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Hanford radiation study III: a cohort study of the cancer risks from radiation to workers at Hanford (1944-77 deaths) by the method of regression models in life-tables

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ABSTRACT This paper reports on results from the study initiated by Mancuso into the health risks from low-level radiation in workers engaged in plutonium manufacture at Hanford Works, Washington State, USA, and attempts to answer criticisms of previous reports by an in-depth study. Previous reports have aroused much controversy because the reported risk per unit radiation dose for cancers of radiosensitive tissues was much greater than the risk generally accepted on the basis of other studies and widely used in setting safety levels for exposure to low-level radiation. The method of regression models in life-tables isolates the effect of radiation after statistically controlling for a wide range of possible interfering factors. Like the risk of lung cancer for uranium miners the dose-response relation showed a significant downward curve at about 10 rem. There may, therefore, be better agreement with other studies, conducted at higher doses, than is widely assumed. The findings on cancer latency (of about 25 years) and the effect of exposure age (increasing age increases the risk) are in general agreement with other studies. An unexplained finding is a significantly higher dose for all workers than for workers who developed cancers in tissues that are supposed to have low sensitivity to cancer induction by radiation.

In 1977 a preliminary analysis[1] of cancer risks from radiation to workers at the Hanford works, Richland, Washington, indicated a risk for bone-marrow cancers among reticuloendothelial system neoplasms, cancers of pancreas and, to a lesser extent, lung among solid tumours. These risks showed a definite relation to radiation doses of individual workers.

That report aroused controversy because the estimated increase in risk (per unit dose) at relatively low dose levels (less than 30 rads) was about 10 to 20 times greater than would have been expected by extrapolating downwards from somewhat higher doses analysed in previous studies, notably the Japanese atomic bomb survivors (ABCC data).[2] Therefore, two independent analyses of essentially the same data by different scientists using different methods were made to see whether our findings could be confirmed.[3 4] Both studies essentially confirmed the findings in relation to bone marrow and pancreatic cancers but drew different conclusions.

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Meanwhile we continued analysing the data[5 6] and showed that an increase in risk was still observable after simultaneous control for the following factors: sex, age at death, year of death, years worked, and level of monitoring for internal exposure to radioactivity (see below). One paper[5] introduced the important concept of concentrating on cancers in tissues that are known (by others) to be sensitive to cancer induction by radiation. In epidemiological studies it is often necessary to subdivide cancers because a particular agent may be inducing some cancers more than others. If this subdivision is done without previous knowledge of tissue sensitivity it will often be necessary to carry the subdivision so far that the subgroups are too small for an adequate statistical test. In the field of cancer induction by radiation this difficulty no longer exists because a wide body of previous experience has shown which tissues are most sensitive.[7 8]

Previous reports by us[1 5 6] and Hutchison *et al*[4] used the methodology of proportionate mortality analysis to relate the proportion of cancers to the cumulative radiation doses. The report by Marks

Table 1 *Hanford study population. (All workers monitored for external radiation)*

Specifications	*Live workers*	*Dead workers†*			*Total*
		A	*B*	*C*	
No of men	18009	503	240	3128	21880
No of women	5756	58	31	237	6082
Age at hire (yr)					
< 25	8850	35	17	224	9126
25-34	9330	143	61	733	10267
35-44	4048	194	69	935	5246
45-54	1341	143	86	1012	2582
⩾55	196	46	38	461	741
Work cohort (calendar years)					
1943-4	3005	215	132	1457	4809
1945-9	5947	231	92	1311	7581
1950-4	4659	83	29	407	5178
1955-	10154	32	18	190	10394
Employment period (yr)					
0-2	8916	206	107	1324	10553
3-7	5812	98	52	626	6588
⩾8	9037	257	112	1415	10821
Levels *of monitoring for internal depositions of radioactive substances					
1	9087	211	119	1479	10896
2	6016	154	78	928	7176
3	2741	114	40	545	3440
4	5921	82	34	413	6450
Totals	23765	561	271	3365	27962

*1 No record of bioassays or whole body counts.
2 Records of these tests but all with negative findings.
3 No record of whole body counts or internal depositions but at least one of the bioassays recorded some radioactivity (positive bioassays).
4 Either definite evidence of internal depositions (225 male workers) or a combination of positive bioassays and whole body counts.
†A Cancers of radiosensitive tissues (see table 3).
B Other cancers.
C Other (non-cancer) deaths.

and Gilbert[3] used the standardised mortality ratio method and thus identified a substantial "healthy worker effect" (or reduced risk of dying), which was possibly due to pre-employment health checks raising the standard of general fitness (see below). According to this study the age and sex standardised death rates for Hanford workers were 75% of national rates for all causes and 89% for cancers. The question arises, how much of this difference is due to inefficient rejection of cancer-prone workers by the pre-employment health checks and how much to radiation? Clearly what is needed is a method of analysis in which *nothing* is assumed about cancer mortality of Hanford employees in the absence of radiation.

Nature of the data

The variables recorded and the method of data collection have been described elsewhere,[9] and only a few relevant facts are noted here. The present analysis includes employees up to 1975 who wore film badges (and deaths up to 1977) and table 1 summarises the main epidemiological facts.

