Kiel

Cancer Risks at Low Dose Levels

Alice M. Stewart

Introduction

In spite of being a common cause of mutations, background radiation is not considered to be an important cause of cancer. This is the opinion of scientists who, knowing that the damage caused by exposing dividing cells to non-lethal doses of gamma radiation may be followed by realignment of broken chromosomes, have postulated the existence of a 'dose rate effectiveness factor' or DREF. By this is meant a molecular repair process whose effects include attenuation of the cancer risk when doses or dose rates fall to the levels that are typical of background radiation and occupational exposures [3].

The DREF concept allows one to assume that, provided there is strict enforcement of ICRP safety recommendations, the cancer risks of radiation workers are reduced to vanishing point. It has also been given as the reason why the Radiation Effects Research Foundation (RERF) has never found any extra cancer deaths at low dose levels either in the Life Span Study (LSS) cohort, which was assembled five years after the bombing of Hiroshima and Nagasaki, or in the cohort of in utero children, which was assembled from 1945 and 1946 birth registrations.

For several months after the two nuclear explosions there were extra deaths from environmental effects of the blast as well as from marrow damage and radiation burns. During this period there must have been strong selection for general fitness. This point has been long conceded by RERF [2]. However, the observed number of deaths for the LSS cohort has remained close to expectations based on national statistics, and in tests of a linear model of relative risk, the non-cancer death rate has never been shown any signs of being dose related [17]. Furthermore, whenever the usual method of risk estimation – by linear extrapolation of high dose effects – was applied to LSS data, the results were essentially the same as in other high dose situations, such as patients being treated for ankylosing spondylitis with radiotherapy [19]. Therefore, among advisers to the nuclear industry there has been longstanding agreement on the following points: all late effects of radiation are the result of mutations; in spite of the early selection the RERF study cohorts are representative of these late effects; and – as a result of DREF – linear extrapolation of high dose effects somewhat exaggerates the cancer risks despite long standing disagreement between RERF and the Oxford Survey of Childhood Cancers (OSCC) on the subject of cancer effects of fetal irradiation.

This disagreement reached a high point in 1970 when OSCC produced a risk estimate – based on prenatal X-rays and cancer deaths before ten years of age – which was much higher than any of the approved estimates for cancer effects of radiation [20]. Despite the fact that OSCC was not alone in finding evidence of a cancer risk from obstetric radiography, the OSCC estimate was refuted by RERF on the grounds that the observed number of cancer deaths in a 10 year follow-up of in utero children was no greater than the expected number [6]. After examining the evidence on both sides of this argument, the US National Council for Radiation Protection decided, that the association

between prenatal X-rays and childhood cancers was caused, not by the radiation, but by the medical reasons for the X-ray examinations [15]. However, a Mantel-Haenszel analysis of OSCC data made this extremely unlikely by showing that, within the group of X-rayed cases, the cancer association was exceptionally strong for "routine X-ray with no abnormal findings" [10]. By the time I was reasonably certain that, at high dose levels, cancer was not the only late effect of radiation [21].

My reasoning took the following form: after the bombing of Hiroshima and Nagasaki there were so many deaths from marrow damage effects of the radiation (and environmental effects of the blast) that a weeding out of infection sensitive persons was inevitable. This dose-related selection probably continued until life in the two cities returned to normal, and must have left survivors with higher levels of resistance to infections than non-survivors, and high dose survivors with higher resistance than low dose survivors. Therefore, without later deaths from incomplete repair of the early injuries to offset this bias, the LSS cohort would have had an exceptionally low death rate, also a rate for non-cancer deaths which was negatively correlated with the radiation dose. This was clearly not the case. So it was reasonable to assume that there was masking of mutational effects of the radiation by the early selection.

Following an analysis of published data which lent some support to these suggestions [22] there was general release of 'Life Span Study Data on Disk'. This provided no information on early injuries but was used to show that, for all causes of death exept neoplasms and cardiovascular diseases, the dose response curve was distinctly U shaped – with the lowest point of the curve close to the threshold dose for marrow damage [23]. This finding has since been confirmed. But RERF is still insisting that the early selection bias has not made the LSS cohort unrepresentative of the much later carcinogenic effects of

Table 1: Source population of the RERF study cohort of in utero children from *Kato* and *Keehn* [7].

