The cohort of the atomic bomb survivors – major basis of radiation safety regulations

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Abstract
Since 1950 about 87 000 A-bomb survivors from Hiroshima and Nagasaki have been monitored within the framework of the *Life Span Study*, to quantify radiation-induced late effects. In terms of incidence and mortality, a statistically significant excess was found for leukemia and solid tumors. In another major international effort, neutron and gamma radiation doses were estimated, for those survivors (*Dosimetry System DS02*). Both studies combined allow the deduction of risk coefficients that serve as a basis for international safety regulations. As an example, current results on all solid tumors combined suggest an excess relative risk of 0.47 per Sievert for an attained age of 70 years, for those who were exposed at an age of 30 years. After exposure to an effective dose of one Sievert the solid tumor mortality would thus be about 50% larger than that expected for a similar cohort not exposed to any ionizing radiation from the bombs.

1 Introduction

After the atomic bomb explosions over Hiroshima and Nagasaki on August 6th and 9th 1945, both cities were almost completely destroyed. Those who were hit close to the hypocentres (the hypocentre is the vertical projection of the point of explosion (epicentre) to the ground) had almost no chance of survival. By end of 1945, about 200 000 inhabitants had died due to the detrimental health effects caused by the high doses of ionizing radiation, the blast wave and the heat.

Acute effects such as epilation, diarrhoea, central nervous system syndrome, etc., however, were not the only consequences of the exposure to ionizing radiation: A few years after the explosions, the first studies indicated an increase of cataracts and leukemia among the A-bomb survivors [1,2]. In the early 1950s a census was initiated by the joint US-Japanese Atomic Bomb Casualty Commission which was later replaced by the Radiation Effects Research Foundation (*RERF*), and about 120 000 survivors were identified. Based on these individuals, various studies have been made since 1950 to investigate any radiation-induced late effects on the health of these survivors.

There are other cohorts that provide important information on radiation-induced late effects such as, for example, (1) the dial painters in the US who incorporated ^{226,228}Rn and showed an excess in bone sarcomas [3], (2) the children in Russia, Belarus and the Ukraine who were exposed to ^{131}I and showed and excess in thyroid cancer after the Chernobyl accident [4], (3) the uranium miners who were exposed to ^{222}Rn and radon progenies and showed an excess in lung cancer mortality [5], (4) members of the tuberculosis Massachusetts cohort who were medically exposed to X-ray fluoroscopies and showed an excess in breast cancer [6], (5) the Mayak workers in Russia who incorporated ^{239,240}Pu and showed an excess of lung cancer [7], (6) the patients who where treated with ^{224}Ra against tuberculosis and ankylosing spondylitis and who showed an excess in bone sarcomas [8], or (7) those who were medically exposed in utero to X-rays in the UK and showed and excess in leukemia and solid tumors [9]. However, the cohort of the A-bomb survivors from Hiroshima and

Nagasaki is unique for various reasons. Those reasons include, for example, (1) the large number of cohort members investigated, (2) the long follow-up period of about 50 years, (3) a composition including males and females, children and adults, (4) a whole-body exposure which is more typical for radiation protection situations than partial-body exposures typical for many medically exposed cohorts, (5) a large dose range from natural to lethal levels, and (6) the fact that the cohort includes an internal control group with negligible doses, i.e. those who survived at large distances to the hypocentres. In spite of these advantages it is noted, however, that some issues must be kept in mind before the results obtained from the A-bomb survivors can be used for general radiation protection: (1) The A-bomb survivors were exposed to a high dose rate which is contrary to the situation involving low dose rates that are typical for many occupational exposures; (2) The consequences of internal exposures cannot be investigated since the survivors were predominantly exposed externally; (3) The results obtained on the Japanese cohort can not necessarily be transferred to western-type populations; (4) Risk estimates for gamma radiation depend somewhat on the biological effectiveness assumed for the neutrons because the survivors were exposed to a mixed neutron and gamma radiation field.

