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***Articolo originale***

# Cancer effects of low level radiation: why the present method of risk estimation is in need of change

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The Oxford Survey of Childhood Cancers (OSCC) with its finding of an association between prenatal X-rays and juvenile neoplasms (Stewart, Webb and Hewitt, 1958) was once the only reason for doubting whether the cancer risk coefficients recommended by the Radiation Effects Research Foundation (RERF), and based on a life span study (LSS) population of A-bomb survivors, have general validity (Beebe, Kato and Land, 1977). Today there are other reasons, including an independent analysis of the Japanese data (Stewart and Kneale, 1990), the result of combining OSCC data with vital statistics and measurements of background radiation (Knox *et al.*, 1988), and a case/control survey involving the Sellafield cluster of childhood leukaemias (Gardner, 1990). But before describing this new evidence it is necessary to explain why so many experts are in favour of cancer risk coefficients being based on survivors from the Hiroshima and Nagasaki bombs.

The present method of cancer risk estimation is the result of both the RERF and the Atomic Bomb Casualty Commission (ABCC) finding that: 1) annual death rates of the LSS population were close to expectations based on national statistics (standardized mortality ratio or SMR analysis), and 2) for non-cancer deaths there was no evidence of any radiation effects but for cancer deaths there was a positive dose trend which was steeper for leukaemia than solid tumours (linear model of relative risk or RR analysis). On the strength of these remarkably consistent findings, RERF and ABCC risk estimates have always been based on the following assumptions: all late effects of the A-bomb radiation were the result of mutations, and the risk of the principal stochastic effect (cancer) was directly proportional to the dose.

There are many powerful committees concerned with radiation protection (including ICRP, UNSCEAR and BEIR) and they have all accepted, without question, the RERF assumption about late effects of radiation. There was also general agreement with ICRP when this Commission voiced the following opinion: «There are biological grounds for assuming that the dose response curve for low LET radiation will generally increase in slope with increasing dose», and consequently, RERF risk coefficients should only be used with great caution and «explicit recognition of the possibility that the actual risk at low doses

may be lower than that implied by a deliberately cautious assumption of proportionality (ICRP, 1977). It was also agreed that, for human populations, knowledge of dose-response relationships was too limited to enable confident prediction of the slopes of the curves at low doses and low dose rates. However, cancer death rates of the LSS population were constantly leaving an impression of a reduced risk at low dose levels. Therefore, from several committees has come the following advice: when a risk model is derived primarily from data on a single instantaneous exposure to radiation (as in LSS data) then application of the model to any situation involving continuous low dose rate exposure (as in occupational exposures or background radiation) will require incorporation of a reduction factor. According to BEIR V (1990) the best estimate of this dose rate effectiveness factor (DREF) is 2.1.

Unfortunately, the assumption of a reduced cancer risk at low dose levels is not borne out by studies of late effects of fetal irradiation. On the contrary, in spite of the OSCC findings for prenatal X-rays, the number of childhood cancers among 1297 survivors from *in utero* exposure to A-bomb radiation was no greater than the expected number (Jablon and Kato, 1970). This finding is still being given as a reason for doubting whether the relationship between prenatal X-rays and childhood cancer has any casual significance (Rose, 1990). However, besides finding evidence of a cancer risk at low dose levels, the Oxford Survey also discovered that there is mounting sensivity to infections during the latent phase of all childhood cancers especially leukaemia (Kneale and Stewart, 1978). Therefore, the negative findings for the Japanese children were probably the result of selection. According to this hypothesis there was, for all infection sensitive persons, an exceptionally high risk of dying from virtually all causes during the period when environmental effects of the two nuclear explosions were still making life difficult, i.e., during the winter of 1945-46, when both city populations were battling with hunger, inadequate protection against cold weather and dislocation of many essential services.

