

# Curvilinearity in the Dose-Response Curve for Cancer in Japanese Atomic Bomb Survivors

Mark P. Little and Colin R. Muirhead

National Radiological Protection Board, Chilton, Oxon, United Kingdom

Recently released data on cancer incidence in Japanese atomic bomb survivors are analyzed using a variety of relative risk models that take account of errors in estimates of dose to assess the dose response at low doses. If a relative risk model with a threshold (the dose response is assumed linear above the threshold) is fitted to solid cancer data, a threshold of more than about 0.2 Sv is inconsistent with the data, whereas these data are consistent with there being no threshold. Among solid cancer subtypes there is strong evidence for a possible dose threshold only for nonmelanoma skin cancer. If a relative risk model with a threshold (the dose response is assumed linear above the threshold) is fitted to the leukemia data, a threshold of more than about 0.3 Sv is inconsistent with the data. In contrast to the estimates for the threshold level for solid cancer data, the best estimate for the threshold level in the leukemia data is significantly different from zero even when allowance is made for a possible quadratic term in the dose response, albeit at borderline levels of statistical significance ( $p=0.04$ ). There is little evidence for curvature in the leukemia dose response from 0.2 Sv upwards. However, possible underestimation of the errors in the estimates of the dose threshold as a result of confounding and uncertainties not taken into account in the analysis, together with the lack of biological plausibility of a threshold, makes interpretation of this finding questionable. — *Environ Health Perspect* 105(Suppl 6):1505–1509 (1997)

Key words: cancer, leukemia, Japanese atomic bomb survivors, threshold, dose-response curve

## Introduction

The shape of the dose-response curve for cancer following ionizing radiation exposure has profound implications for extrapolation of risks at high doses and dose rates to those at low doses and dose rates. It is the possible risks arising from low dose and low dose-rate exposure to ionizing radiation that are central to the setting of standards for radiological protection. For example, the International Commission on Radiological Protection (ICRP) (1) recommended a dose and dose-rate effectiveness factor of 2 on the basis of animal data, the evidence for curvilinearity in the cancer

dose response in the bomb survivor data, and other epidemiologic data. Although the linear-quadratic dose response (with upward curvature) found for leukemia is perhaps the most often employed departure from linearity in analyses of the shape of the cancer dose-response curve in radiation-exposed groups (2,3), other shapes are possible for the dose-response curve (4). For the class of deterministic effects defined by the ICRP (1), it is assumed that there is a threshold dose below which there is no effect. Such a form of dose response has also been used in analyses of brain damage

among those exposed *in utero* to the atomic bombings in Hiroshima and Nagasaki, Japan (5,6). The goal of this paper is to examine the evidence for any possible curvilinearity in the cancer dose-response curve by fitting a variety of relative risk models to recently released cancer incidence data for Japanese atomic bomb survivors (7,8); models allowing for a possible dose threshold will be fitted, as well as models incorporating quadratic terms in dose.

It is recognized that errors in the estimates of dose can substantially alter the shape of the dose-response relationship and hence the evidence for both a dose response as well as any possible curvature in that dose response. The problem of random dosimetric errors for the Radiation Effects Research Foundation (RERF) data has been investigated by Jablon (9), Gilbert (10), Pierce et al. (11), and Pierce and Vaeth (3). Pierce and Vaeth (3) found that after adjustment for dosimetric error there were nonsignificant indications of upward curvature in the solid cancer mortality dose response, whereas the evidence for curvilinearity became rather stronger for leukemia mortality. Because of the marked effect of adjusting for dosimetric errors on the shape of the dose-response curve, all the analyses presented in this paper will employ such dosimetric adjustments, which use the methodology developed by Pierce et al. (11) applied to a richer class of dose-response functions than the linear-quadratic models examined by Gilbert (10) and Pierce et al. (11).