The prime variable is the vector of annual dose of external (or penetrating) radiation as measured by the film badge. Formally these doses are measured in rems to the nearest centirem not rads, but this refinement is an illusion since before 1960 the badge contained only one type of film, and thus it is impossible to separate the effects of gamma rays, neutrons, and x-rays, which have different quality factors. Only cohorts exposed before 1960 are yet old enough to have substantial numbers of deaths, and this is a major limitation to possible conclusions from any analysis.

Files describing basic epidemiological facts about the population, death certificates, and various kinds of radiation exposure are in a good state of quality control and suitable for analysis. The file describing work histories, however, is so poor that Gilbert had to recode all the occupations before using them in her analysis.[10] We have adopted a different approach and, in a first analysis, tried to kill two birds with one stone by using the level of monitoring for internal exposure as an index of job hazard. In any case this level is strongly correlated with the total external dose (as may be seen in table 2) and therefore ought to be included in any analysis of radiation effects.

Table 2 *External radiation doses for four levels of monitoring for internal radiation*

External radiation in rads	Levels of monitoring for internal radiation*				Total
	1	2	3	4	
Men					
< 0·01	2609	494	87	21	3211
0·01- 0·07	1326	611	149	96	2182
0·08- 0·31	1586	1366	376	216	3544
0·32- 0·63	894	1019	338	209	2460
0·64- 1·27	707	822	523	670	2722
1·28- 2·55	321	686	801	1266	3074
2·56- 5·11	76	269	325	1064	1734
5·12-10·23	38	96	173	910	1217
10·24-20·47	27	37	69	686	819
20·48-40·95	3	8	33	675	719
40·96-99·99	2	2	1	193	198
Total	7589	5410	2875	6006	21880
Women					
< 0·01	1391	352	58	8	1809
0·01- 0·07	574	321	81	17	993
0·08- 0·31	829	532	128	43	1532
0·32- 0·63	315	243	71	39	668
0·64- 1·27	138	204	102	103	547
1·28- 2·55	54	84	77	103	318
2·56- 5·11	6	20	21	53	100
5·12-10·23	—	8	16	31	55
10·24-20·47	—	2	8	39	49
20·48-40·95	—	—	3	8	11
40·96-99·99	—	—	—	—	—
Total	3307	1766	565	444	6082

*See table 1 for definition of levels.

Statistical methodology

An ideal methodology should assume nothing about death rates in the absence of radiation. It should also be able to control statistically for any combination of relevant epidemiological variables, as a Mantel-Haenszel analysis can, and be able to include data on both live and dead workers. Ideally it should also be able to estimate parameters of simple dose-effect models—for example, latent period, doubling dose, linearity of dose response etc—as well as testing the null hypothesis of no radiation effect.

A methodology satisfying these criteria was developed during correspondence with interested scientists, but as was pointed out to us the method of Cox[11] on the analysis of regression models in life-tables (originally supposed to be of use only in clinical trials) had simply been rediscovered. Therefore the mathematical explanation (see appendix) is based on the paper by Cox

The method divides into two parts: firstly, a relatively simple calculation to test the null hypothesis of no radiation effects and, secondly, a more complex calculation, based on a transformation of the dose to estimate parameters of a specific dose-effect model. In both calculations the data are first divided into a large number of subgroups by levels of controlling variables. In each subgroup a life-table is constructed, giving for each year of follow-up the total number at risk, the number of deaths from cancer in that year, and the mean doses (transformed doses in the second calculation) of these two categories, cumulated to the year of follow-up or death. Summary variables are then obtained for each subgroup by certain summations over years of follow-up and finally a grand summary by summation over all subgroups. The result is, in the first case, a t statistic with an approximately normal distribution if the null hypothesis is true and, in the second case, a log-likelihood that measures the goodness of fit of the specific dose-effect model according to which the dose transformation was calculated. By varying the parameters of the dose-effect model the maximum likelihood estimates may be calculated in the usual way.

Results

VALIDATION OF THE CONTROLLING FACTORS

Table 1 shows the levels of the controlling factors used and table 3 the definition of group A cancers (or cancers of radiosensitive tissues). This definition is the same as the one in a previous paper[5] except that on the advice of experts we have included all reticuloendothelial system neoplasms, all digestive cancers, and breast cancers.[8]

Before these definitions can be used in the analysis proper, the range of controlling factors must be shown to be adequate. The reason for this necessity may be seen by considering the paper by Sanders.[12] He, in effect, used the same method but without the mathematical basis and with fewer controlling factors. He concluded that radiation exposure, if it did anything, increased longevity because survivors

Table 3 *Detailed specifications of cancers of radiosensitive tissues*

Cancers of radiosensitive tissues (group A)	No of cases		
	Men	Women	Total
Alimentary			
Stomach	44	2	46
Large intestine	68	9	77
Pancreas	52	5	57
Other intestinal	37	3	40
Respiratory			
Pharynx	10	—	10
Lung	215	10	225
Female			
Breast	—	19	19
Reticuloendothelial system			
Lymphoma	40	3	43
Myeloma	10	1	11
Myeloid leukaemia	15	—	15
Other	11	6	17
Endocrine			
Thyroid	1	—	1
Total	503	58	561