As early as 1972, I had an opportunity to discuss this selection hypothesis with the BEIR Committee. However, on the advice of Seymour Jablon, this committee decided that «although some effect of the kind suggested by Stewart may be present in the ABCC data it would, at worst, be quantitatively very small and would have no practical effect on the risk estimates derived from the ABCC data» (BEIR II, 1972). Nevertheless, I felt then (and still feel) that the committee should have asked ABCC for tests of an important corollary of my hypothesis: if there was selection against infection sensitive persons, then members of the LSS cohort, who had not experienced any acute effects of the blast or radiation and had fully recovered from any ill effects of the general devastation, would have a reduced risk of dying from all natural causes, also a death rate which decreased with increasing proximity to the hypocentre. Furthermore, it should be possible to recognize such survivors from the data which were collected in 1950-51 and subsequently used to give each individual an estimated radiation dose.

RERF has never thought it worthwhile to draw a distinction between survivors with and without acute lesions and has always assumed (on the basis of the non-cancer death rate for the LSS population as a whole) that, even if there had been any selection effects of the massively high death rates of 1945-46, they were too short-lived to have any effect on the LSS cohort (Beebe, Land and Kato, 1978). According to this hypothesis, there would be a number of unresolved problems, such as why the LSS death rate for the only distinctive effect of marrow damage (aplastic anaemia) has always been higher than normal as well as strongly dose related, why the opposite was true for deaths from self inflicted injuries, and why there have always been lower rates of mortality in Hiroshima (where 28% of the early survivors had serious injuries) than in Nagasaki (where this proportion was only 14%) (Ohkita, 1975). As a result of these outstanding problems I again found occasion to express doubts about the RERF interpretation of LSS data (Stewart, 1982). Thus, in 1982, I wrote a paper with the following abstract:

«A review of published data relating to A-bomb survivors has led to the conclusion that, since they were based on the mortality experiences of five-year survivors, estimates of radiation effects should have been

controlled for two opposing forces - namely, selective survival of exceptionally fit individuals during the period of heavy acute mortality and residual disabilities. Both effects were dose-related and beyond question, and the disabilities probably included the effects of incomplete repair of bone marrow damage. Therefore, in addition to differences between high and low dose being largely obliterated, there was probably distortion of cancer effects. The two opposing forces are clearly the reason why the change from the high mortality rates of 1945-46 to the low rates of the 1950's was not accompanied by a change from a positive to a negative association with dose, and imperviousness to the residual disabilities is probably the reason why sudden deaths of previously healthy individuals (exemplified by suicides) were an exception to this rule. Finally, impairment of bone marrow function probably accounts for the early epidemic of myeloid leukaemia; the apparent absence of other cancers at this time, and the relatively high, dose-related death rates for blood diseases other than leukaemia» (Stewart, 1982).

There was no response to these suggestions and it was left to Kneale (who only had access to published data) to devise a test of my opposing forces hypothesis (Stewart and Kneale, 1984). His analysis of 1950-1978 deaths did establish a difference between cardiovascular and other non-cancer deaths (of the type which would be expected if there were both selection effects of the early deaths and late effects of marrow damage). But a further search for two, contradictory effects of the nuclear explosions had to wait until 1987, when release of an RERF data tape gave Kneale a second opportunity to refute

**Table 1**

**DEATHS OF A-BOMB SURVIVORS IN FOUR CONSECUTIVE PERIODS**
**EFFECTS OF REPLACING A LINEAR MODEL OF RELATIVE RISK (L) WITH A LINEAR/QUADRATIC MODEL (LQ)**

