Fifty Years of Studying A-Bomb Survivors

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Abstract

Together with other authorities, the Radiation Effects Research Foundation is firmly of the opinion that a lengthy follow-up of A-bomb survivors has provided the world with reliable sources of risk estimates for genetic, teratogenic, and carcinogenic effects of ionising radiation. On this assumption the risk of brain damage is negligible for exposures within 8 weeks of conception, and the cancer risk is lower for exposure after than before 30 years of age. However, alternative analyses of A-bomb data have found evidence of unsuspected biases in the RERF study cohorts, and found new uses for certain records of acute injuries of five year survivors. When added to other variables these records made it possible to see that sensitivity to cancer effects of radiation was much greater towards the beginning and end of the life span than during the intervening years. This evidence of how the age when exposed to radiation affects the cancer risk has brought A-bomb data into line with other studies of low dose effects such as the Oxford Survey of Childhood Cancers and recent surveys of nuclear workers.

Launching of the Fifty Year Follow-up

Included in the survey of A-bomb survivors that has just completed fifty years of follow-up, are three study cohorts assembled by the Atomic Bomb Casualty Commission after coming to Hiroshima and Nagasaki about two years after the bombing [14]. By that time a massive epidemic of acute marrow damage had come and gone [10], and three later effects of the radiation had been identified, namely, lens opacities, brain damage (following *in utero* exposures) and leukaemia [14].

Since it was natural to expect that the marrow damage might have left some of the high dose survivors with residual disabilities, one of the earliest actions of ABCC was to arrange for haematological examinations of more than a thousand survivors with epilation. A first round of blood tests revealed slight lowering of average red and white cell counts in this study population, but this had completely disappeared by the time the examinations were repeated, and there were no other signs of faulty erythropoiesis or leucopoiesis [19]. Therefore, ABCC assumed that there had been full recovery from the marrow damage and turned their attention to other problems. Thus, from pregnant women who had applied for extra rations, they assembled an 'F_1 cohort' for studying second generation effects of the radiation. From registers of live births covering the first nine months after the bombing, they assembled a '*cohort of in utero children*' for studying teratogenic and carcinogenic effects of fetal irradiation. And finally, from the national census, that was held on October 1st 1950, they assembled the *life span study* or LSS cohort for studying later effects of postnatal exposures [14].

F_1 Cohort

Though there has been an enormous investment of time and labour in biochemical, cytogenetic and survival

studies of the cohort that was chosen to represent second generation effects of the A-bomb radiation, this work by ABCC and the Radiation Effects Research Foundation has not yielded any certain evidence of genetic damage. On the contrary, it has shown that, thus far, the F_1 cohort has had *lower* rates of cancer and noncancer mortality than would be expected from national statistics [20]. The possibility that this finding might be the result of selection has never been mentioned by RERF. But given the harsh living conditions that prevailed before ABCC arrived on the scene, the low rates of childhood mortality for the F_1 cohort could easily be the result of extra, dose related deaths leaving adults of childbearing age strongly biased in favour of exceptionally hardy persons.

Cohort of *In Utero* Children

Though A-bomb studies of teratogenic and carcinogenic effects of fetal irradiation have had more in the way of positive findings than studies of second generation effects, recent work has revealed various oversights. Thus there was failure to recognise that there were less than half the expected number of births in April and May 1946 (and that the most likely cause of this deficit was radiation-induced deaths for fetuses that were under 8 weeks of age when exposed) [17]. And there was also failure to appreciate that pre-leukaemic children were far more likely to die from environmental effects of the blast than normal children [7] (and that this might be the reason why there were no cases of childhood leukaemia in the ABCC study cohort) [21].

