of solid tumor cases for the two genders and cities combined and separately. In each dose class, the ratios of the combined numbers (males and females in Hiroshima and Nagasaki, as in Fig. 1) are given using thick lines, and then from left to right the values for the males from Hiroshima and Nagasaki, and for the females in the same order of cities

the two cities with the same gender. The ratios for the females of Nagasaki in the mortality data set in dose classes 2–5 show more than just statistical fluctuation when compared with the ratios for the females from Hiroshima; this observation could warrant further investigation.

No adjustment for calendar time was made; investigations with moving averages have indicated that there is no large calendar time effect, and that it does not have the same size for all ages. A simple calendar time-dependent factor in Eq. (1) would not give a correct picture, and using an age-dependent factor would increase the number of parameters which need to be estimated more than may be justifiable at present. For the comparative analysis done here, possible biases will act in the same way in all dose classes, and thus be of minor importance.

By forming larger dose classes, the statistical errors can be reduced. Even then, direct evidence for significantly increased tumor rates in the group of 100–200 mSv with the given data would be doubtful. The increase in the mortality data within the dose classes 2–4 (5–100 mSv) is not significant and can be completely understood as fluctuations. Thus, direct evidence for significantly increased tumor rates at 50 mSv was not found in this study. Models for numerical risk estimates have to be "calibrated" at doses above 200 mSv. Hazard values in the dose range below this value can only be filled with speculation, until a better quantitative understanding of the molecular mechanism of radiation tumorigenesis is achieved.

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