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STUDIES ON THE HIROSHIMA AND NAGASAKI SURVIVORS, AND THEIR USE IN ESTIMATING RADIATION RISKS

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INVITED PAPER

Abstract — Epidemiological studies of the survivors of the atomic bombings of Hiroshima and Nagasaki have been conducted over many years. These studies have examined, *inter alia*, mortality and cancer incidence among the survivors. This paper summarises the form of the studies undertaken, outlines the main findings and describes how these results can be used in deriving estimates of radiation risks. In doing so, some areas of uncertainty and open issues are highlighted, such as the magnitude of lifetime cancer risks and the evidence for raised risks of non-cancer diseases at low doses. Continued follow-up of the survivors will be important in shedding further light on these issues.

INTRODUCTION

Follow-up of the survivors of the atomic bombings of Hiroshima and Nagasaki in 1945 provides the largest single set of information on the long-term health effects of radiation exposure. In particular, it has played a major role in the work of bodies such as the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR)[1] in deriving radiation risk estimates. This paper aims to review the methodology and main findings for mortality and cancer incidence among the A-bomb survivors, and to highlight issues pertinent to the use of these data in risk estimation, particularly at low doses. Findings for other health outcomes are described on the web site (http://www.rerf.or.jp) of the Radiation Effects Research Foundation (RERF), which is responsible for studying the survivors.

METHODOLOGY FOR MORTALITY AND CANCER INCIDENCE STUDIES

The Life Span Study (LSS) is the main study of mortality and cancer amongst the A-bomb survivors. It is based on a cohort of about 120,000 residents of Hiroshima and Nagasaki identified in a census in 1950. For many years, attention has been focused on about 93,700 survivors who were present in the cities at the time of bombing.

A key strength of the LSS is the availability of radiation dose estimates (both gamma and neutron doses) on an *individual* basis, using, for example, information on the location and degree of shielding for individual survivors, weapon yield and dose transport calculations. Since the mid-1980s, analyses of the LSS have been based on the DS86 dosimetry system. There have been concerns in recent years about an apparent discrepancy between thermal neutron activation measurements in Hiroshima and the corresponding predictions based on DS86. Consequently, following a detailed assessment, a new dosimetry system entitled DS02 will be introduced shortly. However, it is thought that this will lead to little change in risk estimates[2]. Aside from systematic dose errors, it has been estimated that random errors in individual dose estimates may be of the order of 30%, and account has been taken of these in many recent analyses of LSS data.

Another important aspect of the LSS is the good quality of the mortality follow-up, which is based on a mandatory family registration system in Japan (*koseki*). This provides virtually complete national coverage of vital status, and allows emigrants from Japan to be identified, while causes of death can be determined from death certificates. However, death certification may sometimes be inaccurate, and better quality information on cancers can be obtained from cancer registries in Hiroshima and Nagasaki. In contrast to deaths, cancer cases are not identified among survivors who have moved to other parts of Japan, so allowance needs to be made for this in analyses[3]. The registry data are also informative about cancers such as breast and thyroid that have good cure rates.

A subset of about 20,000 survivors in the LSS has been invited by RERF to receive a medical examination every 2 years. This Adult Health Study (AHS) supplements the LSS by providing extra clinical and laboratory data, plus information on lifestyle. For example, general morbidity can be studied, blood samples can be requested for cytogenetic analysis and information on smoking habits can be collected. As well as its contribution to research, the AHS is important in the welfare role of the RERF.

CANCER RESULTS AND DERIVATION OF RADIATION RISK ESTIMATES

The most recent published analysis of cancer

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mortality in the LSS is based on follow-up from October 1950 to the end of 1990[4] (LSS Report 12). A new follow-up to the end of 1997 is due to be published soon (D. L. Preston, personal communication). The Report 12 analysis was based on 7827 cancer deaths among 86,572 survivors with DS86 doses. Of these deaths, it was estimated that around 90 leukaemias and 330 solid cancers may be due to A-bomb radiation (see Table 1). Results for cancer incidence have also been published, both for specific cancer sites from a follow-up to the end of 1987[3,5], and for all solid cancers combined from follow-up to the end of 1994[6]. In the following, the variations in cancer risks by age, time, dose and cancer site will be summarised, with a view to their use in deriving radiation risk estimates.