The first oversight casts doubt on the assumption that there is little or no sensitivity to brain damage effects of radiation before 8 weeks of fetal age [5, 14]. And the second one casts doubt on the assumption that we have in A-bomb survivors a better source of risk estimates for carcinogenic effects of fetal irradiation than the Oxford Survey of Childhood Cancers [13]. The very different estimates for cancer effects of prenatal x-rays, and cancer effects of *in utero* exposure to A-bomb radiation, also made it appropriate to consider the following hypothesis: acute effects of the Hiroshima and Nagasaki bombs are still influencing the death rates of survivors and their offspring, and are making it *especially* difficult to discover whether late effects of the A-bomb radiation included marrow damage as well as cancers.

According to this hypothesis, none of the ABCC study cohorts is a trustworthy source of risk estimates for late effects of radiation. But the LSS cohort could be improved by taking into account the injury data collected by ABCC while checking the exposure positions of five year survivals [6], since this would make it possible to discover whether there were any significant differences between the survivors with and without these early injuries.

LSS Cohort

The fact that risk estimates for radiation workers and other low dose situations are based on the LSS cohort shows that RERF is not alone is assuming that these five year survivors, "apart from their radiation dose, are representative human beings" [12]. On this assumption, which is shared by BEIR V [3], sensitivity to late effects of radiation would have to be independent of sensitivity to early effects, otherwise deaths from acute injuries would have left the LSS cohort short of persons who were exceptionally sensitive to cancer effects of the ra-

diation (positive correlation between the two effects) or exceptionally resistant (negative correlation).

According to RERF and BEIR V, such correlations have been ruled out by the fact that the noncancer death rate of the LSS cohort is not dose related nor significantly different from expectations based on national statistics [2]. However, this assumption is difficult to reconcile either with OSCC data [9] or with a recent study of nuclear workers [8], and is still being challenged by two epidemiologists. Thus, in 1990 Stewart and Kneale used one of the diskettes compiled by RERF from LSS data to show that the noncancer death rate of this cohort had a U shaped dose response curve that could easily be the result of selection and marrow damage having diametrically opposite effects on all diseases with immune system associations [15]. Three years later, they used the same diskette to show that the proportion of high dose survivors (over 1 Gy) was much lower for persons who were under 10 or over 50 years of age in 1945 than for the intervening age groups [17]. And a few months ago they observed the effects of adding to an updated diskette, the injury data compiled by ABCC between 1950 and 1960 [18].

The results of the latest Stewart and Kneale analyses of A-bomb data are still awaiting publication, but they threaten to undermine the position taken by BEIR V after applying to LSS data a 'Poisson regression' model. With this model "the observed number of events in each cell of the cross tabulation is treated as a Poisson variate with parameters given by the predicted number of events under the model" [3]. Therefore, Stewart and Kneale decided that it was appropriate to observe the effects of repeating this analysis after adding the injury data to the usual variables, and using them to obtain several subgroups of the LSS cohort [18].

Reanalysis of the LSS Cohort after Incorporating the ABCC Injury Data

When the incomplete set of injury data compiled by ABCC were added to the RERF diskette it was possible to see that 74,042 members of the LSS cohort had been given an opportunity to claim or deny at least one of the following injuries: flash or fire burns, oropharyngeal lesions, spontaneous bleeding or epilation (Table 1). The total number of claimants was 9,284 or 12.5% of the cohort. But this proportion was much higher for survivors who eventually developed leukaemia (35.6%) than for survivors with other neoplasms (15.1%) or other causes of death (11.8%) and, within the group of leukaemia deaths, the proportion of multiple injuries was also exceptionally high.

Other findings of the unpublished analysis include evidence of a radiation effect for deaths ascribed to cardiovascular disease as well as cancers, and evidence that levels of sensitivity to cancer effects of the radiation were appreciably higher for survivors with than without multiple injuries (Table 2). There was also evidence that this difference was largely the result of exposures after 60 years of age (Fig. 1), and evidence that relations between exposure age and cancer risk were very different for A-bomb survivors and nuclear workers (Fig. 2).