In general, any study on radiation-induced late-effects requires both, information on disease incidence and mortality in the investigated cohort, and information on the doses received by the affected individuals during the exposure to radiation. For the A-bomb survivors both are available – information on disease incidence and mortality is obtained within the framework of the Life Span Study (*LSS*) project [10-14], while individual doses are given in the dosimetry systems such as DS86 [15] and, more recently, DS02 [16]. If the observed health data such as the number of deaths due to solid cancer are plotted on the y-axis versus dose on the x-axis, any radiation-induced effect would appear as a positive correlation (Fig. 1). The slope of a linear correlation can be interpreted as a risk coefficient, i.e. as radiation-induced effect per dose of ionizing radiation.

Below, the *LSS* and the dosimetry of the A-bomb survivors are described in some detail, resulting risk estimates are briefly discussed, and some of the ongoing scientific discussions are sketched. Other studies conducted by *RERF* such as the Adult Health Study (biennial medical examinations of about 24 000 A-bomb survivors), the In-utero Study (investigations on about 3300 individuals who had been exposed in-utero), and the F1-Study (investigations on about 77 000 non-exposed children of A-bomb survivors) also provide valuable information, but are not further discussed here.

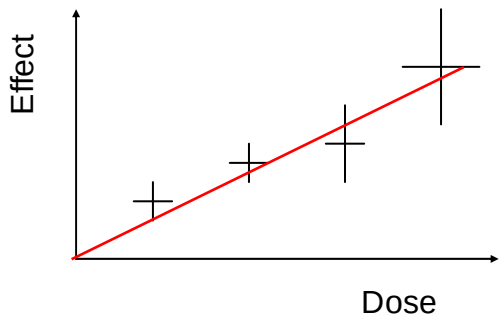

Fig. 1: Principle of a dose response relationship. The slope of a linear fit through the data represents a measure for the effect per dose.

2 Y-axis: the data from the life span study

In a continuous series of reports, *RERF* has published its findings on the incidence and mortality due to leukemia, solid cancer and other diseases, among the members of the *LSS* cohort. Report 12, for example, was based on the follow-up of 86 572 survivors from 1950-1990 [11]. During this period of time, 37 670 individuals died due to various reasons including 7578 individuals who died from solid cancer, and 249 who died from leukemia. While the number of radiation-induced excess cases was quite small compared to the spontaneous cases for solid cancer – in fact, about 334 of the total 7578 cases corresponding to 4.4% (8.2% among those with a nonzero dose) were attributed to the ionizing radiation – it was considerably larger for leukemia (about 87 of the total 249 cases corresponding to 35% [44% among those with a nonzero dose] were attributed to the radiation). Data given in the most recent *RERF* publication that is based on the follow-up 1950-2000 confirm this trend [14]: about 477 of the total 10,085 deaths due to solid cancer, and about 93 of the total 296 deaths due to leukemia were attributed to the radiation.

It is interesting to note that for leukemia, most of the radiation-induced excess cases occurred during the early phase of the follow-up in the 1950s and 1960s, due to the short latency period of this disease (Fig. 2). As mentioned above, extending the follow-up from 1990 to 2000 increased the number of observed leukemia cases from 87 to 93, i.e. by about 7%. Any new leukemia case observed in the *LSS* cohort today is thus rather spontaneous than due to the radiation. For solid tumors, however, the situation appears to be different: during the early phase of the follow-up the radiation-induced fraction of solid tumors was considerably smaller than that for leukemia, but did not decrease significantly in the following decades (Fig. 3). Extending the follow-up from 1990 to 2000 increased the number of excess solid tumor cases from 334 to 477, i.e. by about 43%. This may highlight why it is important to continue this study although more than half a century has already passed since its beginning: for solid tumors, a considerable number of radiation-induced cases is still to come. Those of the *LSS* cohort still alive (in fact, about 48% of the survivors were still alive in 1998 [13]) were exposed at very young ages. Thus, in the future the study is expected to provide new information on the late effects induced by ionizing radiation in children and adolescents.

