



The Hanford Data: Issues of Age at Exposure and Dose Recording

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INTRODUCTION

Along standing belief that the best method of risk estimation for cancer effects of radiation is by extrapolation of the effects observed at high dose levels [1], and that the best source of such data is a life span study (LSS) population of A-bomb survivors [2], is becoming increasingly difficult to reconcile with the cancer experiences of workers in the Hanford nuclear reservation. Compared with these workers, the data relating to A-bomb survivors have the advantage of much larger numbers and a much wider range of radiation doses. But the position of Hanford workers is much closer to two problems of major concern, namely, the size of the health problem posed by the nuclear industry and the cancer risk from unavoidable exposures to background radiation.

In 1990, the U.S. Committee on the Biological Effects of Radiation (BEIR V), addressed these problems and finally decided that, when dose rates fall

to the levels that are typical of occupational exposures and background radiation, spontaneous repair of mutational damage reduces the cancer risk [3]. Therefore, they not only recommended that risk estimates for such exposures be derived from the cancer experiences of the LSS cohort, but also recommended a reduction allowance of approximately 2, to allow for a "dose rate effectiveness factor," or DREF.

Such a decreased effectiveness of low-level radiation in inducing cancer among those exposed (decreased as compared to the effects of high doses) has long been argued by Ethel Gilbert and other DOE funded research workers. For example, in a 1989 analysis of deaths among Hanford workers, Gilbert et al. found that among 36,325 badge-monitored workers, followed from 1945-1981, there was no evidence of any cancer effects in spite of there being a total dose of 831 Sv [4].

Nevertheless, when we came to re-analyzing these data (and integrating more extensive epidemiological data on the deaths of these workers than had previously been made available to outside investigators [5]), the negative findings of Gilbert et al. were not confirmed. On the contrary, by including "exposure age" both among factors that can obscure the relationship between radiation and cancer (confounding variables) and among factors that can alter this relationship (cancer modulating factors), the 1993 analysis revealed an important difference between the nuclear workers and A-bomb sur-

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vivors. Thus, according to our interpretation of the Hanford data, the cancer risk is much greater for exposures after 50 years of age than for earlier exposures [5,6], but, according to repeated analyses of the A-bomb data, exposures after 50 years of age are less dangerous than earlier exposures [7,8].

Since the A-bomb data analyses are solely concerned with persons who were still alive five years after the bombing of Hiroshima and Nagasaki, the most likely cause of a greater risk for young adults than for middle-aged or old persons would be selection—or a much greater risk of dying from acute effects of the A-bomb radiation for persons who were over 50 years of age in 1945 than for younger persons. Evidence of this selection has been found [9], so it is clearly important to understand the finer points of the 1981 and 1993 analyses of the Hanford data.

According to these analyses, the effects of small, repeated doses on workers above a certain age may increase their risk of cancer above what might be expected from an extrapolation of dose-response based on the experience of populations exposed to high doses. In other words, these analyses confirm what we have been arguing for years: that in terms of induction of fatal cancers, repeated low-dose exposures, particular to older people, may be more dangerous than a single exposure to the same total dose (i.e., the opposite of DREF).

We trace here the historical outline of this disagreement and present in some detail the methods and results used in our 1993 re-analysis. It is our view that subsequent analytic work on this population, and on the other worker populations at other nuclear weapons production facilities, employ these methods and include among key variables the age at each exposure, the total duration of exposure, and the socioeconomic status of each worker in successive years.

THE HANFORD CONTROVERSY PRIOR TO 1992

The first sign that low-level radiation exposures might result in excess cancer mortality among worker populations dates back to 1977, when Mancuso, Stewart, and Kneale (MSK) first examined data from Hanford [10]. On that occasion, comparisons between workers who had died from cancer and workers who had died from other causes showed that the former had a higher average dose than the latter. Also established was the fact that this difference was largely the result of radiation received

after 40 years of age (and more than 10 years before death) by men who subsequently developed three types of cancer: myeloma, lung cancer, and cancer of the pancreas.

The sponsor of the 1977 analysis of Hanford data was the U.S. Department of Energy (DOE). The DOE rejected the MSK findings as evidence of a cancer risk. This rejection was apparently justified when Sanders showed that living workers had received greater cumulative radiation doses than those who had died of cancer [11], and when Marks et al. showed that the workforce as a whole had exceptionally low rates of mortality for all diseases, including cancer [12]. These rebuttals of the MSK analysis marked the beginning of the controversy about the correct interpretation of Hanford data [13].

After publication of the 1977 analysis, Kneale was allowed only limited access to the DOE data on Hanford and was much hampered by being unable to correct obvious errors in the recording of job descriptions. Nevertheless, in 1981 and again in 1984, he showed the results of an analysis of the Hanford data that 1) relied upon internal comparisons and included several levels of internal radiation monitoring (IRM) among the controlling factors, 2) adjusted for exposure age and predeath interval, and 3) distinguished between cancers shown by the International Council for Radiation Protection (ICRP) to be sensitive to radiation induction (A cancers) and those (B cancers) that are not [6,14].

