American Journal of Industrial Medicine 23:371–389 (1993)

ARTICLES

Reanalysis of Hanford Data: 1944–1986 Deaths

George W. Kneale, PhD, and Alice M. Stewart, MD

Reanalysis of Hanford data by a method, which is new only in the sense that it makes new uses of standard epidemiological procedures, has produced evidence of a cancer risk at low dose levels. By a conservative estimate, about three per cent of the pre-1987 cancer deaths of Hanford workers had occupational exposures to external radiation as the critical (induction) event. These radiogenic cancers were evenly distributed between five diagnostic groups, but as a result of there being much greater sensitivity to "cancer induction by radiation" after, rather than before, 50 years of age, they were concentrated among the cancers which proved fatal after 70 years of age. The reanalysis provides no support for the idea that radiation is more likely to cause leukemia than solid tumors, or the idea that there is reduced cancer effectiveness of radiation at low dose levels (dose rate effectiveness factor or DREF hypothesis), but the estimated proportion of radiogenic cancers was much higher for the 175 nonfatal cancers (which had other certified causes of death) than for the 1,732 fatal cases.

Finally, according to the latest publication of the US Committee on Biological Effects of Ionizing Radiation (BEIR V), dose rate is more important than exposure age, and even a single exposure to 10 rem would only increase the normal cancer risk by four percent. Nevertheless, for all recorded exposures of Hanford workers, the estimated doubling dose was close to 26 rem; for exposures after 58 years, it was close to 5 rem, and for exposures after 62 years, it was less than 1 rem.

Key words: epidemiology, cancer, radiation, nuclear industry, Hanford data

INTRODUCTION

The following analyses of Hanford data were undertaken to discover whether Gilbert and her associates were correct when, in 1989, they rejected earlier findings of Mancuso, Stewart, and Kneale (MSK) [1981], and concluded that "comparisons by level of radiation exposure within the Hanford worker population provided no evidence of a positive correlation of radiation exposure and mortality for all cancer combined" [Gilbert et al., 1989]. The number of workers is unchanged (44,101), but the number of deaths has increased from 7,249 (for the period 1945 to 1981) to 9,443 (for the period 1944 to 1986).

Department of Public Health and Epidemiology, University of Birmingham, Edgbaston, Birmingham, United Kingdom.
Address reprint requests to Alice M. Stewart, Department of Public Health and Epidemiology, University of Birmingham, Edgbaston, Birmingham, B15 2TT, United Kingdom.
Accepted for publication October 1, 1992.

TABLE I. Hanford Workforce

Group	Race	1944–1978 Recruits Male	1944–1978 Recruits Female	1944–1986 Deaths[a] Male	1944–1986 Deaths[a] Female
Badge monitored workers	White	26,370	7,994	6,571 (*1,494*)	691 (*221*)
	Other	1,025	479	73 (*13*)	7 (*4*)
	Total	27,395	8,473	6,644 (*1,507*)	698 (*225*)
Other workers[b]	White	3,954	3,973	1,469 (*297*)	596 (*185*)
	Other	163	143	25 (*6*)	11 (*5*)
	Total	4,117	4,116	1,494 (*303*)	607 (*190*)

[a]Italics = cancer as the underlying cause of death (ICD No. 140-209, 8th revision).
[b]Not included in the study population.

Study Population

The study population was restricted to 27,395 men and 8,473 women who worked at Hanford between 1944 and 1978, and appeared at least once in annual lists of workers with estimated doses of external radiation (so-called badge monitored workers, see Table I). By 1987, these workers had recorded 5,610 non-cancer and 1,732 cancer deaths (Table II); among the non-cancer deaths, there were 175 instances when cancer was mentioned as a contributory cause of death (nonfatal cancers, see Table III).

The average employment period for badge monitored workers was six and a half years, and for external penetrating radiation the average total dose was 22.3 mSv. Two-thirds of the deaths came from workers who were hired before 1950 (and had an average dose of 28.2 mSv), and one-third from workers who were exposed for more than 10 years (and had an average dose of 63.9 mSv). The proportion of clerical workers was much higher for females (67%) than males (7%), and less than ten percent of the craftspeople and operatives were females. Finally, both the proportion of workers with professional or managerial qualifications (42%) and the proportion who were monitored for internal as well as external radiation (46%) were twice as high for males as females.

Lung cancer accounted for 31% of the fatal and 26% of the nonfatal cancers. For cancers of the digestive system the corresponding proportions were 27% and 23%, and for genitourinary cancers they were 13% and 28%. The high proportion of genitourinary cancers among the nonfatal cases was the result of prostate cancers accounting for 6% of the fatal and 20% of the nonfatal cases. Deaths ascribed to cardiovascular or respiratory diseases (which accounted for 74% of the non-cancer deaths) accounted for 147, or 84%, of the nonfatal cancers; and deaths in Washington State (which accounted for 52% of the non-cancer and 54% of the cancer deaths) accounted for 106, or 60.6%, of the nonfatal cancers.

Method of Statistical Analysis

A detailed description of the methodology can be found in Appendix A. The general principles are similar to the ones adopted by a committee on Biological Effects of Ionizing Radiation (BEIR V), when they decided to base risk estimates on the cancer experiences of A-bomb survivors [BEIR V, 1990]. However, the survivors received a massive dose of radiation at a single point in time, and the Hanford