Source	Hypocentre Distance km	Hiroshima Available	Hiroshima Selected[1)]	Nagasaki Available	Nagasaki Selected[1)]
City Birth Registrations	0.0 – 1.5	270	**265**	55	**55**
	1.5 – 2.0	331	**268**	85	**54**
	2.0 – 3.0	530	**269**	342	**55**
	3.0 – 4.0	862	**267**	1396	**53**
ABCC Master File and 1960 Census	0.0 – 1.5	128	**115**	18	**17**
	1.5 – 2.0	210	**117**	21	**12**
	2.0 – 3.0	292	**116**	103	**18**
	3.0 – 4.0	417	**119**	313	**15**
	Totals	3040	**1536**	2333	**281**

[1)] According to Kato and Keehn [7] "the study sample" included all avaiable subjects within 1500 m of the hypocentre, and three sets of comparision subjects were selected from the distance groups after matching with the study sample for source, city, sex and calender month of birth.

the radiation [18]. This assumption would require the doses of LSS survivors to be independent of the non-cancer death rates which prevailed before as well as after LSS cohort was constructed (from four 'hypocentre distance groups' matched for size, sex and age) [1]. However, when the Disk data were divided into five age groups, the average dose was found to be much lower for the youngest and the oldest groups (i. e. under 10 and over 50 years at the time of the bomb) than for the intervening ones (Fig. 1). This difference must have been the result of a positive association between the early (non-cancer) deaths and the radiation dose and was clearly the result of high doses (over 50 cGy). So we can be reasonably certain that selection against infection sensitive persons was accompanied by the radiation and that this second effect was felt mainly by persons whose radiation doses exceeded 50 cGy.

For further evidence of both types of selection one can turn to the in utero children and the F1 offspring of A-bomb survivors.

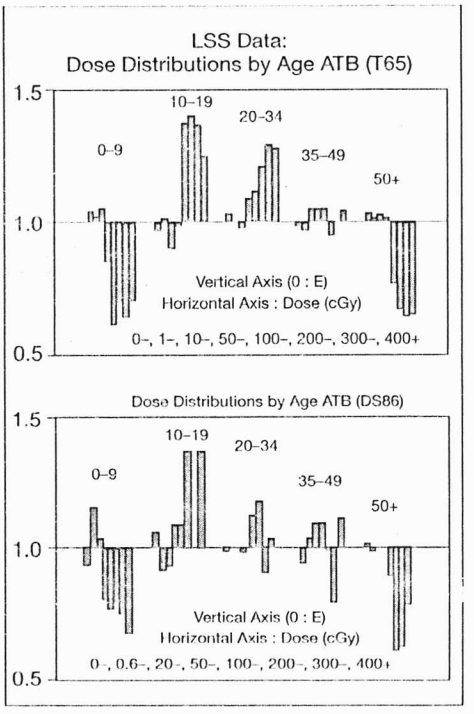

Fig. 1: Life span study data. Upper panel: dose distribution by age ATB (T 65), lower panel: dose distribution by age ATB (DS 86).

In Utero Children

From a source population consisting of 5373 live births in Hiroshima (3040) or Nagasaki (2333) after the bombing and before the following *June, Kato* and *Keehn*, in 1966, made the following selection: "all subjects within the groups within 1500 m [of the hypocentre] were included in the study sample and comparision subjects were selected from 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" [7].

By insisting that each of the comparision groups be as small as the study sample *Kata* and *Keehn* excluded two thirds of the avaiable children from later studies of teratogenic and carcinogenic effects of fetal irradiation and also reduced the Nagasaki representation from 45 to 15 percent (Table 1). But even more unfortunate was the matching for month of birth, since this made it impossible to observe the effects of exposure age on letal doses of radiation. A relatively low dose for embryos was inevitable and the in utero deaths so caused would have serious consequences for later (i. e. teratogenic and carcinogenic) effects of the radiation. But when the time came for these studies there was no mention of an important fact, namely, that both in the original study sample and in the comparision groups, the observed number of

Table 2: Birth months of the in utero children from *Kato* and *Keehn* [7].

Month	Fetal age in weeks	Study sample			Comparision groups		
		Obs.	Exp.[1]	O/E	Obs.	Exp.[1]	O/E
August	37–40	35	26	1.35	153	133	1.15
September	33–36	25	32	0.78	133	164	0.81
October	28–32	31	34	0.91	161	168	0.96
November	24–27	23	32	0.72	136	164	0.83
December	20–23	32	34	0.94	162	168	0.96
January	15–19	66	34	1.94	313	168	1.86
February	11–14	49	28	1.44	245	153	1.60
March	6–10	32	34	0.94	166	168	0.99
April	2–5	19	32	0.59	107	164	0.64
May	0–1	8	34	0.24	42	168	0.25
	Total	320			1618		

[1] Assuming an even distribution of births.

births after March 1946 (i. e. exposures before 6 weeks of fetal age) was less than half the expected number (Table 2).