For A cancers, or the group that included neoplasms of digestive, respiratory, and hemopoietic tissues, there was definite evidence of a radiation effect. However, for B cancers (as well as for non-cancer deaths) there was a negative dose trend (or evidence of insufficient control of factors other than radiation exposure that might relate to cancer induction or death). When A and B cancers were combined, therefore, there was no definite evidence of a radiation effect. Kneale wished to observe the effects of controlling for socioeconomic status (SES) but was not permitted access to this information. Therefore, although he continued to use the Hanford data that had been made available to him, and perfected a method of statistical analysis that required identification of risk sets within cohorts (see below), there was a period of several years when he could do nothing further to influence opinions about cancer risks of low-level radiation.

In 1986, an agreement was reached between the DOE and the Three Mile Island Public Health Advisory Board that ensured the gradual release of all records of epidemiological importance relating to workers at nuclear weapons production facilities. By January 1992, there had been sufficient release of Hanford data for Kneale to include this cohort in a re-analysis, employing his new methodology and using, for the first time, detailed SES data.

THE HANFORD DATA

These data show the results of including one of the largest U.S. nuclear weapons facilities (Hanford) in a series of radiation monitoring programs, and keeping the workforce under continuous mortality surveillance. Several of the reprocessing plants in the Hanford nuclear reservation were fully operative by 1944, and, by 1979, there were 27,395 men and 8,473 women who had been monitored at least once for external penetrating radiation (the study population of badge monitored workers) [5]. By December 31, 1986, the number of ascertained deaths was 7,352, and, included in this series of 1944-1986 deaths and 1944-1978 exposures, there were 1,732 that had cancer as the underlying cause (fatal cancers) and 175 that had cancer as a contributory cause (nonfatal cancers).

For the study population as a whole, there were years of birth that ranged from 1874 to 1958, years of hire that ranged from 1944 to 1978, and exposure ages that ranged from 17 to 71, although only a handful of workers were exposed before age 20 or after age 64. The total cumulative dose averaged 22.3 mSv, with 1.7 mSv as the average for 7,762 workers who were employed for less than one year, and 63.9 mSv as the average for 10,169 workers who remained at Hanford for more than 10 years. Of the 40% of badge-monitored workers who were also tested for internal depositions of radioactive substances, only 3% were contaminated (957 men and 121 women).

Between 1944 and 1964 there was a tenfold increase in the average annual dose (Figure 1). According to Kneale et al., this apparent increase could be the result of monitoring programs (and methods of dose estimation) that were less efficient and less accurate in the 1940s and 1950s than in later years [15,16].

There are thus possibly two factors in the Hanford data, in addition to cancer latency, that might affect the observed relationship between the occupational

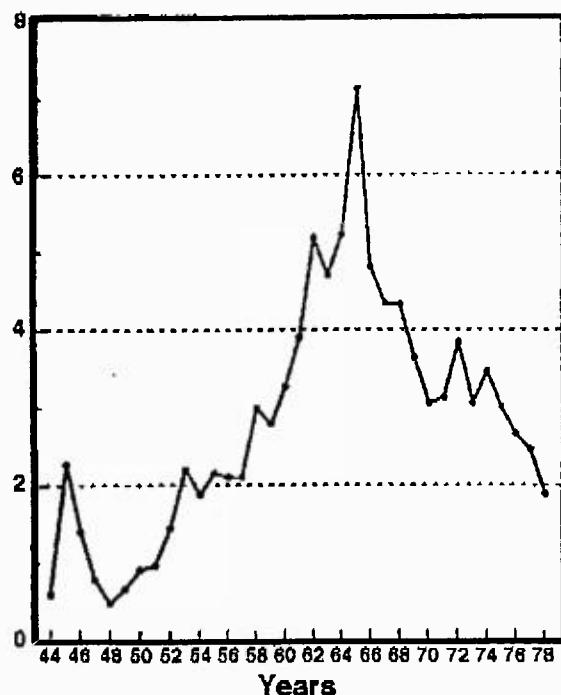


Figure 1. Mean annual dose of external radiation for all badge-monitored workers at Hanford. Reproduced from the journal *Health Physics* with permission from the Health Physics Society. Stewart AM, Kneale GW. A-bomb survivors: further evidence of late effects of early deaths. *Health Phys* 1993;64:467-472.

exposures to radiation and the cancer deaths: the age at each exposure and the date of each recorded dose.

