LOW LEVEL RADIATION
LONG-TERM EFFECTS FOR RADIATION WORKERS AND THE GENERAL PUBLIC

Alice M. Stewart

Cancer Epidemiology Research Unit, Department of Social Medicine,
University of Birmingham, Edgbaston,
Birmingham, England.

ABSTRACT

The Hanford Study has become a source of risk estimates which can be adapted to real life situations because they allow for effects of advancing age and cancer latency. There is also evidence of a dose response which has important implications for storage of radioactive waste and reactor faults on the scale of the Three Mile Island accident.

KEYWORDS

Epidemiology; Cancer; Radiation.

The International Commission on Radiation Protection (ICRP) is a generator of dose level recommendations and a secondary source of risk estimates for radiation workers and tissue sensitivity ratings. [1,2] The original sources of the estimates and ratings are animal experiments and human studies and they include a follow-up of persons who were in Hiroshima and Nagasaki when the cities were bombed and were still alive in October 1950 - so called ABCC data because the Atomic Bomb Casualty Commission was the original sponsor of a life span study of 80,000 survivors out of a total population of 285,000 persons identified through the 1950 Census of Japan.

Analysts of the Japanese data have repeatedly come to the following conclusions:[3] (i) the only delayed effects of the A-bomb radiation were cancers; (ii) the principal and earliest effect for 5-year survivors was myeloid leukaemia, and (iii) over 99% of deaths since the 1950 census have been due to natural causes (Table 1). These conclusions are in reasonably close agreement with ones based on animal experiments and radiotherapy patients.[4] Therefore, although there are many scientists who subscribe to the view that linear extrapolation of high dose observations exaggerates the cancer risks from small doses (threshold hypothesis), the ICRP and other evaluation committees have always equated the risks for radiation workers and the general public with mortality experiences of A-bomb survivors.[1,4,5]

TABLE 1: ABCC Data - 8th Mortality Report(1)

REPRESENTS	All 5-year survivors i.e. 285,000 persons with mean dose of 16.6 rads			
ACTUAL COVERAGE	1950-74 deaths of 79,786 persons with T65 doses			
METHODOLOGY	Relative Risk Analysis with control for sex, exposure age and city			
FINDINGS	No radiation effects apart from Cancer			
RISK ESTIMATES	1950 - 74 Deaths	Nos.	%	Extra Deaths
	Radiogenic:			
	Leukaemias	192	0.3)	415
	Solid Tumours	213	0.3)	
	Natural Causes	70,000	99.4	0

(1) See reference 3

Until recently the only reasons for doubting the general validity of ABCC estimates were negative findings for in utero exposures[6] - which contrasted oddly with positive findings for foetal irradiation in other populations.[7] Today there are more challenging reasons since a study of workers in the nuclear industry[8] has become the source of risk estimates which are in close agreement with the general findings for foetal irradiation and, therefore, an order of magnitude higher than ABCC estimates (see MSK analyses of Hanford data in Table 2).

TABLE 2: MSK Analyses of Hanford Data

MSK Series	Published Reports	Year	Data Base
I	Proceedings H.P.S. (Saratoga Springs)	1976	1944-72 Deaths
	Health Physics	1977	
II	Proceedings IAEA (Vienna)	1978	1944-77 Deaths
	Ambio	1980	
III	Brit. J. Industrial Med.	1981	1944-75 Workforce and 1944-77 Deaths

MSK: Mancuso, Stewart & Kneale
HPS: Health Physics Society
IAEA: International Atomic Energy Association

The first set of MSK estimates was based on a comparative mean dose or CMD analysis of annual radiation doses of workers who died within 28 years of Hanford becoming a producer of plutonium and other radioactive substances on a commercial scale (i.e. 1944-72 deaths of the same workforce).[9,10] The findings of this preliminary analysis included: (i) a radiation effect for three cancer sites, namely, bone marrow, pancreas and lung (and similar but less definite findings for breast cancer); (ii) comparatively low levels of tissue sensitivity (to cancer induction by radiation) at younger ages; and (iii) evidence of long intervals between cancer induction and death (cancer latency effect). The main conclusions were that - assuming linearity of dose response - less than 20 rads might be sufficient to double the normal risk of a cancer death (so called doubling dose which is a measure of relative risk) and less than 2 rads might have the same effect on an exceptionally sensitive tissue, such as bone marrow (see Table 3).

