Longevity of atomic-bomb survivors

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Summary

Background Conflicting claims have been made regarding biological and health consequences of exposure to low doses of radiation. Studies have suggested that certain low-dose exposed atomic-bomb survivors live longer than their peers. Earlier studies in other radiation-exposed populations demonstrated life shortening from mortality from cancer but lacked dosimetry and relied on comparison groups which may introduce bias because of lack of comparability. We have re-examined the effect of radiation on life expectancy in one cohort of survivors of the atomic bombings of Hiroshima and Nagasaki, Japan.

Methods We did a prospective cohort study of 120 321 survivors. The study encompasses 45 years of mortality follow-up with radiation-dose estimates available for most cohort members. We calculated relative mortality rates and survival distribution using internal comparison (cohort-based estimation of background mortality).

Findings Median life expectancy decreased with increasing radiation dose at a rate of about 1·3 years per Gy, but declined more rapidly at high doses. Median loss of life among cohort members with estimated doses below 1 Gy was about 2 months, but among the small number of cohort members with estimated doses of 1 Gy or more it was 2·6 years. Median loss of life among all individuals with greater-than-zero dose estimates was about 4 months.

Interpretation These results are important in light of the recent finding that radiation significantly increases mortality rates for causes other than cancer. The results do not support claims that survivors exposed to certain doses of radiation live longer than comparable unexposed individuals. Because the cohort was intentionally constructed to contain a higher proportion of high-dose atomic-bomb survivors, average loss of life among all exposed atomic-bomb survivors would be less than the 4 months found for the study cohort.

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Introduction

There is an ongoing debate about the effects of low doses of ionising radiation on human health. Some investigators propose hormesis, or beneficial effects, at low doses whereas others cite evidence for harmful effects even at low doses. Numerous studies have shown adaptive responses of specific biological mechanisms to low doses of ionising radiation, but the evidence for such an effect in terms of human health is controversial.[1] Radiation-related life shortening in human beings has been studied for some time, having been shown to occur in numerous animal experiments.[2] Unlike the animal results, it has been claimed that radiation-related life shortening in human beings is limited to cancer deaths. Evidence for this comes from studies of British radiologists,[3] radium dial workers,[4] patients with ankylosing spondylitis in the UK,[5] and atomic-bomb survivors,[6] but is contradicted by a study of US radiologists that found a non-specific radiation-related life-shortening resulting from cancer, cardiovascular diseases, and other causes.[7] With the exception of the atomic-bomb survivor study and ankylosing-spondylitis studies, these studies have been criticised for the use of inadequate comparison groups and lack of dosimetry.[8] The atomic-bomb survivor study was done before the finding of a radiation effect on non-cancer mortality,[9] which therefore raises again the question whether there really is a non-specific life-shortening effect of radiation exposure in man.

Contrary to the evidence for radiation-related life-shortening, it has been reported that certain atomic-bomb survivors exposed to low doses have greater-than-expected life expectancy.[10–15] Such reports presumably form the basis of statements both in the scientific literature[16] and in the US press[17,18] that atomic-bomb survivors outlive their unexposed peers. These reports are based on various comparison populations, raising the crucial epidemiological question of who the survivors' unexposed peers are. Virtually all temporally and geographically comparable individuals (residents of the bombed cities) suffered from the effects of the bombs. Furthermore, atomic-bomb survivor data are "consistent with threshold or non-linear dose-response at low doses".[19]

The Life Span Study (LSS) cohort followed since 1950 by the Radiation Effects Research Foundation (RERF, a joint Japan-US research institute in Hiroshima and Nagasaki, Japan) and its predecessor, the Atomic Bomb Casualty Commission, satisfies stringent epidemiological criteria for large cohort studies. Although the Japanese enjoy one of the longest life expectancies in the world today, and nearly half of the LSS cohort members are still alive, it is now possible to study longevity in this population given complete mortality ascertainment through 1995—a total of 45 years of follow-up and 50 years since the bombings. The risks from radiation for overall mortality, cancer and non-cancer mortality, and cancer incidence in the LSS cohort have been well characterised.[9,20,21]

An advantage of the LSS cohort is that it is a fixed cohort sampled from a well-defined population

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established on the basis of special national censuses. Follow-up began 5 years after exposure, which would eliminate mortality caused by acute radiation effects and other bomb-related trauma, but not most delayed radiation effects (except for a small number of early leukaemia deaths). Mortality related to atomic-bomb radiation dose in the LSS cohort can be assessed by comparison to internally calculated expected death rates to avoid some of the potential biases that can arise from using an external comparison group. In this report we present results of such internally compared mortality analyses and calculate median life expectancy (median age at death) in the LSS using survival analysis without any specific dose-response model.