THE METHODS OF THE 1993 RE-ANALYSIS OF THE HANFORD DATA

Subcohorts and Risk Sets

A novel feature of the 1993 re-analysis of the Hanford data (1944-1986 deaths) was the production of subcohorts and risk sets within these subcohorts. These subcohorts represent stratification of different exposure cohorts according to 10 key demographic and socioeconomic variables (Table 1) of which six were constant through time (20 choices of birth date, 13 choices of hire date, and two choices of employment period, off-site exposure, race, and gender). Controlling for these six variables resulted in 4,160 subcohorts ($20 \times 13 \times 2 \times 2 \times 2 \times 2$).

Each subcohort was then divided into risk sets based on the five socioeconomic groups shown in Table 1, but also drawing a distinction between two discharge intervals, since this would leave some of the cancers initiated before starting work at Hanford in a separate category from later "inductions." The

Table 1. Essential Controlling Factors, Hanford Data¹

Factor	Levels	Details
Sex	2	Male; female
Race	2	White; other
Birth year	20	5 year intervals: 1870-1964
Hire year	13	2 year intervals: 1944-1978
Employment period	2	Under or over 3 years
Facility	2	With or without off-site exposures
Discharge status	2	With or without definite termination date
Potential year of death ²	43	1944-1986
Discharge interval ²	2	Death within 3 years of discharge (or not)
Socioeconomic status ²	6	Census classification of Hanford occupations: 1-199 Professional (1) 400-599 Craftspeople (4) 200-299 Managerial (2) 600+ Other blue collar (5) 300-399 Clerical (3) Not specified (6)

¹The follow-up period runs from January 1944 to December 1986.

²Separate assessment for each calendar year of employment.

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only informative risk sets were the ones that included one or more cancer deaths, but for each cancer death in each of the possible years (1944-1986) there was now a full complement of matched controls (i.e., all matched workers who were still alive at the time of the cancer death even if they eventually experienced a cancer death). Separate analysis of each cancer risk set automatically restricted the socioeconomic status and radiation doses of the matched controls to the correct period, i.e., the years before the cancer deaths.

For a detailed example, turn to the particular risk set presented in Figure 2. This risk set is defined by the following common factors: white males who had worked at Hanford for more than three years, were hired in 1951 or 1952, were born between 1895 and 1899, and had ceased work more than three years before the end of the follow-up period (1986). They also all belonged to social class 5 (the lowest socioeconomic class) and had no record of any off-site exposures.

The dates and doses of each annual exposure are shown together with the dates and causes of all the pre-1987 deaths. There were three cancer deaths for this group, in different years, so no less than three cancer deaths, with all their matched controls, were identified. (See risk set demarcation lines, also in Figure 2.)

For example, the first man to die from cancer (in 1965) had an interval of less than three years between leaving Hanford and dying. Therefore, for this case, there were only two closely matched controls (see the first demarcation line in Figure 2). For the second death, in 1969 (which was also a cancer death), there were 10 closely matched controls, and for the third cancer death, in 1981 (which came sixth in the death sequence,) there were five. Finally, for each cancer case there were observed and expected doses for 13 years (1951-1963) and 13 ages (51 to 64 years). For one of the cases there was an interval of more than 18 years between the last exposure and the date of death. (See Figure 2).

Statistical Methods

With the Hanford data in this subcohort and risk set formation, it was possible to use the conditional likelihood methods of Cox [17] or Breslow and Day [18] to calculate the probability of each set having the observed number of cancer deaths. In addition, several tests of cancer and radiation related factors were employed with the purpose of discovering 1) the amount of radiation needed to double the normal cancer risk, assuming a linear dose-response (the doubling dose); 2) the shape of the dose-response curve (the exponent factor); and 3) the effects of varying exposure age, exposure year, and