Table 4 *Effect of introducing different controls into comparisons between live workers with those dead from various causes*

Sequence of tests	*Controlling factors**	*All deaths*	*t values†*	
			A Cancers	*B Cancers*
1	Sex, work cohorts, and hire age	−4·64	—	—
2	As in 1 plus employment period	−3·60	—	—
3	As in 2 plus monitoring for internal radiation (as in table 1)	−0·48	+2·47	−2·20
4	As in 2 plus monitoring for internal radiation (see text)	−2·15	+1·65	−2·58
5	As in 1 plus job hazard index (see text)	+0·12	+2·24	−1·88

*For factor levels see table 1.
†For the null hypothesis of no radiation effect (using cumulative untransformed doses). For two-sided significance tests $t > 1{\cdot}96$ means $p < 0{\cdot}05$; and $t > 2{\cdot}58$ means $p > 0{\cdot}01$.

had higher doses than non-survivors. In fact, using as controlling factors the obvious set—namely, sex, year of hire, and age at hire—our analysis finds a grand summary t value for comparing all deaths with survivors of $-4{\cdot}6395$ (table 4), which is highly significant and indicative of increasing longevity. But the methods we used can go further and do what Sanders[12] did not—namely, estimate the magnitude of this effect by fitting a model. Practically any model will show that doses of less than 5 rads seem sufficient to reduce the death rate from *all* causes by more than half, or equivalently to extend longevity by 10 years. Inasmuch as a not insubstantial number of workers received over 30 rads they should have longevity extended by 60 years and live to be more than centenarians. Since this conclusion is contrary to the facts, it is obvious that some important factor has been overlooked.

FIRST PROBLEM IN THE ANALYSIS

The discovery that an important difference between live and dead workers had been overlooked was a reminder that, compared with an average American, Hanford workers must be exceptionally healthy because the standardised mortality ratio for all causes of death was only 75.[3] In an industrial setting a reduction in general mortality can be achieved only by selective recruitment of exceptionally fit people. This healthy worker effect may be a natural consequence of some prestigious jobs requiring exceptional strength (as in the coal industry where coal face workers are both stronger and better paid than surface workers) or the result of workers being made to pass a special fitness test before holding certain positions. Either way the bias in favour of exceptional fitness is unlikely to apply with equal force to all grades of workers. Therefore, the fact that live workers at Hanford have higher radiation doses than dead workers could result from the healthy worker effect already noted by Marks and Gilbert.[3]

To test this hypothesis we needed an index of the hazards of the work (constructed from the occupational data of individual workers without reference to their radiation records) for inclusion among our controlling factors. The census classification of occupations, however, which provides the basis of Hanford work records, is ill-suited for this purpose. So much time-consuming work had to be done before even the records were in a manageable form that we decided to have, as a first approximation to this index, a classification based on the workers' bioassay records (see table 1). Why we felt justified in using these records to obtain an indirect measure of the dangerousness of the work performed by individual workers is described elsewhere.[6]

TESTS OF THE NULL HYPOTHESIS

After deciding what factors to have as essential controls, tests of the null hypothesis (of no radiation effect) were allowed to go forward using the definitions in tables 1 and 3. Table 5 shows one of the many life-tables intermediate in the calculations; table 4 shows the results of having three causes of death as first, second, and third test groups and having different combinations of controlling factors in each test. The differences between the first two tests and later ones are obvious, and the differences between the later tests are as follows.

Third test—For this the bioassay levels corresponded to the highest level reached by each worker on a four-point scale, as in table 1. The highest level was chosen because, although a worker might take some time to reach this level, he could easily be doing dangerous work for several years before personally reaching the level for the job. The test was successful inasmuch as the t statistic for the first test group (all deaths) was no longer indicative of a significant difference between live and dead workers.

Fourth test—This was done to meet the objections of one critic who thought there might be bias (as between live and dead workers) if a worker was treated as having a bioassay level he had not yet reached. The test shows the results of allowing each worker to progress through the bioassay levels, changing at the date of any appropriate test. The effect of this alteration was to increase the difference between live and dead workers without altering the relative positions of the three test groups. Therefore

Table 5 *Life-table for typical cohort**

Year of follow-up	*Survivors to beginning of year (R_{tg})*		*Cancers of radiosensitive tissues dying in year (A_{tg})*		*Deviation (rads)*	*Variance (square rads)*	*t value*
	No	*Mean dose*	*No*	*Mean dose*			
1-11	414	1·68	—	—	—	—	—
12	414	1·99	—	—	—	—	—
13	414	2·34	—	—	—	—	—
14	414	2·75	—	—	—	—	—
15	414	3·17	—	—	—	—	—
16	413	3·61	—	—	—	—	—
17	413	4·09	—	—	—	—	—
18	410	4·66	—	—	—	—	—
19	409	5·17	1	29·30	+24·13	61·00	+3·09
20	407	5·60	—	—	—	—	—
21	406	6·15	—	—	—	—	—
22	402	6·62	—	—	—	—	—
23	397	6·93	—	—	—	—	—
24	392	7·13	1	0·79	− 6·34	106·8	−0·61
25	387	7·42	2	15·28	+15·69	228·6	+1·04
26	378	7·63	1	4·76	− 2·87	121·0	−0·26
27	374	7·73	1	6·96	− 0·77	127·4	−0·07
28	267	7·50	1	2·17	− 5·33	115·1	−0·50
29	162	7·90	—	—	—	—	—
30	134	8·21	4	3·98	−16·92	404·8	−0·84
31	5	8·39	1	12·83	+ 4·44	27·3	+0·85
32	3	8·60	—	—	—	—	—
33	1	2·21	—	—	—	—	—
Σ	11543 man-years	3·50	12	8·60	+12·03	1192·0	+0·34

