

Risks Associated with Low Doses and Low Dose Rates of Ionizing Radiation: Why Linearity May Be (Almost) the Best We Can Do¹

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Deterministic and stochastic effects associated with high-dose ionizing radiation (x-ray) exposure have been known for almost as long as ionizing radiation itself (1–3). At lower doses, radiation risks are primarily stochastic effects, in particular, somatic effects (cancer) rather than the deterministic effects characteristic of higher-dose exposure (4–6). In contrast to deterministic effects, for stochastic effects, scientific committees generally assume that at sufficiently low doses there is a positive linear component to the dose response—that is, that there is no threshold (4–6). This does not preclude there being higher-order (eg, quadratic) powers of dose in the dose response that may be of importance at higher doses. It is on this basis that models linear (or linear-quadratic) in dose are often used to extrapolate the experience of the Japanese atomic bomb survivors (who were typically exposed at a high dose rate to moderate doses [average, 0.1 Sv]) to estimate risks from low doses and low dose rates (4–6). Most population-based cancer risk estimates are based primarily on the Japanese atomic bomb survivor Life Span Study (LSS) cohort data (4–6). However, evidence of excess risks comes from a large number of other studies as well.

In the parallel editorial (7), evidence is presented for possible real (or at least “practical”) thresholds or “hormetic” (beneficial) effects of low doses of ionizing radiation. As we summarize here, and in contrast to the arguments of Tubiana et al (7), we judge that there is little epidemiologic or biologic evidence for these for cancer. The arguments are of three forms: (a) assessment of the degree of curvature in the cancer dose response within the Japanese atomic bomb survivors and other exposed groups (in particular, departure from linear or linear-quadratic curvature), (b) consistency of risks between

the Japanese and other moderate- and low-dose cohorts, and (c) assessment of biologic data on mechanisms.

Most of the information on radiation-induced cancer risk comes from (a) the Japanese atomic bomb survivors, (b) medically exposed populations, (c) occupationally exposed groups, and (d) environmentally exposed groups (6). In the higher-dose radiation therapy studies, where doses received are very much higher than in the LSS, sometimes in the range at which cell sterilization occurs, excess cancer risks per unit dose tend to be less than in comparable subsets of the LSS (8,9). However, as we show, risks in moderate- and low-dose medically and occupationally exposed groups are generally consistent with those in the LSS.

Evidence for Departures from Linear or Linear-Quadratic Curvature in the Dose Response in Moderate-Dose Exposed Cohorts

The dose response for most cancer sites in the LSS and in other radiation-exposed cohorts is well described by a linear dose response (6,10–14). The major exceptional sites in this respect are leukemia and nonmelanoma skin cancer in the LSS (10–12,14,15) and bone cancer in radium dial painters (16,17). When all solid cancers are analyzed together, there is no evidence of significant departure from a linear dose response in the latest LSS cancer incidence data, although there are suggestions of modest upward curvature in the latest LSS mortality data

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(6,13,14). The evidence for breast cancer, where there is reasonable power to study the risks at low doses, suggests that the data are most consistent with linearity (18). It should be noted that, in addition to modifications in carcinogenic effectiveness (per unit dose) relating to the total dose delivered, there are also possible variations in effectiveness as a result of dose fractionation (the process of splitting a given dose into a number of smaller doses suitably separated in time) and dose rate (19). This is not surprising in radiation biologic terms; by administering a given dose at progressively lower dose rates (ie, giving the same total dose over longer periods of time) or by splitting it into many fractions, the biologic system has time to repair the damage, so that the total damage induced will be less (19).

This plus the modest upward curvature exhibited in the solid cancer mortality dose response overall (13) and for certain specific cancer sites (6,14,15), as well as the rather larger curvature in the leukemia dose response (13), as discussed above, provide some justification for using a dose and dose rate effectiveness factor (DDREF) other than 1 when linear models are employed to extrapolate to low doses and low dose rates. The DDREF is the factor by which one divides risks for high-dose and high-dose-rate exposure to obtain risks for low doses and low dose rates. The International Commission on Radiological Protection (ICRP) (5) recommended that a DDREF of 2 be used together with models linear in dose for all cancer sites, on the basis largely of the observations in various epidemiologic data sets. The Biological Effects of Ionizing Radiations VII Committee (4) estimated what they termed an "LSS DDREF" to be 1.5 (95% confidence interval [CI]: 1.1, 2.3) on the basis of estimates of curvature from experimental animal data and from the latest LSS data on solid cancer incidence. The United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) (6) has reviewed the various values proposed for DDREF, as well as the criteria used to determine the range of applicability in dose and dose rate, and suggested that a DDREF of no more than 3 be used in conjunction with linear models.