TABLE II. Specifications of Badge Monitored Workers, Hanford, WA

Specifications	1944–1978 Recruits		1944–1986 Deaths[a]		Average cumulative dose mSv
	Male	Female	Male	Female	
Cohort or year of hire					
1944–	10,358	2,070	35,078 (*1,119*)	480 (*145*)	28.2
1950–	3,863	1,322	902 (*224*)	115 (*37*)	39.9
1955–	1,796	749	210 (*54*)	44 (*22*)	28.1
1960–	2,188	395	140 (*31*)	10 (*4*)	31.4
1965–	2,357	901	119 (*32*)	28 (*11*)	10.0
1970–	2,220	975	75 (*25*)	8 (*5*)	8.3
1975–78	4,613	2,061	120 (*22*)	13 (*1*)	4.8
Employment period in years					
under 1	5,916	1,846	1,570 (*335*)	138 (*37*)	1.7
1–2	6,400	2,671	1,069 (*254*)	140 (*48*)	4.5
3–4	3,158	1,275	518 (*135*)	75 (*26*)	8.9
5–9	3,437	996	908 (*210*)	84 (*31*)	12.9
10+	8,484	1,685	2,537 (*573*)	261 (*83*)	63.9
First occupation[b]					
Professional	10,723	1,875	979 (*254*)	184 (*58*)	13.4
Managerial	872	52	228 (*58*)	5 (*2*)	9.7
Clerical	1,910	5,656	402 (*80*)	380 (*132*)	8.5
Craftsperson	5,332	43	1,736 (*417*)	3 (*1*)	42.4
Operative, etc.	8,558	847	3,299 (*698*)	126 (*32*)	35.2
Final levels of internal radiation monitoring (IRM)					
Never or zero	14,924	6,498	4,363 (*966*)	524 (*162*)	4.2
Suspect	11,106	1,809	2,256 (*531*)	174 (*63*)	44.8
Nonsignificant[c]	408	45	10 (*7*)	0 (*0*)	60.1
Significant[d]	957	121	15 (*3*)	0 (*0*)	96.8
Total	27,395	8,473	6,644 (*1,507*)	698 (*225*)	22.3

[a]See footnote to Table I.
[b]Census Code: Professional and technical 1–199, Managerial 200–299, Clerical 300–399, Craftsperson 400–599, Operatives and Service 600–999.
[c]Result > S.E.
[d]Result > 2 S.E.

workers received a much smaller dose distributed over many years. Consequently, BEIR V was dealing with a situation where some cancer effects of the radiation could be assumed, and we were dealing with a situation where there was no certainty of any such effects. As a result of this difference, explicit risk models, which were needed only for the final stage of the BEIR V analysis, were needed from the start of our analysis.

As pointed out by the BEIR committee, when using epidemiological data to estimate cancer effects of radiation, it is important to distinguish between factors which are liable to create false impressions by influencing radiation doses as well as cancer induction risks (essential controlling factors or confounding variables), and factors which modify radiation effects by influencing the neoplastic process (modulating factors or modifiers of any radiation effects), even though the same factor may belong to both classes. For example, in Hanford data, the final age of the workers influenced exposure periods, cancer induction risks, cancer growth rates, and proportions of fatal cancers.

TABLE III. Stated Causes of 1944–1986 Deaths of Badge Monitored Workers, Hanford, WA

ICD Nos.	8th Revision	Males	Females	Total
1–138	Infective	31	3	34 (3)[a]
140–209	Neoplasms, malignant	1,507	225	1,732
210–239	Neoplasms, other	12	0	12 (1)
240–279	Endocrine & Metabolic	128	18	146 (1)
280–289	Blood Diseases	9	3	12
290–389	Neurological	103	18	121 (5)
390–458	Cardiovascular	3,390	246	3,636 (120)
460–517	Respiratory	453	48	501 (27)
520–577	Digestive	250	43	293 (11)
580–629	Genitourinary	65	3	68 (1)
630–796	Other & unspecified	76	20	96
800+	Trauma	620	71	691 (6)
Total		6,644	698	7,342 (175)
Malignant neoplasms				
140–149	Mouth & pharynx	41	—	41 (3)
150–159	Alimentary	413	48	461 (41)
160–163	Respiratory	490	42	532 (46)
170–174	Bone & C.T.	39	67	106 (3)
180–189	Genitourinary	196	27	223 (49)
190–194	Brain & endocrine	52	7	59 (4)
195–199	Nonspecific	166	12	128 (11)
200–203	Lymphomas	97	15	112 (7)
204–209	Leukemias	63	7	70 (11)

[a]Cancer was a contributory cause of a non-cancer death.

TABLE IV. Essential Controlling Factors, Hanford Data*

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 offsite exposures
Discharge status	2	With or without definite termination date
Potential year of death[a]	43	1944–1986
Discharge interval[a]	2	Death within 3 years of discharge (or not)
Socioeconomic status[a]	6	Census classification of Hanford occupations: 1–199 Professional (1) 200–299 Managerial (2) 300–399 Clerical (3) 400–599 Craftspeople (4) 600+ Other blue collar (5) Not specified (6)

*The follow-up period runs from January 1944 to December 1986.
[a]Separate assessment for each calendar year of employment.

In the BEIR V analysis, the essential controlling factors were sex, city, exposure age, and age at death; and the modulating factors were exposure age and interval (or period between exposure and death). In our analyses, there are usually three

modulating factors (exposure age, exposure year, and interval) and the ten controlling factors in Table IV. By having a fixed position for each controlling factor and a specific number of levels for each factor, we also obtained a series of eight figure numbers to describe each worker's annual position vis à vis each of the ten essential controlling factors. As explained in Appendix A, these numbers were used to identify all the closely matched controls of each cancer case.

For example, Figure 1 shows the annual radiation doses of all the badge monitored workers who had the following factors in common: they were white males who worked at Hanford for more than three years, were hired in 1951 or 1952, had no offsite exposures, and a definite termination date; they also belonged to the fifth socioeconomic level in Table IV, were born in the period 1895–1899, and were still alive at the time of the first cancer death (in 1965). This death occurred within three years of the termination date. Therefore, it belonged to a risk set which included only three workers (see 9th controlling factor in Table IV and the first risk set demarcation line in Fig. 1). For the second cancer death (in 1969), there was a much longer interval between leaving Hanford and dying and, consequently, this case belonged to a risk set which had ten controls. Finally, the third man to die from cancer (in 1981) also had a long post-employment period, but as a result of there being four non-cancer deaths between 1969 and 1981, this case had only five matched controls.

Since all the A-bomb radiation was received at the same time, it was possible for BEIR V to deal with the effects of two modulating factors separately from the effects of a single radiation dose. For Hanford workers, there were annual doses recorded on film badges worn during working hours. Therefore, there was a need for a model which not only calculated the combined effect of several distinct exposures at different ages, but also showed how the different exposures ages and exposure years of individual workers influenced the ultimate cancer risk. This was done by applying to Hanford data the method used by BEIR V to calculate the cancer effects of the annual exposures to background radiation which make up a lifetime exposure to this source of gamma radiation. In BEIR V, these effects of background radiation are calculated from a model which a) is based on A-bomb data; b) takes into account two modulating factors (i.e., age at each exposure and interval between each exposure year and death); and c) obtains a final risk estimate by summing the effects of each person's annual dose.