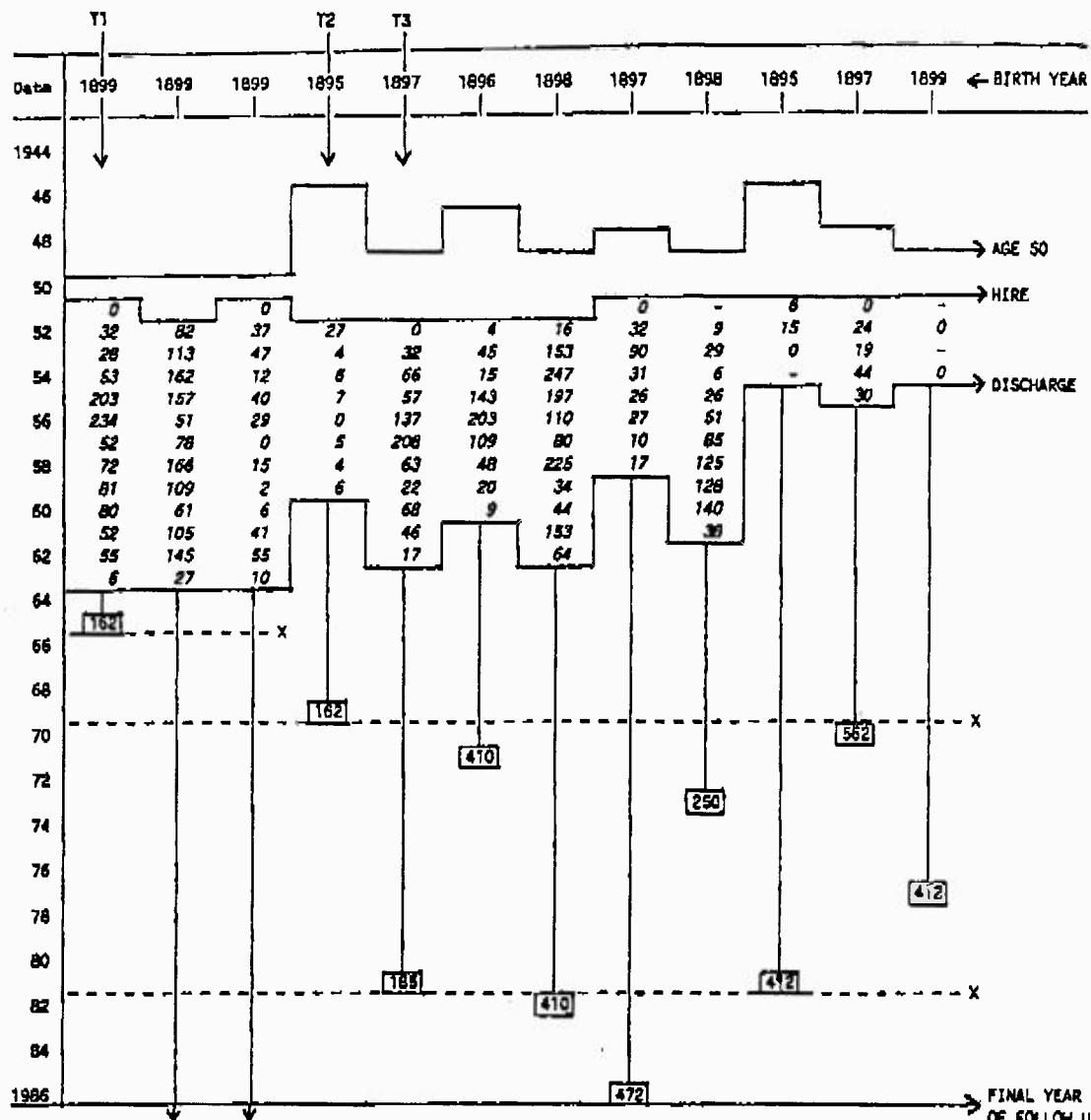


Figure 2. Specifications of three cancer cases and their exactly matched controls; Hanford data. T, Test cases or cancer deaths before the end of the follow-up. \square , ICD codes of all deaths before the end of the follow-up. *Italics*, Radiation doses in 0.1 mSv. ----X, Demarcation lines for three risk-sets with cancer cases. Reprinted, with permission, from Kneale GW, Stewart AM. Reanalysis of Hanford data: 1944-1986 deaths. Am J Ind Med 1993;23:371-389. © 1993 Wiley-Liss, Inc.

interval between exposures and death.

It was necessary early on in this analysis to resolve a problem of numbers. For example, with the Breslow and Day method, where "sets" of exposure factors are compared with standard sets, the formula for relating relative risk to standard risk is given by the exponential of a linear combination of all sets of case/control differences. In the Hanford data, this linear combination is currently the weighted sum of 34 annual doses (since the exposure period stretches for 34 years, from 1944 to 1978). Therefore, in order to allow the effects of three fac-

tors in addition to annual radiation doses, direct application of the Breslow and Day method to the Hanford data would require a risk model with more than a hundred parameters (3×34).

In the 1993 analysis of the Hanford data, Kneale resolved this problem by retaining other elements of the Breslow and Day method, but allowing the weight of each annual dose to be a function of three estimated parameters (interval period, exposure age, and exposure year) [5]. In this way, an impossibly large number of case/control comparisons was reduced to a single difference between two weight-

ed doses. Kneale also made good use of the following BEIR V recommendation: "at least with respect to cancer induction and hereditary genetic defects, the frequency of such effects increases with low-level radiation as a linear, nonthreshold function of dose" [3]. With this as an acceptable hypothesis, it was possible to employ a much simpler, linear formula for relative risk, namely, unity plus the weighted dose, rather than the Breslow and Day exponential formula.