## Methods

The relative risk in the Japanese atomic bomb survivor cancer incidence data in stratum  $i$  with sex  $s$ , average age at exposure (AAE)  $a$ , average time since exposure (TSE)  $t$ , and true dose  $D$ , was assumed to be given by:

$$RR(i, D) = \max \left[ 1 + 1_{\{D > D_i\}} \cdot \left\{ \alpha_s \cdot (D - D_i) + \beta_s \cdot (D - D_i)^2 \right\} \cdot \exp\{\delta \cdot a + \epsilon \cdot t\}, 0 \right]$$

This is a linear-quadratic relative risk model with a hypothetical dose threshold  $D_i$ , where  $\alpha_s$  is the linear excess relative risk (ERR) coefficient ( $\text{Sv}^{-1}$ ) in sex  $s$ ;  $\beta_s$  is the quadratic ERR coefficient ( $\text{Sv}^{-2}$ ) in sex  $s$ ;  $\delta$  is the factor determining the log-linear

This paper is based on a presentation at the International Conference on Radiation and Health held 3–7 November 1996 in Beer Sheva, Israel. Abstracts of these papers were previously published in *Public Health Reviews* 24(3–4):205–431 (1996). Manuscript received at *EHP* 28 February 1997; accepted 23 May 1997.

The authors are grateful for the detailed comments of the two referees. This report makes use of data obtained from the Radiation Effects Research Foundation (RERF) in Hiroshima, Japan. RERF is a private foundation funded equally by the Japanese Ministry of Health and Welfare and the U.S. Department of Energy through the U.S. National Academy of Sciences. The conclusions in this report are those of the authors and do not necessarily reflect the scientific judgment of RERF or its funding agencies. This work was funded partially by the Commission of the European Communities under contract FI4P-CT95-0009.

Address correspondence to Dr. M.P. Little, National Radiological Protection Board, Chilton, Didcot, Oxon, OX11 0RQ, U.K. Telephone: 044 1235 822806. Fax: 044 1235 833891. E-mail: mark.little@nrpb.org.uk

Abbreviations used: AAE, age at exposure; AML, acute myeloid leukemia; ERR, excess relative risk; GSD, geometric standard deviation; Gy, gray; ICRP, International Commission on Radiological Protection; LET, linear energy transfer; LSS, Life Span Study; RERF, Radiation Effects Research Foundation; Sv, sieverts; TSE, time since exposure.

adjustment to the ERR for AAE  $a$  (year<sup>-1</sup>);  $\epsilon$  is the factor determining the log-linear adjustment to the ERR for TSE  $t$  (year<sup>-1</sup>); and where  $1_{\{D>D_t\}}$  is 1 if  $D>D_t$  and 0 otherwise. In general, the true dose,  $D$ , is not known; the only observable dosimetric quantity in any stratum is the nominal (or estimated) dose,  $d$ . Approximately unbiased parameter estimates were obtained by replacing  $RR(i,D)$  by  $\text{avg}[RR(i,D)|d]$  in the model fitting, in which this last expression represents the average of the relative risk  $RR(i,D)$  over the stratum with average nominal dose  $d$ . The true dose distribution in each of the two cities was modeled by a Weibull distribution in which the probability of the true dose being greater than  $D$  is given by  $\exp(-\theta \cdot D^\phi)$  and the distribution of the nominal dose,  $d$ , given the true dose,  $D$ , is assumed to be log-normal with median  $D$ . Jablon (9) investigated the errors in the Japanese atomic bomb dosimetry and found that the errors were most likely to be log-normal, with a geometric standard deviation (GSD) of about 30%. Following the example of Pierce et al. (11) for various assumed values of the GSD, the parameters of the Weibull models were chosen to give approximately the same distribution of nominal dose as seen in the solid cancer (7) and leukemia and lymphoma (8) incidence datasets. The fitting of the Weibull distribution parameters  $\theta$  and  $\phi$  was achieved by minimizing the sum of squares of the differences between observed and predicted cumulative distributions of the nominal dose at the average dose within each nominal dose band. In general, all models predicted a nominal dose distribution that agreed well with that observed. The analyses in this paper assume 35% GSD errors; it can be shown that results are not sensitive to the precise choice of GSD in the range of 0 to 45% (12).