Kato and *Keehn* followed their selection procedures with an analysis of deaths before 18 years of age (which showed that the younger deaths were male biased) and, since then, there has been both a study of brain damage effects of radiation, based on 1599 in utero children [16], and a study of cancer deaths before 40 years of age, based on 1630 of these children [26]. The brain damage study came to the conclusion that there was much greater vulnerability to this (teratogenic) effect of the radiation between 8 and 15 weeks of fetal age than between 0 and 8 weeks. But this was probably an artifact caused by under representation of embryos among high dose survivors (Table 3). Thus, for recipients of more than 50 cGy there were six times as many survivors in the older age group as in the younger one.

The 40 year follow-up of 1630 in utero children succeeded in identifying 18 cancers, but there were no childhood leukaemias and only four male cancers (Table 4). By national standards both the number of cancers diagnosed before 20 years of age and the number diagnosed between 30 and 40 years of age were excessive, but much the greatest excess was in the intervening age group – which accounted for all but one of the male cancers. By any standard the sex ratio, the ratio of leukaemias to solid tumours, and the ratio of deaths before and after 10 years of age, were too low, and by comparision with British and American children, the peak incidence of the radiogenic cancers was too late. Therefore, it is reasonable to assume that the cancer experiences of the in utero children were influenced both by acute effects of the radiation (causing selective loss of embryos) and by the general devastation (causing selective loss of infection sensitive children). Both effects would involve males more than females, and the devastation effect would have a disproportionate effect on pre-leukaemic children – or chil-

Table 3: Observed and expected numbers of children included in a study of brain damage effects of the radiation.

Radiation dose cGy	Exposure age[1)]	Observed	Expected	O/E
under 50	0–7	217 (1)	309	0.70
	8–15	364 (6)	309	1.18
	16–25	467 (6)	387	1.21
	26–40	497 (4)	541	0.92
over 50	0–7	3 (0)	10.6	0.28
	8–15	19 (9)	10.6	1.79
	16–25	20 (3)	13.2	1.52
	26–40	11 (1)	18.6	0.59

[1)] weeks from conception

dren whose infection sensitivity was the result of early involvement of the immune system in a neoplastic process.

Offspring of A-bomb Survivors

According to *Kato, Schull* and *Neel* "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" [8]. Nevertheless, "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" [27]. On the contrary, the ratio of observed to expected numbers was below unity both for all causes of death (0.72) and for neoplasms (0.81).

According to *Yoshimoto et al.* "a variety of explanations can be advanced for this discrepancy from an expected ratio of 1" and "arguably, the most important of these centres in the appropriateness of the national statistics as the basis for determining the expectations". But a far more likely cause is the unusual experiences of the parents since, with thousands of extra deaths distinguishing sharply between persons with weak and strong constitutions, the way would be paved for a second generation effect of "survival of the fittest" – or an extension of the early selection which overruled all the F1 generation effects of the radiation but possibly left a further trail of genetic damage.

Oxford Survey of Childhood Cancers

Compared with the RERF cohort of in utero children the Oxford Survey has many advantages including the much larger size of the case group, the wide range of matched and unmatched factors, and the strong links with official vital statistics which have been so successfully exploited by *Kneale* [12]. Besides showing that fetal irradiation is a cause of childhood cancers, this analysis has shown that immunisations against infections have cancer inhibitor effects, and that infections are both cancer promoters and competing causes of death. Therefore, although there is now a strong presumption that background radi-

Table 4: Cancer experiences in 1630 in utero children from *Yoshimoto* [27].

Sub Groups		765 males			865 females		
		Obs.	Exp.	O/E	Obs.	Exp.	O/E
DS86 Dose Estimate cGy	0.00	-	**3.70**	-	5	**4.10**	1.22
	0.01–0.21	2	**3.50**	0.87	5	**4.00**	1.25
	0.40–2.13	2	**1.20**	1.67	4	**1.40**	2.86
Onset Age in Years	5–9	-	**0.12**	-	1	**0.10**	10.00
	10–19	-	**0.42**	-	2	**0.38**	5.26
	20–29	3	**0.80**	3.75	4	**0.29**	4.35
	30–39	1	**1.87**	0.53	7	**2.50**	2.80
	Total	4	**3.21**	1.03	14	**3.90**	3.59
Cancer Sites	Genito Urinary	1			8		
	Digestive	1			4		
	Haemopoietic	2			1		
	Thyroid	-			1		

ation is an important cause of human cancers, it is probable that immune system control of foreign cells has the last say in the etiology of neoplastic as well as infective diseases.