For the linear dose-response model, which is recommended by all radiation protection committees, the background dose model of BEIR V was equivalent to summing individual annual doses (after weighting by the effects of two modulating factors) and thus obtaining a final "effective dose" which could be plugged into their single dose (or A-bomb data) model. For our purposes, it was also necessary to establish a relation between the actual dose of each worker and the "cancer effective dose," which was similar to the relation between "absorbed dose" (in gray) and "dose equivalent" (in sievert). This was done by equating the cancer effective dose of each worker with the sum of his or her actual (annual) doses, after weighting of these by estimated effects of three modulating factors.

Provided one person has an effective dose (Z) by a particular date, and provided there is a model with an assumed doubling dose (β) and power law exponent (ϵ), it is possible to calculate the risk of dying from a radiogenic cancer (R) relative to the risk of a simultaneous death from an idiopathic cancer—since R equals $1 + (Z/\beta)^{\epsilon}$, where ϵ has been introduced into the model to take account of any nonlinearity of

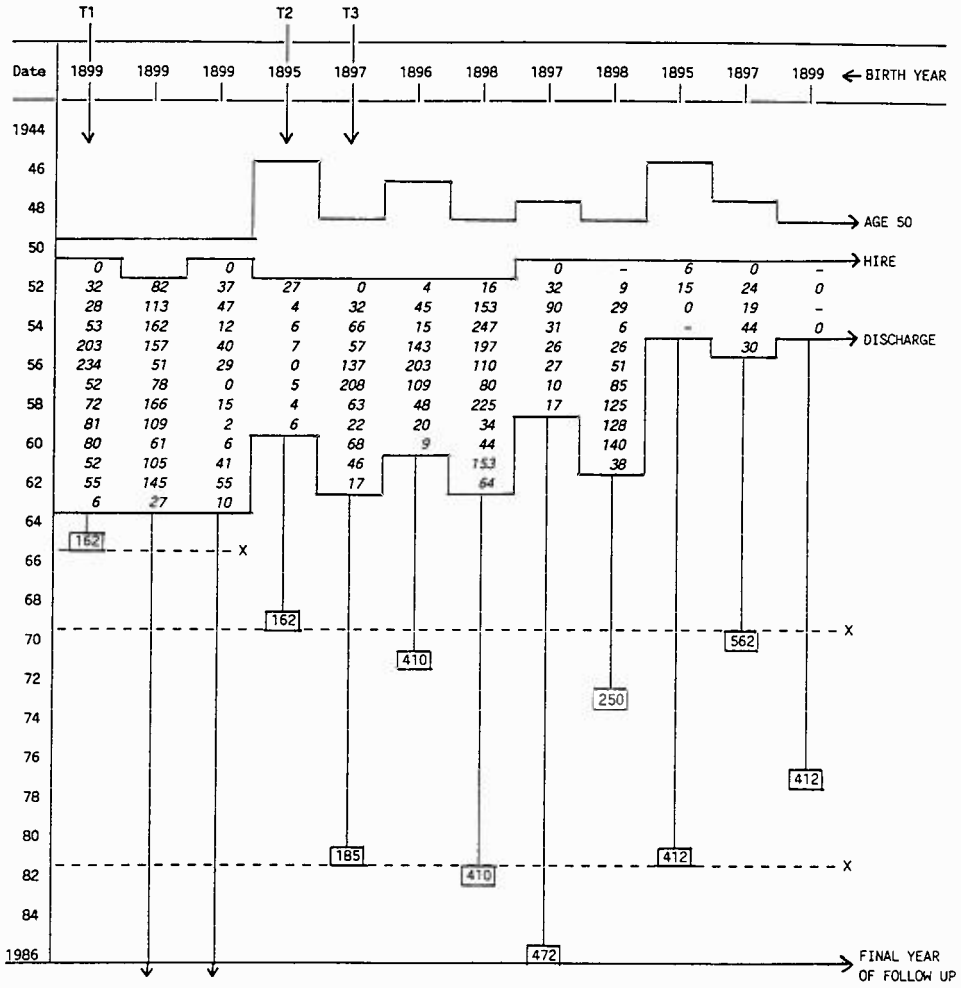

Fig. 1. Specifications of three cancer cases and their exactly matched controls; Hanford data. T, Test cases or cancer deaths before the end of the follow-up. □, ICD codes of all deaths before the end of the follow-up. Italics, Radiation doses in 0.1 mSv. ---X, Demarcation lines for three risk-sets with cancer cases.

dose response. In order to estimate the doubling dose (by maximum likelihood) from the cancer experiences of a large cohort of nuclear workers, one must know the shape of the dose response curve for each modulating factor. Therefore, our Hanford model has the three parameters, which are shown in Table V as lag period (δ), exposure age (α), and exposure year (γ), in addition to the two main parameters of doubling dose (β) and power law exponent (ϵ).

With this model it was a simple matter to specify a computer algorithm which stratified the data into cohorts by essential controlling factors and also identified all the risk sets with cancer cases. Following these identifications, the Breslow and Day [1980] method of "conditional logistic regression for matched sets"—modified for use with our Hanford model of relative risk rather than the exponential model envis-

TABLE V. Maximum Likelihood Tests of Hanford Data*

Risk models		Main parameters		Critical values of modulating factors			Results				
Series[a]	No.	Doubling dose mSv	Power law exponent	Lag period in years	Exposure age in years	Exposure year	EDC[b]	Estimated radiogenic cancers	Chi-square equivalent[c]	d.f.	Statistical significance of each model
		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	*[e]
	III	6.0	*DV*[d]	17+	62+	1979–	34	15.3	12.49	4	*
	IV	8.6	1.48	17+	62+	*DV*	34	12.5	13.45	4	**[f]
	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	*

*Risk models with two main parameters, and critical values of three modulating factors.
[a]Series F = fatal cancers only; Σ = fatal and nonfatal cancers.
[b]EDC = cancers with *effective doses* greater than zero, after allowing for the critical step function values of each modulating factor (see text).
[c]Actually $-2 \times$ log-likelihood (see text).
[d]DV = default value.
[e,f]Significance levels: * $p > 0.05$; ** $p > 0.01$; ns, not significant.

aged by Breslow and Day—was used to calculate the probability of each risk set having the observed number of cancer deaths. From these "conditional likelihoods" were obtained all the necessary maximum likelihood values by suitable adjustment of the risk model parameters. In terms of generality and statistical power, the maximum likelihood procedures (which are described in Appendix A) have already been justified by one of us (G.W.K.) as a generalization of the Cox method of regression models in life tables [Kneale et al., 1981]. The explanatory diagrams included in one of the MSK reports [Mancuso et al., 1981], and the Breslow and Day text book [1980], should be compared with Figure 1.