Relative risk models were fitted to Japanese atomic bomb survivor incidence data by maximum likelihood (13), in which it is assumed that the expected number of cases of whichever type cancer is under consideration (various sorts of leukemia or solid cancer) in stratum  $i$  with average nominal dose  $d$  (in Sv), is given by:

$$PYR_{id} \cdot \lambda_i \cdot \text{avg}[RR(i,D)|d]$$

where  $PYR_{id}$  is the number of person-years in stratum  $i$  with average nominal dose  $d$ ;  $\lambda_i$  is the base cancer rate in stratum  $i$ .

The solid cancer incidence data are those used in the analysis of Thompson et

**Table 1.** Estimates of threshold value  $D_t$  in fit of linear threshold and linear-quadratic threshold models to cancer incidence data.<sup>a</sup>

Cancer site	Linear threshold = $D_t$ (Sv) (+95% CI)	Linear-quadratic threshold = $D_t$ (Sv) (+95% CI)
<b>Solid cancers</b>		
Stomach	0.06 (<0.00, 0.27)	0.10 (<0.00, 0.31)
Colon	0.50 (0.09, >1.00)	0.64 (<0.00, >1.00)
Liver	0.13 (<0.00, 0.71)	0.30 (0.08, 0.75)
Other digestive organs	0.36 (<0.00, >1.00)	0.04 (<0.00, >1.00)
Lung	<0.00 (<0.00, 0.25)	<0.00 (<0.00, 0.35)
Nonmelanoma skin	0.45 (0.18, 0.75)	0.92 (0.53, >1.00)
Female breast	0.03 (<0.00, 0.14)	0.04 (<0.00, 0.19)
Urinary	0.04 (<0.00, 0.36)	0.03 (<0.00, 0.37)
Thyroid	0.04 (<0.00, 0.19)	0.05 (<0.00, 0.29)
Other solid cancers	<0.00 (<0.00, 0.90)	<0.00 (<0.00, >1.00)
All solid cancers	0.04 (<0.00, 0.16)	0.08 (<0.00, 0.23)
<b>Leukemias</b>		
Acute lymphocytic leukemia	0.06 (<0.00, 0.18)	0.05 (<0.00, 0.18)
Acute myeloid leukemia	0.30 (0.08, 0.60)	0.32 (<0.00, 0.76)
Chronic myeloid leukemia	0.15 (0.00, 0.28)	0.15 (<0.00, 0.30)
All leukemias	0.13 (0.04, 0.27)	0.12 (0.01, 0.28)

<sup>a</sup>Shielded-kerma dose < 4 Gy and (for solid cancers) colon dose < 4 Sv or (for leukemias) bone-marrow dose < 4 Sv; 35% dosimetric GSD assumed.

al. (7), whereas the leukemia incidence data are those used in the analysis of Preston et al. (8). The dose used for the solid cancer data was that to the colon, whereas the bone-marrow dose was used for leukemia; in both cases a neutron relative biological effectiveness of 20 was assumed, as recommended by the ICRP (1). The  $\alpha_i$  are free to vary, with  $\beta_i$  and  $D_t$  also free to vary as appropriate;  $D_t$  was constrained to be nonnegative in all fits. The AAE adjustment coefficient,  $\delta$ , was allowed to vary and the TSE adjustment coefficient,  $\epsilon$ , set to 0, for the model fits to the solid cancer data; both the  $\delta$  and  $\epsilon$  were allowed to vary for the fits to the leukemia data to allow for the known variations in the data of ERR (or lack of them) with age and time (7,8). Further details on the methods used are found in a recent study by Little and Muirhead (12).