According to BEIR V it is just possible to reconcile the OSCC and the RERF risk estimates for fetal irradiation [3]. But even this doubtful accord would require two cancer deaths of in utero children before 10 years of age, and there was, in fact, only one such death. Therefore OSCC data lend no support to the DREF concept.

Nuclear Workers

The starting point of a fierce controversy about the cancer risks of nuclear workers [24] was a study of occupational mortality rates in Washington State USA which found that the ratio of cancer to non-cancer deaths was exceptionally high for men who had worked at the Hanford nuclear facility [14]. This observation was followed by an analysis of a much larger sample of Hanford deaths which showed that, although the annual doses of external radiation were only a tiny fraction of the "permitted doses" the average total dose was significantly higher for the cancer than the non-cancer deaths [13]. This difference was largely the result of radiation received more than ten years before death by men who were over 40 years of age and later developed either myelomas, pancreatic cancers or lung cancers, and, according to *Mancuso, Stewart* and *Kneale* (MSK), this made it reasonable to assume that there was a causal relationship between the radiation exposures and the cancer deaths – in which the case the cancer risks of nuclear workers were much greater than was generally supposed.

There was prompt rejection of this suggestion by the nuclear establishment on the ground that, according to an independent analysis of the same data by *Gilbert* and *Marks*, the cancer death rate of Han-

ford workers was both lower than normal (SMR analysis) and showed no signs of being dose related (RR analysis) [4]. There followed a lengthy argument about the best method of risk estimation – with *Gilbert* insisting that there was no evidence of any radiogenic cancers apart from myeloma [5] and insufficient allowance for a dose related bias caused by selective recruitment of well paid and well educated men into more dangerous occupations [11].

With limited access to Hanford data (and no means of controlling for socio-economic factors) it was not possible for MSK to do more than show that, with control for the frequency of monitoring for internal radiation (IRM factor), there was evidence of an external radiation effect for a relatively large group of cancers (i. e. cancers which rated high in an ICRP classification of "tissue sensitivity to cancer induction by radiation"). However, a recent events have given *Kneale* and *Stewart* renewed access to the records of workers in the US nuclear industry. The first use of this opportunity has been to observe the effects on Hanford workers of replacing the IRM factor with a job classification which did not exist at the time of the MSK analysis. According to this new (and as yet unpublished) analysis there is a significant dose trend for three groups of neoplasms, namely, haemopoietic, respiratory and digestive, though demonstration of this low dose effect requires either control for socio-economic status occupations or control for IRM levels.

Meanwhile, from other sources has come similar evidence that the cancer risks of nuclear workers are much greater than offical recommendations [9, 25]. According to these studies of British as well as American workers the employment requirements for work in the nuclear industry have left successful applicants with relatively low rates of cancer and non-cancer mortality (healthy worker effect), but within the industry cancer death rates are dose related. Therefore, evidence that there is no attenuation of the cancer risk at low dose levels is no longer confined to OSCC data.

Discussion

Risk estimates for cancer effects of background radiation and other low dose exposures are currently based on LSS data with an allowance for DREF. However, there is no certainty that spontaneous repair of mutational damage reduces the cancer risk, and a distinct possibility that cancer is not the only late effect of radiation.

According to this hypothesis the extra deaths of A-bomb survivors from aplastic anaemia and other blood diseases (which continued long after 1950 [2]) were late effects of marrow damage whose principal effect was loss of immunological competence. In addition there is a period of several months after the two nuclear explosions when there were qualitative as well as quantitative differences between high and low dose survivors. Thus, above the marrow damage threshold there was selection against persons who were at high risk of late effects of mutations as well as selection against infection sensitive persons (combined effects of marrow aplasia and blast injuries). But below this level there was only selection against infection sensitive persons (environmental effects of the blast). As a result of this difference, there was more masking of cancer effects of the radiation by other effects of the bombing at high than low dose levels. But even at low dose levels there was sufficient masking to create a false impression of no cancer risk at the dose levels likely to be encountered by radiation workers.

There is no way of recognising cancer induction effects of radiation and the only distinctive effect of marrow damage (aplastic anaemia) may have cancer as the underlying cause. But before assuming that cancer is the only late effect of radiation, we should be quite certain that the non-cancer death rate is the same for the LSS survivors who had apparently recovered from acute radiation injuries, and other (uninjured) survivors. The necessary data for this analysis exist, and the finding of selection against high radiation doses as well as infection sensitivity has brought it to the forefront of problems requiring the attention of RERF.

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Correspondence: *Stewart, Alice M.,* Dr. med., Department of Public Health and Epidemiology, University of Birmingham, Birmingham B15 2TT, UK