Final Form of the Analysis

Numerous tests of the procedures described in Appendix A were performed before deciding the final form of our risk estimates. The starting point of this preliminary work was the 1981 analysis of Hanford data by Kneale et al. According to this analysis, the risk of a cancer death was positively correlated with exposure age and pre-death interval, and provided a) the essential controlling factors included the intensity of the internal radiation monitoring (so-called IRM factor which was based on the records of urine tests and whole body counts) and b) the modulating factors included exposure age, there was definite evidence of a radiation effect for a large subgroup of cancers. These were the so-called A cancers, which were formed by grouping together all neoplasms whose tissue of origin was deemed by the International Commission for Radiological Protection (ICRP) to be "sensitive to cancer induction by radiation" [ICRP, 1969]. However, for the remaining (B) cancers (and for all non-cancer deaths) the effect of adding the IRM factor to other controlling factors was merely to reduce the slope of a strongly *negative* dose response curve. Therefore, for A and B cancers combined (832 cases), there was only doubtful evidence of a radiation effect.

In the 1981 analysis of 1944–1977 deaths, there were two models, both of which were consistent with a radiation effect for A cancers. It was naturally expected that the addition of 1978–1986 deaths would improve the fit of both models. But although this was so for the model with four parameters (doubling dose, power law exponent, latency, and exposure age), the opposite was found for the model with only two parameters (doubling dose and power law exponent). This difference led to the discovery that the A cancer association was exceptionally strong for workers who were born before 1900, hired before 1946, and exposed before 1960. This was probably an artifact caused by less complete recording of doses before than after 1960 [Kneale et al., 1991]. Therefore, in all analyses of the enlarged data base, there has been control of exposure year as well as exposure age. The first of these analyses had as one objective to observe the effects of having, as one of the controlling factors, six levels of socio-economic status instead of four levels of monitoring for internal radiation, as in the earlier analysis.

The different levels of IRM were clearly the result of different occupations. In the only source of Hanford data which was available to MSK, there were so many "job titles" and so many workers with unlikely sequences of these code numbers, that it was not possible for Kneale et al. [1981] to observe the effects of controlling for occupations rather than IRM levels. Gilbert was aware of this problem, and by 1989 all the job titles had been recoded to conform with a census classification of U.S. occupations [U.S. Department of Labor, 1970]. Even so, there was no attempt

by Gilbert to observe the effects of controlling for the six socioeconomic levels listed in Tables II and III.

The first use of the statistical procedures described in Appendix A was to show the effects of a) having exposure age as a modulating factor, and b) controlling for six levels of socioeconomic status instead of four levels of internal radiation monitoring. As a result of this change, the negative association between B cancers and radiation dose was reduced to negligible proportions and the positive dose trend for all fatal cancers (1,732 cases) achieved statistical significance. Once this evidence of a general cancer effect was firmly established (by including the data in several analyses involving several different models), the next consideration was how best to represent the effects of modulating factors in the risk estimates.

These effects could be represented either as smooth functions (based on exponential or power laws) or as step functions (with a yes/no choice for each factor depending upon whether the value lay above or below a critical level). Thus, with a step function curve, each cancer effective dose would equal the sum of all the annual doses which lay within a certain "window" whose frame was determined by critical values of the modulating factors. In other words, any cancer modulating effect of exposure age in Hanford data would receive the same treatment as in the leukemia model of BEIR V, and any latency effects would be equated with "lagging." Therefore, we have, in Table V, the results of applying step function curves to three modulating factors, whose critical values were determined by the statistical procedures described in Appendix A.

The merit of step function curves is that they provide a simplistic interpretation of epidemiological data—but they are clearly less informative than smooth curves. For example, the recent discovery that, until 1960 or thereabout, there was systematic under-recording of Hanford doses required the use of smooth functions to determine the full extent of certain exposure age and exposure year effects [Kneale et al., 1991]. Therefore, by ignoring this dose recording bias and giving high priority to comparability with BEIR V (thus allowing step function curves to take precedence over smooth curves), we have deliberately erred on the side of underestimating the cancer risks of nuclear workers.

RESULTS

In Table V, there is a choice of seven figures for "estimated numbers of radiogenic cancers." This is the result of a) having a risk model with five parameters; b) sometimes including and sometimes excluding nonfatal cancers; and c) sometimes allowing a "default value" to take the place of an "estimated value" (see Appendix A). For example, the linear hypothesis made it appropriate to observe the effects of replacing estimated values of the power law exponent (ϵ) with a default value of unity. Furthermore, there were no workers under 16 years and no exposures after 65 years and after 1978. Therefore, it was possible to observe the effects of ignoring exposure age and exposure year (by having default values for these parameters).

Included in Table V are both the number of cancer cases whose effective dose was greater than zero, after allowing for the critical step function values (EDC cases) and the statistical significance of the estimated number of radiogenic cancers. The significance levels were calculated from the log likelihood (since $-2 \times$ log likelihood is approximately distributed as chi-square whose degrees of freedom correspond