It has been customary to model the dose response in fits to biologic (19) and epidemiologic data (6) by a linear-quadratic (upward-curving) function of dose, and this form of dose response is strongly indicated for leukemia in various radiation-exposed groups (4,6,10,12,20). Various other possible departures from a linear dose response have been used; for example, exponential cell-sterilization adjustments to the linear-quadratic term in the dose response have been employed in fits to biologic (19) and higher-dose epidemiologic data (11,15,20–24).

Evidence for threshold effects has also been examined by using the LSS data. Little and Muirhead (11,12,25) fitted linear threshold and linear-quadratic threshold models to the LSS incidence and mortality data for various solid cancer subtypes and leukemia, while adjusting for measurement error. There was no evidence of threshold departures from linearity or linear-quadratic curvature in the solid cancer data by subtype or overall; when using a linear-quadratic model, for the mortality data, the central estimate of the threshold was less than 0 Sv (95% CI: <0, 0.15), and for incidence, the central estimate of the threshold was 0.07 Sv (95% CI: <0, 0.23) (25). Pierce and Preston (26) also fitted linear threshold models to the LSS solid cancer incidence data, with an extra 7 years of follow-up (to the end of 1994), and estimated the threshold as 0 Sv (95% CI: <0, 0.06); the somewhat tighter upper bound is perhaps because of the extra years of follow-up data and the use of a linear threshold rather than a linear-quadratic threshold model.

Little and Muirhead (25) found evidence at borderline levels of statistical significance for departures from linear-quadratic curvature for leukemia incidence, but not for mortality; with a linear-quadratic model, for the mortality data, the central estimate of the threshold was 0.09 Sv (95% CI: <0, 0.27) ($P = .16$), and for incidence, the central estimate of the threshold was 0.11 Sv (95% CI: 0.003, 0.27) ($P = .04$). As Little and Muirhead (12) document, the LSS leukemia mortality and incidence data are fairly similar (most leukemia

cases were fatal in the 1950s and 1960s). Little and Muirhead (12,25) concluded that the most likely explanation for the difference in findings between the leukemia incidence and mortality data is the finer disaggregation of dose groups in the publicly available version of the mortality data compared with the incidence data.

The ICRP has recently carefully reviewed the issue of possible thresholds and their effect on risk estimates (27) (but see also the article by Land [28]). The ICRP's survey of the epidemiologic data indicates that there are a number of groups exposed at low doses and dose rates that exhibit excess risk, compatible with extrapolations from risks observed at moderate to high doses and dose rates (27), and these we now discuss.

Direct Evidence for Risk in Groups Exposed to Low and Moderate Doses and Compatibility with Risks in Japanese Atomic Bomb Survivors

Direct epidemiologic evidence exists of excess cancer risk in a number of groups exposed at low doses or low dose rates (6,27). In particular, excess cancer risk is associated with radiation exposures on the order of a few tens of milligrays from diagnostic x-ray exposures in the Oxford Survey of Childhood Cancers (OSCC) and in various other groups exposed in utero (29–31). However, the interpretation of these in utero studies remains controversial (32,33), in particular because there is no specificity in risk—the risk for all childhood solid tumors is increased, at about 40%, by the same magnitude as that for childhood leukemia, implying a possible bias. The ICRP (33) has carefully reviewed all of these studies, in particular the OSCC, and has noted a number of methodologic problems, in particular possible selection and recall biases; the ICRP noted that "although the arguments fall short of being definitive because of the combination of biological and statistical uncertainties involved, they raise a serious question of whether the great consistency in elevated [relative risks], including embryo-

nal tumours and lymphomas, may be due to biases in the OSCC study rather than a causal association." Doll and Wakeford (34) and Wakeford and Little (35) also carefully reviewed the literature and concluded that most of the criticisms of these studies could be addressed; Doll and Wakeford concluded that "there is strong evidence that low dose irradiation of the fetus in utero...causes an increased risk of cancer in childhood." The "negative" studies highlighted by Tubiana et al (7) are of low power to detect excess risk, because of the generally low prevalence of obstetric radiography and the lower doses received from modern x-ray equipment.