*Men for the 1945-9 cohorts who were: (*a*) aged 25-34 when hired; (*b*) employed for more than eight years; and (*c*) had 4th grade of monitoring for internal radiation.

it seems to us that our original argument about the bioassay data is probably closer to the truth.

Fifth test—In the final test the bioassay data have been replaced by an index of the hazards of the work performed by each worker, which was based on job specifications without any reference to film badge readings or bioassays. The results show, firstly, that the healthy worker effect has been brought under control by an index that is independent of the radiation records (see *t* statistic for all deaths) and, secondly, that there has been firm rejection of the null hypothesis by the cancers of radiosensitive tissues.

For the reasons we have given, the fifth test was applied much later than the earlier test. Therefore, in the detailed model fitting, described below, the controlling factor was the final state of the bioassay level for each worker as in table 1. The figures in table 4 show that a switch to the new index would have made very little difference and would still have left us with an unexpected problem—namely, the negative findings for cancers of relatively insensitive tissues in all tests of the null hypothesis (see group B in table 1).

SECOND PROBLEM IN THE ANALYSIS

The negative findings for group B cancers have nothing to do with the healthy worker effect because they feature in all proportional mortality analyses whether by us or by Hutchison *et al.*[1 4–6] Nor are they the result of biased selection of the two groups of cancers because this grouping is based on the work of other scientists done by them without any knowledge of the Hanford data. There was a distinct impression of some kind of problem related to accuracy of diagnosis because, up to 56 years of age, the doses for group B cancers were higher than the doses for non-cancer deaths.[6] Final resolution of the problem had to wait until the death certificate data were subjected to close scrutiny (table 6).

The death certificate data included place of death and showed that most of the certificates had been signed by doctors who were probably less aware of the occupational hazards of Hanford workers than doctors in Richland and other cities in the State of Washington. In the more distant places the proportion of high doses (over 2·5 rads) was distinctly lower for cancers than non-cancers, and everywhere the proportion was lower for cancers than for typically sudden deaths—that is, myocardial infarctions and accidental deaths. We therefore decided to test the hypothesis of under-reporting of cancer deaths by repeating the proportional mortality analysis after excluding all deaths ascribed to myocardial infarction and accidents and including place of death among the controlling factors. We actually used the three levels of place of death shown in table 6 and found that there was no longer a

Table 6 *Additional specifications of dead workers. (Figures in parentheses show the number of cases in the highest dose group—that is, over 2·54 rads)*

Age at and stated cause of death	*Place of death*†					
	A		*B*		*C*	
< 56						
Acute myocardial infarction*	117	(16)	125	(12)	207	(8)
Accidents and suicide*	57	(10)	134	(15)	220	(7)
Other non-cancers	105	(12)	137	(14)	282	(5)
A-series cancers	42	(9)	70	(9)	125	(3)
B-series cancers	34	(7)	20	(—)	54	(2)
All deaths	355	(54)	486	(50)	888	(25)
> 56						
Acute myocardial infarction*	215	(50)	279	(27)	462	(20)
Accidents and suicide*	26	(11)	56	(9)	113	(4)
Other non-cancers	298	(73)	444	(46)	944	(29)
A-series cancers	132	(45)	134	(24)	250	(6)
B-series cancers	64	(10)	67	(4)	127	(1)
All deaths	735	(189)	980	(110)	1896	(60)
All ages						
Acute myocardial infarction*	332	(66)	404	(39)	669	(28)
Accidents and suicide*	83	(21)	190	(24)	333	(11)
Other non-cancers	403	(85)	577	(60)	1226	(34)
A-series cancers	174	(54)	204	(33)	375	(9)
B-series cancers	98	(17)	91	(4)	181	(3)
All deaths	1090	(243)	1466	(160)	2784	(85)

*Excluded from some of the comparisons between cancers and non-cancer deaths (see text).
†A Washington State, Richland.
B Washington State, elsewhere.
C Other US States.

negative finding for group B cancers (t value − 0·14) and still a positive finding for group A cancers (t value +2·07).

Model fitting: I

Having shown that cancers of radiosensitive tissues gave a significant positive result in the test of the null hypothesis, an attempt was made to fit a simple model (table 7). The first model only allows for variation of the assumed doubling dose and a parameter measuring non-linearity of dose response. Equal weights were given to doses of radiation at whatever age they were received or at whatever interval before death, so no allowance was made for cancer latency. The log-likelihoods (relative to no radiation effect) for various combinations of the parameters (table 7) are plotted as log-likelihood curves in fig 1, and sample dose-response curves equivalent to typical combinations of parameters are plotted in fig 2. Both theoretical and practical considerations show that in plotting log-likelihood curves the parameter D (doubling dose) should be measured on an *inverse* scale for best possible interpolation on the curves.