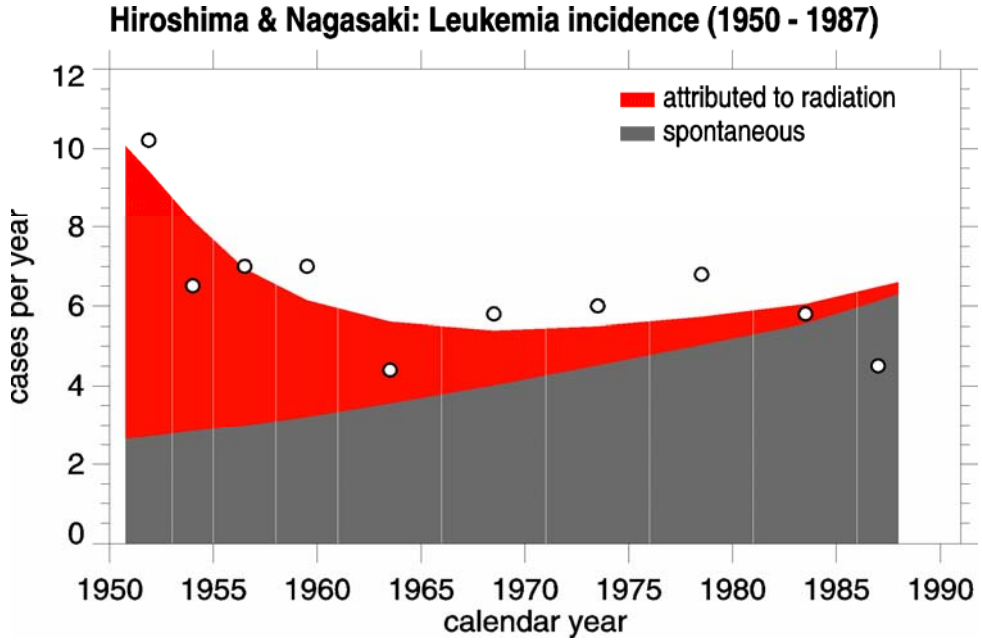

Fig. 2: Leukemia incidence in Hiroshima and Nagasaki, based on a follow-up 1950–1987

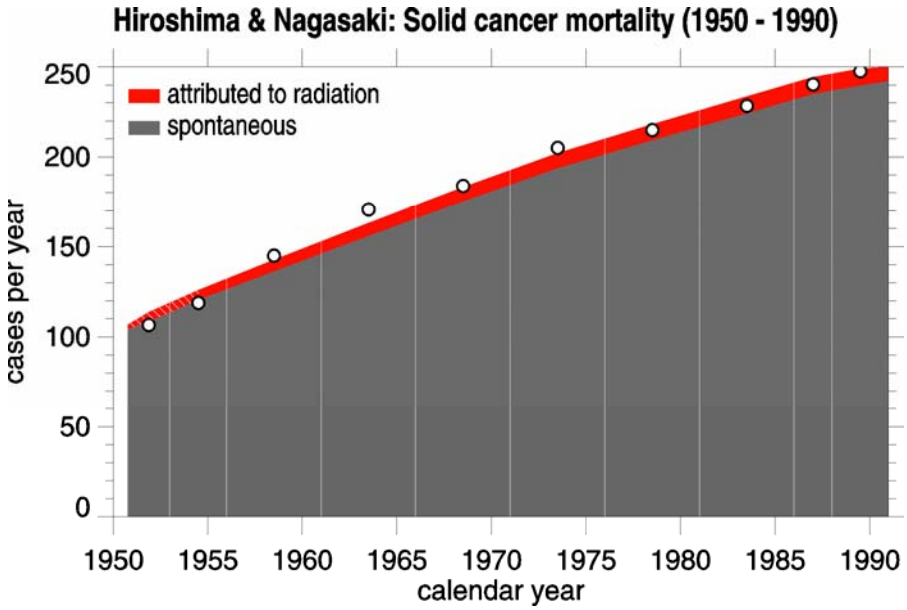

Fig. 3: Solid cancer mortality in Hiroshima and Nagasaki, based on a follow-up 1950–1990