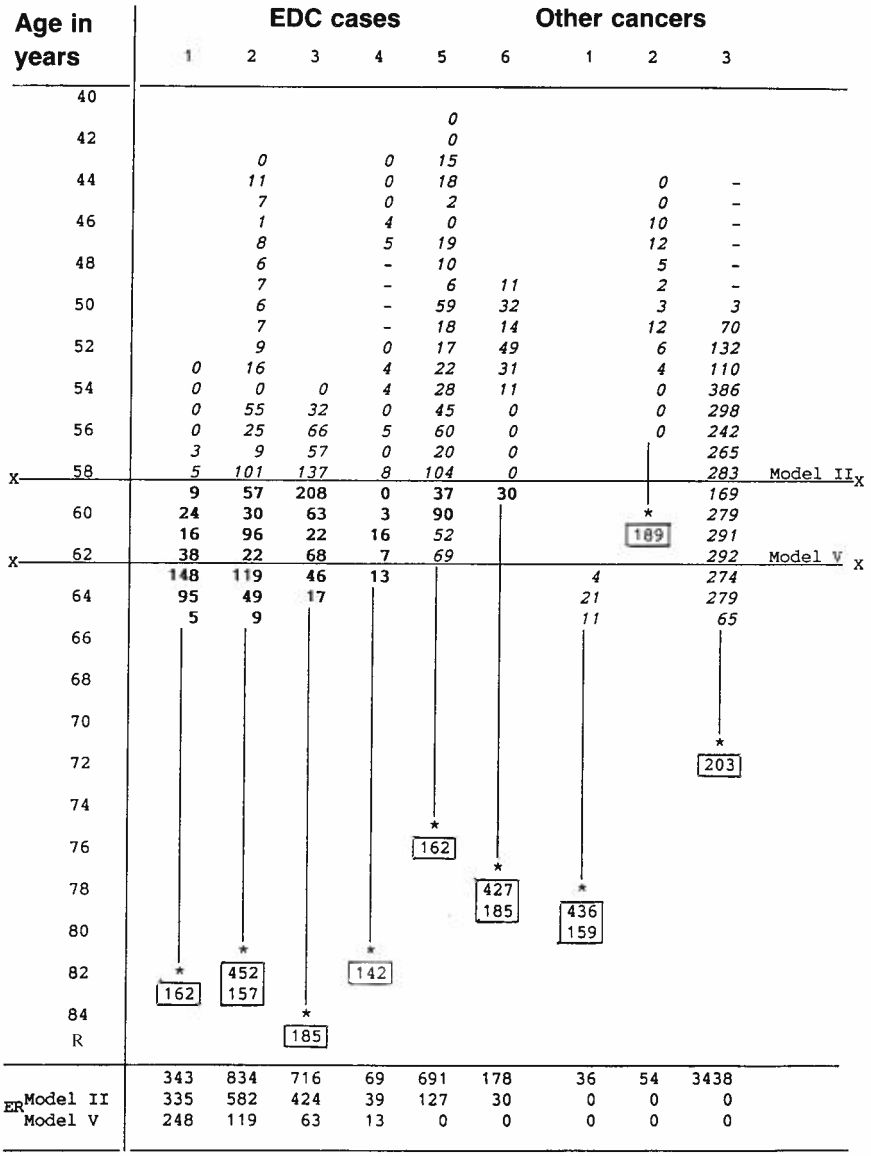

Fig. 2. Examples of actual and effective doses for fatal and nonfatal cancers, Hanford data. Bold figures, effective dose; italics, other doses. R, total cumulative dose. ER, total effective dose. □, ICD codes of deaths. X——X, demarcation for Model II and Model V.

to the number of parameters with estimated values). The EDC cases were needed for comparison with the total number of cancer cases, and examples of such cases can be found in Figures 1 and 2. In Figure 1, which shows the year-specific doses of three cancers, there is only one EDC case (T3); but in Figure 2, which shows the age-specific doses of nine cancer cases, there are either four or six of these cases, depending on whether Model V or Model II determines the number of cancers whose

effective dose exceeded zero. For these cases, the two choices of effective doses are shown alongside the actual total dose.

The figures for Chi-square and d.f. (degrees of freedom) in Table V should be interpreted in the following way: 1) each Chi-square value increases with increasing goodness of fit of the model and a zero value implies NO radiation effect; 2) each d.f. value corresponds to the number of free (estimated) parameters in the model; and 3) any improvement in the goodness of fit (by changing the model) is measured by the difference of the two chi-squares and d.f. For example, the only model with a default value for exposure age is Model I. Therefore, the big difference between this model (with a Chi-square of 1.12 and 3 d.f.) and either Model II (with a Chi-square of 9.46 and 4 d.f.) or Model III (with a Chi-square of 11.37 and 4 d.f.) shows that exposure age was exerting a very strong influence.

In spite of Models II and IV having the same number of free parameters, they were not identical, since in one case (Model II) the free parameters yielded a *local* maximum to the likelihood function, and in the other case (Model IV), they yielded the *global* maximum (see Appendix A). For Model IV, which has a default value for exposure year, the Chi-square (13.45 with 4 d.f.) was virtually the same as for Model V (13.45 with 5 d.f.), which has no default values. Therefore, we can safely assume that exposure year was not important. Finally, for Model III, which has a default value for the power law exponent, the chi-square was almost the same as for Model V. Therefore, seemingly nothing would be gained by having a nonlinear instead of a linear dose response model. In Appendix A can be found the reasons why we have not included any standard errors in Table V.

If we exclude the power law exponent, Model I is no different from the one used by Gilbert et al. in their 1989 analysis of Hanford data. It is also the only one of the present models which a) makes no allowance for any exposure age effects and b) has an estimated number of radiogenic cancers which fails to reach statistical significance. Model II (which, in common with Models I and IV, shows the results of ignoring exposure year) has "58 years" as the critical value for exposure age, but the later models have "62 years." These include Model III, which shows the effects of assuming a linear relationship between doses (by having a default value for ϵ); Model IV, which shows the effects of ignoring exposure year (by having a default value for γ); and Model V, which shows the effects of not having any default values.

For Models III and V, there are two sets of results depending upon whether nonfatal cancers are included or excluded. For the 1,732 fatal cancers, the estimated numbers of EDC cases and radiogenic cancers was the same for Models IV and V (i.e., 34 and 12.5). This tells us that, provided four of the parameters (i.e., β, ϵ, γ, and α) have fixed maximum likelihood values, it is unnecessary to include exposure year among the modulating factors. Finally, since the proportion of radiogenic cancers among the EDC cases was smaller for Model V (36.8%) than for Model II (45.0%), one can appreciate that a smooth (exponential) curve for exposure age would have been preferable to a step function curve.