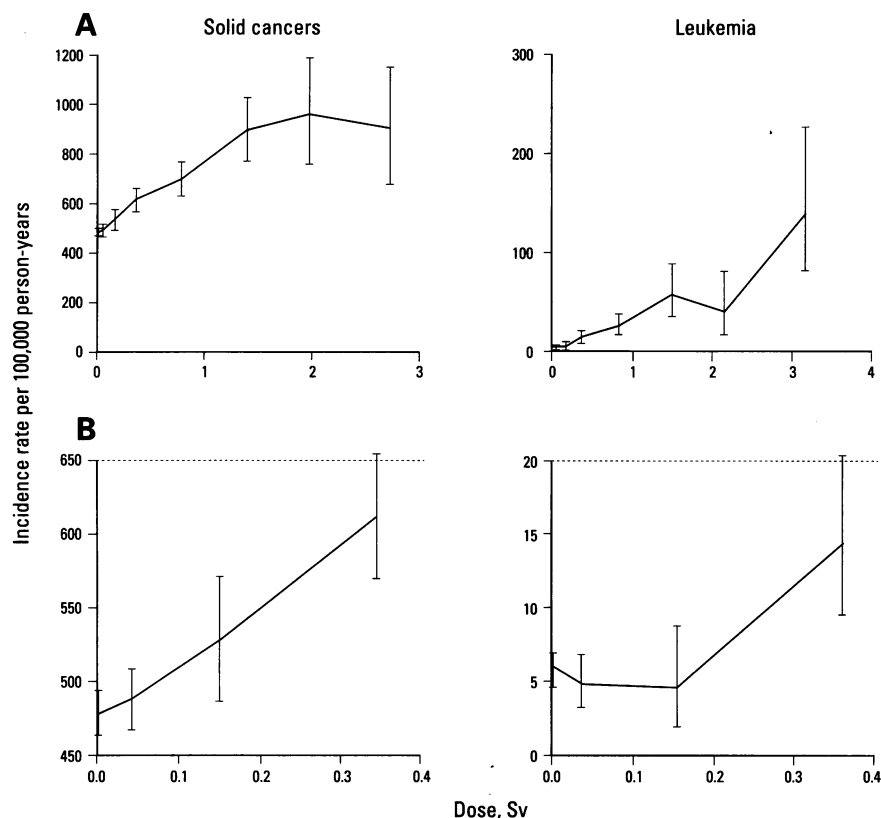
## Results

Table 1 and Figure 1 show that overall there is little evidence for curvilinearity for the solid cancer data. For example, if a linear threshold model is fitted to the solid cancer data, the value of the threshold dose below which no elevation in risk is assumed is not significantly greater than zero (best estimate 0.04 Sv, 95% CI <0.00, 0.16). Table 1 also shows that in general there is no stronger evidence of curvilinearity for particular subtypes of solid cancer. Only for non-melanoma skin cancer is there compelling evidence for the presence of a threshold. For leukemia, there are stronger indications of curvilinearity in the dose response. Table 1 shows that if a linear model with a threshold

is fitted to the leukemia data, the value of the threshold dose below which no elevation in risk is assumed is statistically significantly greater than zero ( $p < 0.01$ ); the best estimate is 0.13 Sv (95% CI 0.04, 0.27). Surprisingly, much the same result ( $p = 0.04$ ) is found when a linear-quadratic threshold model is fitted (best estimate 0.12 Sv, 95% CI 0.01, 0.28). The improvement in fit of the linear-quadratic threshold model compared with that of the linear threshold model is not statistically significant ( $p = 0.60$ ). This last result shows that the curvature in the leukemia dose response takes place at low doses (< 0.2 Sv), as Figure 1 also shows. If a linear threshold model is fitted separately to each of the three leukemia subtypes, only for acute myeloid leukemia (AML) is there strong evidence ( $p < 0.01$ ) for a dose threshold (best estimate 0.30 Sv, 95% CI 0.08, 0.60), perhaps reflecting the fact that the largest number of leukemia cases (102 of 190) are of this subtype. There also is evidence at borderline levels of statistical significance ( $p = 0.05$ ) for a dose threshold for chronic myeloid leukemia. For the other main leukemia subtype (acute lymphocytic leukemia) the best estimate of the threshold is positive, although not significantly so. However, it is clear from Table 1 that for each leukemia subtype considered separately, the curvature in the dose response is adequately described by a linear-quadratic model.