3 X-axis: the dosimetry of the A-bomb survivors

While early dose estimates for the gamma and neutron radiation doses in Hiroshima and Nagasaki had been performed already in the 1950s and 1960s [17,18], it was in the early 1980s that extensive modelling allowed the estimation of organ doses to the survivors on an individual scale. The so-called DS86 model included, for example, calculation of the neutron and gamma radiation emitted by the exploding bombs ("source terms"), hydrodynamic simulation of the atmosphere disturbed by the explosions, coupled neutron and gamma ray transport calculations from the points of explosions ("epicentres") to the ground, quantification of the shielding by Japanese houses and other structures, and calculation of the shielding by the human body itself [15]. Figure 4 shows, as an example, the location of about 58 000 survivors from Hiroshima at the time of bombing (*atb*). The color code represents DS86 colon doses for these survivors. Figure 4 demonstrates the wide dose range to which the *LSS* cohort was exposed: doses of a few mSv for those who were located beyond about 2500 m from the hypocenter on the one hand, and doses up to several Sv for those few who could survive at a distance of less than 1000 m from the hypocenter on the other.

Results of various measurements that had been made in the 1950s and 1960s during test explosions on the Nevada Test Site proved the reliability of the DS86 methodology [15]. Measurements on environmental samples from Hiroshima containing quartz allowed the retrospective determination of the gamma radiation doses from the A-bomb by means of the thermoluminescence method. The results indicated somewhat lower experimental doses than calculated by DS86 close to the hypocenter, and slightly higher values at distances beyond 1000 m. For example, at a distance of about 1400 m from the hypocenter, the experimental data were about 20%-30% higher than those calculated [15]. In order to reconstruct the fast neutrons from the Hiroshima A-bomb that were responsible for the neutron doses to the survivors, early efforts concentrated on the detection of ^{32}P (half-life: 14.2 days) that was produced by fast neutrons in samples that contained sulfur [19,20]. Results of these studies showed reasonable agreement with DS86 calculations close to the hypocentre, but did not allow firm conclusion to be drawn at distances larger than about 700 m. Since these data were the only data on fast neutrons available until recently, an experimental corroboration of the neutron doses to the members of the LSS cohort who survived beyond about 1000 m from the

hypocenter (see Fig. 4) did not exist. From the 1960s until the mid 1990s, work on neutron fluence reconstruction concentrated on those radioisotopes that had been produced by thermal neutrons such as ^{60}Co [21], ^{152}Eu [22] and ^{36}Cl [23-25], due to a lack of alternatives. See [26] for a more complete list of references. Similar to the results on gamma radiation, most of the experimental results on thermal neutrons were somewhat lower close to the hypocentre of Hiroshima, compared to DS86 calculations. Contrary to the thermoluminescence data, however, the thermal activation measurements showed significantly higher results than DS86 approaching factors between 10 and 100 at distances beyond 1500 m. Interestingly, the few data available for Nagasaki appeared to support DS86 calculations even at large distances. A detailed description of the situation as it appeared by 1998 is given in [26].

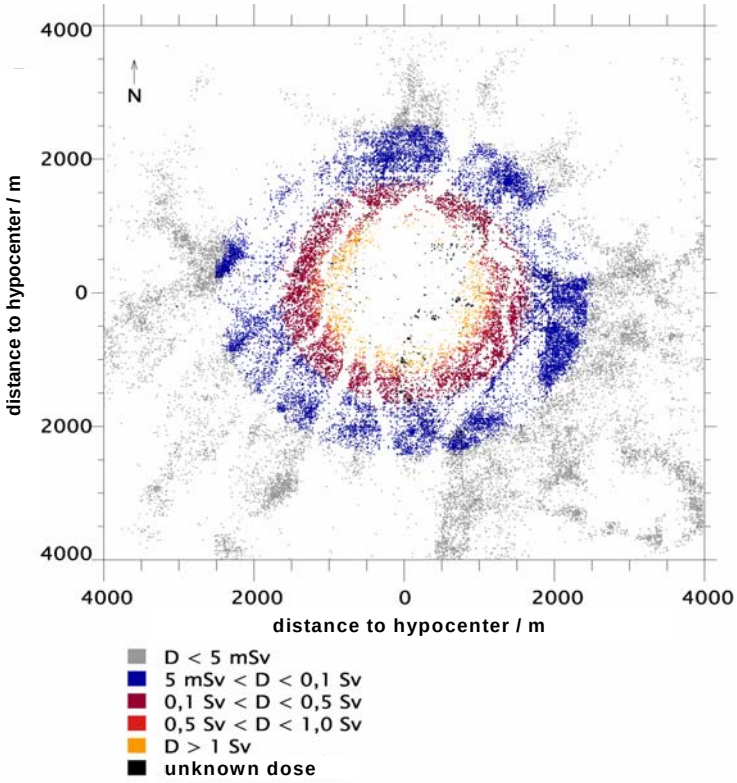

Fig. 4: Location of about 58 000 survivors in Hiroshima, at the time of bombing. The color code represents dose estimates for the colon obtained from the DS86 model (figure produced by M. Chomentowski, Radiobiological Institute, University of Munich, during a stay at *RERF* Hiroshima).