Methods

Study population and follow-up

The LSS cohort of atomic-bomb survivors includes Japanese citizens identified through censuses done between 1950 and 1953, whose place of residence at the time of the bombings was either Hiroshima or Nagasaki. "Exposed" individuals were, by definition, within 10 km of the hypocentre at the time of one of the bombings (either Hiroshima on Aug 6, 1945, or Nagasaki on Aug 9, 1945), regardless of their direct atomic-bomb radiation dose,[22] even if it is estimated as zero because of shielding or distance from the bomb. Doses less than 0·005 Gy were rounded to zero. Residents who were away ("not in city") at the time of the bombing are called "unexposed", although some of these people may have been exposed to fallout or to residual radiation because they entered the cities shortly after.

Among survivors who met the above eligibility requirements, all of those who were within 2·5 km of the hypocentre at the time of the bombing were included in the cohort. Random samples of survivors further away than 2·5 km, and unexposed residents, were also included. Mortality follow-up via death certificates is virtually complete for the entire cohort by virtue of the *koseki* family registration system in Japan. Among the 120 321 cohort members, 121 could not be followed, leaving 120 200 individuals that were used in our analyses. Follow-up is from the time of census to the end of 1995.

Statistical analysis

We analysed mortality by Cox[23] regression with age as the primary time scale, adjusting for city, sex, year of birth, and age at start of follow-up. Two types of model were fitted, both adjusted for these factors. In one model, we used indicator variables for dose/distance groups to estimate relative risk (relative rates of mortality) compared with the in-city, zero-dose individuals. In the other model, we stratified the Cox regression on dose and distance groups to estimate median survival age within each dose and distance group. Dose and distance groups were the same in both models and are defined in the table, which also shows number of individuals and mean dose/distance in each group. We also included interactions of city and sex by birth-year and sex by age in the Cox models. We allowed more flexible models by using sex-specific quadratic regression splines[24] for birth-year with knots at 1910, 1920, and 1930 and a quadratic function for age at start of follow-up. For city and sex we used mean-centered indicator variables so that results reflected the population average of these two variables. From the Cox regression we calculated covariate-adjusted, smoothed baseline hazard functions and confidence bands for each dose/distance stratum. From these we derived the survival functions and their corresponding confidence bands[25] median life expectancy (age at death, conditional on being alive at the time of census and standardised to average age at entry of 34 years) and CIs were obtained as the 50% points of the survival functions and corresponding bands.[26]

All analyses were done using Epicure software (Hirosoft International Corporation, Seattle, USA, version 2.10).

Results

Figure 1 shows relative mortality by dose, or distance from the hypocentre in the case of individuals with an estimated dose of zero. Radiation risk is generally expressed as a function of continuous dose rather than dose group as in figure 1; these groups are used to illustrate the effect of choice of comparison group on the

Dose (Gy)	Distance (km)	Mean dose (Gy)	Mean distance (km)	Number of people	Number of deaths	Life expectancy (years/days) median (95% CIs*)
Zero dose						
Not in city, late entrants (entered after 1 month)	>10†	NA	>10	21 923	9645	81y 115d (76y 180d–86y 55d)
Not in city, early entrants (entered within 1 month)	>10	NA	>10	4608	2579	81y 330d (76y 77d–86y 332d)
In city at time of bomb‡	≤10	NA	4·14	34 064	16 775	81y 30d (76y 69d–86y 18d)
	7–10	NA	8·83	1992	881	80y 130d (73y 339d–85y 248d)
	3–7	NA	4·22	23 532	11 864	80y 338d (75y 345d–85y 352d)
	2·8–3·0	NA	2·90	5421	2480	81y 203d (75y 336d–86y 231d)
	≤2·8	NA	2·70	3119	1547	81y 298d (75y 282d–87y 273d)
Non-zero dose						
0·005–0·249	1·94–2·77	0·06	2·09	40 403	19 641	81y 9d (76y 87d –85y 331d)
0·250–0·499	1·74–2·58	0·36	1·45	4899	2548	80y 159d (74y 317d–86y 71d)
0·500–0·749	1·58–2·18	0·61	1·32	2427	1296	80y 25d (73y 205d–86y 66d)
0·750–0·999	1·37–2·03	0·86	1·25	1360	693	80y 114d (71y 176d–86y 334d)
1·000–1·499	1·22–1·82	1·22	1·20	1527	802	79y 281d (72y 152d–86y 39d)
1·500–2·499	1·13–1·67	1·90	1·09	1160	619	77y 363d (69y 175d–86y 45d)
<2·500	0·33–1·28	3·04	0·93	732	411	75y 314d (65y 153d–85y 88d)
Unknown	0·11–3·00	··	1·60	7097	3151	80y 345d (75y 163d–86y 53d)