Table 7 *Fitting of simple model. Let* X_j = *dose in follow-up year* j, *and let the relative risk in follow-up year* i *be given by* $R_i = 1 + (\sum_{j=1}^{i} X_j/D)^E$ *where* D *is the assumed doubling dose and* E *is the exponent for non-linearity* (E = *1·0 gives a linear dose-response relationship*)

Model No	*E*	*D rads*	*Log-likelihood relative to no radiation risk*
1	1·0	∞	0·0000
2	1·0	100	1·7046
3	1·0	50	2·5307
4	1·0	25	2·8818
5	1·0	15	2·1187
6	1·0	10	0·3942
7	2·0	∞	0·0000
8	2·0	50	1·1697
9	2·0	25	−0·6964
10	2·0	15	−9·7484
11	0·5	∞	0·0000
12	0·5	50	3·8979
13	0·5	25	4·3815
14	0·5	15	4·5278
15	0·5	10	4·4394
16	0·3333	∞	0·0000
17	0·3333	25	3·9659
18	0·3333	15	3·9173
19	0·3333	10	3·7579

Inspection of the curves in fig 1 shows that for all values of D, the log-likelihood is higher for E = 0·5 (corresponding to a half-power law for the dose response) than for any other value of E, in particular E = 1·0 (corresponding to a linear dose response). This is interesting because a similar dose response

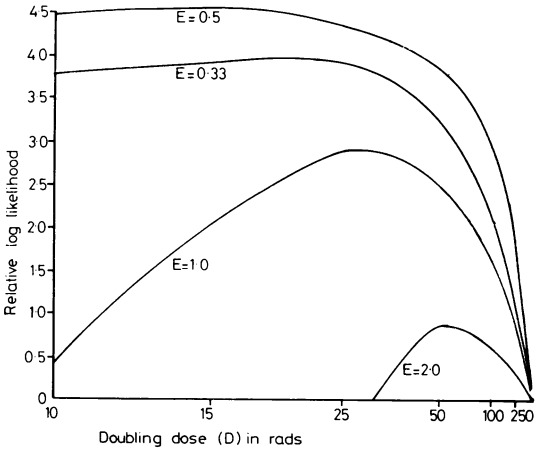

Fig 1 *Curves of log-likelihood against assumed doubling dose (D) for various values of the exponent for non-linearity (E) arising in the fitting of the simple model. Relative risk (R) = 1 + (Σx/D)^E where Σx is cumulative dose.*

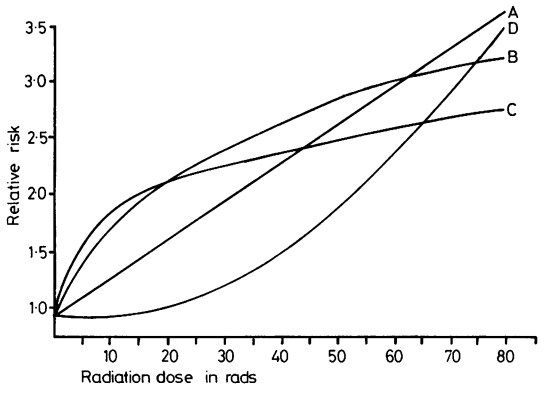

Fig 2 *Typical dose-response curves of relative risk (R) against cumulative dose (Σx) for various values of the parameters (D and E) in the simple model: $R = 1 + (\Sigma x/D)^E$. Curve A: D = 30 rads, E = 1·0 (linear law). Curve B: D = 15 rads, E = 0·5 (square-root law). Curve C: D = 15 rads, E = 0·3333 (cube-root law). Curve D: D = 50 rads, E = 2·0 (quadratic law).*

was found in a recent study of uranium miners.[13] Moreover, if the differing estimates of doubling dose (assuming linearity) from ABCC and Hanford data were to be reconcilable, one would expect the true dose-response relationship to have such a downward curve. By inspection of fig 1 the maximum likelihood estimate of doubling dose is about 30 rads for the linear model and 15 rads for the half-power model.

Model fitting: II

After these encouraging results with a simple model a more complicated model (allowing for cancer latency and variation in sensitivity with age at exposure) was fitted (table 8).

The results for this model are as follows.

(1) *Non-linearity of dose-response (E)*—A maximum likelihood estimate for E of 0·5 (half power dose-response law) with E = 1·0 rejected at the 1% level.

(2) *Doubling dose (D)*—A maximum likelihood estimate for D of 15 rads with a 95% confidence interval of 2-150 rads.

(3) *Interval between cancer induction and death (L)*—A maximum likelihood estimate of L = 25 years.

(4) *Effect of age on sensitivity to cancer-induction by radiation (S)*—A maximum likelihood estimate of the amount by which age at exposure must increase in order to increase sensitivity by e (that is, the base of natural logarithms) is given by S = 8 years (with equal sensitivity at all exposure ages, or S = ∞, rejected at the 1% level).