In the 1990s, the situation prompted major international efforts to improve the A-bomb dosimetry. Those efforts included novel approaches for measuring the radioisotope ^{63}Ni produced by fast neutrons in copper samples from Hiroshima, additional measurements of radioisotopes produced by thermal neutrons, and a complete re-evaluation of all computational aspects of the DS86 dosimetry model.

In a joint Japanese-US-German project, five copper samples could be identified in Hiroshima that had been exposed to fast neutrons from the A-bomb. The nickel in those samples was extracted by means of a specially developed chemical method [27], and the ^{63}Ni measured at the Munich MLL Laboratory by means of accelerator mass spectrometry [28]. The results indicated, within their experimental uncertainties, good agreement for four samples that were located at distances beyond about 1000 m where people had survived (Fig. 5). Thus, a major discrepancy that had been reported in the literature for thermal neutrons was not confirmed for fast neutrons [29].

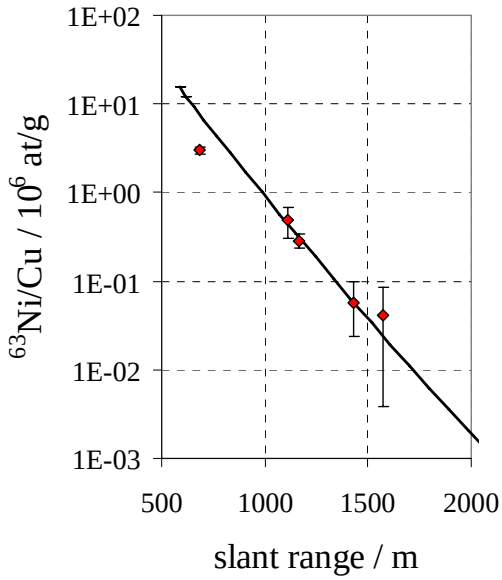

Fig. 5: Measured ^{63}Ni nuclei per gram copper (symbols) compared to DS86 calculation (solid line), as a function of distance from the epicentre

A joint Japanese-German collaboration was the first to show that new measurements of ^{36}Cl produced by thermal neutrons in Hiroshima were in agreement with DS86 calculations at distances beyond 1000 m from the hypocentre where previous measurements suggested a major discrepancy (Fig. 6) [30-33]. This finding was confirmed by other studies (for example, Ref. [16]). A detailed description of the work that was done to improve the dosimetry of the A-bomb survivors and that led to an updated Dosimetry System DS02 will soon be published [16].

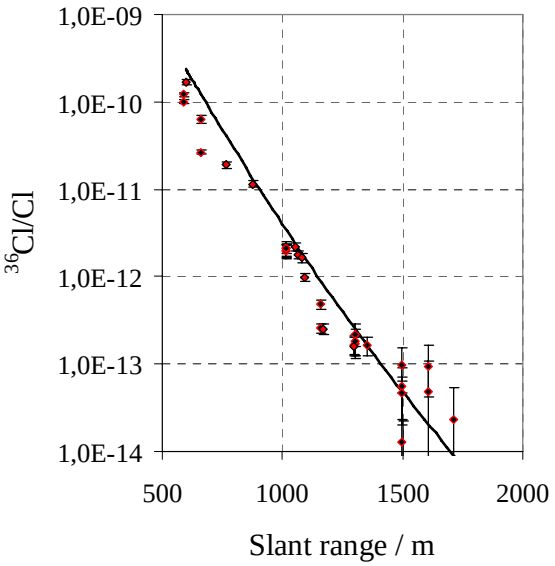

Fig. 6: Measured ^{36}Cl/Cl ratios (symbols) compared to DS86 calculation (solid line), as a function of distance from the epicentre