Choice of Functions for Cancer Modulating Factors: Step Function or Smooth Curve. Intervals between the start of a neoplastic process (cancer induction) and the development of clinically recognizable disease (cancer onset) may be less than five or more than 30 years (cancer latency periods). Therefore, in any survey of cancer effects of radiation that has a limited follow-up period, it is important to be able to address the issue of the time at which each exposure occurred. To address this cancer latency problem, it is common practice to ignore all exposures in an arbitrary "lag period" or pre-death interval of, say, five, 10, or 15 years. This practice amounts to 1) recognizing the existence of one "cancer modulating factor," 2) giving a weighting value of zero to all exposures in "forbidden" or "ignored" periods, and 3) giving a weighting value of unity to all earlier exposures. This practice is equivalent to creating a step function representation of one cancer modulating factor whose estimated parameter is equal to a "critical lag period."

An alternative to having a step function curve as a means of weighting doses is to have a smooth curve whose weights gradually increase from zero to unity. This method would be more in keeping with the possible effects of cancer latency (or exposure age) than a step function, and it was, in fact, the formula used in the 1981 analysis of the Hanford data [6]. In 1981, we used a risk model whose parameters included only two modulating factors (cancer latency and exposure age), but there was weighting by smooth curves, instead of step functions. The actual curve for exposure age is shown in Figure 3, together with two step functions from a later analysis of data from several DOE nuclear facilities, including Hanford [16].

If two or more factors other than dose are influencing an observed relationship between radiation and cancer, it is plausible that the overall weighting is the product of the separate weights. This relation-

ship would allow the overall weighting for cancer latency and exposure age to take the form of a unimodal curve, if there was smooth curve weighting, or a "window," if weighting was arrived at through a step function methodology. A "window" includes the sum of all the annual doses of radiation falling within the time frame defined by a set of critical modulating factors. Thus, in Figure 4, the lower edge of a window (which is superimposed on a unimodal curve and has unit weights for "inside" doses

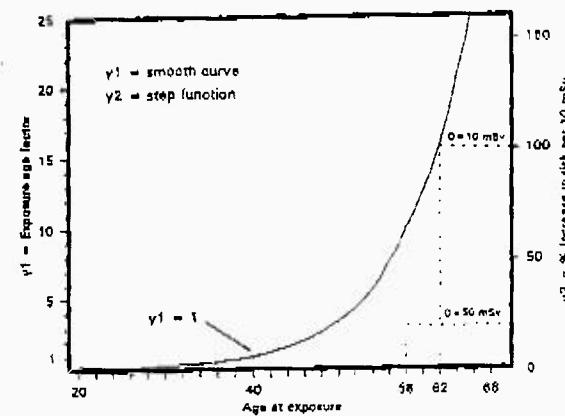


Figure 3. Vertical axis: Exposure age effect (y^1) according to Kneale GW, Mancuso TF, Stewart AM. Hanford radiation study III—a cohort study of the cancer risks from radiation to workers at Hanford (1944-1977 deaths) by the method of regression models in life tables. Br J Ind Med 1981;16:156-166. Horizontal axis: percentage increase in risk per 10 mSv (y^2) according to Kneale GW, Stewart AM. Further results of a 1993 analysis of data from five nuclear facilities. Am J Ind Med 1993, in press.

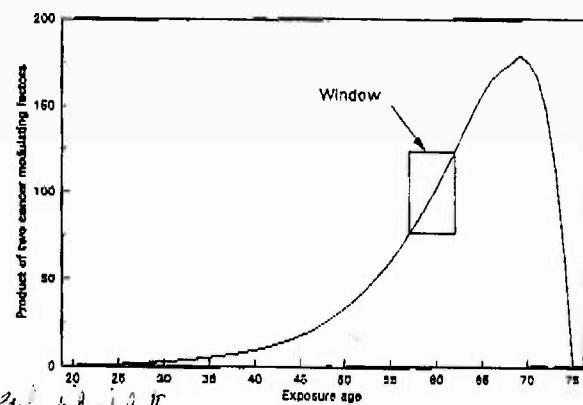


Figure 4. Weighting for cancer latency and exposure age takes the form of a unimodal curve. The "window" includes the sum of all the annual doses of radiation falling within the time frame defined by a set of critical modulating factors. *for a worker who died of cancer at 75y.*

Table 2. Maximum Likelihood Tests of Hanford Data¹

Risk models		Critical values of modulating factors					Results			Statistical significance of each model	
		Doubling dose mSv	Power law exponent	Lag period in years	Exposure age in years	Exposure year	EDC ³	Estimated radiogenic cancers	Chi-square equivalent ⁴		
Series ²	No.	β	ϵ	σ	α	λ					
F	I	263	1.87	24+	DV	DV	776	7.5	1.12	3	ns
	II	44.8	0.39	14+	58+	DV	157	50.9	9.46	4	* ⁶
	III	6.0	DV ⁵	17+	62+	1979-	34	15.3	12.49	4	*
	IV	8.6	1.48	17+	62+	DV	34	12.5	13.45	4	*** ⁷
	V	8.6	1.48	17+	62+	1979-	34	12.5	13.45	5	*
Σ	III	11.0	DV	14+	62+	1979-	84	25.3	14.07	4	**
	V	8.7	0.76	14+	62+	1979-	84	30.1	14.80	5	*

¹Risk models with two main parameters, and critical values of three modulating factors.