Table 8 *Fitting of more complex model. Let radiation received* k *years before death have to be multiplied by a factor* W_k *to give the effective dose, where* $W_k = (k/L) \exp[1-(k/L)]$ *and* L *is the optimum latent period in years* (W_k *is less than 1·0 for all* k *except* k *equal to* L). *Let radiation received at age* a *have to be multiplied by a factor* U_a *to give the effect of age at exposure, where* $U_a = \exp[(a-40)/S]$ *and* S *is the amount in years by which age at exposure must increase to increase sensitivity by a factor* e (*2·7183*). U_a *is standardised to give a sensitivity of 1·0 at exposure age 40. Let the radiation received in follow-up year* j *be* X_j *and let the cumulative effective dose by follow-up year* i *be* Z_i, *where* $Z_i = \sum_{j=1}^{i} W_{(i-j)}U_{(h+j)}X_j$ *and* h *is the hire age in years. Let the relative risk in follow-up year* i *be given by* R_i *where* $R_i = 1 + (Z_i/D)^E$ *and* E *is the exponent for non-linearity and* D *is the assumed doubling dose for radiation received at age 40 and death after the optimum latent period* (L *years*)

Model No	*L years*	*S years*	*E*	*D rads*	*Log-likelihood*
1	any	any	any	∞	0·0000
2	10	∞	0·5	15	4·8748
3	20	∞	0·5	15	5·0972
4	30	∞	0·5	15	5·0483
5	25	20	0·5	30	6·4304
6	25	−20	0·5	30	2·6846
7	20	20	0·5	30	6·4806
8	20	15	0·5	30	7·0649
9	20	10	0·5	30	8·0644
10	20	5	0·5	30	7·3960
11	20	2	0·5	30	0·8342
12	20	8	0·5	30	8·5601
13	15	8	0·5	30	8·3384
14	25	8	0·5	30	8·6314
15	25	8	1·0	30	1·6531
16	25	8	0·3333	30	8·0394
17	25	8	0·5	20	8·8489
18	25	8	0·5	50	8·0931
19	25	8	0·5	100	7·0663
20	25	8	0·5	10	8·6104
21	25	8	0·5	15	8·8558

Conclusions

Before the Hanford study the main data on the carcinogenic effects of penetrating radiation in man were from the ABCC study[2] and the study of ankylosing spondylitics.[14] Both these studies broadly agree that the dose-response effect above 100 rem shows no evidence of curvilinearity within experimental error and that the doubling dose for radiosensitive cancers (see table 3) is in the region of 200 rem. The two sets of data on latent periods broadly agree with one another (and with us), showing an effect continuing and in some cases still increasing after 20 years. Less has been written on the effects of age at exposure, but what has been published tends to show that the risk increases with age, though the measured effect is much less than our estimate.

It is also interesting to compare the estimates of

this paper with those from the study of lung cancer in uranium miners[13] since in both studies an approximately square root relationship of effect to estimated exposure was found. It is extremely difficult, however, to compare other parameters of the dose response because the uranium miners' exposure included alpha particles from radon daughters, which have very different linear energy transfer and relative biological effectiveness from the penetrating gamma radiation measured in this study.

Thus the main area of disagreement between our second analysis of Hanford data[5] (which gave a doubling dose of about 15 rad assuming linearity of dose response) and other human data on the effects of external or penetrating radiation lies in the dose-response effect and, specifically, the doubling dose which implies an effect about 15 to 20 times greater than earlier estimates.

If, however, the dose-response relationship estimated in this paper, which implies major downward curvature in the region of 10 rads, is extrapolated upwards to the dose levels covered in earlier studies—that is, over 100 rems—then it predicts an effect two to three times lower than linear extrapolation. The effect of this is to halve the difference between the two estimates. For the reasons already given the Hanford study cannot separate the greater radiobiological effect of neutrons from the lesser effects of gamma radiation. Therefore, although no precise figure can be given for the neutron effect, one should probably reduce the difference still further and thus be left with an unexplained component of the difference that is only two or three times higher than the earlier estimates.

This difference is sufficiently small enough to be accounted for by increased liability of precancer in general and preleukaemia in particular to latent period deaths. Heightened sensitivity to infections during the terminal phase of cancer latency has recently been confirmed in children[15] and is probably a feature of adult cancers also. Therefore, changed reactions to other diseases during the preclinical phase of adult cancers could make all the difference since there is a strong healthy worker effect at Hanford (see above) whereas A-bomb victims were exposed to the aftermath of a catastrophe and the patients with ankylosing spondylitis were at risk of dying from a disease that lowers resistance to respiratory infections.

Thus putting all the data together can give a reasonably consistent explanation of observed differences and resemblances between several surveys. But one discrepancy remains to be accounted for—that is, the prediction that background radiation, amounting to about one-tenth of a rem a year, would (by our estimates of risk) account for more cancers than actually exist. This apparent reductio ad absurdum can be accounted for by three factors. Firstly, progressive increase in sensitivity to cancer-induction by radiation with advancing age means that most of any one person's life-time exposure to background radiation is occurring at relatively insensitive ages. Secondly, long intervals between cancer-induction and death mean that any effects of background radiation will only find expression among individuals who live to an advanced age. Thirdly, the assumption that each death from cancer has only one cause is certainly an over-simplification. The method of calculation used in this paper is such that if, for example, radiation worked jointly with other chemicals to produce lung cancer, then radiation would have contributed to the risk even in the presence of a sufficient cause—namely, excessive smoking. In fact, smoking was not measured in Hanford data, but for other industrial chemicals there are records that we hope will be incorporated in later analyses.

