A-bomb Survivors

Further evidence of late effects of early deaths

by

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Abstract

Reanalysis of A-bomb survivor data has shown that in the life span study cohort there is a significant deficit of high doses in two age groups (under 10 and over 50 years in 1945) and in the cohort of *in utero* children there is a similar finding for person who were under 8 weeks of fetal age when exposed. Also discussed is how this selection bias has affected our perceptions of marrow damage, brain damage, carcinogenic and second generation effects of the radiation.

Key Words

A-bomb, Epidemiology, Radiation, Selection

Introduction

According to several authorities, including BEIR V (1990) and ICRP 60 (1991), the most reliable source of risk estimates for cancer effects of radiation is the life span study (LSS) cohort which was assembled 5 years after the bombing of Hiroshima and Nagasaki. This consensus is largely the result of all radiation protection committees agreeing with the Radiation Effects Research Foundation (RERF) on the following points: 1) the LSS cohort has a normal risk of dying from all natural causes including non-radiogenic cancers; 2) all acute effects of the A-bomb radiation (which included wholesale destruction of the hemopoietic stem cells of red marrow) were exhausted in less than 5 years, and 3) all later effects of the radiation were the result of somatic or germ cell mutations (Beebe *et al* 1978, Preston *et al* 1987) It is also the result of rejecting an hypothesis which was first advanced by Stewart (1982, 1985). According to this there are fundamental and longstanding differences between individuals in their state of health (or resistance to diseases) which are linked to differences in socioeconomic grouping, lifestyle, genetics and other factors influencing the general competence of the immune system.

The relevance of this hypothesis to the interpretation of A-bomb survivor data is two-fold. Firstly, in the year immediately after the bombing, and to a lesser extent in the remaining four years till the LSS cohort was assembled, there was a very high death rate, especially from diseases where resistance demands high levels of immunological competence. Consequently, we would expect the LSS cohort, when finally assembled, to be selected in favour of exceptionally healthy individuals, and especially so close to the hypocenter where injuries were most common (selection hypothesis). Secondly, ionizing radiation is known to be especially

damaging to areas of bone marrow where stem cells of the immune system are located. As a consequence of this, high dose survivors would have impaired levels of immunological competence (marrow damage hypothesis), thus allowing two effects of the A-bombs to cancel one another. Therefore, the aim of this paper is to pin point features of RERF data which suggest that, in spite of this cancellation, we could be dealing with two, valid hypotheses.

Life span study (LSS) cohort

In favour of there being partial cancellation of a selection effect by late effects of marrow damage, is an analysis of LSS data by Stewart and Kneale (1991) which showed that, for non-cancer deaths, a negative dose trend between 0 and 1 Gy was accompanied by a positive dose trend between 1 and 4 Gy . This observation has since been confirmed by RERF, but although Shimizu *et al* (1991) found that "non-cancer mortality in the period 1950-85 exhibits a significant non-linear dose response with excess risks apparent at doses of 2 or 3 Gy and over", they finally concluded that, since "this evidence is limited to only the older ages ATB in the initial years of study", selection was unlikely to have affected the cancer risk. Nevertheless, outright rejection of the selection hypothesis is difficult for another reason.

The LSS cohort of 5 year survivors was assembled from 4 zones or 'hypocenter distance groups', and each of these groups was matched for size sex and age (Beebe *et al* 1962). Therefore, if there had not been any selection against 'immunological incompetence' (during the aftermath of the two nuclear explosions) the proportion of high dose survivors in the LSS

cohort would be roughly the same for each exposure age. But, given such selection - which would necessarily affect future liability to cancer as well as infections - the proportion of high dose survivors would certainly be lower for the exposure age groups which were relatively infection sensitive (e.g. children and old persons) than for the more resistant age groups (e.g. young or middle-aged adults).