Selection Hypothesis

The importance of the Stewart and Kneale analyses of A-bomb data lies in the fact that they allow one to see that a) the study cohorts chosen by ABCC to represent late ef-

fects of radiation were not typical of the nonsurvivors, b) the atypical characteristics of the LSS cohort were the result of deaths from acute injuries being concentrated among person who (by virtue of their age) were exceptionally sensitive to all causes of death, including the cancer caused by the A-bomb radiation. [18]

One of the reasons why it has taken so long to realise that the A-bomb survivors were not typical Japanese citizens was because analysts of LSS data failed to grasp the true significance of there being both too many deaths from aplastic anaemia and too few suicides among the high dose survivors [1]. A possible cause of the extra deaths was residual marrow damage. But according to Beebe *et al* this was ruled out by the 'normal' noncancer death rate (and the normal haematological findings for survivors with epilation) and left, as the most likely cause of the extra deaths, the profound anaemia which characterises the terminal phase of leukaemia and other malignant diseases. This conclusion made it relatively easy to regard the low suicide rate as a fluke. And though we can now see that, in a population that was still suffering from residual effects of marrow damage, a small group of '*sudden deaths from self inflicted injuries*' might provide the only evidence of selection, this was not obvious twenty years ago. Even today the strongest support for the selection hypothesis comes from two unpublished observations, namely, the differences between A-bomb survivors with and without multiple injuries in Table 2, and the differences between the survivors and the nuclear workers in Fig. 2.

We also have in Table 1 some support for a recent suggestion, namely, that it is only when the dose is sufficient to cause extensive tissue destruction that late effects of radiation include a batch of leukaemias with exceptionally short latent periods [16]. At this dose level (over 1 Gy) radiation effects include a granulocytosis followed by leucopenia and extreme infection sensitivity [14]. This makes death within two weeks of exposure a likely consequence, but an obvious alternative is a *special* leukaemia effect caused by the combined effects of the granulocytosis and the immune incompetence. Besides accounting for the leukaemia findings in Table 1, this sequence of events would explain why the special relationship between leukaemia and radiation is confined to myeloid cases, and has only been observed in surveys where the dose was sufficient to cause extra deaths from aplastic anaemia [4, 14].

In short, although much has been learnt from fifty years of studying A-bomb survivors, much has been missed by biostatisticians who too readily assumed that a normal blood picture ruled out immune system damage, and too readily assumed that the usual effect of age on sensitivity to all diseases need not apply to late effects of radiation.

References

1 Beebe GW, Kato H, Land CE. Life Span Study Report 8. Mortality experience of atomic bomb survivors, 1950-74. Technical Report RERF TR 1-77.

2 Beebe GW, Land CE, Kato H. The hypothesis of radiation-accelerated ageing and the mortality of Japanese A-bomb victims. *In* Late Radiological Effects of Ionising Radiation IAEA Vienna 1978;**1**:3-27.

3 BEIR V. Health effects of exposure to low levels of ionizing radiation. Natn Acad Press, Washington DC, USA 1990.

4 Court Brown W, Doll R. Leukaemia and aplastic anaemia in patients irradiated for ankylosing spondylitis. Medical Research