TABLE 3: MSK Early Estimates of Cancer Risks[1]

Cancer Sites	MSK I[2]		MSK II			
	Cases	Doubling Dose[3]	Cases	Doubling Dose	95% Confidence limits	
Bone Marrow	11	0.8	25	3.6	1.7	10.3
Marrow and Lymph nodes	64	2.5	-	-	-	-
Pancreas	49	7.4	-	-	-	-
Pancreas, Stomach & Large Intestine	-	-	165	15.6	7.3	55.0
Lung	192	6.1	215	13.7	7.3	28.7
Group "A"	-	-	456	13.9	8.4	21.2
All Sites	670	12.2	743	33.7	15.2	79.2

(1) See references 10 & 11
(2) These are over-estimates of risk due to the accidental inclusion of non-monitored persons among the zero doses
(3) Doubling Dose - the amount of radiation needed to exactly double the normal risk (i.e. the lower the doubling dose the higher the risk)

From the reports it was clear that there were too few cancer deaths to do more than touch lightly on the problem of relative sensitivity of different tissues. Also, one analysis, involving reference to bioassay tests (i.e. routine tests for internal deposits of radioactive substances), revealed differences between live and dead workers which were suggestive of selective recruitment of exceptionally fit persons into really dangerous occupations (healthy worker effect). Therefore there was early realisation of the fact that any cohort-based estimates of risk would be very misleading unless there was adequate control of this elusive factor.

After publication of the Health Physics paper it was discovered that non-exposed workers (who were equated with zero doses) included some persons who had never been monitored for external radiation. It was also clear that various aspects of the preliminary analysis were ill understood and were meeting with a very bad press. Therefore, as soon as possible, the CMD analysis was repeated on a larger series of deaths (i.e. 1944-77 deaths of the 1944-75 workforce) after first

justifying the method and then excluding all workers who were never issued with film badges.[11,12] The problem of how to control for the healthy worker effect without invoking bioassay data had not yet been solved but it was clear that most of the criticisms of the earlier papers were unfounded. The later papers also showed that the small number problem could be brought under control by combining the usual (anatomical) classification of cancers with ICRP ratings of tissue sensitivity (Table 4).

TABLE 4: Specifications of A & B Cancers

Group	Tissues(1)	ICD Nos. (8th Revision)	Cases	
			Male	Female
A Cancers (Sensitive Tissues)	Pharynx	145-149	10	-
	Digestive	150-159	201	19
	Respiratory	160-163	215	10
	Female Breast	174	-	19
	Thyroid	193	1	-
	Haemopoetic	200-209	76	10
B Cancers (Other Tissues)		Remainder		
	Other Sites	140-209	199	28
	Other Unspecified	195-199	41	3

(1) See references 2 & 22

This regrouping of the cancer deaths had a direct bearing on the problem of cancer risks from radiation and made it possible to work with only two diagnostic groups, namely, cancers of tissue which were known or suspected of being sensitive to radiation (Group A) and cancers of other and unspecified sites (Group B). A by-product of regrouping was the discovery of under-reporting of cancers in older age groups since there happened to be more involvement of Group B cancers in this bias than of Group A cancers (Fig. 1).

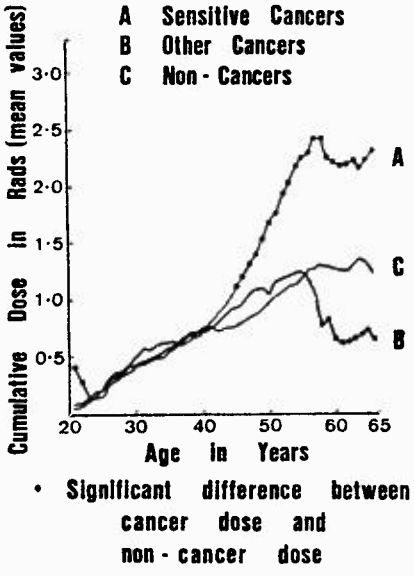

Fig. 1 Age Trend of Cumulative Dose for three groups of male workers

Though the preliminary findings had been confirmed the bad press continued[13] and made it difficult to realise that the objections raised by scientists who had independent access to Hanford data referred to conclusions not observations.[14,15,16] However, the preferred conclusion, namely, that an unidentified correlate of dose (not radiation) was the cause of all the cancer associations, must now be reconciled with a cohort analysis of 1944-77 deaths (by the method of regression models in life tables) which has gone out of its way to show, (i) the effects of not controlling for the healthy worker effect, and (ii) how two, independent measures of this effect compare.[17]