| Cause of death | Period | Cases | L-L/Q[2] | L/Q model of relative risk[1] | | | |
|---|---|---|---|---|---|---|---|
| | | | | $\alpha(10^{-3})$ | SE | $\beta(10^{-6})$ | SE |
| All causes | 1950-1958 | 7426 | 13.6*** | −1.40 | 0.43*** | +4.10 | 1.11*** |
| | 1959-1966 | 7615 | 0.0 | +0.36 | 0.46 | 0.00 | 1.12 |
| | 1967-1974 | 7899 | 1.2 | +0.18 | 0.46 | +1.34 | 1.14 |
| | 1975-1982 | 8103 | 1.3 | +0.23 | 0.45 | +1.39 | 1.14 |
| Excluding neoplasms | 1950-1958 | 6204 | 10.3*** | −1.65 | 0.45*** | +3.55 | 1.11*** |
| | 1959-1966 | 6040 | 0.0 | +0.01 | 0.50 | −0.26 | 1.17 |
| | 1967-1974 | 6127 | 3.5 | −0.54 | 0.49 | +2.20 | 1.24 |
| | 1975-1982 | 6090 | 6.0** | −0.99 | 0.47* | +2.93 | 1.22* |
| Excluding neoplasms and CVS[3] | 1950-1958 | 4064 | 10.8*** | −2.07 | 0.53*** | +4.39 | 1.34*** |
| | 1959-1966 | 3182 | 0.7 | −0.71 | 0.65 | +1.26 | 1.57 |
| | 1967-1974 | 2700 | 9.2** | −1.53 | 0.72* | +5.51 | 1.91** |
| | 1975-1982 | 2588 | 3.5 | −1.16 | 0.72 | +3.29 | 1.84 |
| Neoplasms | 1950-1958 | 1222 | 3.6 | +0.10 | 1.33 | +7.01 | 3.67 |
| | 1959-1966 | 1575 | 0.0 | +1.99 | 1.17 | 0.00 | 0.00 |
| | 1967-1974 | 1772 | 0.8 | +2.66 | 1.12* | −1.96 | 2.73 |
| | 1975-1982 | 2013 | 2.2 | +4.59 | 1.12*** | −4.74 | 2.72 |
| CVS | 1950-1958 | 2140 | 0.9 | −0.95 | 0.83 | +1.92 | 2.04 |
| | 1959-1966 | 2858 | 1.4 | +0.85 | 0.78 | −1.96 | 1.79 |
| | 1967-1974 | 3427 | 0.2 | +0.43 | 0.68 | −0.93 | 1.63 |
| | 1975-1982 | 3502 | 2.6 | −0.91 | 0.65 | +2.75 | 1.68 |

[1] $RR = 1 + \alpha D + \beta D^2$ where D is the T65 radiation dose.

[2] On the assumption of no quadratic component of relative risk, L-L/Q would be distributed according to $X^2$ with on degree of freedom. Therefore, the critical values are: 4.0 = $p < 0.05$*
6.6 = $p < 0.01$**
10.8 = $p < 0.001$***

[3] Including deaths from trauma (1,708), tuberculosis (1,393), diseases of the digestive system (2,373), blood diseases (162) and other unspecified causes (6,898).

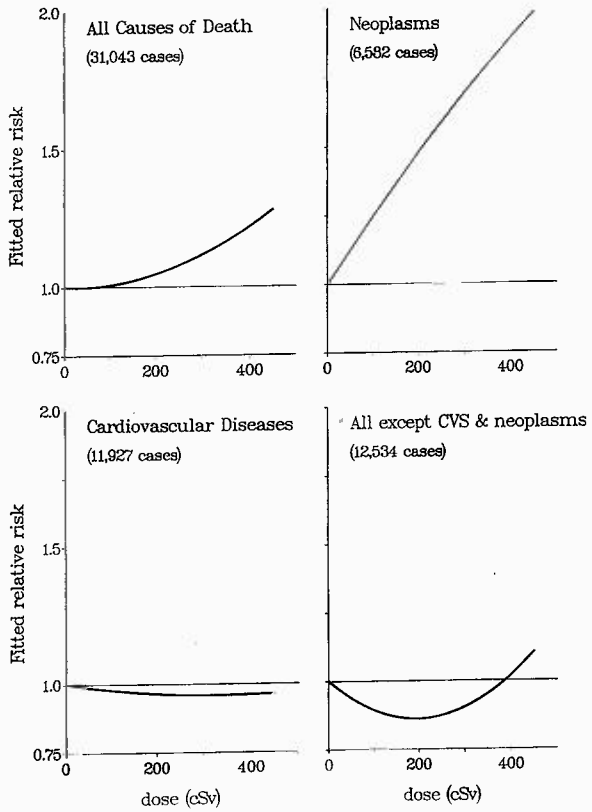


**Fig. 1.** Fitted relative risk for specified causes of death (1950-1982).

the hypothesis of no late effects of the A-bomb radiation other than cancer (Stewart and Kneale, 1990).

