A-bomb Survivors as a Source of Cancer Risk Estimates:

Confirmation of Suspected Bias.

by

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Abstract

It was inevitable that the chaos caused by the Hiroshima and Nagasaki bombs would leave survivors more disease resistant than a normal population (selection effect of environmental damage and other acute effects of the radiation) and it was also possible that an epidemic of acute bone marrow depression had caused irreparable damage to blood forming tissues (crippling effect of an illness never previously observed).

To discover whether either or both of these effects had lasted for more than 5 years, mortality patterns of a survivor cohort were examined. The results of comparing linear and linear quadratic models of relative risk for various causes of death are described and shown to be compatible with prolonged effects of both selection and marrow damage. One implication of these findings is that published analyses of the mortality experiences of A-bomb survivors have repeatedly underestimated the radiogenic cancer risk.

Key words: A-bomb radiation; cancer; marrow damage; selection.

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Introduction

In addition to causing radiation burns, and the first ever epidemic of acute bone marrow depression[1], the Hiroshima and Nagasaki bombs had environmental effects which rapidly became independent causes of infection deaths (e.g. destruction of houses and dislocation of essential services). These indirect effects of the radiation were the result of high doses but they involved everyone exposed to the aftermath of the nuclear explosions with or without direct exposure to the radiation. Therefore, there was a period of several months when an exceptionally high death rate was not only taking a heavier toll of infection sensitive than infection resistant personsbut also having effects below the threshold dose for burns or marrow damage which were probably dose related via hypocentre distances.

If selection in favour of infection resistant persons had not been followed by harmful effects of marrow damage, survivors would have recorded exceptionally low death rates, also rates which were inversely related to radiation doses and lower for infections than other causes of death. If, however, recovery from acute effects of marrow damage had been followed by defective functioning of replacement cells, as in animal experiments[2], extra deaths from infections (faulty leucopoesis) and aplastic anaemia (faulty erythropoesis) would have continued and might have left high dose survivors with above average death rates for these diseases.

For the survivor population which was assembled in October 1950 and included, with Not-in-City or NIC controls, in the Life Span Study or LSS

cohort)[3], this model would predict a negative trend with radiation dose for infection deaths up to but not beyond the level where radiation induced marrow damage outweighed any selective advantage of the early deaths. Therefore this report has two objectives: to discover whether, for infection deaths of five year survivors, there is a U-shaped curve of dose response, and, to consider how this type of dose response would affect estimated numbers of radiogenic cancers.

Method

The following analysis of 1950-82 deaths of A-bomb survivors is based on tabulations compiled by the Radiation Effects Research Foundation before the recent revision of dose estimates[4]. For 8 dose levels and 5 exposure age groups of each sex and city there were separate tabulations for 36 selected causes of death in 8 periods. Therefore, for 8 dose levels of 160 standardized cohorts, it was possible to obtain an average radiation dose (D); the number of person years at risk of dying; and the actual number of deaths from certain causes. The 36 cause-of-death categories were based on the ICD classification[4] but did not allow separate identification of all infection deaths. However, by removing from all causes of death (31043 cases) neoplasms (6582), cardiovascular diseases (11927), blood diseases (162) and trauma (1708) one could obtain a large residual group containing virtually all the infection deaths (10664 cases of infections etc).

Therefore the data relating to 4 causes of death (all causes, neoplasms, cardiovascular and infections etc) in 5 periods (1950-58; 1959-66; 1967-

74; 1975-82 and 1950-82) were divided into 8 dose levels of 160 cohorts before fitting, by maximum likelihood, both a simple linear model of relative risk ($RR = 1 + \alpha D$) and a linear quadratic model ($RR = 1 + \alpha D + \beta D^2$).

Results

The main results of the model fitting are shown in Table I (log likelihood values for each model) and Table II (alpha and beta coefficents of the linear quadratic model). In Figure I observed deaths for the whole follow-up period (1950-82) are compared with the predictions of the two models, and in Table III the observed deaths for infections etc in 4 periods are compared with 3 sets of expected numbers: 1) assuming no radiation effect (null hypothesis or E^1); 2) assuming an exact fit with the linear model (E^2) and 3) assuming an exact fit with the linear quadratic model (E^3). Also included in Table III are the E^3 to E^1 ratios after normalization at zero dose since these show the shape of the dose response curves for infections etc. and provide a numerical basis for graphic representation of the dose response curve for 1950-82 deaths (Figure II).