4 Dose-response relationships obtained from the LSS data

4.1 Shape of the dose-response curve for solid cancer

Recently, *RERF* published the results of a detailed follow-up of the *LSS* cohort, based on the period from 1950 to 1997 [13]. These results are summarized here in terms of the excess relative risk (*ERR*) as a function of weighted colon dose. The *ERR* is defined as the difference between the number of observed solid cancer cases (O) in the cohort, and the number of solid cancer cases expected for the cohort (E) if no additional exposure due to A-bomb radiation was present, normalized to this number (see Eq. 1). The *ERR* is a function of dose, sex, age-at-exposure, and age-attained. All data given here were calculated for those aged 70 years who were 30 years old *atb*, and are gender-averaged.

$$ERR = (O - E)/E \tag{1}$$

where:

- O is the number of cases observed in the exposed cohort,
- E is the number of cases expected in an identical (hypothetical) cohort not exposed to A-bomb radiation.

The weighted colon dose as used by *RERF* is the sum of the colon absorbed dose from the gamma radiation, and the ten fold colon absorbed dose from the neutrons (Eq. 2). The factor 10 accounts for the increased relative biological effectiveness (*RBE*) of the densely-ionizing neutron radiation compared to that of the sparsely-ionizing gamma radiation.

$$D = D_\gamma + 10 \cdot D_n \tag{2}$$

where:

- D is the weighted absorbed dose to the colon,
- D_γ is the absorbed dose to the colon due to the gamma radiation,
- D_n is the absorbed dose to the colon due to the neutrons radiation.

It is important to note that with the chosen value of 10 for the neutron weighting factor, the contribution of the neutrons to the weighted colon dose is relatively small. Based on *DS86* or *DS02*, for example, the contribution of the neutrons is less than 10%, at a distance of 1000 m from the hypocenter in Hiroshima, and about 1% at a distance of 2000 m. In other words, the major fraction of the late effects observed in the LSS is attributed to the gamma radiation if a value of 10 for the neutron weighting factor is used.

The dose-response relationship obtained by *RERF* for solid tumors is shown in Fig. 7. As a major finding is noted that for all solid cancer combined “There is little evidence against a simple linear dose response, with the only apparent curvature being a flattening for those with dose estimates above 2 Sv that is not statistically significant ($p > 0.5$)” [13]. Based on a linear dose-response curve, an ERR/Sv of 0.47 ± 0.06 is obtained for survivors who are 70 years old, and were exposed at an age of 30 years. Until recently, the linear dose-response curve was somewhat surprising since it was not observed for leukemia which showed a significant upward curvature [11]. Additionally, based on animal experiments, biological experiments and on theoretical considerations, a linear-quadratic rather than a pure linear dose-dependence was expected, for the sparsely-ionizing gamma radiation.