Without control of the healthy worker effect all non-survivors had significantly lower doses than all survivors. But with control - either by a scale of bioassay tests or a fitness rating for each job - there was (i) near equality between survivors and non-cancer deaths, (ii) below average doses for Group B cancers, and (iii) above average for Group A cancers. The negative findings for Group B cancers were clearly the result of reporting bias whose demonstrated effects made it possible to conclude that although observed differences between survivors and Group A cancers were statistically significant they were not as great as the true differences.

With these results it was possible to use maximum likelihood tests to identify the effects of radiation and cancer-related factors and thus obtain a closer fit between the risk estimates and real life situations. The results of these tests can be summarised as follows (see Table 5 and Fig. 2):

(i) There is non-linearity of the dose response and the curve is probably obeying the square root law. This is strong evidence against the threshold hypothesis and in favour of linear extrapolation of high dose observations <u>under-estimating</u> cancer effects of low doses.

(ii) For adults there is progressive increase in sensitivity to cancer effects of low level radiation with advancing age, and as a result of this we can expect the addition of 8 years to double the cancer risk of the original age. In other words, the shape of the curve is similar to the shape of the curve of general mortality.

(iii) Short intervals between cancer induction and death are possible but not likely. The maximum risk of dying is probably 25 years after induction but this estimate is based on data which had 32 years as the longest possible interval.

(iv) For cancers of sensitive tissue, which normally account for three-quarters of all cancer deaths, the doubling dose decreases progressively with age and is in the region of 15 rads for a typical man aged 40 years.

TABLE 5: MSK III Results of Model Testing after confirming a Radiation Effect for Group A Cancers

Radiation Effects	Maximum Likelihood Estimate
Dose Response (E)	Non linear, with E = 0.5
Doubling Dose (D)	D = 15 rads (95% limits 2 - 150)
Latency (L)	Interval between cancer induction and death, L = 25 years
Exposure Age (S)	The age addition which increases sensitivity by e, the base of natural logarithms S = 8 years

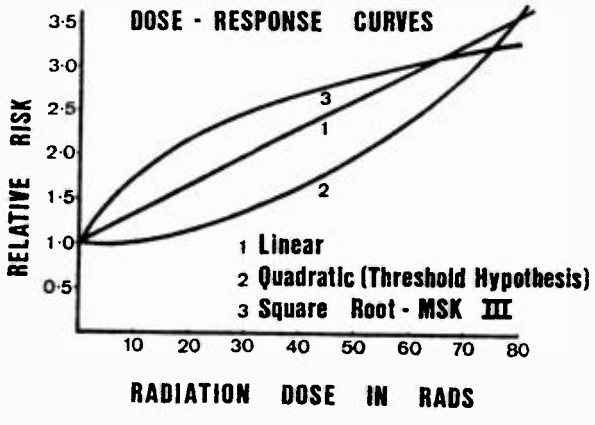

Fig. 2 Typical Dose Response Curves of Relative Risk against Cumulative Dose for Various Parameters

There has not yet been time for the ICRP to react to these findings but pressures against continued dependence upon ABCC risk estimates are rising, as can be seen from the following story. In ICRP 26[1] there are risk factors for several types of cancer including one for breast cancer which gives 25 as the expected number of extra (radiogenic) cancers if one million women were exposed to 1 rem of ionizing radiation. This estimate of absolute risk (and MSK estimates of relative risk) can now be compared with a real life situation because a follow-up of 1110 women who worked in the radium luminizing industry in World War II has identified 16 breast cancer deaths when the expected number (on the basis of national statistics) was 10.3.[18] For all causes of death the observed number (89) was smaller than the expected number (112.0). Therefore it was concluded that, in spite of there being a healthy worker effect, there was a genuine excess of breast cancer deaths, and that the relative risk was 16 ÷ 10.3 = 1.55.