*CIs for median life expectancy are given for completeness but are not recommended for inference about individual dose-distance groups.[24] †Met residence criteria but were beyond 10 km at the time of the bombing. ‡All dose estimates below 0·005 Gy were rounded to zero. NA=not available.

Median life expectancy by radiation dose or distance from hypocentre of bomb

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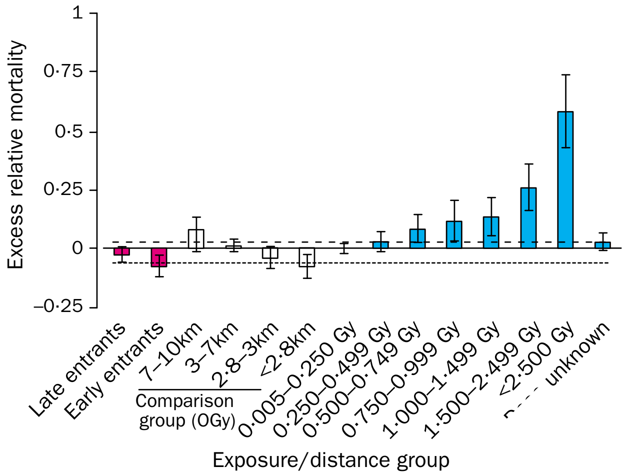

Figure 1: **Excess relative mortality by radiation dose or distance from hypocentre of bomb**

From left to right is increasing proximity to the hypocentre. The comparison group (baseline mortality, or excess relative mortality 0; solid line) is all in-city individuals with estimated doses of zero (all dose estimates below 0·005 Gy were rounded to zero). Blue bars show the excess relative mortality for radiation-exposed individuals grouped by radiation dose. White bars show the excess relative mortality of individual in-city, zero-dose groups. Pink bars show the excess relative mortality for the two not-in-city groups (early and late entrants). Dotted and dashed lines show the effects on baseline of changing the definition of comparison group. Dotted line: all proximal (<3 km) in-city zero-dose individuals (<2·8 km and 2·8–3·0 km combined). Dashed line: all distal (3–10 km) in-city zero-dose individuals (3–7 km and 7–10 km combined). Radiation dose is shielded whole-body kerma (Gy).

risk estimates without assuming any particular dose-response model. The estimated relative mortality was 1·0 or greater in all non-zero dose groups compared with the combined in-city zero-dose group. There was substantial heterogeneity in death rates with distance among the in-city, zero-dose groups (likelihood ratio test statistic 21·25; 3 degrees of freedom, $p<0·001$). The choice of comparison group can affect inference about risks at low doses. Excess relative mortality (relative risk minus 1) at any non-zero dose differed substantially depending on the comparison group, and can be seen by the alternative baselines in figure 1. In particular, the lowest-dose group (0·005–0·249 Gy) had a relative mortality of less than 1·0 compared with the distal (>3 km) zero-dose individuals. The not-in-city group, especially the late arrivals, had an overall mortality similar to that of the proximal (≤3 km) zero-dose survivors. This may reflect some unobserved selection factor or it may be that the not-in-city group was more comparable to the proximal survivors than the distal survivors with respect to factors not related to the bombs.