For Model II, the maximum likelihood value for the power law exponent ϵ was below unity (0.39), and for Model V it was above unity (1.48). Neither of these values was significantly different from unity, but the low value for the model which ignored exposure year is a reminder that when a smooth curve for exposure age was calculated (as in the 1981 MSK analysis) the estimated power law exponent was significantly below unity [Kneale et al., 1981]. A possible reason for the low values

TABLE VI. Dose distributions of Hanford Workers for Age-Based Exposure Periods*

	Exposure period age in years	Dose Groups (0.1 mSV)														Mean dose mSV
		0	1	2	4	8	16	32	64	128	256	512	1024	2048	4096	
All workers	20+	1401	80	232	279	325	534	266	208	163	99	75	44	35	5	9.8
	30+	13553	136	283	446	556	740	809	923	1288	768	555	446	337	108	18.2
	40+	13555	89	183	344	439	617	745	1121	1455	709	601	491	372	118	16.8
	50+	13384	72	166	288	409	605	827	1160	1005	506	414	342	245	9	10.6
	58+	11200	73	144	265	435	623	665	684	403	251	227	168	14	0	4.7
	62+	9674	55	173	282	399	438	377	263	177	122	110	9	0	0	1.8
Fatal and nonfatal cancers	20+	17	0	5	2	1	2	2	1	4	0	2	1	0	0	11.1
	30+	233	1	6	11	18	22	27	37	61	20	23	21	11	13	37.4
	40+	633	7	10	16	29	38	54	82	143	64	43	35	39	17	30.9
	50+	1005	3	10	30	30	66	81	147	126	62	50	48	36	1	17.5
	58+	1204	2	17	13	57	87	110	101	52	42	41	27	1	0	6.8
	62+	1253	11	25	38	57	68	68	34	32	23	22	1	0	0	2.6

*In each exposure period or 'window' are all contemporary and subsequent exposures of workers who had their first exposure at or before the stated age.

TABLE VII. ICD Classification of Four Groups of Cancers

	All cases[a]		EDC cases[b]			
Series[a]	Nos.	%	Model II[c]		Model V	
Fatal cancers						
150–159	461	26.6	37	23.6	16	25.0
160–163	532	30.7	51	32.5	22	34.4
180–189	223	12.9	32	20.4	10	15.6
200–209	182	10.5	14	8.9	6	9.4
Other and unspecified	334	19.3	23	14.6	10	15.6
Total	1,732	100.0	157	100.0	64	100
Nonfatal cancers						
150–159	41	23.4	10	23.8	7	35.0
160–163	46	26.3	12	28.6	5	25.0
180–189	49	28.0	12	28.6	4	20.0
200–209	18	10.3	4	9.5	2	10.0
Other and unspecified	21	12.0	4	9.5	2	10.0
Total	175	100.0	42	100.0	20	100

[a]See Table III.
[b]See Table V.
[c]Includes nonfatal cancers not listed in Table V.

of ϵ in Model II is given in Appendix B. What is certain is that nothing in Table V provides any support for the idea, favored by BEIR V [1990], that the cancer effectiveness of radiation is reduced at low dose levels.

According to Model V, the proportion of radiogenic cancers among the EDC cases was roughly the same for 1,732 fatal cancers (35.8%) and the 1,907 fatal and nonfatal cancers (36.8%); but there was no mistaking the fact that the proportion of EDC cases was much higher for the 175 nonfatal cancers (28.6%) than for the 1,732

fatal cancers (2.0%). In spite of this big difference, an ICD classification of the cancers failed to reveal any difference between the cases with a cancer effective dose (EDC cases) and the other non-radiogenic cancers (Table VI). Thus, for 1,732 fatal cancers, the proportion of lung cancers and renal cancers as 30.7% and 12.9%. For the EDC cases in this series, the corresponding figures were either 32.5% and 20.4% (Model II) or 34.4% and 15.6% (Model V). For the 175 nonfatal cancers, the corresponding proportions were 26.3% and 28.0% for all cases, and either 28.6% and 28.6% for EDC cases (Model II), or 25% and 20% (Model V).

Since exposure age has proved to be of such importance, Table VI has been introduced. This shows how the population is restricted by various "exposure age windows" (including the ones for Models II and V), and also shows, for all workers and for fatal and non-fatal cancers, the relevant dose distributions for six of the "restricted" populations. It will be noted that in each group the mean dose was higher for the cancer cases than for all workers.

DISCUSSION

Renewed access to Hanford data, after an interval of more than ten years, has provided an opportunity to clarify certain assumptions of an earlier (MSK) analysis and make a few changes. For example, a longer follow-up and the inclusion of non-fatal cancers made it unnecessary to distinguish between A and B cancers, and improved coding of occupations made it possible to control for six levels of socio-economic status, instead of four levels of monitoring for internal radiation. New ways of treating confounding variables and cancer modulating factors are explained, and reasons are given for temporary use of "windows," or step function curves, for estimating cancer effects of exposure age, exposure year, and interval. Also explained is 1) how a seemingly new method of statistical analysis is merely a new way of combining standard methods of cohort and case/control analysis; 2) how new combinations of familiar statistical procedures will affect future studies of occupational exposures to small doses of ionizing radiation; and 3) why the "Hanford Controversy" made it desirable to keep strictly in line with an authoritative source of risk estimates, such as BEIR V.

The Hanford Controversy is the name given to a prolonged dispute about the effects of radiation, when doses and dose rates fall to the levels which are typical of background radiation and occupational exposures [Stewart and Kneale, 1991]. For example, as a result of A-bomb data constantly leaving an impression of a reduced cancer effectiveness of radiation in these circumstances, the risk estimates in current use include an allowance for a "dose rate effectiveness" factor, or DREF. However, the 1981 analysis of Hanford data by Kneale et al. left exactly the opposite impression and, although a later analysis by Gilbert et al. [1989] found no evidence of a general cancer risk, there were findings for myeloma which were difficult to reconcile with DREF. Furthermore, since 1989, there have been two studies of nuclear workers with positive findings: one in the United States [Wing et al., 1991] and one in Britain [Kendall et al., 1992]. In these circumstances, it was clearly desirable for a reanalysis of Hanford data to avoid all controversial issues and follow procedures recommended by BEIR V.

By the use of windows instead of smooth curves for estimating the effects of exposure age and other modulating factors, we may have weighted the odds against detection of what we were seeking, namely, evidence of any extra cancers among

27,395 adults who had an average exposure period of six and a half years, and had received a total dose of 611 Gy of gamma radiation, over and above a background dose of 3.6 mGy per annum (or a total dose of 641 Gy from this source alone). However, by accepting these conditions, we were hoping to make things easier for readers of BEIR V. In the event, our reanalysis of Hanford data has found evidence of a cancer induction risk at low dose levels, and has also shown that our risk estimate is much more strongly age-related than are any of the numerous estimates based on A-bomb data.