The figures in table 1 and fig. 1 are based on the same sample LSS data which was included in the Stewart and Kneale (1990) analysis. They show the results of a) stratifying by sex and city; b) recognising 5 exposure ages and 8 dose levels on the T65 scale; c) comparing observed and expected numbers, assuming no interaction between age and dose (Mantel-Haenszel analysis) and d) using the method described, in the 1990 analysis, to estimate the terms of any interaction between exposure age and dose, assuming either a linear or a quadratic relation with each of the 5 age groups. In addition, Fig. 2 shows the results of replacing the T65 dose estimates with the DS84 estimates.

On both dose scales the proportion of high dose survivors (over 0.5 Gy) was smaller for the youngest and oldest exposure ages (under 10 and over 50 years in 1945) than for the intervening ages. This significant difference was the result of a quadratic interaction between dose and age, so it could be described as a typically a high dose effect with maximum impact on children and old persons.

This finding makes it reasonable to assume that, in the LSS cohort, there was under-representation of persons who (by virtue of their age in 1945, and their exposure positions) were most at risk of dying from

radiogenic and non-radiogenic cancers during the next 20 or 30 years. Together with the earlier finding of a positive dose trend for non-cancer deaths at high dose levels (Stewart and Kneale 1990), the new finding makes it probable that some of the cancers currently ascribed to mutational effects of the radiation, were actually the result of defective immune responses, or cancer promotion effects of marrow damage. They also show that it is no longer safe to assume, either that the RERF study cohort of *in utero* children (Kato and Keehn 1966) is a straightforward source of risk estimates for fetal irradiation; or that the study cohort of F1 offspring of A-bomb survivors (Kato *et al* 1966) is a straightforward source of second generation effects of radiation.

In utero children

From a source population consisting of 5373 *"in utero children"*, defined as children whose mothers were exposed and they themselves were born "from the time of the bomb to 31 May, 1946", Kato and Keehn (1966), made the following selection: "all subjects in the groups within 1500m [of the hypocentre] were included in the study sample and comparison subjects were selected for each of the distance groups 1500-1999m, 2000-2999m, and 3000-3999m having the same source, city and sex, and the closest match possible for month of birth".

As a result of this selection 1) only 1817 or one-third of all the *in utero* children were ever included in later studies of fetal irradiation effects (Table 2); 2) the Nagasaki proportion was reduced from 45-15%, and 3) it was not possible to discover whether a special effect of fetal irradiation (abortion risk) was felt outside the central zone (Table 3).

According to a Kato and Keehn (1966) analysis of the 1288 city birth registrations in Table 2, the number of *in utero* children who were born before 1946 (591) was less than the expected number, assuming a constant daily rate of live births (676.8). For these children, who were obviously at greater risk of dying from the general turbulence than later births, the estimated exposure age (measured from conception) was 23-40 weeks. For children who were born in the next two months (and had estimated exposure ages of 11 to 19 weeks) the observed number was larger than the expected number (411 and 273.5), but for children who were born after March 1946 (and had estimated exposure ages of 0-7 weeks) the observed number was again lower than the expected number (122 and 204.0). These frequencies were determined by 320 children from the central zone, whose exposure positions were within half a kilometer of the hypocenter. Therefore, in this high risk group, which is shown separately in Table 3, there is evidence that, for embryos (or fetuses who were still at risk of an early abortion), the probability of surviving a high dose exposure was much smaller than for other, more mature fetuses.

Brain damage effects of fetal irradiation

Extra abortions or perinatal deaths would necessarily mask the true frequency of teratrogenic or carcinogenic effects of the A-bomb radiation. Nevertheless, in studies of *in utero* children there has never been any allowance for a well known fact, namely, that the lethal dose is much smaller for embryos than for mature fetuses (Russell 1954). For example, in the Otake and Schull (1983) study of brain damaged children, which was based on 1,599 *in utero* children, the apparent insensitivity to this teratrogenic effect in the youngest age group (under 8 weeks of fetal age)

was probably an artifact caused by the low dose needed for an abortion. Evidence in favour of this suggestion can be found in Table 4 where one can see that, in the youngest of 4 exposure age groups (under 8 weeks of fetal age), the proportion of high doses (over 0.5 Gy) was much smaller (1.4%) than it was in the oldest age group (over 26 weeks, with 5.0% of high doses).