The introduction of a quadratic component of relative risk made no significant difference to neoplasms and cardiovascular diseases but it considerably improved the risk predictions for all causes of death and infections etc (Table I and Figure I). For the complete series of 31,043 deaths there was a negative alpha coefficient and a positive beta coefficient, but only the latter had a statistically significant value (Table II). The virtual absence of a linear dose trend for all deaths was

the result of neoplasms and infections etc having dose trends in opposite directions. Thus for neoplasms there was a constant positive trend which achieved statistical significance 21 years after the exposure dates and for infections etc there was a constant negative trend which was steeper for deaths 5 to 13 years after the exposure dates than for later deaths. The significant beta coefficient for all deaths was clearly the result of infections etc, but in the first period a significant positive quadratic component of relative risk owed something to neoplasms and cardiovascular diseases as well as infections.

For infections etc the improvement of fit of the linear quadratic model (with respect to either the linear model or the null hypothesis) was greater for 1950-58 than later deaths but in all four periods there was a markedly U-shaped curve of dose response (Tables II and III and Figure II). Within this residual group there were 24% of tuberculosis deaths from 1950-54 and 4% from 1979-82. Therefore we can safely assume that the proportion of infection deaths was much higher towards the beginning than the end of the follow-up period.

Discussion

Before embarking on an analysis of 1950-82 deaths of A-bomb survivors we had envisaged the following situation: the sheer volume of the 1945-46 deaths caused by the two nuclear explosions conferred a lasting advantage on the survivor populations but thereafter there was continual erosion of this advantage by late effects of the radiation which included marrow

damage as well as cancers. Hence the prediction, made several years ago, of a U shaped dose response curve for infection deaths[6], and the need to confirm this mortality pattern when an opportunity arose. The tabulations recently released by RERF made it possible to compare the predictions of two models of relative risk (linear and linear quadratic) with the null hypothesis of no radiation effects. In this way it was discovered that, for a large group of infection related deaths, there has always been a negative trend with radiation dose up to but not beyond the dose required for extensive marrow damage.

This finding makes it impossible to agree with Land that by far the best source of risk estimates for low level radiation is the LSS cohort of A-bomb survivors[7]. This opinion was based on an analysis of these data which purported to show that there were no late effects of the radiation apart from cancer. However, according to our analysis of essentially the same data, there were several effects of the two nuclear explosions which lasted for more than 30 years, including extensive marrow damage. With this legacy from the 1945 epidemic of acute bone marrow depression[1] there is no need to insist that leukaemia was the sole cause of later deaths from aplastic anaemia[8]. There is also a reason why these normally rare diseases might coexist and thus hasten the onset of radiogenic leukaemias. With this (dual) effect restricted to high doses such cases might follow exposure to therapeutic doses of x-rays[9] as well as A-bomb radiation but would not be observed in studies of radiation workers or pregnancy x-rays[10,11].

The findings for infection deaths make it unlikely that reliable risk estimates for cancer effects of radiation will ever be derived from the mortality experiences of A-bomb survivors. This use of the mortality data would require a piecing together of information from various sources to discover the effects which pre-1950 deaths would have had on cancer mortality rates of survivors if there had been no radiogenic cancers and no marrow damage. If the early deaths had left the same mark on cancer and infection mortality, certain selection factor values might be derived from the findings for low dose groups in Table III. How these would affect estimated numbers of radiogenic cancers is shown in Table IV where there is one set of estimates based on the usual assumption of no selection effects (official estimates) and one which assumes that, relative to the zero dose group, selection had reduced the cancer risk by 1% for the 1-9 rad group, by 5% for the 10-49 rad group and by 14% for the 50-99 rad group (modified estimate, see E^3 to E^1 ratios for 1950-58 deaths in Table III). According to the official estimates 120 or 3.5% of the 3402 cancer deaths in three low dose groups were radiation induced, and according to the modified estimate there were 301 or 8.8% of these cases.

Needless to say pre-1950 deaths were unlikely to have had the same effect on different diseases. However, with marrow damage causing deaths from infections and blood diseases after as well as before 1950, there would certainly be some modification of the cancer risks of five year survivors. Therefore the official estimates in Table 4 are certainly underestimates and, however inaccurate, the modified estimates should remind the reader of how complex are late effects of all disasters involving large numbers of

persons, and how essential an understanding of this complexity is for correct interpretation of the cancer mortality rates of A-bomb survivors.