Variations in radiation risks by age and time

Whereas most of the risk of radiation-induced leukaemia appeared to arise in the first few decades after exposure, mortality rates for all solid cancers combined were still raised towards the end of the most recent follow-up period[4]. Furthermore, as indicated in Table 1, the relative increase in the total risk of solid cancers was higher for those exposed at young ages than for those exposed at older ages. However, most of the estimated excess solid cancer deaths arose among those exposed at ages of 20 years or more. This reflects the higher baseline rates at older attained ages, which survivors exposed at young ages were reaching only towards the end of the follow-up period.

There has been much interest in describing the age and temporal patterns in solid cancer risks, in order to make predictions of the risk of radiation-induced cancer over a lifetime. In its 2000 report, UNSCEAR[1] used two risk projection models. Under the 'age-at exposure' model, the excess relative risk (ERR), i.e. the relative risk minus 1, is assumed — for a fixed dose — to vary only by gender and age at exposure, and to be constant with time since exposure. Consequently, for a given age at exposure, the excess absolute rate (EAR) increases with increasing time since exposure as the baseline rate of solid cancers increases. In contrast, under UNSCEAR's 'attained-age model', the ERR for a fixed dose varies only by gender and attained age. In particular, for a given age at exposure, the relative risk decreases with increasing time since exposure under this model. However, the EAR increases over time, although at a slower rate than under the age-at-exposure model. UNSCEAR concluded that neither of these models describes all of the variation on solid cancer risks in the LSS, although both models provide a reasonable fit to these data. Based on the age-at-exposure model, UNSCEAR estimated the lifetime excess absolute risk of solid cancer mortality following an acute dose of 1 Sv to a Japanese population of all ages to be about 9% for males and 13% for females[1]. Estimates based on the attained-age model were about 30% lower, and this difference was greater for risk estimates based on childhood exposure. Continued follow-up will be important to determine to which, if either, of these models provides a better estimate of lifetime cancer risks.

Variations in risk with dose

Although the LSS is often viewed as being exclusively a high-dose study, about 15,000 survivors included in the Report 12 analysis had received a dose between 0.1 and 1 Sv, and the majority of survivors received less than 0.1 Sv[4]. Consequently, the LSS provides information on risks over a wide dose range, down to low values, as illustrated in Table 2. Some caution should be attached to the interpretation of values for individual dose categories in this table because of statistical varia-

Table 1. Mortality in the Life Span Study (LSS), 1950–1990, according to age at the time of bombing (based on Pierce *et al*[4]).

Age at time of bombing in 1945	No of people in LSS in 1950	Percentage surviving to 1991	Solid cancers		Leukaemia	
			Observed deaths	Estimated excess[a]	Observed deaths	Estimated excess[b]
0–9	17,824	94	227	24	35	15
10–19	17,557	86	662	66	43	17
20–29	10,882	77	816	62	32	12
30–39	12,270	51	1688	78	50	20
40–49	13,489	16	2370	72	59	22
50+	14,550	1	1815	32	30	1
Total	86,572	56	7578	334	249	87

[a]Estimated number, based on a model under which the excess relative risk (ERR) varies with dose according to a linear relationship, and such that the ERR decreases with increasing age at exposure and is greater for females than for males.
[b]Estimated number, based on a model under which the excess absolute rate (EAR) varies with dose according to a linear–quadratic relationship, and also varies by age at exposure, time since exposure and gender.

bility and the possibility of artefacts due to multiple comparisons. In general, inferences from modelling of dose–response relationships are likely to be more soundly based than those that involve examining individual dose categories in turn.