## Discussion

Analysis using a variety of models reveals little evidence for curvilinearity for solid cancers overall. In particular there is no



**Figure 1.** Dose response for solid cancers and leukemia in A-bomb survivors (+95% CI). Shielded-kerma dose < 4 Gy and (for solid cancers) colon dose < 4 Sv or (for leukemia) bone-marrow dose < 4 Sv. (A) all data; (B) low-dose region of A.

evidence for a dose threshold with fairly tight upper bounds ( $\approx 0.2$  Sv) on how large a threshold there could possibly be. These findings confirm the results of previous analyses by the RERF of the dose response for cancers other than leukemia in the Life Span Study (LSS) cohort of the Japanese atomic bomb survivors (2,7), which also found little evidence for any curvature in the dose response. The RERF analyses considered a more restricted set of dose-response models (generally only linear quadratic) than that employed in this study and, unlike the analyses described above, did not consider random errors in dose estimates (2,7). There is little evidence for curvilinearity in the dose response for solid cancers in any other group exposed to low linear energy transfer (LET) radiation (14,15). The dose response for solid cancer following exposure to high LET radiation also is generally linear (16,17), although there is some evidence of nonlinearity in the dose response for bone sarcomas in U.S. women who work with radium dials (18).

In contrast to the results found for solid cancers, those in the analysis by the RERF

and other groups of the dose-response curve for leukemia incidence and mortality in the LSS cohort exhibited a marked quadratic component, i.e., a significant upward curvature (2,8). The evidence for nonlinearity in the incidence data is strongest for AML (8). The fact that when both linear threshold and linear-quadratic threshold models are fitted to this data there is a barely significant ( $p=0.04$ ) threshold is also consistent with a high degree of curvilinearity in the dose response.

Although our analysis considers the effects of random errors in dose estimates, it does not take into account possible systematic biases in the atomic bomb dosimetry. Recently there have been indications of inconsistencies between the most current set of neutron dose estimates for the Hiroshima bomb survivors (dosimetry system 1986) and those measured by neutron activation in mineral and metal samples (19). It has been argued, however, that these dosimetric uncertainties imply only slight adjustments to the slopes of the cancer dose-response curves in the Japanese LSS cohort (20). Our analysis also does not

take into account the contribution of natural background radiation and other non-bomb sources of radiation e.g., medical X-rays, although there is no reason to suppose that the doses from these sources would be different for survivors in different atomic bomb dose groups (21,22). The contribution to total dose (and therefore also the contribution to uncertainties in dose) made by radiation sources other than atomic bombs would be relatively more important at low (atomic bomb) doses rather than at high doses.

It should be noted that given the statistical uncertainties as well as the impact of possible bias and confounding in epidemiologic studies, a low-dose threshold would be difficult to observe directly. For these reasons this study's estimation of thresholds in the dose response uses a model-fitting approach to the Japanese dataset, a cohort exposed to moderate doses (average  $\approx 0.1$  Sv) at a high dose rate. The dangers of this modeling approach must be recognized, namely that the evidence for (or against) a threshold at low doses may be partially driven by the patterns of risk in the higher dose parts of the Japanese incidence data.