Median life expectancy (averaged for city and sex) is shown in the table. There was slight downward curvature to the link between median life expectancy and mean dose values: slope −1·16 years/Gy, curvature −0·18 years/Gy^2. Median loss of life was therefore about 1·3 years at 1 Gy and 0·12 years at 0·1 Gy. Women lived an average 7 years 141 days longer than men (median life expectancy in the ≤10 km zero-dose individuals was 84 years, 14 days among women and 76 years 237 days among men). Median life expectancy was virtually identical in the two cities (81 years 56 days in Hiroshima, 81 years 15 days in Nagasaki). There was no significant difference in radiation-related mortality by sex (female:male mortality relative risk was 1·05 times higher in the non-zero-dose group compared with the in-city, zero-dose group; p=0·11). Sex-averaged survival curves for certain exposure/distance groups are shown in figure 2. Median life expectancy was 81 years 30 days for all in-city, zero-dose individuals. Among survivors with non-zero estimated doses, those exposed to below 1 Gy (mean dose 0·14 Gy) had a median life expectancy of 80 years 321 days, shorter than that of the zero-dose individuals by 70 days. Survivors with dose estimates greater than 1 Gy (mean dose 2·25 Gy) had median life expectancy of 78 years 169 days, shorter than the in-city, zero-dose individuals by about 2·6 years. The small number (3419) of survivors exposed to 1 Gy or more represents a small total loss of life within the entire cohort. The median life expectancy for all survivors combined who had estimated doses of at least 0·005 Gy (mean dose 0·27 Gy) was 80 years 265 days, about 4-months shorter than the zero-dose individuals.

Discussion

Epidemiological studies of atomic-bomb survivors who were exposed primarily to direct instantaneous gamma radiation with a small component of neutrons are the primary source of data on long-term effects of radiation exposure in human beings. Although these studies have been ongoing for more than 50 years, late effects in individuals exposed at very young ages are only now beginning to emerge. Analyses of longevity reported here remain speculative for the youngest survivors since most of them have not yet reached the median life expectancy. However, the follow-up so far suggests that their patterns of mortality and excess death rates are similar to older survivors and that these effects last throughout life.[9,20]

Previous reports have revealed and refined estimates of the radiation risks for mortality and cancer incidence in the LSS cohort.[9,20,21] Risk of death from all solid cancers increases linearly with dose, with an excess relative risk at 1 Sv of 0·375 for men and 0·774 for women among those exposed at age 30 years.[20] Risk of death from diseases other than cancer may be non-linear

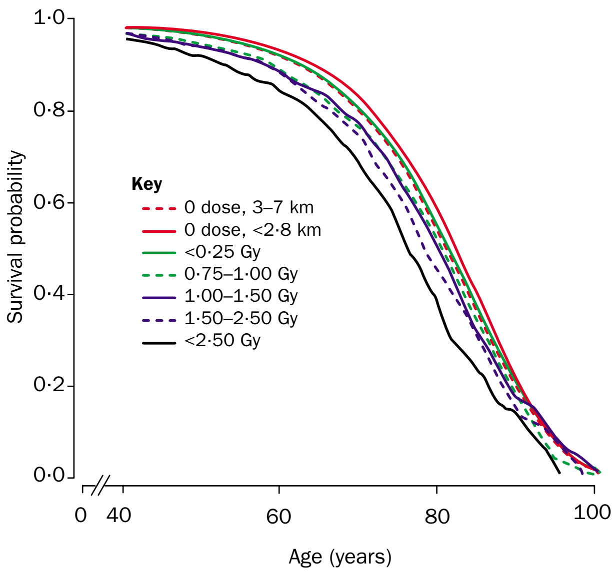

Figure 2: Survival by age

Adjusted for age at start of follow-up, birth year, city, and sex. Seven of the dose-distance groups from the table are shown: 0 Gy, <2·8 km; 0 Gy, 3–7 km; 0·005–0·250 Gy; 0·75–1·00 Gy; 1·0–1·5 Gy; 1·5–2·5 Gy; and ≥2·5 Gy. The 0 Gy comparison groups consist of in-city individuals with estimated dose less than 0·005 Gy.

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with an excess relative risk of about 0·1 at 1 Sv.[9] Although these relative-risk estimates imply shorter life expectancy with increasing dose, they do not convey an accurate impression of the effect on longevity because the background mortality occurs predominantly at older ages. Compared with the dramatic early effects that resulted in death soon after exposure (such as acute radiation syndrome or leukaemia), a large excess relative or absolute rate for effects occurring late in life does not imply a large decrease in individual length of life.