Increased breast cancer risk has been observed among young women exposed to moderately high cumulative doses (mean, 0.8 Gy) from multiple thoracic fluoroscopic x-ray exposures delivered in fractions that were, on average, on the order of 10 mGy (36–38). A typical chest fluoroscopic examination in the period between 1930 and 1950 would last about 15 seconds, and patients would receive 0.01–0.10 Gy (38). These fluoroscopic exposures did not occur at low dose rates, although because the fluoroscopic examinations would be performed every 2 weeks for 3–5 years, the wide temporal separation of such fractionated low-dose exposures should, theoretically, result in a linear dose-response relationship directly applicable to the estimation of low-level effects (19,39). Excess (absolute) breast cancer risks per unit dose in these groups are comparable to those in the LSS (18,38). However, there is no comparable excess risk of lung cancer among patients who underwent fluoroscopy, even though lung doses were comparable to breast doses (40,41). The difference between the breast and lung cancer findings among patients who underwent fluoroscopy suggests that there may be variation among cancer sites in terms of fractionation effects, but possible residual confounding effects of cigarette smoking cannot be ruled out, nor can possible misdiagnosis of lung cancer as tuberculosis. Increased breast cancer risk has also been observed in a study of

patients who underwent multiple diagnostic x-ray examinations as part of the diagnosis of scoliosis (42).

A pooled analysis of data from five studies of thyroid cancer following irradiation during childhood (43), including Israeli patients with tinea capitis, the youngest (age at exposure, <15 years) atomic bomb survivors, two populations treated with x-rays for enlarged tonsils or lymphoid hyperplasia, and a population treated for supposedly enlarged thymus, obtained an overall excess relative risk (ERR) per gray of 7.7 (95% CI: 2.1, 28.7). The highest risk of thyroid cancer was observed among the Israeli patients with tinea capitis, for whom the ERR per gray was 32.5 (95% CI: 14.0, 57.1), on the basis of 44 cases among the exposed and 16 cases among the nonexposed, and this largely accounted for the significant interstudy heterogeneity that was observed. Although the doses to the thyroid gland in the Israeli tinea capitis study were low, averaging 90 mGy (range, 40–500 mGy), they were very uncertain, and Ron et al (43) point out that only minor dosimetric adjustment in this cohort is required to make the ERR compatible with that in the other four studies. No significant thyroid cancer excess was observed in a much smaller U.S. group of patients given similar treatment (average thyroid dose, 60 mGy) (44), but the difference in risk estimates between this study and the comparable Israeli study was not statistically significant (44). Two Swedish studies of patients with skin hemangioma with low-dose and low dose rate exposures to radium 226 obtained risk estimates that were similar to those in the pooled analysis of Ron et al (43): an ERR per gray of 7.5 (95% CI: 0.4, 18.1) on the basis of an estimated mean thyroid dose of 120 mGy (45) and an ERR per gray of 4.9 (95% CI: 1.3, 10.2) on the basis of a mean dose of 260 mGy (46).

There have been a number of studies of occupationally exposed persons, who generally receive low doses and low dose rates of ionizing radiation (47–49). In all of these worker studies, it is important to recognize that individual doses were accumulated in daily incre-