Certain approximations are made in this study. The analysis uses the average for a given nominal dose,  $d$ , of the relative risk  $RR(i,D)$  evaluated at true dose  $D$ :  $\text{avg}[RR(i,D)|d]$ . The dataset used for analyses of both leukemia and solid cancers is in grouped form, with the strata defined in each case by the variables for city, sex, AAE, TSE, and dose. For each such stratum,  $i$ , the average nominal dose over the persons in that stratum ( $\text{avg}_i[d]$ ) is available. Ideally one should calculate for each stratum  $\text{avg}_i[\text{avg}[RR(i,D)|d]]$ , i.e., the average of  $\text{avg}[RR(i,D)|d]$  over all individuals in stratum  $i$ . It is impossible to calculate this quantity using the grouped data publicly available, so this analysis evaluates  $\text{avg}[RR(i,D)|\text{avg}_i[d]]$ , i.e., the value of  $\text{avg}[RR(i,D)|d]$  evaluated at the average nominal dose ( $\text{avg}_i[d]$ ) within stratum  $i$ . Even for linear dose-response models there are potential differences between  $\text{avg}[RR(i,D)|\text{avg}_i[d]]$  and  $\text{avg}_i[\text{avg}[RR(i,D)|d]]$ . Table 2 demonstrates that when 35% GSD dosimetric errors are assumed, this approximation does not introduce appreciable errors for the optimal linear quadratic and linear-quadratic threshold models for leukemia. Even for the smallest values of AAE and TSE, when the ERR is largest and therefore when the proportional errors in  $\text{avg}[RR(i,D)|\text{avg}_i[d]]$  are the most

**Table 2.** Errors in averaging hazard function for optimal leukemia models.<sup>a</sup>

NDI, Sv	Percentage error <sup>b</sup>			
	L-Q		L-Q threshold	
	M	F	M	F
0.005-0.1	-0.47	-0.05	-4.20	-5.76
0.1-0.2	-0.33	-0.10	-3.62	-3.79
0.2-0.5	-1.12	-0.42	-0.51	0.37
0.5-1.0	-1.10	-0.49	-0.42	0.31
1.0-2.0	-1.48	-0.79	-0.66	0.44
2.0-3.0	-0.49	-0.28	-0.22	0.22
3.0-4.0	0.01	0.05	0.07	0.21

Abbreviations: F, females; L-Q, linear-quadratic; M, males; NDI, nominal dose interval. <sup>a</sup>35% dosimetric GSD assumed; AAE 0.5 years; TSE 7.5 years; averages evaluated using 100 random samples from nominal dose distribution. <sup>b</sup>100 • {avg[RR(i,D)|avg<sub>i</sub>[d]]/avg<sub>i</sub>{avg[RR(i,D)|d]}-1} (person-years) averaged over city.

significant, errors are at most 5% for the linear-quadratic threshold model; the errors are somewhat less (generally < 1%) for the linear-quadratic model (Table 2). The magnitude of the relative error in avg[RR(i,D)|avg<sub>i</sub>[d]] from this source is much the same for Hiroshima and Nagasaki (results not shown). At least for the linear-quadratic threshold model, in the higher dose groups the relative error in avg[RR(i,D)|avg<sub>i</sub>[d]] tends to be of equal magnitude but of opposite sign for males compared to that for females (Table 2).

It should be noted that the use of threshold models is generally problematic,

since the asymptotic ( $\chi^2$ ) distribution of the deviance difference statistic employed for significance tests is not guaranteed because of lack of sufficient smoothness in the likelihood function (23). However, this problem is circumvented by the likelihood averaging techniques used in this paper and in a companion analysis (12) (at least when the dosimetric GSD is assumed to be non-zero).

The admittedly weak indications of a possible threshold in the leukemia dose response found in this analysis should be considered in a wider context. In particular, the biological plausibility of such a threshold must be questioned. There is some evidence from animal data for substantial low-dose curvilinearity, and even possible threshold effects, in the induction of skin cancer (24) and leukemia (25) in mice. There are indications of beneficial or hormetic effects of very low-dose irradiation (0.004 Gy) in some large chromosomal aberration studies (26), although there may be problems with these data, the findings from which have not been duplicated in other studies (27). Cancers in general, and leukemias in particular, are assumed to be stochastic effects for which there generally are no expectations of a dose threshold; however, a threshold might be expected for certain other categories of deterministic effects such as sterility or cataract induction (1). Because significant excess leukemia risk has been observed in various occupationally exposed groups (28) in which total doses

generally are administered in a hyperfractionated manner and also among those exposed to small doses (< 20 mSv) of X-irradiation *in utero* (29), it is highly likely that there is no threshold in the leukemia dose response.