Even with these data it was not possible to separate injured from uninjured survivors or to identify the deaths most likely to have been influenced by environmental effects of the bombs and by lasting damage to the immune system (i.e. deaths from the classical killers of all destitute persons, namely, primary and secondary infections). Even so, Kneale was able to show the effects of 1) replacing a linear model of relative risk with a linear quadratic model, 2) dividing the follow-up period into 4 sections, and 3) recognizing two causes of death besides cancer (Table 1; figs. 1, 2). The final conclusions of this analysis were as follows:

«Cancer risk coefficient for ionizing radiation are currently based on the assumption that, after the bombing of Hiroshima and Nagasaki, there were no late effects of early selection (survival of the fittest) or acute marrow damage. These negative findings were the result of applying a linear model of relative risk to the deaths of 5 year survivors. By applying a linear-quadratic model to these deaths (i.e. a model with more than one degree of freedom), we have obtained evidence of long-standing competition between effects of the early deaths and other radiation effects and also evidence that late effects of radiation include marrow damage as well as cancer. Consequently, the present method or risk estimation – by linear quadratic extrapolation of high dose effects – should no longer be used for estimating the cancer effects of occupational exposures or background radiation» (Stewart and Kneale, 1990).

Another reason for suspecting that the present method of risk estimation is underestimating the risk of low dose situations (and suspecting that the LSS population will never have a normal risk of dying from natural causes) can be found in a recent extension of the Oxford survey (Knox *et al.*, 1988). This is no place to describe the intricacies of this ongoing case/control survey. But it should be understood that the new contribution to the problem of cancer effects of low level radiation was the result of combining three data sets, i.e. interview data for 22,351 case/con-

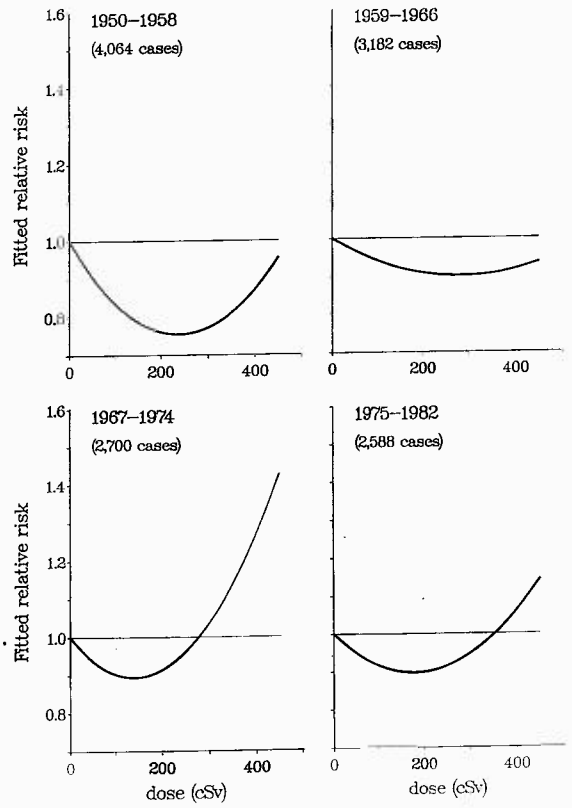


**Fig. 2.** Fitted relative risk for all causes of death except neoplasms and cardiovascular diseases in four periods.

**Table 2**

**CANCER EFFECTS OF FETAL IRRADIATION. ESTIMATES BASED ON A REGRESSION ANALYSIS OF OSCC DATA**

| | | |
|---|---|---|
| 3rd trimester medical X-rays | Regression analysis[1] β value | 0.7413 |
| | Relative Risk[2] | 1.90 |
| | Proportion of x-rayed cases | 14% |
| | Proportion of extra (radiogenic cases) | 6.6% |
| Continuous exposure to background gamma radiation | Regression analysis (TGR) β value | 0.0034 |
| | Average TGR dose | 32 nGy/h |
| | Relative Risk (TGR) | 1.11 |
| | TGR as proportion of background gamma | 22% |
| | Proportion of extra (background) cases[3] | 50% |