Carcinogenic effects of fetal irradiation

There has also been a follow-up of 1,630 *in utero* children by Yoshimoto *et al* (1990) which first identified 10 fatal and 8 non-fatal cancers with onsets before 40 years of age, and then used these cases to obtain incidence based as well as mortality based risk estimates (Table 5).

Only 4 of the 18 cases were males. Therefore, the sex ratio (0.29) was much lower than the usual ratio for cancer deaths before 40 years of age (circa 1.05). In addition, there were no cases of childhood leukemia (and only 2 older cases) and only one solid tumour death before 18 years. Therefore, since data from the Oxford Survey of Childhood Cancers (OSCC) have shown a) that infection deaths are a special risk of preleukemic children (Kneale 1971), and b) that this infection sensitivity is the result of direct involvement of the immune system in the cancer process (Stewart and Kneale 1982), it is reasonable to assume that, in the RERF cohort of *in utero* children, carcinogenic effects of the radiation were competing not only with a high abortion risk (radiation effect) but also with a high risk of dying from postnatal infections (turbulence effect). The abortion risk would probably affect males more than females, and the infection risk would certainly be greater for leukemia than for solid

tumours. Therefore, there are several features of the 18 cancer cases which could be explained by assuming that there were lasting effects of an exceptionally strong selection bias.

F1 Offspring of A-bomb Survivors

Over 20 years ago Kato *et al* (1966) prefaced a report on F1 offspring of A-bomb survivors with the following words: "The genetic effects to be expected in the first generation progeny of mammals exposed to radiation is a shortening of the life span due to the action of deleterious mutations". This expectation was based on "a considerable body of data concerned with such experimental species as mice, rats and swine". Nevertheless, in 1991, Yoshimoto *et al* found that "continued surveillance of mortality among the live born children of A-bomb survivors has not revealed a significant increase in the relative risk of mortality from all diseases except neoplasms, nor from neoplasms, following parental exposure to A-bomb radiation". On the contrary, the ratio of observed to expected numbers was well below unity both for all causes of death (0.72) and for neoplasms (0.81).

According to the later report "a variety of explanations can be advanced for this discrepancy from an expected ratio of 1" and "arguably, the most important of these centers in the appropriateness of the national statistics as the basis for determining the expectations [since] these statistics are derived from all Japan including rural areas". However, rural areas usually have much lower rates of infant mortality than urban areas. Therefore, a more likely cause of the low (F1) death rates is the unusual experiences of the parents of these children. For example, the

number of deaths from trauma related infections in 1945 alone would be sufficient to leave survivors with exceptionally high levels of immunological competence, this would pave the way for a second generation effect of 'survival of the fittest' which, in terms of general or cancer mortality, would more than offset any comparable effects of the genetic damage caused by the radiation.

Discussion

The assumption that all RERF study cohorts provide straightforward sources of risk estimates for carcinogenic or teratrogenic effects of radiation is largely the result of discovering that the non-cancer death rate of the LSS cohort has always been close to expectations based on national statistics (standardized mortality ratio or SMR analysis) and has never shown any signs of being dose related (linear model of relative risk or RR analysis). But it is now necessary to find solutions to the following problems: why is there U-shaped curvature of dose response for all causes of death except neoplasms and cardiovascular diseases (Stewart and Kneale 1990); why is the proportion of high doses much lower for persons who were under 10 and over 50 years of age in 1945 than for the intervening age groups (Table 1); why are the cancer experiences of *in utero* children so different from the cancer experiences of children who are involved in obstetric x-ray examinations (Yoshimoto *et al* 1990 and Stewart *et al* 1958); why is the F1 cohort showing signs of being exceptionally healthy (Yoshimoto *et al* 1991); and, finally, why is the LSS cohort death rate for blood diseases other than leukemia (which is dominated by deaths from aplastic anemia) so strongly dose related (Beebe *et al* 1978).