Council Special Report Series 295 HMSO London 1957.
5 International Commission on Radiological Protection: Developmental effects of irradiation on the brain of the embryo and fetus. Annals of the ICRP 16.1986:1-43.
6 Jablon S, Ishida M, Yamasaki M. Studies of the Mortality of A-bomb Survivors. 3. Description of the sample mortality, 1950-1960. Rad Res 1965;**25**:25-52.
7 Kneale GW, Stewart AM. Pre-cancers and liability to other diseases. Br J Cancer 1978;**37**:448-457.
8 Knox EG, Stewart AM, Kneale GW, Gilman EA. Prenatal irradiation and childhood cancer. J Rad Prot 1987;**7**;(4):3-15.
9 Kneale GW, Stewart AM. Factors affecting recognition of cancer risks of nuclear workers. Occup & Env Med 1995;**52**:515-523.
10 Ohkita T. Review of thirty years study of Hiroshima and Nagasaki atomic bomb survivors. Acute Effects. Journal of Radiation Research 1975;**16**:49-66.
11 Preston DL, Kato H, Kopecky KJ, Fujita S. Studies of the mortality of A-bomb survivors : 8 Cancer mortality, 1950-1982. Rad Res 1987;**111**:151-178.
12 RERF. Minutes of a meeting of the Scientific Council of the Radiation Effects Research Foundation. RERF Annual Report 1987:98.
13 Rose KSB. Epidemiological surveys on the effects of low level radiation dose: A comparative assessment. *In* AEA Environment and Energy, 1990. AEA-EE-0001 (AERE R12045 Vol B).
14 Schull WJ. Effects of Atomic Radiation: A half-century of studies from Hiroshima and Nagasaki. Wiley Liss, Inc., New York 1995
15 Stewart AM, Kneale GW. A-bomb radiation and evidence of late effects other than cancer. Health Physics 1990;**58**;(6):729-735.
16 Stewart AM. Relative sensitivity of myeloid and lymphatic stem cells to mutational and cell killing effects of ionizing radiation. Leukemia Research 1991;**15**;(12):1089-1090.
17 Stewart AM, Kneale GW. A-bomb survivors: Further evidence of late effects of early deaths. Health Physics 1993;**64**;(5):467-472.
18 Stewart AM, Kneale GW. Acute injuries of A-bomb survivors: Their epidemiological importance. 1996 (unpublished)
19 Yamasawa, Yoshimichi. Hematologic studies of irradiated survivors in Hiroshima, Japan. Archives of Internal Medicine 1953;**91**:310-314.
20 Yoshimoto Y, Schull WJ, Kato H, Neel JV. Mortality among the offspring (F_1) of atomic bomb survivors, 1946-85. RERF Technical Report Series RERF TR 1-91, Research Project 4-75.
21 Yoshimoto Y, Kato H, Schull WJ. Risk of cancer among children exposed *in utero* to A-bomb radiations, 1950-84. Lancet 1988;**ii**:665-669.

Table 1
A-bomb survivors. 74,042 persons with acute injuries.
(From Stewart and Kneale [18])

Specifications[1]		Claimants Nos.[2]	Claimants %[2]
Number of Injuries	One	6,683	9.0
	Two	1,737	2.3
	Three	708	1.0
	Four	156	0.2
Types of Injury	Burns	5,552	7.5
	Oropharyngeal Lesions	3,613	4.9
	Spontaneous Bleeding	2,432	3.3
	Epilation	1,308	1.8
	All Types	12,905	17.4
Vital Status	Alive: (45,305)	5,640 (1,529)	12.4 (3.4)
	Dead:		
	Leukaemia (202)	72 (41)	35.6 (20.3)
	Other Neoplasms (6,022)	909 (308)	15.1 (5.1)
	CVS (11,164)	1,346 (362)	8.3 (3.2)
	Other Deaths (11,349)	1,317 (361)	11.6 (3.2)
	Alive and Dead	9,284 (2,601)	12.5 (3.5)

1 Unless otherwise stated the number of survivors is 74,042
2 Figures in brackets are for multiple injuries

Table 3
Tests of uniform levels of sensitivity to late effects of radiation.
(From Stewart and Kneale [18])

Series (1)	df	Causes of Death: All Causes	Leukaemia	Other Malignant Neoplasms	CVS	Other Diseases
		χ^2 tests of radiation effects(1)				
A	(8)	41.1	32.8	25.8	17.1	3.3
B+C	(8)	45.2	39.2	40.0	28.6	6.8
D+E	(8)	45.5	37.7	48.5	33.4	11.3
B+D+F(2)	(16)	50.7	41.3	63.2	40.7	20.7
		χ^2 tests of uniform levels of radiosensitivity				
A-(B+C)	(8)	4.1	6.6	*14.2**	11.5	3.5
A-(D+E)	(8)	4.3	4.9	*22.7**	*16.3**	8.0
A-(B+D+F)(2)	(16)	9.6	8.5	*37.4**	*23.5**	17.3

(1) see Table 2
*italics** indicates non-uniform levels of sensitivity to late effects of radiation within the LSS cohort