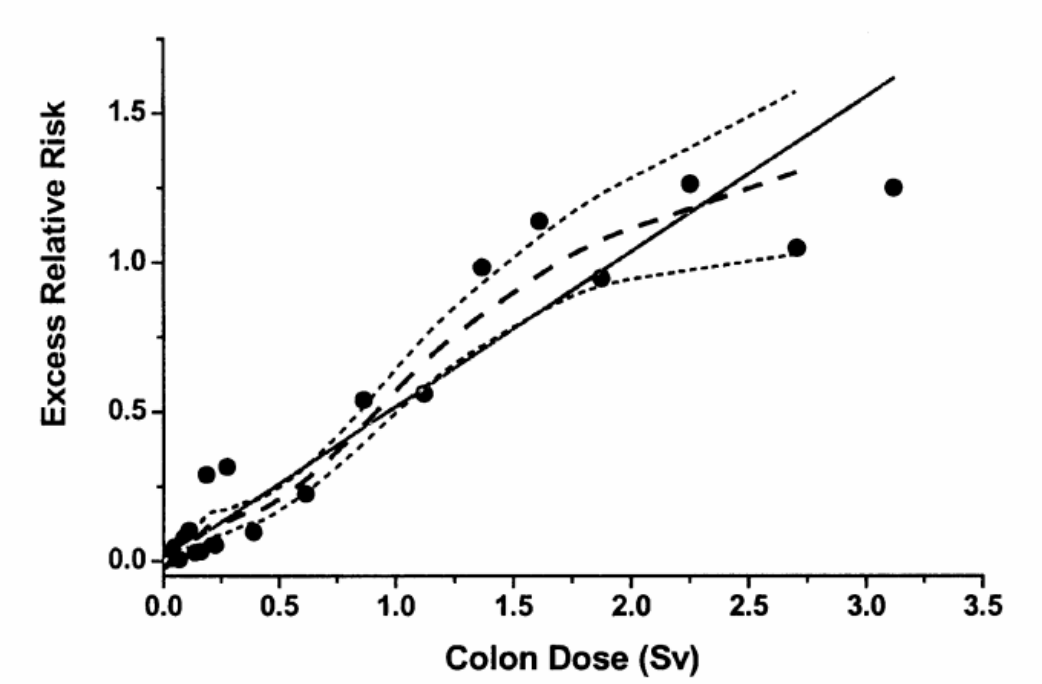

Fig. 7: Excess relative risk for all solid tumors combined versus weighted colon dose (Eq. 2). The linear fit through the data corresponds to a slope of (0.47±0.06)/Sv [13].

Preston and coworkers were able to find a statistically significant increase of the ERR with dose for those survivors whose doses were below 120 mSv. If the analysis was restricted to those whose doses were below 100 mSv, however, a statistically significant slope of the dose-response was not observed [13].

About one year later, *RERF* published a further report that included an additional three years follow-up. While the motivation of this article was primarily to provide a first discussion of the new *DS02* doses, it is also important for another reason: for the first time a significant upward curvature was found in the solid cancer mortality data [14]. This result was independently confirmed by Walsh and coworkers who used the earlier follow-up (1950-1997) for their analysis [34]

4.2 The role of the neutrons

As has been mentioned earlier, the chosen value of 10 for the *RBE* of the neutrons implies that most of the observed late effects are attributed to the gamma radiation. There are reasons to believe, however, that values greater than 10 provide a more realistic description of the biological effectiveness of the neutrons. In fact, animal experiments, chromosome aberrations measured in peripheral blood of about 1800 A-bomb survivors, and recommendations published by the International Commission on Radiological Protection (ICRP) [35] would suggest higher values [36–38], as well as a detailed analysis of organ-specific risk estimates obtained for solid cancers [39].

Qualitatively speaking, the use of higher *RBE* values for the neutrons implies that a larger fraction of the observed radiation-induced late effects (e.g. solid cancer or leukemia) is attributed to the neutrons. As a consequence, a smaller fraction is attributed to the gamma radiation and thus the risk estimates deduced from the LSS cohort for gamma radiation will also become smaller. This effect is demonstrated in Figs. 8 and 9. While Figure 8 shows the results of a conventional analysis of the solid cancer mortality data (1950-1990) with an assumed *RBE* value of 10 for the neutrons, Fig. 9 shows the results based on *RBE* values of 20, 35, and 50.