The first two anomalies can be explained by assuming that competition between selection effects of the early deaths and marrow damage effects of the radiation has been constantly creating an impression of normality, whose spurious nature has recently been uncovered by meticulous inspection of deaths from causes other than cancer. The unusual cancer experiences of *in utero* children can be explained by assuming that, for these children, competing causes of death included abortions (radiation effect with a selective effect on embryos) and infections (turbulence effect with a selective effect on leukemias), and the low death rates of the F1 cohort is probably the result of genetic selection being a natural consequence of any disaster situation. Finally, given the massive epidemic of acute bone marrow depression in 1945 (Ohkita 1975), the extra deaths from aplastic anemia in the LSS cohort are far more likely to be the result of this, cell death effect of the radiation, than to be the result of Japanese doctors constantly mistaking leukemia for aplastic anemia (Beebe *et al* 1977).

Though evidence in favour of lasting effects of the early deaths seems to us to be exceptionally strong in the cancer study of Yoshimoto *et al* (1990), these data have not been given this interpretation by BEIR V (1990). Furthermore, although RERF has conceded a need "to confirm the suggestion of a radiation-related increase in mortality from causes other than cancer" (Shimizu *et al* 1991), it remains the prevailing view that, only mutational effects of the radiation prevented the holocaust from having no long term consequences. Even so, we find it impossible to believe, either there are no lasting effects of extensive marrow damage, or that there are no lasting effects of survival of the fittest.

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Table 2 Potential and actual size of the RERF cohort of *in utero Children*; from Kato and Keehn, 1966.

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Table 4 1599 *In utero children* included in a study of brain damage effects of radiation; from Otake and Schull (1983)

Table 5 Cancer experiences of 1630 *in utero children*; from Yoshimoto *et al* (1988)

Figure 1 T65 Dose distribution for 5 exposure ages

Vertical axis : Ratio of observed to expected nos.

Horizontal axis : dose in cGy : 0-, 1-, 10-, 50-, 100-, 200-, 300, 400+

Figure 2 DS86 Dose distribution for 5 exposure ages

Vertical axis : Ratio of observed to expected nos.

Horizontal axis : dose in cGy : 0-, 0.6-, 20-, 50-, 100-, 200-, 300-, 400+

Table 1. LSS Cohort of A-bomb survivors
Relation between exposure age and T65 doses

T65 dose cGy	Exposure age (Y) 0-9		10-19		20-34		35-49		50+	
	Obs.	O:E	Obs.	O:E	Obs.	O:E	Obs.	O:E	Obs.	O:E
0-	6171	1.04	6012	0.97	5668	1.03	6843	0.99	4786	1.03
1-9	4953	1.02	5085	1.01	4412	1.00	4952	0.97	3518	1.01
10-49	2500	1.05	2241	0.90	2319	0.98	2920	1.05	1901	1.02
50-99	589	0.85	716	0.99	730	1.09	813	1.05	526	1.01
100-199	323	0.61	749	1.37	527	1.12	584	1.05	298	0.77
200-299	165	0.69	347	1.40	252	1.21	230	0.95	112	0.67
300-399	68	0.64	149	1.35	125	1.29	114	1.00	49	0.64
400-600	105	0.70	190	1.24	166	1.28	163	1.04	70	0.65
Total	14874	1.00	15489	1.00	14199	1.00	16619	1.00	11260	1.00

Expected persons (E) assume an even distribution of radiation doses between the 5 exposure age groups after stratifying by sex and city.

Interaction terms between exposure age and dose:-
(1) assuming a linear relation with age group = $9.65.10^{-5}$ (SE 0.0021, not significant).
(2) assuming a quadratic relation with age group= -0.0114 (SE 0.0012, $p<0.001$).

For the quadratic model the chi-square, with 2 fd, was 97.35 ($p>0.001$).