The mean absorbed dose for the 1110 luminizers was 38.5 rems. Therefore, if one million women had been exposed to 1 rem the number of extra deaths would have been

$$\frac{(16 - 10.3)\ 10^6}{1110 \times 38.5} = 134$$

which is between 5 and 6 times higher than the ICRP estimate of absolute risk. Equivalence with MSK III estimates of relative risk is not so easily obtained (see Table 5) but it can be done by postulating the existence of a woman who was born in 1915, worked as a luminizer from 1940 to 1945 with an annual dose of 6.4 rems, and died from a breast cancer in 1970 (Table 6). For such a worker the actual dose would be 38.4 rems and the transformed or "cancer effective" dose would be 8.2 rems. Therefore, assuming a typical (curvilinear) dose response and comparability with other cancers of radio-sensitive tissues, the relative risk would be 1.74 which is only a fraction higher than the original estimate.

TABLE 6: Application of MSK III Risk Estimates to a typical Radium Luminizer(1)

Year(2)	Age	Dose in Rads		Relative Risk
		Actual	Transformed	
1940	25	6.4	1.00	
1941	26	6.4	1.08	
1942	27	6.4	1.27	
1943	28	6.4	1.39	
1944	29	6.4	1.60	
1945	30	6.4	1.86	
	Total	38.4	8.20	1.75

(1) See reference 18
(2) Date of Death - 1970 Cause - Breast Cancer

The odd thing about this story is that the authors of the survey evidently thought that their findings were supportive of ICRP recommendations and, therefore, supportive of the idea that all MSK estimates grossly exaggerate the cancer risks of low level radiation. Since cosmic and terrestial radiation fall into this category we will now compare MSK estimates of risk for a background dose of 0.1 rems per annum (Table 7) with a study of cancer mortality in 329 regions of Japan with known levels of background radiation[19] (Table 8).

TABLE 7: Background Radiation (0.1 rads per annum) and Cancer Mortality

Death Age	Cumulative Dose		Radiogenic[2] Cases
	Actual	Transformed[1]	
			%
40	4.0	2.6	22
45	4.5	2.8	23
50	5.0	3.3	24
55	5.5	4.2	26
60	6.0	6.8	30
65	6.5	9.9	34
70	7.0	15.0	38

(1) See reference 17
(2) As proportion of all cancer deaths

TABLE 8: Cancer Mortality and Background Radiation in 329 Japanese locations[1]

Sex	Background Radiation	Cancer Mortality[2]
	in millirems	rate per 10^5
Males	under 60	753
	60 - 79	839
	80 - 99	840
	100+	868
Females	under 60	464
	60 - 79	541
	80 - 99	554
	100+	567

(1) See reference 19
(2) Deaths over 40 years of age in the period 1969-70

According to MSK III, background radiation is influencing cancer mortality and deaths from this source could be making a 22% contribution to deaths between 40 and 45 years and a 38% contribution to deaths after 70 years. The Japanese study was restricted to cancer deaths after 40 years of age. For males there was an increase in the death rate (per 10^5) from 753 for the lowest of 4 dose levels (under 0.06 rems per annum) to 868 for the highest level (over 0.10 rems per annum); and for females the corresponding figures were 464 and 567. These results are a further reason for suspecting that the mortality experiences of A-bomb survivors are not reliable indicators of radiation risks in populations which have not experienced acute radiation effects.

My views on this subject are contained in a paper which is still under review by the British Journal of Epidemiology and Community Health.[20] They can be summed up

by saying that an obvious weakness of ABCC risk estimates is that there has never been any control for two, certain effects of the explosions and one, probable effect. The certain effects are natural selection (healthy survivor effect) and incomplete repair of serious injuries (unhealthy survivor effect), and the probable effect is incomplete repair of bone marrow damage and consequent effects on infection sensitivity and primary anaemias. In support of this hypothesis are (i) the findings for blood diseases other than leukaemia - which are suggestive of an elevated and a dose related death rate for primary anaemias; (ii) the findings for suicide - which require sudden deaths of physically healthy persons to be uninfluenced by bone marrow function; (iii) the city differences - which require more intense, as well as more localised, effects from the bomb which exploded over a narrow valley surrounded by hills (Nagasaki) than the bomb which exploded over a delta (Hiroshima); and (iv) the findings for cerebrovascular accidents and tuberculosis - which require the former deaths to be much less affected by bone marrow damage than the latter.