²Series F = fatal cancers only; Σ = fatal and nonfatal cancers.

³EDC = cancers with effective doses greater than zero, after allowing for the critical step function values of each modulating factor (see text).

⁴Actually $-2 \times \log$ -likelihood.

⁵DV = default value.

^{6,7}Significance levels: * $p > 0.05$; ** $p > 0.01$; ns, not significant.

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and zero weights for "outside" doses) is determined by the age at death (75 years) and a "critical exposure age" (58 years), and the upper edge is determined by a "critical lag period" (14 years).

Use of Five Relative Risk Models. The 1993 analysis of the Hanford data is based on a decision to use step function weighting for three critical modulating factors, which resulted in a choice of five relative risk models (Table 2). For each model there are two estimated parameters (doubling dose and power law exponent) and either one, two, or three additional parameters: exposure age, exposure year, and interval or lag period. There are four models whose estimated parameters include a "critical exposure age" (II to V). Since Model I, the preliminary model, lacks this key parameter of critical exposure age, it is virtually the same as the model used by Gilbert et al. in their 1989 analysis of the same data [4]. Gilbert and her associates found no evidence of a correlation between radiation dose and cancer risk, and this was also true of Model I in the 1993 analysis. This was also the only model in the later analysis that had a nonsignificant number of estimated radiogenic cancers, and the only one to have an estimated doubling dose that was not a great deal lower than any estimate based on A-bomb data.

For the two models in the 1993 analysis that allowed for exposure age effects but not for different standards of dose recording in different years

(Models II and IV), there was a local maximum to the likelihood function (Model II) and a global maximum (Model IV). Statistically, this result suggests marked variance in the maximum likelihood estimates, which may well reflect the wide variation in dose recording that occurred over these years. This finding also serves as a reminder that there were several results of the 1981 analysis (of deaths before 1978) that were not confirmed in the 1993 analysis (of deaths before 1987) and vice versa. For example, it was only in the 1993 analysis that there were positive findings for all cancers combined, and only in the 1981 analysis that there were sufficiently low values for the exponent of dose-response (ϵ) to doubt the validity of the linear hypothesis.

RESULTS OF THE 1993 REANALYSIS

The results of re-analyzing the Hanford data, on the basis of access to more complete socioeconomic data and by using the techniques described above, are presented in Table 2 (which shows the effects of excluding or including exposure age among "estimated" parameters of the 1993 risk model) and in Figure 3 (where a smooth curve estimate of the exposure age effects is shown alongside two step function estimates). In Table 2 the estimated excess risk—which is shown as a doubling dose, or the amount of radiation needed to exactly double the normal cancer risk—varies according to the number of estimated parameters of the 1993 risk model. But

it is possible, by recognizing five variants of this model, to see that:

1. The effect of including exposure age among the estimated parameters was to reduce the doubling dose estimate from 263 mSv (Model 1) to less than 12 mSv (Models II to V).
2. For cancer latency, or the critical interval between cancer induction and death, there are three estimates: i.e., over 14 years (Models II, III, and V), over 17 years (Models II and IV), and over 24 years (Model I).
3. In Table 2, there are two choices of critical age for any cancer effects from a radiation exposure: either over 58 years (Model II) or over 62 years (other models). But according to Figure 3, where these step function estimates are shown alongside a smooth curve estimate, a twofold increase in an initially small risk between 20 and 40 years was followed by a fivefold increase between 50 and 60 years.
4. For the exponent of dose-response (ϵ) there were five choices ranging from 0.39 (Model II) to 1.87 (Model I). However, none of these values was significantly different from 1.0. Therefore, an earlier impression of nonlinearity of dose-response (see below) was not confirmed when using the 1993 risk model.
5. Provided the cancer effective dose was restricted to the total dose received after 58 years of age and more than 14 years before death (Model II), or during equivalent periods for other models, the estimated number of radiogenic cancers (i.e., the cancers caused by an occupational exposure) lay between 12 and 51 for fatal cancers (average 22.8) and between 25 and 31 for all fatal and nonfatal cancers (average 27.7). Each of these estimates required identification of the workers whose effective dose exceeded zero (see EDC cancers in Table 2) and the number of these high-risk cases ranged from 34 to 157 for fatal cancers (Models II to V) and was 84 for all the fatal and nonfatal cancers (Models III and V).
6. When identifying the EDC cases, each exposure year could be included, since the critical value for this factor (1979-) included all the exposure years (1944-1978).