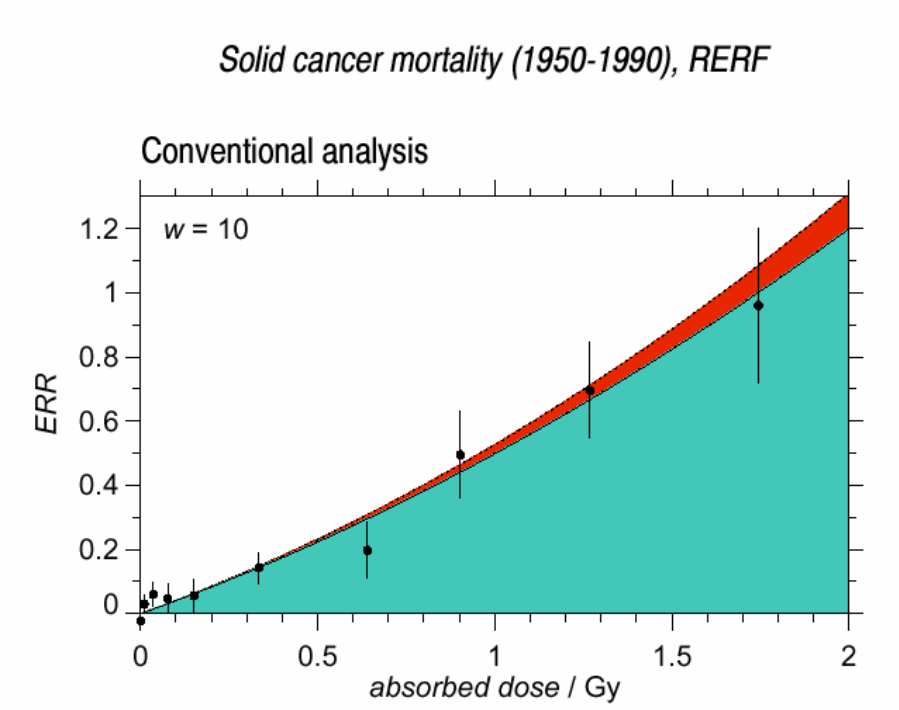

Fig. 8: Excess relative risk for solid cancer mortality, versus weighted colon dose; a value of 10 is used for the neutron *RBE* [40]

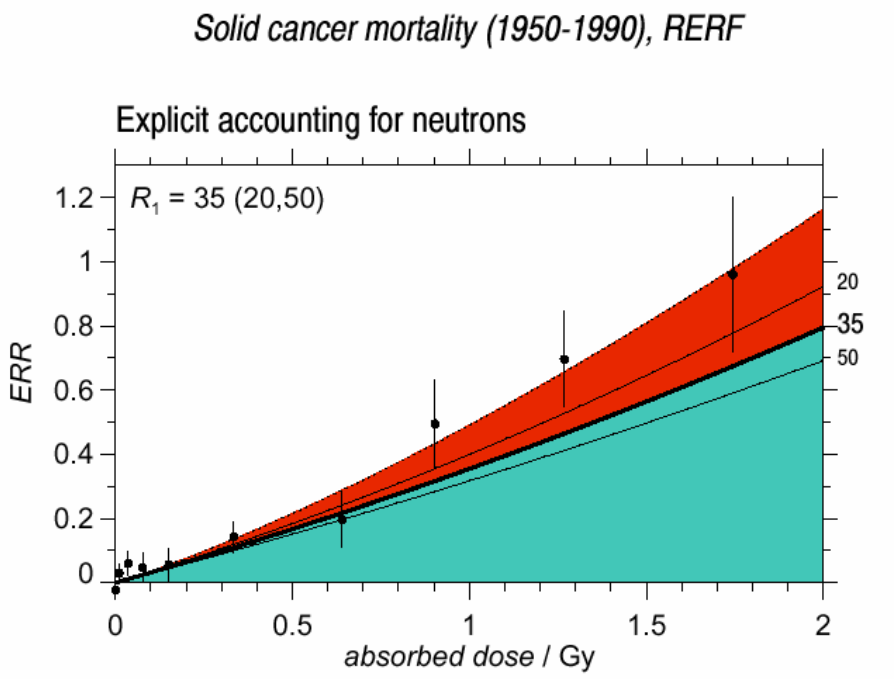

Fig. 9: Excess relative risk for solid cancer mortality, versus weighted colon dose; values of 20, 35, and 50 are used for the neutron *RBE* [40].

5 Conclusion

Data obtained on the A-bomb survivors from Hiroshima and Nagasaki serve as a major basis for radiation protection regulations. For more than half a century, considerable efforts have been made to quantify the morbidity and mortality of initially about 100 000 individuals. Recently, a major international effort came to an end that included re-evaluation of all aspects of A-bomb dosimetry. It was concluded that – while previous measurements suggested a significant discrepancy between neutron activation measurements and calculations for thermal neutrons – results of more recent measurements turned out to be in agreement with these calculations. While current analyses attribute most of the observed radiation-induced effects such as leukemia and solid tumors to the gamma radiation, more recent analyses suggest the neutrons having contributed considerably to these effects. It is expected that a final decision on how to interpret the effect contribution of the neutrons will be made in the next couple of years.

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