We estimate that there is a 2·6 year average loss of life expectancy for survivors with dose estimates greater than 1 Gy (mean dose 2·25 Gy). The average decrease in life expectancy for those in the Life Span Study cohort with non-zero dose estimates below 1 Gy (mean 0·14 Gy) is about 2 months. For the 40 403 (43%) of exposed survivors in the cohort with non-zero dose estimates less than 0·25 Gy (mean 0·055 Gy), the decrease in life expectancy is estimated as 21 days. Individuals exposed to high doses were less likely to survive the short-term radiation and non-radiation effects of the bombs. Thus, the distribution of doses among the survivors in the cohort with non-zero estimated doses is heavily weighted towards low doses and the average loss of life among all exposed survivors in the cohort with non-zero estimated doses is a little more than 4 months. Because the LSS cohort was intentionally constructed to include a greater proportion of high-dose survivors, the average loss of life among the larger population of all atomic-bomb exposed individuals who survived acute causes of death would be less than 4 months.

Most of the previous reports of radiation and logevity in human beings suggested that life shortening was primarily caused by radiation-related cancer.[3–6] An effect of radiation on non-cancer mortality has now been elucidated in the atomic-bomb survivor population and shown not to be the result of confounding by socioeconomic or lifesyle factors.[9] A higher rate of mortality with radiation exposure translates into a reduction in length of life. To apportion the total loss of life shown here among various causes of death, however, is difficult. This is because an individual dying of one cause related to radiation might have died of another cause if not exposed to radiation, and median age at death differs for different causes of death. However, we esimated the portion of total life lost for cancer and other causes of death, with the assumption that people would have died from the same cause if not exposed to radiation. At 1 Gy the proportion of total life lost was about 60% from solid cancer, 30% from illness other than cancer, and 10% from leukaemia. Because of non-linearity in the leukaemia mortality dose response and possible non-linearity in the non-cancer mortality dose response, solid cancer might contribute a greater share to total life lost at lower doses.

Other studies[10–15] of mortality and longevity in atomic-bomb survivors, not including the LSS, have been based on lists of survivors obtained through voluntary registration for health benefits using variously selected comparison groups, and are not population based. Those studies have suggested that overall longevity may be greater in certain survivors, particularly those in the low-dose to mid-dose range. One set of studies utilised only distal (>3 km) survivors as the comparison group;[10,13] use of the >3 km individuals as a comparison group in the present analysis would lead to the conclusion that survivors with doses between 0·005 and 0·25 Gy had slightly greater longevity than distally (>3 km) exposed individuals whose doses were less than 0·005 Gy (figure 1). Variation in mortality rates among zero-dose groups could be because of geographical differences in lifestyle, socioeconomic status, and regional differences in health care and/or occupation. Other studies have compared atomic-bomb survivors with the present-day general population[14] which was not exposed to non-radiation factors associated with the bombings, and therefore cannot directly address the question of whether radiation leads to longer or shorter life expectancy.

Although radiation dose was primarily a function of distance from the hypocentre—decreasing very rapidly with distance—it also depended to a lesser extent on shielding and other factors.[22] Thus, survivors do not generally know their dose. Nevertheless, the aforementioned health benefits could affect our results if the propensity to register were related to dose in the cohort. Overall, 55% of cohort members registered; the proportion was not related to dose or distance (data not shown), but the proportion was smaller among not-in-city individuals. There was no change in our conclusions when we restricted the analysis to those registered, with follow-up beginning at the time of registration.

The issue of radiation-related life shortening has been considered in numerous animal studies, as summarised in the 1982 UNSCEAR report.[2] In an attempt to overcome the problems with interspecies comparisons, results are usually given as a percentage of life lost relative to median or mean survival age. In the UNSCEAR report it was estimated that for various species of mice and rats there is a 5% loss of life expectancy per Gy of acute X-ray or gamma-ray exposure, with, at low doses, neutrons having five times this effect. Our findings for the atomic-bomb survivors suggest that life shortening in human beings is about 1–2% per Gy.

Contributors

Both investigators planned the work, did the analyses, and wrote the paper.

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