There is substantial evidence that oncogenesis occurs because of damage to a single cell and in particular because of damage to genetic material (DNA) in the cell nucleus that takes the form of stable gene or chromosome mutations (4). In the case of leukemia there is strong evidence for the involvement of specific chromosome rearrangements in the neoplastic process (30). For there to be an ionizing-radiation dose threshold for leukemia, it would be necessary to assume either *a*) that single tracks of ionizing radiation cannot induce the necessary damage in the target tissue (cells in the bone marrow) or *b*) that there is a totally efficient error-free system of repair after damage from relatively small doses of ionizing radiation. There is evidence that single tracks of all types of ionizing radiation can induce a variety of damage including DNA double-strand breaks (31,32), which are believed to be critical lesions in radiation response. There is also a body of experimental evidence that argues against an error-free DNA repair system operating at low doses of ionizing radiation that might result in a dose threshold for the induction of gene and chromosomal mutations (27,33).

## REFERENCES

- International Commission on Radiological Protection (ICRP). 1990 Recommendations of the International Commission on Radiological Protection. Ann ICRP 21, Pts 1-3 (1991).
- Shimizu Y, Kato H, Schull WJ. Studies of the mortality of A-bomb survivors. 9. Mortality, 1950-1985: Part 2. Cancer mortality based on the recently revised doses (DS86). Radiat Res 121:120-141 (1990).
- Pierce DA, Vaeth M. The shape of the cancer mortality dose-response curve for the A-bomb survivors. Radiat Res 126:36-42 (1991).
- United Nations Scientific Committee on the Effects of Atomic Radiation. Sources and Effects of Ionizing Radiation. New York:United Nations, 1993.
- Otake M, Schull WJ, Yoshimaru H. A Review of Radiation-Related Brain Damage in the Prenatally Exposed Atomic Bomb Survivors. RERF Commentary and Review CR 4-89. Hiroshima:Radiation Effects Research Foundation, 1990.
- Otake M, Schull WJ. Radiation-related small head sizes among prenatally exposed A-bomb survivors. Int J Radiat Biol 63:255-270 (1993).
- Thompson DE, Mabuchi K, Ron E, Soda M, Tokunaga M, Ochikubo S, Sugimoto S, Ikeda T, Terasaki M, Izumi S et al. Cancer incidence in atomic bomb survivors. Part II: solid tumors, 1958-1987. Radiat Res 137:S17-S67 (1994).
- Preston DL, Kusumi S, Tomonaga M, Izumi S, Ron E, Kuramoto A, Kamada N, Dohy H, Matsuo T, Nonaka H et al. Cancer incidence in atomic bomb survivors. Part III: leukemia, lymphoma and multiple myeloma, 1950-1987. Radiat Res 137:S68-S97 (1994).
- Jablon S. Atomic Bomb Radiation Dose Estimation at ABCC. ABCC Tech Rep TR 23-71. Hiroshima:Atomic Bomb Casualty Commission, 1971.
- Gilbert ES. Some effects of random dose measurement errors on analyses of atomic bomb survivor data. Radiat Res 98:591-605 (1984).
- Pierce DA, Stram DO, Vaeth M. Allowing for random errors in radiation dose estimates for the atomic bomb survivor data. Radiat Res 123:275-284 (1990).
- Little MP, Muirhead CR. Evidence for curvilinearity in the cancer incidence dose-response in the Japanese atomic bomb survivors. Int J Radiat Biol 70:83-94 (1996).
- McCullagh P, Nelder JA. Generalized Linear Models. 2nd ed. London:Chapman and Hall, 1989.
- Little MP. Risks of radiation-induced cancer at high doses and dose rates. J Radiol Prot 13:3-25 (1993).
- Muirhead CR, Cox R, Stather JW, MacGibbon BH, Edwards AA, Haylock RGE. Estimates of late radiation risks to the UK population. Docs NRPB 4(4):15-157 (1993).