Included in the unpublished paper are the results of making some correction for the healthy survivor effect which are here shown in Table 9. The correction factor equated the Hiroshima death rate for cerebrovascular accidents with the risk of dying from natural causes and showed that on this assumption two-thirds of the extra (radiogenic) deaths were non-cancers, and the total number of these deaths was over 10 times higher than the ABCC estimates in Table 1.

TABLE 9: ABCC Data - Effect of correcting for the Healthy Survivor Effect

BASIC REQUIREMENT	A cause of death not affected by the unhealthy survivor effect which can be compared with national statistics				
PROVISIONAL CHOICE	Cerebrovascular Accidents				
CORRECTION FACTOR	O:E ratio for Hiroshima survivors = 0.70				
RISK ESTIMATES	(For 1950-72 deaths of 82,244 survivors)(1)				
	Deaths	Obs.	Expected (Original)	Expected Corrected	"Extra"
	Neoplasms	3744	(3283)	2298	1446) 4399
	Other Causes	14782	(16899)	11829	2953)

(1) See reference 23

DISCUSSION

The assumption that linear extrapolation of high dose observations exaggerates the cancer risks from small doses (threshold hypothesis) is based on the knowledge that there is always some repair of chromosomal damage following exposure to radiation, and the assumption that this repair is necessarily beneficial. However, in theory at least, incomplete repair of chromosomal damage could add to the cancer risk by increasing the viability of damaged cells. In support of this hypothesis is the shape of the dose response curve for Hanford exposures[17] also the data relating to workers in the radium luminizing industry[18] and different

levels of background radiation in Japan.[19]

A dose response which is obeying the square root law has important implications for the storage of radioactive waste and for reactor faults on the scale of the Windscale accident of 1957 and the Three Mile Island (TMI) accident of 1979. Storage of radioactive substances is affected because with such a response it would be important for dilute sources of radioactivity to be treated with the same respect as concentrated sources; and reactor faults are affected because with such accidents there is usually involvement of persons living in the vicinity of the reactor as well as workers.

Presumably there was involvement of workers in the Windscale and TMI accidents. Therefore there is still a possibility of doing for the British workers what has already been done for luminizers, and for the American workers what has already been done for Hanford workers. Each accident provided an opportunity to include workers and others exposed in the equivalent of an A-bomb survivor follow-up , and though it is too late to identify the British "survivors", the research potential of the TMI accident is actually better than the research potential of the A-bomb explosions.

TABLE 10: Neonatal Deaths (Quarterly Rates)

Year	Quarter	Pennsylvania	TMI (10 mile radius)
1977	1st	107	124
	2nd	111	85
	3rd	101	61
	4th	101	105
1978	1st	99	86
	2nd	111	76
	3rd	93	10
	4th	105	108
1979	1st*	93	172
	2nd*	104	186
	3rd	90	79
	4th	104	96

* Periods affected by the TMI accident (28th March-6th April)

Statistical Tests of Homogeneity: Pennsylvania - Yes
TMI - No

Heterogeneity of TMI region:
(1) Not due to seasonal factors
(2) Main contributors are 3rd quarter of 1978 (downward)
1st and 2nd quarter of 1979 (upward)

We already know that in two periods affected by the TMI accident (i.e. the first and second quarters of 1979) the neonatal death rates for a local population were higher than the corresponding rates for Pennsylvania (Table 10), and we have since learnt of a similar difference for hypothyroidism of the new born.[21] Furthermore, there is no reason why the steps which were taken (in 1950) to discover how many persons were exposed to A-bomb radiation in 1945 should not be repeated. For this purpose all that is needed is inclusion of an appropriate question in the next

U.S.A. census. Identification of a population at risk could then be followed by identification of deaths (through Social Security death benefit claims) and congenitally defective children in the F1 generation (through Social Security disability claims for dependants of insured persons).

REFERENCES

1 ICRP Publications 26, Radiation Protection, Recommendations of the International Commission on Radiological Protection.