Table 2. Potential and actual size of the RERF cohort of *in utero children*; from Kato and Keehn (1966)

In utero children	Hypocenter distance Km	City birth registrations	ABCC master file and 1960 census
Available	0-	325 (55)[a]	146 (18)[a]
	1.5-	416 (85)	231 (21)
	2.0-	872 (342)	395 (103)
	3.0-4.0	2258 (1396)	730 (313)
	Total	3871 (1878)	1502 (455)
Selected	0-	320 (55)	132 (17)
	1.5-	322 (54)	129 (12)
	2.0-	324 (55)	134 (18)
	3.0-4.0	322 (55)	134 (15)
	Total	1288 (219)	529 (62)

a ( ) Nagasaki births

Table 3. Birth months of 1288 *in utero children*; from Kato and Keehn (1966)

Month	Estimated fetal age (D)	Study sample			Comparison groups		
		Obs[a]	*Exp*[b]	t-value	*Obs*[a]	*Exp*[b]	t-value
Aug	257-280	35	27.4	+1.45	81	83.8	-0.31
Sept	227-256	25	34.3	-1.58	81	104.8	-2.32[c]
Oct	196-226	31	35.4	-0.74	97	108.3	-1.09
Nov	166-195	23	34.3	-1.93	88	104.8	-1.61
Dec	135-165	32	35.4	-0.57	98	108.3	-0.99
Jan	104-134	66	35.4	+5.14[d]	178	108.3	+6.70[d]
Feb	76-103	49	32.0	+3.00[e]	148	97.8	+6.09[d]
March	45-75	32	35.4	-0.57	102	108.3	-0.61
April	15-44	19	34.3	-2.67[d]	69	104.8	-3.50[d]
May	1-14	8	16.0	-2.00[c]	26	48.9	-3.27[e]
	Total	320		55.75[f]	968		115.57[f]

a Cut off date May 31st, see Kato and Keehn (1966)
b Assuming a constant rate from August 7th to May 14th

c $p>0.05$
d $p>0.01$
e $p>0.001$
f Chi-square (with 9df.) $p>0.01$

D Days from conception

Table 4. 1599 *In utero children* included in a study of brain damage effects of radiation; from Otake and Schull (1983)

Fetal exposure age (W)	DS86 Dose cGy	*In utero children* Obs.	Exp.	t-value
under 8	0-	156 (1)[a]	217.0	-4.14[b]
	1-	61	92.2	-3.25[c]
	50+	3	10.6	-2.33[d]
	Total	220 (1)	*1.4%*[e]	
8-15	0-	253 (1)	217.0	+2.44[d]
	1-	112 (5)	92.2	+2.06[d]
	50+	19 (9)	10.6	+2.58[c]
	Total	384 (15)	*5.0%*[e]	
16-25	0-	324 (3)	271.3	+3.20[c]
	1-	143 (3)	115.2	+2.59[c]
	50+	20 (3)	13.2	+1.87
	Total	487 (9)	*4.1%*[e]	
26-39	0-	352 (4)	379.7	-1.42
	1-	145	161.4	-1.29
	50+	11 (1)	18.6	-1.77
	Total	508 (5)	*2.2%*[e]	

a ( ) Brain damaged children

b p>0.001
c p>0.01
d p>0.05

e percentage of high dose exposures (over 50 cGy)

W Weeks from conception

Table 5. Cancer experiences of 1630 *in utero children*; from Yoshimoto *et al.* (1988)

Specifications		Cancer cases *Obs.*	Cancer cases *Exp.*	Significance test
				t-value
DS86 Dose cGy	0.00	5	7.9	-1.03
	0.01-0.21	7 (2)[a]	7.5	-0.18
	0.40-2.13	6 (2)	2.6	+2.11[c]
				p-value[b]
Onset age (Y)	5-9	1	0.22	0.198
	10-19	2	0.80	0.191
	20-29	7 (3)	1.09	0.0001
	30-39	8 (1)	4.37	0.076
		Alive	Dead	Total
Diagnostic groups	Genitourinary	3 (1)	6	9 (1)
	Digestive	3 (1)	2	5 (1)
	Hemopoietic	1 (1)	2 (1)	3 (2)
	Thyroid	1	-	1