ments over a protracted period of many years. For example, in the International Agency for Research on Cancer (IARC) 15-country study (49), average cumulative doses were 19.4 mSv, and less than 5% of workers received cumulative doses exceeding 100 mSv. Risks in these studies are generally consistent with those seen in the LSS. For example, Muirhead et al (47) estimated that the ratio of the leukemia ERR coefficient in United Kingdom nuclear workers to that estimated from the linear part of the leukemia dose response in the LSS was 1.18 (90% CI: <0, 3.73), and the corresponding ratio for all malignant neoplasms, excluding lung cancer and leukemia, was 0.89 (90% CI: <0, 3.65). The IARC 15-country study (49) risk for leukemia, an ERR of 1.93 per sievert (95% CI: <0, 8.47), was similar to that in an age-matched subset of the LSS, with the linear coefficient (in fits of a linear-quadratic model) being 1.54 per sievert (95% CI: -1.14, 5.33), although for solid cancers there were (statistically nonsignificant) indications of higher relative risks than in the LSS: an ERR of 0.97 per sievert (95% CI: 0.14, 1.97) compared with an ERR of 0.32 per sievert (95% CI: 0.01, 0.50) in an age-matched subset of the LSS. The ratio of lung cancer risk coefficients in the LSS and for the Colorado Plateau uranium miners is very close to the value suggested by the latest ICRP model of lung dosimetry (50,51). Precise estimation of cancer risks after low doses of radiation exposure requires very large studies with long-term follow-up (52). Absence of significantly elevated risks observed in some occupational studies therefore should not be taken as evidence of lack of risk. In particular, this shows that use of a "practical" threshold, as proposed by Tubiana et al (7), may not be wise: Just because one cannot detect a risk does not mean that it is not there.

Of relevance to these epidemiologic studies is the study of stable chromosome exchanges in the peripheral blood lymphocytes of populations with protracted exposures. Chromosome changes play a major role in carcinogenesis, and there is increasing evidence that the

presence of increased frequencies of chromosome aberrations in peripheral blood lymphocytes in healthy individuals could be a surrogate for the specific changes associated with carcinogenesis and could therefore be indicative of risk (53–55). Tawn et al (56) demonstrated a linear dose response for chromosome translocations in workers exposed occupationally to low linear energy transfer radiation. For low doses of radiation, the production of a chromosome exchange generally occurs within a few hours of the initial lesions, and the International Atomic Energy Agency (57) considers that when interfraction intervals of more than 6 hours occur, the exposures can be considered to be isolated events, with the induced aberration yields being additive. The occupational doses received by the workers in the Sellafield study (56) were accumulated in small daily increments of less than 0.4 mSv. While the effect of any one daily increment is too small to measure, their cumulative effect conforms to expectations on the basis of the linear component of dose-response curves derived from *in vitro* experiments using acute exposures. Thus, linearity must extend below 1 mSv, at least for the induction of chromosome aberrations, and there is no evidence to support suggestions of novel mechanisms operating at these very low doses. Studies of U.S. radiologic technologists with cumulative discrete exposures to low doses of diagnostic x-rays have produced similar findings (58).

Biologic Evidence for Departures from Linearity in the Dose Response

We briefly survey here themes touched on in more detail in the parallel editorial (7). For the class of deterministic effects defined by the ICRP (5), it is assumed that there is a threshold dose below which there is no effect, and the response (probability of effect) smoothly increases above that point. Biologically, it is much more likely that there is a threshold for deterministic effects than for stochastic effects; deterministic effects ensue when a sufficiently large number of cells are damaged within a

certain critical time period that the body cannot replace them (59). As outlined by Harris (60) (but see also the 1993 UNSCEAR report [19]), there are compelling biologic data to suggest that cancer arises from a failure of cell differentiation and that it is largely unicellular in origin. Canonically, cancer is thought to result from mutagenic damage to a single cell, specifically to its nuclear DNA, which in principle could be caused by a single radiation track (19), although there is emerging evidence, largely *in vitro*, that other targets within the cell may also be involved (61,62). A low linear energy transfer dose of 1 mGy corresponds to about one electron track hitting a cell nucleus (19,63). As Brenner et al (64) point out, this means that at low doses (≤ 10 mGy over a year) it is unlikely that temporally and spatially separate electron tracks could cooperatively produce DNA damage. Brenner et al (64) surmise from this that in this low-dose region, DNA damage at a cellular level would be proportional to dose.