Analyses of leukaemia risk based on both mortality and incidence data indicate a linear–quadratic dose–response relationship over the range below 3 Sv. In particular, UNSCEAR[1] estimated the radiation-induced leukaemia risk at 0.1 Sv to be about one-twentieth of the risk at 1 Sv (the latter being about 1%). Whilst it has been suggested that the LSS leukaemia data support a threshold in risk at low doses, detailed analyses indicate that the evidence is weak[7,8]. For all solid cancers combined, both the mortality and incidence data are generally consistent with a linear dose–response over the range below 3 Sv. This linear model was used by UNSCEAR[1] in estimating solid cancer risks for acute doses of both 0.1 Sv and 1 Sv. Kellerer *et al*[9] derived slightly lower solid cancer risks for gamma ray exposure, owing to a different way of taking account of neutrons and because of some other methodological differences. The mortality data provided some suggestion of a higher risk per unit dose below 0.05 Sv than over the wider dose range[4]. However, this was not found to the same extent in the corresponding incidence data, perhaps reflecting a small bias due to differential misclassification of deaths among people known to be A-bomb survivors. It is notable that the incidence data showed a statistically significant trend in the risk of all solid cancers combined for doses over the range up to 0.1 Sv; furthermore, the upper confidence limit for any dose threshold in risk was 0.06 Sv[6]. Among individual types of solid cancer, only for non-melanoma skin cancer incidence was there a suggestion of non-linearity in the dose–response[7,10].

Thus, the LSS provides statistically powerful information on cancer risks down to relatively low doses, although it is uninformative about the effects of protracted or fractionated exposures. Based on other information, UNSCEAR[1] noted that estimates based on the LSS for solid cancer risks following acute exposures might be halved when considering chronic exposures, although the uncertainty in this reduction factor could be of the order of 2. For leukaemia, UNSCEAR[1] did not recommend any further reduction in risk for chronic exposures, over and above that arising from using the linear–quadratic dose–response model to extrapolate from high to low doses.

Variations in risk by cancer site

In contrast to many studies of medical exposure, in which only a few organs were irradiated to a sizeable degree, the A-bomb survivors received whole-body irradiation. Consequently, the LSS provides information on cancer risks for a wide range of cancer sites. Given the difficulties in synthesising results from other studies, the site-specific risk estimates calculated in the UNSCEAR 2000 report[1] were based on the LSS.

Pierce *et al*[4] showed that the ERR per sievert did not vary to a statistically significant extent between a

Table 2. Mortality in the Life Span Study (LSS), 1950–1990, by radiation dose (based on Pierce *et al*[4] and Shimizu *et al*[14]).

Dose (Sv)[a]	No of people in LSS in 1950[b]	Solid cancers		Leukaemia		Non-cancer diseases	
		Observed deaths	Estimated excess[c]	Observed deaths	Estimated excess[d]	Observed deaths	Estimated excess[e]
<0.005	36,459	3013	−42	73	9	11,484	−106
0.005–0.1	32,849	2795	85	59	−3	10,293	155
0.1–0.2	5467	504	18	11	0	1743	−52
0.2–0.5	6308	632	77	27	15	2018	20
0.5–1.0	3202	336	73	23	16	950	64
1.0–2.0	1608	215	84	26	22	446	40
2.0 or more	679	83	39	30	28	183	50
Total	86,572	7578	334	249	87	27,117	171

[a]Based on dose to the colon for solid cancers and for non-cancer diseases, and on dose to the red bone marrow for leukaemia, with a weighting factor of 10 for neutrons in each case.
[b]Numbers subdivided according to weighted colon dose.
[c]Estimated number, based on a model under which the excess relative risk varies with dose according to a linear relationship.
[d]Estimated number, based on a model under which the excess absolute rate varies with dose according to a linear–quadratic relationship.
[e]Estimated number, based on a model under which the excess relative risk varies with dose according to a linear–quadratic relationship.

wide range of cancer types, although there may be some underlying variation owing to differences in aetiology. In contrast, the EAR per sievert varied to larger extent, owing to differences in baseline rates between cancer types. Ron *et al*[11] found that for all solid cancers combined, both the ERR and EAR at 1 Sv were higher in the incidence than in the mortality data, owing to the greater diagnostic accuracy of the incidence data and the under-representation of cancers such as breast and thyroid in the mortality data. In contrast to these latter two cancers, radiation risks for some cancer types were lower in the incidence data than in the mortality data. In particular, unlike the mortality data, data on the incidence of multiple myeloma did not show a clear association with radiation, owing in part to a review of diagnoses[5].