[1] β = change in the relative risk per unit change of each factor (x-ray units: yes/no; TGR units: 1 nGy/h) (Knox *et al.*, 1988)

[2] $RR = \frac{\beta(exp) - 1}{\beta(exp)}$

[3] Assuming the same effect from TGR and other components of background radiation.

trol pairs (representing 27 years of early cancer deaths), annual numbers of births for a thousand districts of England, Scotland and Wales, and terrestrial gamma radiation dose rates for each district. The findings for two sources of fetal irradiation (medical X-rays and background radiation) are summarized in Table 2. They include an estimate of the cancer risk from background radiation which is not only much greater than any RERF equivalent but is also indicative of a higher relative risk for these continuous as well as inevitable exposure (2.69) than for the brief, third trimester exposure to medical X-rays (1.90).

The latest contribution to the problem of cancer effects of low level radiation has come from an attempt by Gardner and his associates to discover the cause of a cluster of childhood leukaemia in the vicinity of Sellafield (Gardner, 1990). Since Sellafield is a reprocessing plant, an obvious factor to suspect was environmental pollution with pluto-

**Table 3**

**INCIDENCE OF LEUKEMIAS AND LYMPHOMAS IN CHILDREN OF FATHERS EXPOSED TO GAMMA RADIATION BEFORE CONCEPTION[1]**

| Fathers | | Leukaemias (0-14 yrs) | | | Leukaemias and lymphomas (0-24 yrs) | | |
|---|---|---|---|---|---|---|---|
| | | Cases | Controls[2] | RR | Cases | Controls[2] | RR |
| All fathers | | 46 | 288 | 1.00 | 66 | 404 | 1.00 |
| Sellafield workers | | | | | | | |
| anytime | | 12 | 65 | 1.35 | 14 | 72 | 1.01 |
| before diagnosis | | 8 | 53 | 1.17 | 11 | 72 | 0.97 |
| at birth | | 8 | 32 | 2.07 | 10 | 37 | 2.14 |
| at conception | | 8 | 25 | 2.79 | 10 | 34 | 2.44 |
| before conception | | 9 | 36 | 1.97 | 11 | 47 | 1.77 |
| Radiation doses of Sellafield workers | | | | | | | |
| Total dose (msv) | 1-49 | 3 | 19 | 1.12 | 4 | 27 | 1.06 |
| | 50-99 | 1 | 11 | 0.69 | 2 | 13 | 1.16 |
| | 100+ | 4 | 5 | 6.25 | 4 | 5 | 6.42 |
| Exposure within 6 months of conception date | | | | | | | |
| Dose (msv) | 1-49 | 3 | 18 | 1.30 | 5 | 22 | 1.80 |
| | 50-99 | 1 | 3 | 3.54 | 1 | 4 | 2.41 |
| | 100+ | 4 | 5 | 7.17 | 4 | 8 | 4.33 |

[1] From Gardner *et al.*, 1990.

[2] Matched for sex, date of birth and region.

nium and other fission products; but according to Gardner the salient difference between his cases and controls concerned paternal exposure to occupational sources of gamma radiation shortly before the conception dates (Table 3). This finding (of an excess of such exposures among children who later died from leukaemia or lymphoma) has added a new dimension to the etiology of childhood cancers, by showing that some of these cases may have prezygotic origins as well as a new dimension to the radiation problem, by drawing attention to the possibility that exposure of mature spermatozoa to mutational effects of background radiation might be one route for the development of human cancers.

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