One reason why it was not immediately obvious that cancer was not the only late effect of the Hiroshima and Nagasaki bombs was because harmful effects of marrow damage and beneficial effects of selection were targeted on the same diseases. There were other problems including the fact that the only distinctive effect of marrow damage (aplastic anaemia) can also be caused by leukaemia. But the main reason for the long delay in recognising the two opposing forces was a statistical analysis which not only required as evidence of any radiation effect a significant linear dose trend, but also attached no importance to infection deaths even after several reminders about possible effects of selection and marrow damage[6].

As two separate events (or events targeted on different diseases) the selection and marrow damage would have produced dose response curves which merely increased or decreased with radiation dose (monotone dose effects). But as simultaneous events targeted on the same diseases this was impossible. Therefore both effects might have escaped recognition if the threshold had not been much lower for environmental effects of the radiation than other acute effects. The former not only affected the zero dose group but also lasted long enough to affect the "early entrant" subgroup of the NIC controls[3,12]. For these persons there would be no erosion of any selection advantage by later effects of the radiation.

Therefore, since they have always had lower death rates than either "late entrants" or the zero dose group[12], there might be more to be learnt about cancer effects of selection by comparing these three groups than by concentrating on the low dose groups in Table IV.

At the opposite end of the dose scale both the infection death rate and the cancer death rate increased with dose, and the number of extra deaths from leukaemia was almost matched by the number of extra deaths from other blood diseases[8]. Therefore, in spite of various attempts to prove the opposite, the hypothesis of life shortening effects of radiation other than cancer still stands - with irreparable damage to blood forming tissues as the most likely cause of extra non-cancer deaths[13]. On this assumption the present method of risk estimation for cancer effects of small doses of radiation - by linear extrapolation of high dose observations - is clearly in need of replacement. We can no longer assume that cancer is the only late effect of radiation at high doses. Therefore, there is probably no alternative except to base future risk estimates on direct observations of small dose effects in situations where it is both possible to identify cancer deaths long after exposure to measured doses of radiation, and possible to identify (and control for) indirect effects of the radiation and other confounding variables.

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Table I

Results of Fitting RERF data to Two Models of Relative Risk[1]

Diagnostic Groups	Calendar Years	Cases	Deviance Values for Two Models of Relative Risk[2] Linear L	Linear Quadratic L/Q	L-L/Q[3]	Significant Improvement
All Causes of Death	1950-58	7246	356.72	343.12	13.60	Yes
	1959-66	7615	282.01	282.01	0.0	-
	1967-74	7899	282.92	281.77	1.15	-
	1975-82	8103	291.86	290.55	1.31	-
	Total	31043	1212.14	1183.07	29.07	Yes
Neoplasms	1950-58	1222	293.23	289.69	3.54	Marginal
	1959-66	1575	315.16	315.16	0.0	-
	1967-74	1772	315.17	314.35	0.82	-
	1975-82	2013	280.17	277.97	2.20	-
	Total	6582	1205.35	1205.09	0.26	-
Cardiovascular Diseases	1950-58	2140	243.53	242.65	0.88	-
	1959-66	2863	223.28	221.85	1.43	-
	1967-74	3429	208.92	208.71	0.21	-
	1975-82	3502	285.05	282.41	2.64	-
	Total	11932	903.84	902.90	0.94	-
Infections etc	1950-58	3536	287.23	276.95	10.28	Yes
	1959-66	2684	222.78	221.45	1.33	-
	1967-74	2228	259.52	255.26	4.26	Yes
	1975-82	2216	256.49	253.89	2.60	-
	Total	10664	1031.95	1014.74	17.21	Yes

(1) fitting by maximum likelihood after division into 8 dose levels of 160 cohorts (see text)

(2) Deviance value is -2 x natural logarithm (fitted likelihood)

(3) This difference is approximately distributed according to X^2 with 1 d.f on the assumption that there is no significant quadratic component of risk. Therefore the critical value is close to 4.0 for 5 percent significance.