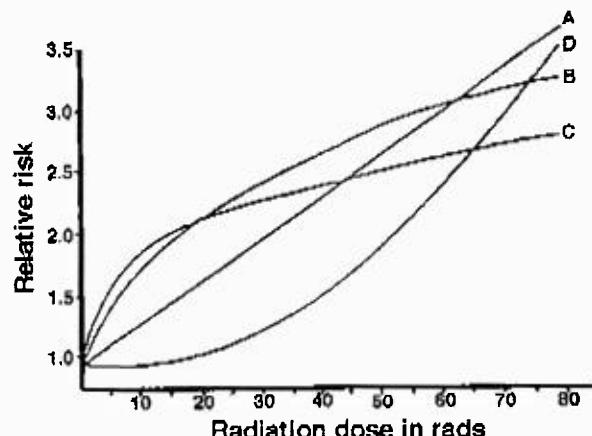


Figure 5. Typical dose-response curves of relative risk (R) against cumulative dose (Σx) for various values of parameters (D and E) in the simple model: $R = 1 + (\Sigma x/D)^E$. Curve A: $D = 30$ rads, $E = 1.0$ (linear law). Curve B: $D = 15$ rads, $E = 0.5$ (square root law). Curve C: $D = 15$ rads, $E = 0.3333$ (cube root law). Curve D: $D = 50$ rads, $E = 2.0$ (quadratic law). From Kneale GW, Mancuso TF, Stewart AM. Hanford radiation study III - a cohort study of the cancer risks from radiation to workers at Hanford (1944-1977 deaths) by the method of regression models in life tables. *Br J Ind Med* 1981;16:156-166.

7. Model V was alone in having a full complement of estimated parameters. Therefore, according to the 1993 risk model, the best estimates of doubling dose are 8.6 mSv for fatal cancers, and 8.7 mSv for all fatal and nonfatal cancers.

Not shown in Table 2 are the results of dividing the fatal and nonfatal cancers into A cancers (1,280 cases) and B cancers (627 cases). For the larger group, the Model V estimate for EDC cases was 58 or 4.5%, and for the smaller group it was 58 or 4.1%. Therefore, the earlier impression of no radiation effects for B cancers was not confirmed in the 1993 analysis.

DISCUSSION OF THE RESULTS OF THE 1993 RE-ANALYSIS

The Shape of the Dose-Response Curve

In the 1981 analysis of the Hanford data, the exponent of dose-response had an estimated value of 0.33, whereas, in the 1993 analysis, the exponent of dose-response was always closer to unity, or 1.0. This discrepancy between our two analyses required consideration of two possible reasons why the dose-response from repeated exposure to small doses of radiation might appear, in the 1981 analysis, to be

taking the form of a supralinear curve (Figure 5, curve C) rather than a straight line (Figure 5, curve A).

The first reason is that in large populations, even rare effects of extreme sensitivity to cell killing effects of radiation might reduce the cancer risk following exposure to low as well as high doses (thus allowing susceptible cells to be killed rather than maimed). This reason, although theoretically plausible, could not be further explored in the context of a retrospective population-based study relying on radiation monitoring data. Furthermore, this factor would have applied equally in the 1981 and 1993 analyses. The second reason is that errors in estimating annual doses might prevent the dose-response curve for a study population of workers from obeying a linear law, even if this law described the true relationship between dose and cancer risk.

In short, the fact that the exponent of dose-response had much lower values in the 1981 analysis of Hanford deaths before 1978 than in this later 1993 analysis of the same data with a longer follow-up time (and thus a less truncated series of deaths) was probably the result of less accurate recording of annual doses before 1960 than in later years (see Figure 1). Such "internal heterogeneity" (or different standards of dose recording within the same location) would account both for the rising trend of Hanford doses between 1944 and 1964 [15], and for a similar trend in Oak Ridge doses [19]. Furthermore, comparisons between Hanford and Oak Ridge nuclear facilities have produced evidence of "external heterogeneity" (or different standards of dose recording in different locations) [16], and detailed inspection of the Oak Ridge data, by Wing and his associates, has shown how different monitoring programs produced different patterns of low doses [20].

The possibility of different standards of dose recording in different nuclear facilities should occasion no surprise. It is important because the World Health Organization is currently assembling records from several facilities with the intention of using the pooled data to test the validity of risk estimates based on the LSS population exposed to the A-bomb. The need for such tests is not in doubt but there is also a need to be sure that all unnecessary errors in dose recording have been eliminated. This necessity will require a new "dose reconstruction" program. Given the present reasons for doubting the general validity of the A-bomb data [9], such a program might be thoroughly worthwhile.