Since lung cancers account for a high proportion of radiosensitive cancers a further word should perhaps be said about the possibility of smoking being an interfering factor. As mentioned above, there is no record of the smoking histories of Hanford employees. It is hardly surprising that this item was not included in the workers' medical records when the plant was first set up in 1943, since on-site smoking was strictly prohibited. By 1964, when an epidemiological study of this population was first promulgated, it was too late to obtain off-site smoking habits from workers who had left the industry. But although we are not in a position to observe any joint effects of radiation and smoking it is still possible that off-site smoking was correlated with the radiation exposures. This remote possibility has been tested in a preliminary fashion by measuring the association between radiation exposures and deaths from chronic respiratory diseases other than cancer (which should include most non-cancer deaths with smoking associations).[6] This test showed no statistically significant evidence for the postulated association.

Mention should be made at this point of the different treatments of exposure age in this paper and one by Gofman.[16] We conclude that within work cohorts defined by hire age (and other controlling factors) the effect of a given yearly dose of radiation is greater at high exposure ages. Gofman did not have data on individual yearly doses but only on the total amount of radiation received by each worker. Consequently, he was forced to define exposure age in terms of hire age. Therefore, what he has noticed is that, as between different hire ages, the effect of radiation is greatest in the youngest age groups.

This conclusion may well be correct, but it is of doubtful relevance to the problem of when—that is, at what age—radiation has its greatest effect, since, in the Gofman analysis, there could be any number of confounding variables, including the fact that a high dose and a long period of employment usually requires entry to the industry at an early age.

Finally, although we have shown the importance of controlling for internal monitoring levels when testing for external radiation effects, it should be noted that extensive monitoring of Hanford workers identified only 225 men with definite evidence of internal radiation (see footnote to table 1). This sample is clearly too small for measuring any health effects of internal radiation. An earlier analysis, however, found that apparent effects from external contamination (disclosed by monitoring for internal radiation) were much less after controlling for external radiation than in a crude analysis.[5] Therefore, we may safely assume that, compared with external radiation, any cancer effects of internal radiation were very small.

Appendix

REGRESSION MODELS IN LIFE-TABLES

A life-table contains information on individuals exposed to various treatments and followed up for several years. A characteristic feature is that the final fate of some individuals is not known—that is, their survival time is censored and all that is known is that they were alive at the end of follow-up. A crucial assumption is that this censoring time is statistically independent of the final fate, whatever it may be. The question at issue is whether the survival curves differ between treatments. In the seminal paper by Cox[11] only one kind of ultimate fate was considered; in other words, if an individual was not alive at the end of follow-up any cause of death was considered of interest. The present problem differs in that only cancers are supposed a priori to be susceptible to radiation induction, so two kinds of ultimate fate, cancer and non-cancer, must be considered. The probability of non-cancer is assumed independent of any radiation, and if the plausible assumption is made that the probability of censoring is also independent of radiation (though it will obviously depend on other treatment factors such as work cohort) then the censored and non-cancers can be considered together, which greatly simplifies the statistical analysis.

Because the data give the radiation doses in yearly exposures and not more finely divided it is convenient to work in discrete time units of one year. The basic method is to divide the data into a large number of treatment subgroups (480 in the present paper) by the cross-classification of non-radiation controlling factors. The survival curve of cancers in each subgroup in the absence of radiation is considered arbitrary and estimated by maximum likelihood. The survival curve in the presence of radiation is assumed related to that in its absence by a simple regression model whose parameters can then be estimated by maximum likelihood.

DERIVATION OF LIKELIHOOD FORMULA

Let the data be divided into G subgroups indexed by g. Let the follow-up years be indexed by i and j. Let there be K individuals indexed by k. Let individual k be in subgroup G_k and be followed up to year I_k. Let a_k be one if individual k dies of cancer and zero otherwise. Let b_k be one if individual k dies of non-cancer or is censored and zero otherwise. Let λ_A (i, g) be the probability of dying from cancer in subgroup g and follow-up year i. Let λ_B (i, g) be the corresponding probability of dying from non-cancer or of being censored. Then $[1 - \lambda_A(i, g) - \lambda_B(i, g)]$ is the probability of surviving year i in subgroup g. Let X_{ki} be the radiation dose of individual k in year i. Let x_k be a vector of length I_k containing these doses. Let the model of radiation effects be that the relative risk of cancer for individual k in year i is increased by the factor $(1 + E(x_k, i))$ where E is a simple function specifying the model. For example, a very simple model has $E(x_k, i) = (\sum_{j=1}^{i} X_{kj}/D)$ with equally weighted doses and a constant doubling dose D. Then the overall likelihood is given by

$$\prod_{k=1}^{K}\{\pi[1 - \lambda_A(i, G_k)(1 + E(x_k, i)) - \lambda_B(i, G_k)]^{I_k}_{i=1} [\lambda_A(I_k, G_k)(1 + E(x_k, I_k))]^{a_k}[\lambda_B(I_k, G_k)]^{b_k}\}$$