There are several reasons why the mortality experiences of A-bomb survivors might not be an appropriate guide to the subject matter of BEIR V, namely, "Health Effects of Exposure to Low Levels of Ionizing Radiation." Two of them, namely, the massively high death rates of 1945 and 1946, and the early epidemic of acute immune system depression, were the subject matter of a recent paper by Stewart and Kneale [1990]. Still awaiting publication is a second paper which shows that, among the A-bomb survivors whose estimated doses exceeded 1 Sv, there was gross underrepresentation of persons who were over 50 years of age in 1945 [Stewart and Kneale, in press]. Therefore, the A-bomb evidence in favor of there not being any cancer risk at low dose levels and only a weak effect of exposure age—which is conspicuous by its absence in Hanford data—could be an artifact caused by unrecognized effects of two nuclear explosions, while the Hanford evidence, in favor of there being both a cancer risk at all dose levels and a strong exposure age effect—which is conspicuous by its absence in A-bomb data—could be a genuine finding caused by advancing age progressively undermining resistance to all potential causes of disease, including the mutations caused by low level radiation.

ACKNOWLEDGMENTS

We are indebted to the TMI Public Health Fund for obtaining the data we have examined, and for defraying the full cost of the analysis.

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APPENDIX A
Statistical Method

Practically all the details of the statistical method have already been described in other contexts by various authors, and all that is new is the context and certain combinations of standard procedures.

In any epidemiological study, it is convenient to draw a distinction between factors of special or immediate interest and nuisance factors, that inevitably influence the final outcome, and so must be taken into account if possible, but are not of immediate interest. In the present study of Hanford workers, the factors of special interest are the radiation doses and their relationship to certain (modulating) factors; and the nuisance factors are the essential controlling factors listed in Table IV. Other factors, such as smoking or medical histories, might well be considered appropriate to be placed among the modulating or nuisance factors, but, unfortunately, records of the workers' smoking habits and medical histories are not available.

The standard method of treating nuisance factors in a case/control study is by dividing the data into strata by each combination of levels of the nuisance factors, and then the statistical evidence from each stratum about the effects of factors of interest can be combined by Mantel-Haenszel [1959] techniques or, more generally, by the conditional likelihood method of Breslow and Day [1980]. These methods are standard and well known. Less well known is the fact that Mantel [1966] suggested, Cox [1972] proved, and Kneale et al. [1981] generalized the idea, that these methods designed for case/control studies can be applied to cohort studies by simply treating each example of what Cox calls "a risk-set within a cohort" as a separate stratum in the above mentioned stratum combination methods. Thus, the difference between our analysis of Hanford data and the standard person-year approach, which is described

in the second volume on methodology by Breslow and Day, is that the latter is primarily concerned with (as factors of special interest) those factors that differentiate between the cohorts, or those factors that affect the basic hazard rate (in the Cox terminology), or, in other words, those factors that in the present study would be considered as nuisance factors.

An understanding of the basic difference between the two approaches can be seen in the way they treat "impossible person-years." In the standard approach, a fairly complicated algorithm, provided by Clayton (see Breslow and Day [1980]), is necessary for deciding whether a particular person-year is informative, and if so, into what expression it should go as a denominator. In our approach, any risk set which includes at least one cancer and one non-cancer death or survivor to the next year is necessarily informative, since there was a positive probability of dying of cancer in the corresponding person-year.

Another disadvantage of the person-year, as opposed to the risk-set, approach is that the natural method of programming a computer (for it) often involves arrays of tens of millions of computer words, a size that may overrun even a modern large computer. On the other hand, it is easy to see that, in the risk-set approach, only those risk-sets that contain at least one cancer actually contribute to the final statistics; in consequence, a computer program for this method can use a hash-table technique, as explained in Knuth [1975], and this hash-table need only be a few times larger than the actual number of cancers, i.e., a few tens of thousands of computer words.

In the paper by Cox and the book by Breslow and Day, the basic method of combining the statistical evidence of a large number of strata (or risk-sets) is by the conditional likelihood, using a logistic dependence of the probability of cancer on the explanatory factors. This logistic dependence of the probability implies an exponential dependence of the relative risk. In a radiobiological context, the natural assumption is that the relative risk of cancer is a linear function of dose rather than an exponential one. Furthermore, in the present context there are the effects of many small doses to be combined and a necessity to have only a few parameters in the final model to obtain reasonable statistical efficiency. There is also the precedent of BEIR V in estimating the effects of background radiation by summing the effects of each year's individual dose as if these annual doses acted in combination like the sum of their separate effects individually calculated by the final BEIR V model. All these suggest a model of the relative risk as depending linearly, or at least monotonically, on a total *effective dose,* calculated as explained in the main text, by the sum of the individual annual doses weighted by the effects of the modulating factors, each modulating factor introducing one parameter which determines the shape of its weighting curve. Thus, the final relative risk model is more complicated than the simple exponential one used by Cox or Breslow and Day. However, as Cox mentions in passing and as is shown explicitly by Kneale, the method of combining strata, by adding the conditional log-likelihoods for each stratum (derived from the relative risks, according to the chosen model, of the individuals in the stratum), retains its optimum statistical properties, even if a more complicated model of the relative risk is used.

Even if the simple model is used, the computational problems of using the exact conditional likelihood and its derivatives are very daunting, especially when there are many large strata with several cancers each. This happens because, as is shown in Breslow and Day, the denominator of the likelihood for a single stratum is the sum

of products, of relative risks, over all possible samples of size equal to the actual number of cancers in the stratum, of persons selected with equal probability, but without replacement, from the total number of persons, both cancer and non-cancer, in the stratum. This computational problem can be surmounted in two ways. First, as was suggested by Peto, in the discussion of Cox [1972], and separately by Kneale (in Kneale et al. [1981]), one can substitute in the above definition "with replacement" for "without replacement." This leads to a much simpler computation for an approximation to the exact conditional likelihood that Peto calls the "rough probability." Second, as was suggested by Howard, also in the discussion of Cox [1972], one can take advantage of the fact that the above definition is of a symmetric function (if two persons in the stratum are interchanged, the value remains the same) and all symmetric functions can be calculated by a simple iteration from the power sums; in this case, the sums, over all the persons in the stratum, of the relative risks raised to various powers. It was this second method, of using power sums, that was used in this paper.