16. U.S. National Academy of Sciences Committee on the Biological Effects of Ionizing Radiations. Health Risks of Radon and other Internally-deposited Alpha-emitters (BEIR IV). Washington:National Academy Press, 1988.
17. Lubin JH, Boice JD, Edling C, Hornung RW, Howe GR, Kunz E, Kusiak RA, Morrison HI, Radford EP, Samet JM et al. Lung cancer in radon-exposed miners and estimation of risk from indoor exposure. *J Natl Cancer Inst* 87:817-827 (1995).
18. Rowland RE, Stehney AF, Lucas HF. Dose-response relationships for female radium dial workers. *Radiat Res* 76:368-383 (1978).
19. Straume T, Egbert SD, Woolson WA, Finkel RC, Kubik PW, Gove HE, Sharma P, Hoshi M. Neutron discrepancies in the DS86 Hiroshima dosimetry system. *Health Phys* 63:421-426 (1992).
20. Preston DL, Pierce D, Vaeth M. Neutrons and radiation risk: a commentary. In: RERF Update, Vol 4, No 4. Hiroshima: Radiation Effects Research Foundation, 1992;5.
21. Aoyama T, Radford EP, Yonehara H, Kato H, Sakanoue M. Radon Concentrations in Residential Housing in Hiroshima and Nagasaki. RERF Tech Rep TR 8-91. Hiroshima: Radiation Effects Research Foundation, 1993.
22. Kato K, Antoku S, Sawada S, Russell WJ. Organ doses received by atomic bomb survivors during radiological examinations at the Radiation Effects Research Foundation. *Br J Radiol* 64:720-727 (1991).
23. Schervish MJ. *Theory of Statistics*. New York:Springer-Verlag, 1995.
24. Papworth DG, Hulse EV. Dose-response models for the radiation-induction of skin tumours in mice. *Int J Radiat Biol* 44:423-431 (1983).
25. Mole RH, Papworth DG, Corp MJ. The dose-response for X-ray induction of myeloid leukaemia in male CBA/H mice. *Br J Cancer* 47:285-291 (1983).
26. Pohl-Rüling J, Fischer P, Haas O, Obe G, Natarajan AT, Van Buul PPW, Buckton KE, Bianchi NO, Larramendy M, Kučerová M et al. Effect of low-dose acute X-irradiation on the frequencies of chromosomal aberrations in human peripheral lymphocytes *in vitro*. *Mutat Res* 110:71-82 (1983).
27. Lloyd DC, Edwards AA, Leonard A, Deknudt GL, Verschaeve L, Natarajan AT, Darroudi F, Obe G, Palitti F, Tanzarella C et al. Chromosomal aberrations in human lymphocytes induced *in vitro* by very low doses of X-rays. *Int J Radiat Biol* 61:335-343 (1992).
28. Cardis E, Gilbert ES, Carpenter L, Howe G, Kato I, Armstrong BK, Beral V, Cowper G, Douglas A, Fix J et al. Effects of low doses and low dose rates of external ionizing radiation: cancer mortality among nuclear industry workers in three countries. *Radiat Res* 142:117-132 (1995).
29. Kneale GW, Stewart AM. Age variation in the cancer risks from foetal irradiation. *Br J Cancer* 35:501-510 (1977).
30. Rabbitts TH. Chromosomal translocations in human cancer. *Nature* 372:143-149 (1994).
31. Goodhead DT. Initial events in the cellular effects of ionizing radiations: clustered damage in DNA. *Int J Radiat Biol* 65:7-17 (1994).
32. Goodhead DT, Nikjoo H. Track structure analysis of ultrasoft X-rays compared to high- and low-LET radiations. *Int J Radiat Biol* 55:513-529 (1989).
33. Thacker J. Radiation-induced mutation in mammalian cells at low doses and dose rates. *Adv Radiat Biol* 16:77-124 (1992).