Let R_{ig} be the survivors to the beginning of year i in subgroup g. Let A_{ig} be the cancers dying in year i in subgroup g and B_{ig} be the corresponding number of non-cancers and censored. So the survivors to the next year are given equivalently by $R_{(i+1)g}$ or $(R_{ig} - A_{ig} - B_{ig})$. Then, using the notation $\sum_{k \in R_{ig}}$ to mean summation over the R_{ig} individuals surviving to year i in subgroup g and a similar notation for summation over the A_{ig} cancers dying in that year, the overall log-likelihood is given by

$$\sum_{ig}\{\sum_{k \in R_{ig}} \ln[1 - \lambda_A(i, g)(1 + E(x_k, i)) - \lambda_B(i, g)] + A_{ig} \ln[\lambda_A(i, g)] + \sum_{k \in A_{ig}} \ln[1 + E(x_k, i)] + B_{ig} \ln[\lambda_B(i, g)]\}$$

OPTIMUM TEST OF THE NULL HYPOTHESIS

Since by year i the doses for years less than i and consequently $E(x_k, i)$ and also R_{ig} are all fixed, the only term in the log-likelihood that actually depends on any connection between the doses and the number of

cancers is $\sum_{ig}\{\sum_{k\in A_{ig}} 1n[1 + E(x_k, i)]\}$ and consequently by sufficiency arguments the difference between two such terms is the optimum statistic for testing which of two fully specified models, corresponding to two forms for E, is the better fit. If the null hypothesis of no radiation effect is true the function E and the term it specifies are both identically zero, and so the term corresponding to the model of some effect is the optimum test of that model compared to the null hypothesis. For the very simple model with equal weights and a constant doubling dose the best statistic becomes $\sum_{ig}\{\sum_{k\in A_{ig}} 1n[1 + (\sum_{j=1}^{i} X_{kj}/D)]\}$. If the doubling dose under test is large and fixed, then by expanding the logarithm and neglecting a constant of proportionality the effective statistic becomes $\sum_{ig}\{\sum_{k\in A_{ig}} (\sum_{j=1}^{i} X_{kj})\}$ or the total dose of the cancers. Its distribution under the null hypothesis of no radiation effect may be found from the following considerations. If the null hypothesis is true the A_{ig} cancers dying in year i in subgroup g will be a random sample of the R_{ig} survivors who started the year. Therefore the mean under the null hypothesis of the test statistic will be $\sum_{ig}\{(A_{ig}/R_{ig}) \sum_{k\in R_{ig}} (\sum_{j=1}^{i} X_{kj})\}$ and its variance can be found by finite population sampling formulae. Hence a *t* statistic can be constructed from the observed value and its mean and variance under the null hypothesis. If the number of cancers is reasonably large this *t* statistic will be approximately normally distributed under the null hypothesis.

FITTING A GENERAL MODEL OF THE RADIATION EFFECT

If one is attempting to fit a general model with adjustable parameters in the function E, because the null hypothesis has been rejected by the previously derived test, one cannot use sufficiency arguments that work for fully specified models since the function E appears in more than one place in the expression for the log-likelihood. So an approach via general maximum likelihood theory appears suitable. Because of the number of parameters it would be better to estimate the parameters in λ_A and λ_B by maximum likelihood for a fixed function E, substitute these estimates in the likelihood, and then estimate the parameters in E. This approach is made simpler if the likelihood function is first suitably approximated.

Let $E_{ig} = \sum_{k\in R_{ig}} E(x_k, i)/R_{ig}$ be the estimated mean excess relative risk in year i in subgroup g. Then if $\lambda_A(i, g)E_{ig}$, the estimated proportion of radiogenic cancers in the R_{ig} individuals who started year i in subgroup g, is small compared with one, the term in the expression for the log-likelihood involving summation over R_{ig} can be approximated by $\sum_{ig}\{R_{ig}1n[1 - \lambda_A(i, g)(1 + E_{ig}) - \lambda_B(i, g)]\}$. With this approximation the maximum likelihood estimate for $\lambda_A(i, g)$ is $A_{ig}/[(R_{ig} + A_{ig} + B_{ig})(1 + E_{ig})]$ and the corresponding value for $\lambda_B(i, g)$ is $B_{ig}/(R_{ig} + A_{ig} + B_{ig})$. The justification for using maximum likelihood estimates at all if R_{ig} is small, when the estimates will be very erratic, is given in terms of the power it gives against the most general forms for λ_A and λ_B in the paper by Cox.[11] Substituting these estimates into the expression for the log-likelihood, simplifying and neglecting constant terms, the log-likelihood becomes $L = \sum_{ig}\{\sum_{k\in A_{ig}} 1n[1 + E(x_k, i)] - A_{ig} 1n[1 + E_{ig}]\}$ or, in other words, the sum over the cancers of the difference between the logarithms of the actual estimate of the relative risk and the mean estimate of matching individuals.

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