As Tubiana et al (7) point out, and has been known for some time, the efficiency of cellular repair processes varies with dose and dose rate (19,63), and this may be the reason for the curvature in cancer dose response and dose rate effects observed in epidemiologic and animal data. DNA double-strand breakage is thought to be the most critical lesion induced by radiation (19), although, as above, there is evidence of other targets within the cell (61,62). Repair of double-strand breaks relies on a number of pathways, even the most accurate of which, homologous recombination, is prone to errors (63); other repair pathways (eg, nonhomologous end joining, single-strand annealing) are intrinsically much more error prone (27,63). The variation in efficacy of repair that undoubtedly occurs will affect the magnitude of unrepaired and misrepaired damage and, whereas unrepaired damage is likely to result in cell death, misrepaired damage will invariably result in mutation.

Tubiana et al (7) mention a number of novel radiation biologic responses that they believe could affect the shape

of the dose-response curve for stochastic health effects at low doses. Low-dose hypersensitivity has been shown to occur for cell killing, *in vivo* and *in vitro* (65,66), with suggestions that this is the result of a failure to activate repair processes and will very likely effectively remove any potentially genetically altered cells. However, chromosome rearrangements and gene mutations, both of which arise as a result of misrepair, have been shown to be inducible *in vitro* at doses on the order of 0.01 Gy with a linear no-threshold dose response relationship (63), and, as discussed above, chromosome translocations have been reported in blood lymphocytes from occupationally exposed workers. Adaptive response has been documented *in vivo* and *in vitro* and has been thoroughly reviewed by the ICRP and the UNSCEAR (27,67), which observed that generally, the protective effect of the conditioning dose appears to last only for a few hours, and the ability to induce an adaptive response differs between individuals, with some failing to respond at all (27,67). Also, the excess risk after the challenge dose is reduced by the previous adapting dose but is still generally increased (27,67), so that this mechanism would not account for a possible threshold or hormetic effect at low doses.

Observations of responses in neighboring cells that have not been directly hit have led to suggestions that at low doses these nontargeted effects could contribute to the adverse consequences of radiation exposure (68). As Tubiana et al (7) observe, it has been suggested that such bystander effects could be part of a sensitive response system and could thus be protective (69). Bystander effects have been observed largely *in vitro* (61,62), although one recent study (70) provides evidence for bystander induction of cancer in a patched mouse model of brain cancer after very high-dose (3, 8.3 Gy) partial-body radiation exposure. The relevance of this work to low-dose risk in humans is unclear, but it suggests, as do some other reports (61,62), that bystander effects can act to increase rather than decrease risk. In any event, Tubiana et al (7) note the absence of a bystander effect in epide-

miologic studies of cancer, a view supported by studies of lung cancer following exposure to the α -emitting radionuclide radon and its decay products (71). The dose response shows no substantial departure from linearity over a wide dose range, from the doses received by underground miners to the doses received in homes.

Tubiana et al (7) also rule out a role for the induction of persistent radiation-induced genomic instability in carcinogenesis. Although there appears to be substantial evidence of radiation inducing persistent genomic instability in hemopoietic cells in vitro and some limited support for the effect to be transmissible in vivo, to date there has been little evidence produced to indicate in vivo induction and transmission (62). Suggestions that radiation-induced genomic instability has played a role in the induction of leukemia in the Japanese atomic bomb survivors (72,73) have been criticized following reanalysis of the data (74,75). Follow-up studies of chromosome aberration frequencies in individuals with known exposures to radiation do not show evidence of a continuing expression of genomic instability (76–80).

As Tubiana et al (7) point out, studies of gene transcription find evidence for low-dose and high-dose responses differing (81,82). However, such studies have yet to identify coherent sets of genes that respond differentially to high and low doses (83), and it is therefore premature to draw conclusions on the similarities and differences between high- and low-dose effects. The relevance of such early changes in expression to cancer is also unknown.

Conclusion

In summary, excess cancer risks observed in the Japanese atomic bomb survivors and in many medically and occupationally exposed groups exposed at low or moderate doses are generally statistically compatible. For most cancer sites, the dose response in these groups is compatible with linearity over the range observed. The available data on biological mechanisms do not provide

general support for the idea of a low-dose threshold or hormesis. This large body of evidence does not suggest, and indeed is not statistically compatible with, any very large threshold in dose or with possible hormetic effects.

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