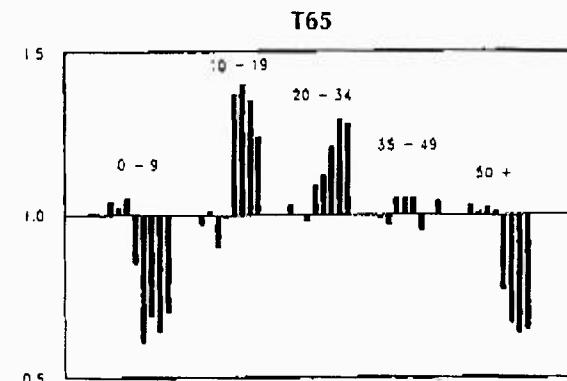


Figure 6A. RERF analysis of data from the Life Span Study (LSS) cohort of A-bomb survivors. Horizontal axis: T65 dose distribution of average dose in cGy (0-, 1-, 10-, 50-, 100-, 200-, 300-, and 400+) for each of 5 exposure age groups at time of the bomb (1945). Vertical axis: the ratio of observed to expected numbers at time of observation (1993). Reproduced from the journal *Health Physics* with permission from the Health Physics Society. Stewart AM, Kneale GW. A-bomb survivors: further evidence of late effects of early deaths. *Health Phys* 1993;64:467-472.

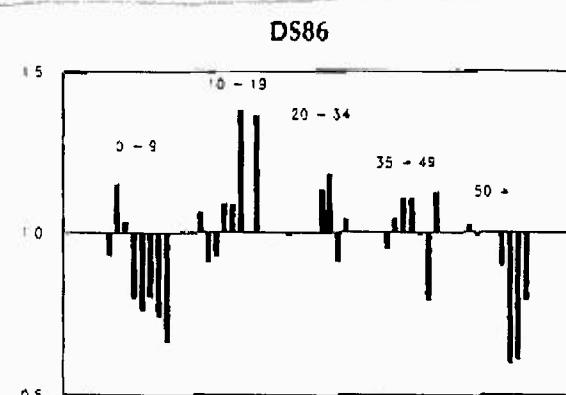


Figure 6B. RERF analysis of data from the Life Span Study (LSS) cohort of A-bomb survivors. Horizontal axis: DS86 dose distribution of average dose in cGy (0-, 0.6-, 20-, 50-, 100-, 200-, 300-, and 400+) for each of 5 exposure age groups at time of the bomb (1945). Vertical axis: the ratio of observed to expected numbers at time of observation (1993). Reproduced from the journal *Health Physics* with permission from the Health Physics Society. Stewart AM, Kneale GW. A-bomb survivors: further evidence of late effects of early deaths. *Health Phys* 1993;64:467-472.

The Effect of Age of Exposure on Risk of Subsequent Cancer

The LSS cohort, which was assembled five years after the bombing of Hiroshima and Nagasaki, has always had a normal noncancer death rate even at high dose levels. Therefore, it is a source of risk estimates based on the assumption that (in spite of the

massively high death rates of 1945-1946) there were no selection effects of these deaths that lasted for more than five years and no long-lasting damage to the immune system that predisposed survivors to death from other causes, such as infections [21].

However, whether the older or new A-bomb dosimetry estimates are used, it is only necessary to divide the LSS cohort into eight dose levels on the T65 scale (or on the DS86 scale) to see that the proportion of high-dose survivors (over 1 Gy) is much smaller for persons who were under 10 or over 50 years of age in 1945 than for the intervening age groups (Figure 6A and B, which shows the dose distribution within each of five exposure ages).

The LSS cohort originally included equal numbers of persons from four zones (measured from each hypocenter) and each zone was also matched for age and sex. Therefore, the age group differences in Figure 6 are clearly the result of children and old persons experiencing more deaths from acute and subacute effects of the bombing than did the intervening age groups. As a result of these age-related differences, we can safely assume that there was, in the LSS cohort, a gross shortage of persons who (by virtue of their age in 1945 and their exposure positions) were most at risk of dying either from nonradiogenic or radiogenic cancers in the subsequent 20 or 30 years.

The effect of these age-related differences on the survivor cohort would fully justify the Stewart and Kneale hypothesis that the appearance of normal non-cancer death rates in this population is false. This appearance of normality derives from the constant masking of (favorable) selection effects of the early deaths by (unfavorable) effects of marrow aplasia [21], producing, each year, a near normal rate for non-cancer deaths. These age-related differences also make it unnecessary to expect comparability between A-bomb survivors and nuclear workers.

CONCLUSIONS

There are three main points to take home from this re-analysis.

1. It is necessary, when evaluating the risk of cancer from low-level ionizing radiation, to include each and every exposure age, since age dramatically affects the risk.
2. The results of applying to Hanford data a 1993 risk model with five estimated parameters (Model V in Table 2) cast serious doubts upon the validity

of risk estimates based on extrapolation of the high-dose effects observed in the LSS cohort of A-bomb survivors.

3. Nonuniform standards of dose recording at Hanford call for a dose reconstruction program before allowing these data to be pooled with other cohorts of nuclear workers.

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