The baseline rates for some types of cancer have tended to differ between Japan and many Western countries; for example being higher for stomach cancer and lower for lung and female breast cancer in Japan compared with Western countries. There is uncertainty about how to transfer radiation cancer risks based on the LSS when making risk estimates for other countries. For female breast cancer, parallel analyses of the LSS and medically exposed groups in North America suggest that it may be best to transfer the EAR across countries, i.e. the absolute increase in risk[12,13]. In contrast, there is some indication that for stomach cancer, the ERR (i.e. the relative increase in risk) may be more stable across the LSS and studies of medical exposures in Western countries[1]. However, it has been difficult to assemble information in a uniform fashion to analyse this topic for other cancer types. UNSCEAR[1] showed that ranges for cancer site-specific risk estimates, using both absolute and relative measures to transfer risks from the LSS to other countries, could be wide in some circumstances. In contrast, the method of transfer has relatively little impact on estimates of the total risk of radiation-induced cancer in other countries.

MORTALITY FROM NON-CANCER DISEASES

Shimizu *et al*[14] have analysed about 27,000 deaths from non-cancer diseases in the LSS during 1950–1990. Some of these data are presented in Table 2, although, as noted earlier, caution should be attached to the interpretation of results for individual dose categories. The analysis by Shimizu *et al* strengthened the evidence noted in earlier follow-ups for a dose-related increase in non-cancer disease mortality, particularly for diseases of the circulatory, digestive and respiratory systems. For those members of the LSS who were also in the AHS, clinical examinations have shown statistically significant dose–response trends for myocardial and cerebral infarctions and for various indicators of atherosclerotic changes and hypertension[15]. For a dose of 1 Sv, Shimizu *et al*[14] estimated that rates of non-cancer disease mortality were raised by about 10% relative to unexposed survivors; this is a lower relative increase than that for cancer. In absolute terms, the number of excess non-cancer deaths in the LSS up to the end of the 1990 was estimated to be around 140–280[14], which compares with the estimate of about 420 radiation-induced cancer deaths in the same population[4]. However, there is uncertainty in the form of the putative dose–response relationship and hence in estimates of excess non-cancer deaths at low doses. Shimizu *et al*[14] noted that the data are consistent with various possible dose–response relationships, including both a linear trend and non-linear functions under which there is essentially no raised risk at doses below 0.5 Sv. Also, the authors were unable fully to explain the non-cancer findings on the basis of dose misclassification, confounding variables or selection effects. It should be noted that the evidence for excesses of non-cancer diseases in other groups exposed to medium or low radiation doses appears largely to be weak. Consequently, in the absence of an understanding of relevant biological mechanisms, the extent to which the LSS findings on non-cancer mortality may influence radiation risk estimates at low doses is unclear. UNSCEAR is currently addressing this topic, and will take account of the extended follow-up of the LSS that is due to be published shortly.

CONCLUSION AND PERSPECTIVE

Follow-up of the Japanese A-bomb survivors has provided a considerable amount of information on the late health effects of radiation. This reflects several notable advantages of the LSS, including:

- the large cohort of survivors, of all ages and both genders;
- the wide range of doses received from essentially whole-body exposure, and the availability of individual dose estimates;
- the long-term, mostly prospective, follow-up of both mortality and cancer incidence; and
- the high statistical precision to analyse trends in risk with dose.

As in any epidemiological study, the LSS also has some limitations, such as:

- the lack of systematic follow-up in the first 5 years after exposure, which has led to discussion about the potential impact of selection effects[16,17];
- the lack of information on chronic or fractionated exposures; and
- the fact that the findings to date have been influenced largely by those who received medium or high doses.

There are still uncertainties about the shape of the dose–response, both for cancer and for non-cancer diseases, below about 0.1 Sv. A concern for future investigations of this topic is that any small residual bias, which might distort risks by only a few per cent, could

have a large impact on inferences at very low doses. In addition, analyses of site-specific cancer risks will continue to be affected by changing patterns in baseline cancer rates in Japan as this population moves towards a Western lifestyle. However, further follow-up of the A-bomb survivors will be important in addressing both these issues and the estimation of lifetime cancer risks for those exposed when young. This is because, as indicated in Table 1, about half of the survivors (including about 90% of those aged under 20 years at the time of bombing) were still alive in 1991 and many of them are still alive today. Not only has LSS already provided much information on radiation risks, but it will continue to do so for many years to come.

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