Table 2
Radiation effects of acute injuries. With chi squares to show the results of applying a Poisson regression model to the enlarged data base and recognising seven exposure ages. (From Stewart and Kneale [18])

Causes of Death		Series A (74,042)	B (63,027)	C (10,970)	D (2,601)	E (71,441)	F (8,369)
Neoplasms	Leukaemia	201	121	80	41	160	39
	Other Malignant	5,491	4,487	1,004	293	5,196	708
	Benign	273	224	49	12	261	37
	Total	5,965	4,832	1,133	349	5,616	784
Other Causes	CVS	10,676	9,073	1,603	362	10,314	1,241
	Other Diseases	9,079	7,721	1,358	309	8,770	1,049
	Trauma	1,410	1,181	229	52	1,358	177
All Causes of Death		27,130	22,807	4,323	1,072	26,058	3,251
		Chi Squares (8 df)					
Neoplasms	Leukaemia	32.8**	35.0**	4.2	34.0**	3.7	2.6
	Other Malignant	25.8**	31.9**	8.1	27.7**	20.8**	10.5
	Benign	5.1	5.2	5.0	4.1	4.2	4.7
	All Neoplasms	58.6**	58.6**	7.7	40.7**	17.6*	9.7
Other Causes	CVS	17.1*	6.0	22.7**	8.9	34.5**	0.2
	Other Diseases	3.3	4.2	2.6	5.5	5.9	10.6
	Trauma	1.9	2.4	5.1	2.8	7.8	9.3
All Causes of Death		41.1**	29.6**	15.7*	30.3**	15.2*	5.9

Figures in brackets show the size of each series
Other figures in the upper half of the table are numbers of cases
The Chi Squares in the lower half of the table are Poisson regression tests of radiation effects

* $p<0.5$
** $p<0.1$

Series
A = the LSS cohort as a whole
B = all four injuries denied
C = A minus B
D = multiple injuries
E = A minus D
F = A minus (B+D)

Note: A = B+C = D+E = B+D+F

Fig. 1
Excess relative risk of a cancer death at 1 Gy for all neoplasms at seven exposure ages (From Stewart and Kneale [18])

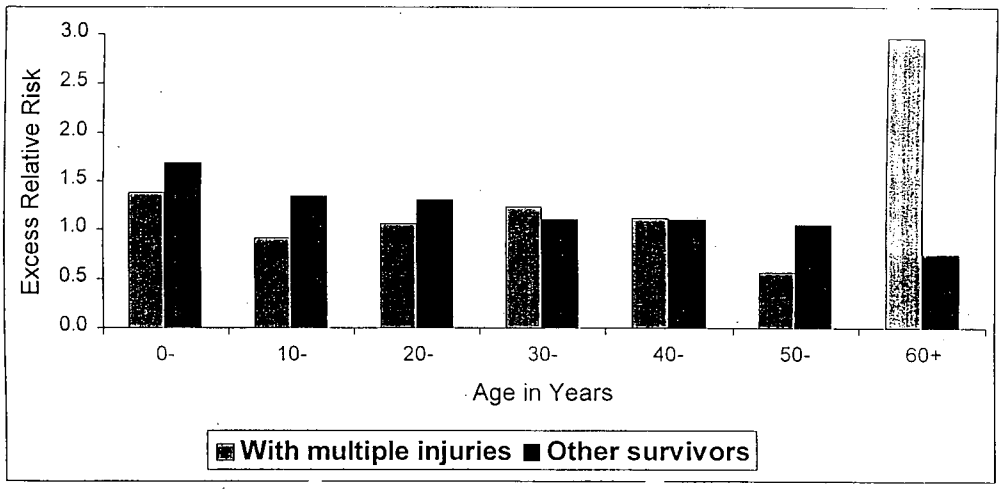

Fig. 2
The effect of the age when exposed on the cancer risk for 1 Gy (with allowance for cancer latency) for two study populations: (A) nuclear workers [9] and (B) A-bomb survivors [11].