Table II

Values of Alpha and Beta Coefficients of the Linear Quadratic Model

Diagnostic Groups	Calendar Years	Linear Quadratic Model(1)					
		Alpha (10^{-3})	S.E.		Beta (10^{-6})	S.E.	
All Causes of Death	1950-58	- 1.40	0.43	***	+ 4.10	1.11	***
	1959-66	+ 0.36	0.46		0.00	1.12	
	1967-74	+ 0.18	0.46		+ 1.34	1.14	
	1975-82	+ 0.23	0.45		+ 1.39	1.14	
	Total	- 0.07	0.20		+ 1.54	0.57	**
Neoplasms	1950-58	+ 0.10	1.33		+ 7.01	3.67	
	1959-66	+ 1.99	1.17		0.00	0.00	
	1967-74	+ 2.66	1.12	**	- 1.96	2.73	
	1975-82	+ 4.59	1.12	***	- 4.74	2.72	
	Total	+ 2.54	0.59	***	- 0.78	1.48	
Cardiovascular Diseases	1950-58	- 0.95	0.83		+ 1.92	2.04	
	1959-66	+ 0.85	0.78		- 1.96	1.79	
	1967-74	+ 0.43	0.68		- 0.93	1.63	
	1975-82	- 0.91	0.65		+ 2.75	1.68	
	Total	- 0.25	0.32		+ 0.38	0.94	
Infections etc	1950-58	- 2.19	0.58	***	+ 4.52	1.47	***
	1959-66	- 1.08	0.69		+ 2.56	1.68	
	1967-74	- 1.23	0.82		+ 4.32	2.15	*
	1975-82	- 1.16	0.81		+ 3.28	2.12	
	Total	- 1.47	0.35	***	+ 3.51	0.90	***

(1) Linear Quadratic Model $R = 1 + \alpha D + \beta D^2$ where D is the radiation dose in rads

* $p > 0.05$ ** $p > 0.01$ *** $p > 0.001$

Table III

Observed and Expected Numbers of 1950-58 Deaths from Infections etc.

Period	T65 Dose in rads	Infections etc[1] Obs. Nos.	E^1 Nos.	E^2 Nos.	E^3 Nos.	DRC[2]
1950-58	0	1471	1438.7	1452.9	1478.2	100
	1 - 9	1174	1139.2	1149.3	1163.2	99
	10 - 49	580	578.6	578.6	567.3	95
	50 - 99	127	167.6	164.0	149.6	86
	100 - 199	100	113.7	107.6	91.3	78
	200 - 299	32	47.5	42.8	35.9	74
	300 - 399	21	21.2	18.1	17.0	78
	400 +	31	29.6	22.9	33.5	110
1959-66	0	1121	1104.1	1110.2	1117.4	100
	1 - 9	868	841.3	845.4	848.6	100
	10 - 49	423	450.2	450.2	445.4	98
	50 - 99	127	131.5	129.9	124.6	93
	100 - 199	75	84.4	81.8	76.7	90
	200 - 299	36	35.5	33.5	32.0	89
	300 - 399	12	15.8	14.5	14.9	93
	400 +	22	21.2	18.5	24.4	114

Continued .../

Table III continued .../

1967-74	0	923	929.8	920.9	936.5	100
	1 - 9	702	681.6	675.7	683.7	100
	10 - 49	359	375.8	375.9	369.1	97
	50 - 99	101	107.4	109.7	101.1	93
	100 - 199	74	72.1	75.8	66.2	91
	200 - 299	27	30.7	33.7	29.6	96
	300 - 399	13	12.9	14.8	14.2	109
	400 +	29	17.6	21.6	27.5	155
1975-82	0	963	909.5	907.2	919.3	100
	1 - 9	641	685.4	683.8	690.1	99
	10 - 49	373	379.0	379.0	374.0	98
	50 - 99	110	107.4	108.0	101.5	93
	100 - 199	66	75.1	76.1	68.5	90
	200 - 299	28	30.2	30.9	27.9	91
	300 - 399	13	13.0	13.5	13.0	99
	400 +	22	16.4	17.4	21.6	130

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(1) E^1, E^2, E^3 } Expected Deaths { Null Hypothesis; Linear Model; Linear Quadratic Model

(2) Dose Response Curve or ratio of E^3 to E^1 after normalization at zero dose (see Figure II).

Table IV

Risk Estimates for cancer effects of A-bomb Radiation (LSS cohort).

With and without some allowance for selection effects of pre-1950 deaths.

T65 Dose in Rad	Cancer Deaths	Selection Factors(1)	Fitted Relative Risk(2) R^1	Fitted Relative Risk(2) R^2	Radiogenic Cancers Estimated Nos. R^1	Radiogenic Cancers Estimated Nos. R^2
0	2556	1.00	1.00	1.00	0	0
1 - 9	1920	0.99	1.01	1.04	19	74
10 - 49	1143	0.95	1.05	1.15	54	149
50 - 99	339	0.86	1.16	1.30	47	78
1 - 99	3402				120	301

(1) see E^3 to E^1 ratios in Table III

(2) R^1 relative risk assuming no selection, see RERF 10th mortality report(4)

R^2 relative risk after inclusion of the selection factor values in column 3.