a ( ) male cases

b single-tailed poisson test

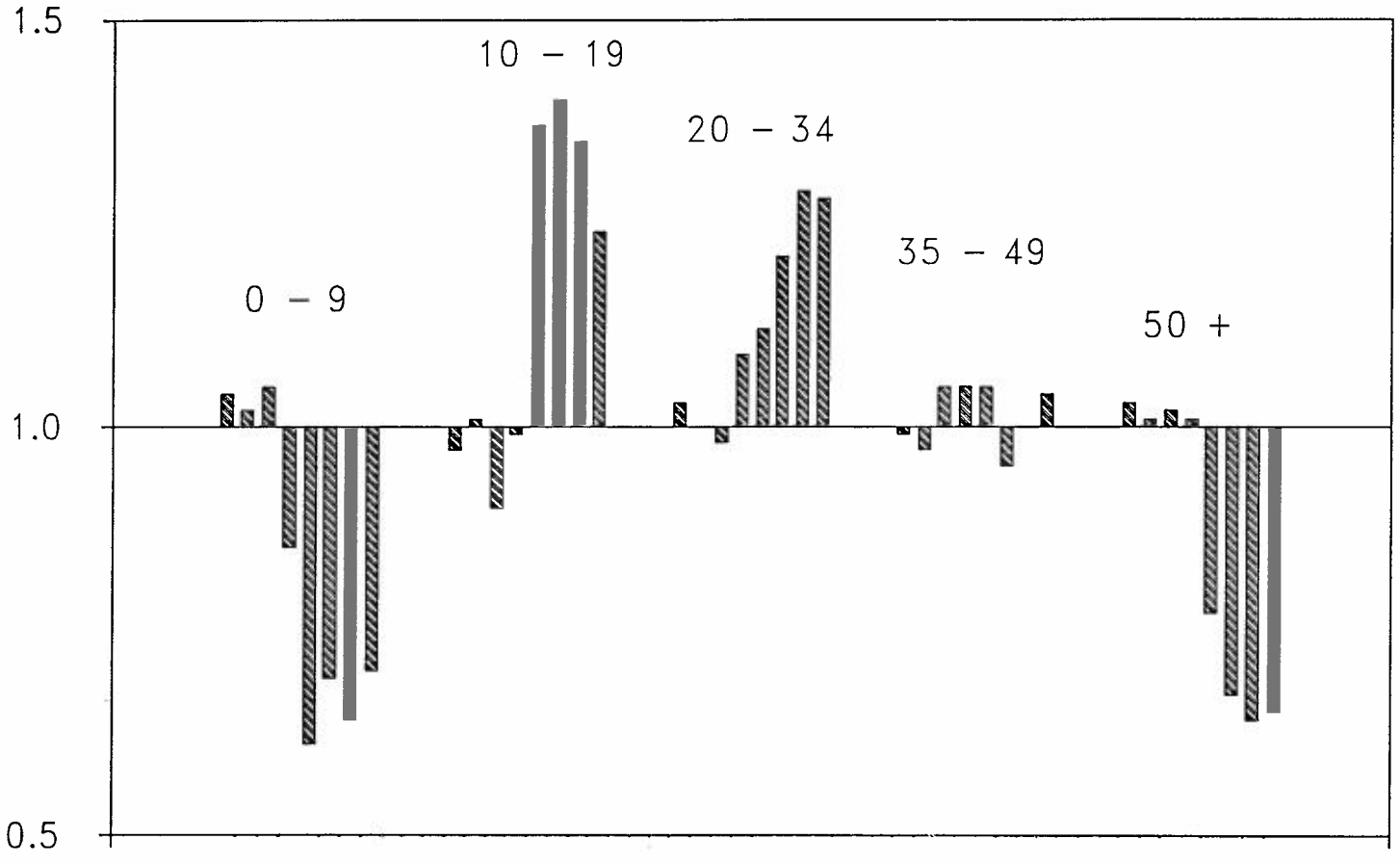
c $p>0.05$

The cohort included 765 males and 865 females; the 2 fatal leukemias had onset ages of 18 and 29 y.

Expected numbers for each dose level assume an even dose distribution for the two sexes and no radiation effects.

Expected numbers for each age group are derived from national statistics.

LSS Cohort



LSS Cohort