When a more complicated risk function than the simple exponential is used, the calculation of differential coefficients is very complicated, even using power sums, and so in the final maximum likelihood calculation, using all the above ideas, a method of calculation that needed only function values (a variation of the Simplex method due to Nelder and Mead [1965]) was employed. An advantage of this method is that, since it does not use function derivatives and is very robust to function discontinuities, it even works when the underlying parameters are discrete, provided the initial simplex size is large enough. Thus it produces maximum likelihood estimates even for parameters describing step functions, as in the present application. Such parameters are effectively confined to integer values, since the windows derived from them either do, or do not, include in the effective dose the annual dose for any given year.

Unfortunately, the Simplex method of maximization does not lend itself to giving good estimates of the variances, or estimated standard errors, of the maximum likelihood estimates it provides. Thus, the only way of testing whether or not a particular value of a parameter, such as a default value, is consistent with the data as a whole, is by standard nested likelihood ratio tests. For this reason, a constant was added to the final $-2 \times$ log-likelihood statistic so that it would be zero if all the relative risks in all the risk sets were equal to 1.0, i.e., if the basic null hypothesis, of no radiation effect at all, were true. Because the underlying relative risk model is more complicated than the simple exponential, the likelihood function is not guaranteed to have a single unique maximum, and may have local maxima less than the unique global maximum; an example of this phenomenon is mentioned in the text.

APPENDIX B

Reasons Why the Observed Dose-Response Relationship May Be a Sub-Linear Power Law

There are basically two reasons why a sub-linear power law may be a better approximation to the observed dose-response relationship than the simple linear law. The first takes into account heterogeneity at the individual level of the parameters of the radiobiologically plausible model known as linear quadratic with cell killing, and the likely correlation of these parameters, if they are in fact heterogeneous between

individuals. The second assumes an exact linear dose-response relationship between the probability of the response (cancer) and the unobserved "true" dose; the "measured" dose from the film badge reading is assumed to be statistically distributed about the true dose with an experimental error in measurement uncorrelated with the actual response. If the parameters of this experimental error distribution are known, and some intuitive guess can be made of the parameters of the intrinsic heterogeneity distribution of the true doses, then the observed dose-response relationship between the measured doses and the observed responses can be calculated and will not, in general, be linear or even of similar slope to the underlying true dose-response relationship.

In the first argument with a heterogeneous population of individuals and the linear quadratic model with cell killing, the cancer induction parameters of the model (for an individual), are likely to be correlated with the cell killing parameters (for the same individual), because the biological mechanisms of defense against each outcome are likely to be similar at the biochemical level, and both determined by factors such as genetics or the stage of the cell cycle which happened to be irradiated.

The exact dose-response relationship that will be observed for such a heterogeneous population obviously depends on the precise correlations between the parameters and their population average values, and cannot easily be calculated. However, an indication of the way an observed dose-response for a heterogeneous population will differ from the response that would be observed if the population were homogeneous, with the same average values, can be obtained by a simple model.

Suppose the distribution of the parameters (of the linear quadratic model with cell killing) in the population is such that 1% of the population is 100 times as sensitive to both cancer induction and cell killing as the average, and 10% is similarly 10 times as sensitive, and there is a similar tail of less sensitivity than average in the direction of low sensitivity; then, at very low doses, the slope of the observed dose-response will be 3 times what it would be if the population had been homogeneous. Similarly, at low to moderate doses, the slope will be 2 times that for a homogeneous population, since the very sensitive 1% will have been killed off. In fact, taking into account the whole distribution of sensitivities, it can be seen that at the low dose end of the dose-response relationship, the relationship will be distorted from the underlying linear-quadratic in the direction of a sub-linear power law.

The second argument can be made much more exact and algebraic. Let x be the measured dose and let ξ be the true dose. Let the distribution function of the measured dose about the true dose be $f_e(x|\xi)$ and let the distribution function of the true doses be $f_i(\xi)$. Then, by Bayes theorem, the distribution function of the true dose given the measured dose is $f_i(\xi)f_e(x|\xi)/\int f_i(\xi)f_e(x|\xi)d\xi$. Let the relative risk of cancer given the true dose be the linear function $1 + \beta\xi$, where β is the regression constant on the true dose. Then the regression on the measured dose is $1 + \beta\int\xi f_i(\xi)f_e(x|\xi)d\xi/\int f_i(\xi)f_e(x|\xi)d\xi$ which is obviously not necessarily linear, nor, even if it did indeed happen to be linear, would the regression constant necessarily be β, as for the true dose. This general result, in the context of Hanford data, was first noted by Gilbert [1991].

In order to progress further and see what the regression on the measured dose is likely to be, one must make some assumptions about the form of f_e and f_i. The error in measurement of the true dose, estimated by repeat exposures of film badges from the same batch of film to known doses, is estimated to be about 30%, and, since a film

badge reading is necessarily positive, f_e is likely to be approximately log-normal. So, let ln(x) be normally distributed about ln(ξ) with variance σ_e^2. Now the marginal distribution of x is observed to be a good approximation to log-normal with an extra discrete lump at zero dose, which lump is almost certainly due to doses below the detectable limit. So it is likely that the unobservable distribution $f_i(\xi)$ is also approximately log-normal. Let ln(ξ) be normally distributed about ln(μ) with variance σ_i^2, where μ is the grand median of all individual doses.

Then the above complicated expression, giving the regression of the cancer relative risk on the measured dose, can be evaluated by repeated application of the following formula: $\int\exp(Ax^2 + Bx + C)dx = \sqrt{(4\pi/A)}\exp(C-B^2/4A)$ which can be verified as a generalization of the ordinary Normal integral. The result is that the regression is given by $1 + \beta\lambda\exp[\ln(x)\sigma_i^2/(\sigma_i^2 + \sigma_e^2)]$ where λ is a constant depending in a complicated way on σ_e, σ_i, and μ. The exponential term does of course describe a sub-linear power law for dependence on x, with the power law exponent equal to the proportion of the total variance (on a logarithmic scale) that is intrinsic and not due to errors of measurement.