Captions to Figures

Figure I. Comparison between two models of Relative Risk

Figure II. Shape of the Dose Response Curve for 1950-58 deaths from infections etc.

Figure I

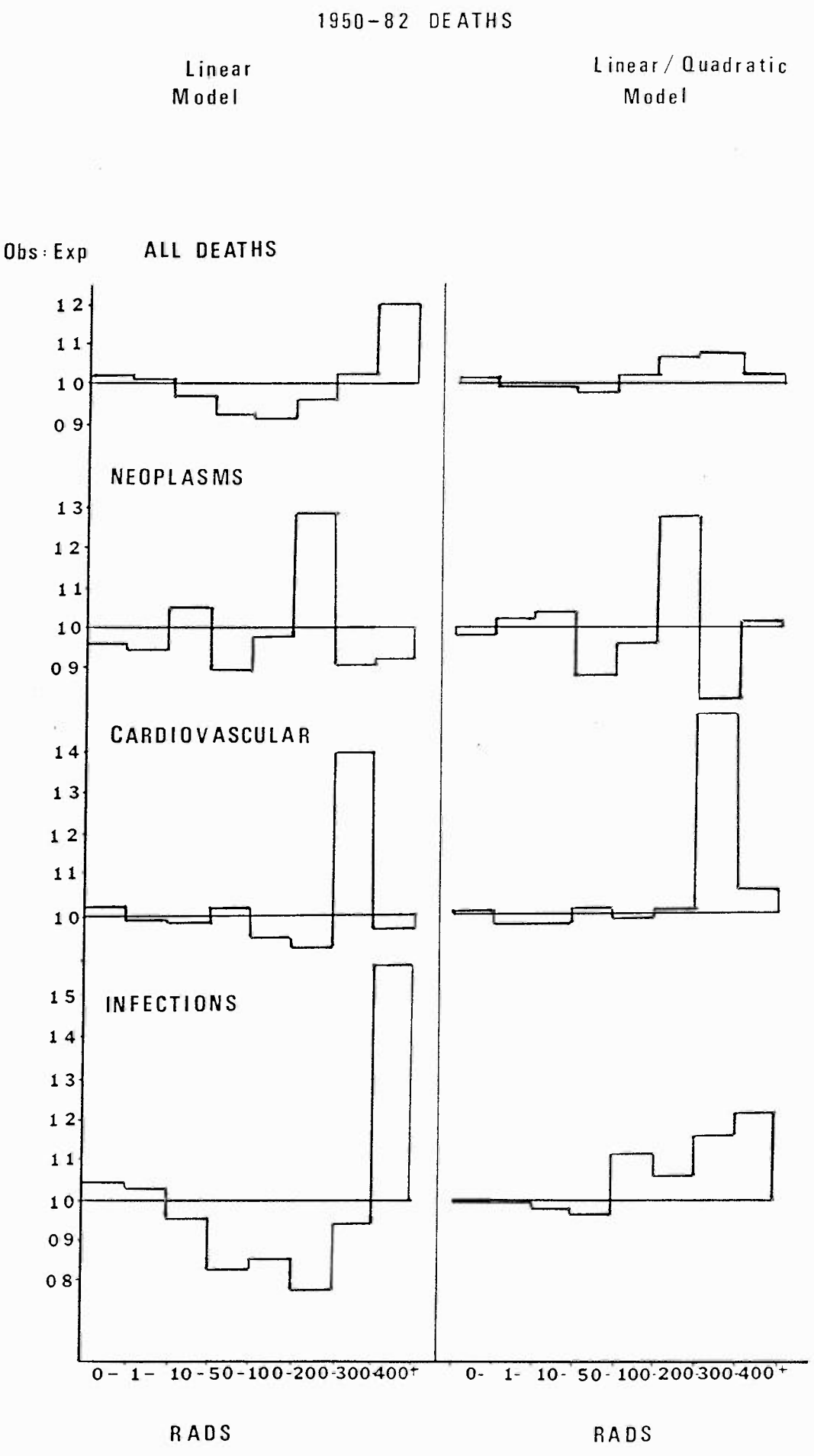
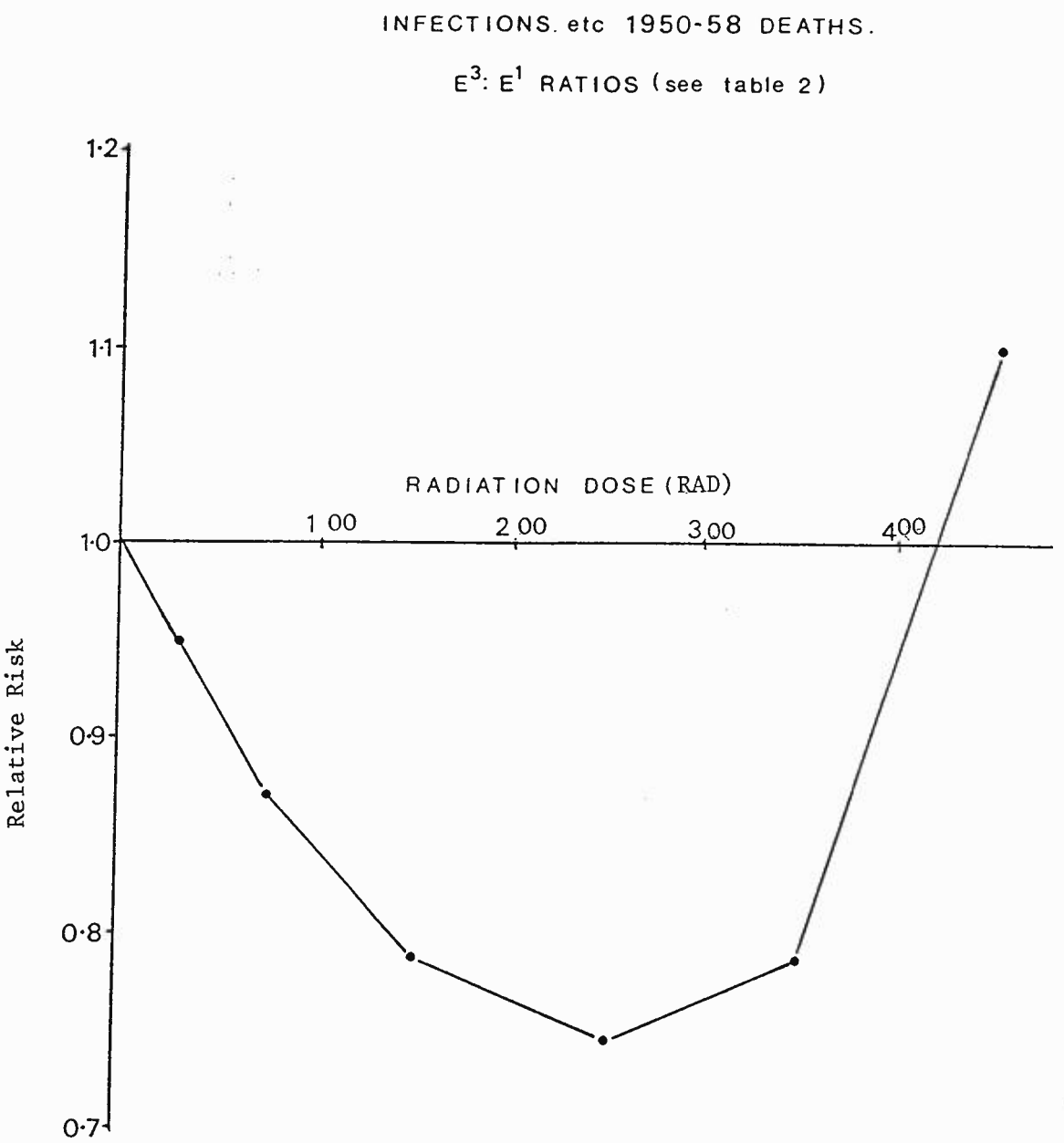

1950-82 DEATHS
Linear Model
Linear / Quadratic Model
Obs:Exp
ALL DEATHS
NEOPLASMS
CARDIOVASCULAR
INFECTIONS
0- 1- 10- 50- 100- 200- 300- 400+
RADS

Figure II


INFECTIONS. etc 1950-58 DEATHS.
E3: E1 RATIOS (see table 2)
1·2
1·1
1·0
0·9
0·8
0·7
Relative Risk
RADIATION DOSE (RAD)
1 00
2 00
3 00
4 00