2 Radiosensitivity and Spatial Distribution of Dose (1969), ICRP Publication 14 Pergamon Press.

3 Beebe,G.W., Kato,H. and Land,C.E. (1977), Mortality experience of atomic bomb survivors 1950-74. Life Span Study Report 8. Washington D.C.: U.S. National Academy of Science, RERF TR 1-77.

4 The Effects on Populations of Exposure to Low Levels of Ionizing Radiation (1972), Report of the Advisory Committee on the Biological Effects of Ionizing Radiation.

5 Radiation Effects on Prenatal Development (1977), in Sources and Effects of Ionizing Radiation, UNSCEAR.

6 Jablon,S. and Kato,H., (1970), Childhood Cancer in relation to prenatal exposure to A-bomb radiation, Lancet, ii, 1000-1003.

7 Stewart,A. and Kneale,G.W. (1970), Radiation dose effects in relation to obstetric x-rays and Childhood Cancers, Lancet, i, 1185.

8 Mancuso,T., Sanders,B. and Brodsky,A. (1971), Proc. 6th Ann. Health Physics Soc. Topical Symposium, Vol. III, Study of the Lifetime Health and Mortality Experience of Employees of AEC Contractors.

9 Mancuso,T.F., Stewart,A.M. and Kneale,G.W. (1976), Radiation Exposures of Hanford Workers dying from various causes, 10th Midyear Topical Symposium of the Health Physics Society, Proc. of papers presented at Saratoga Springs, 204-230, Rensselaer Polytechnic Inst. Troy, NY. 12181.

10 Mancuso,T.F., Stewart,A.M. and Kneale,G.W. (1977), Hanford I: Radiation Exposures of Hanford Workers dying from Cancer and Other Causes, Health Physics, 33, 369-384.

11 Kneale,G.W., Mancuso,T.F. and Stewart,A.M. (1978), Re-analysis of Data relating to the Hanford Study of the Cancer Risks of Radiation Workers - Hanford IIA, in Late Biological Effects of Ionizing Radiation, 1, 387-410, IAEA.

12 Stewart,A.M., Kneale,G.W. and Mancuso,T.F. (1980), Hanford IIB: The Hanford Data - A Reply to Recent Criticisms, Ambio, 9, 66-73.

13 Reissland,J.A. (1978), An Assessment of the Mancuso Study, NRPB - R 79, National Radiological Protection Board, Harwell, Didcot, Oxon, OX11 ORQ., England.

14 Marks,S. and Gilbert,E.S. (1978), Cancer Mortality in Hanford Workers, in Late Biological Effects of Ionizing Radiation, 1, 369-384, IAEA.

15 Hutchinson,G.B., MacMahon,B., Jablon,S. and Land,C.E. (1979), Review of Report by Mancuso Stewart & Kneale of Radiation Exposure of Hanford Workers, Health Physics, 37, 207-220.

16 The Comptroller General of the United States, Problems in Assessing the Cancer Risks of Low-Level Ionizing Radiation Exposure, General Accounting Office, P.O. Box 6015, Gaithersburg Md., 20760.

17 Kneale,G.W., Mancuso,T.F. and Stewart,A.M. (in press 1981), A Cohort Study of the Cancer Risks from Radiation to Workers at Hanford (1944 to 1977 deaths) by the Method of Regression Models in Life-Tables, Brit. J. Indus. Med.

18 Baverstock,K.F., Papworth,D. and Bennart,J. (1981), Risks of Radiation at Low Dose Rates, Lancet 21st Feb., 430-433.

19 Ujeno,Y. (1978), Carcinogenic Hazard from Natural Background Radiation in Japan, J. Rad. Res., 19, 205-212.

20 Stewart,A.M. (in press), Delayed Effects of A-bomb Radiation - A Review of recent mortality rates and risk estimates for 5-year survivors, Brit. J. Epidemiology and Community Health.

21 Bertell,R., Understanding the Three Mile Island accident (Unpublished)

22 Mole,R.H. (1978), The Sensitivity of the Human Breast to Cancer Induction by Ionizing Radiation, Brit. J. Radiology, 51, 401-405.

23 Moriyama,I.M. and Kato,H., Mortality Experience of A-bomb Survivors 1970-72, 1950-72, ABCC Life Span Study Report 7, RERF TR 15-73.