EXTRAPOLATING RADIATION-INDUCED CANCER RISKS FROM LOW DOSES TO VERY LOW DOSES

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Abstract—There is strong evidence that ionizing radiation increases cancer risks at high doses (e.g., ≥ 1 Gy), and persuasive, if controversial, epidemiological evidence that cancer risks are increased at low doses (~ 10 mGy). Discussed here are the issues related to extrapolating radiation risks from low radiation doses to very low doses (≤ 1 mGy) — for which purpose we are forced to rely on radiobiological evidence and biophysical arguments. At high doses, cells are typically hit by many tracks of radiation, while at low doses most cells are typically hit by a single track of radiation; at very low doses proportionately fewer cells are hit, again only by a single track of radiation. Thus, in comparing low doses to very low doses, the damage to hit cells remains essentially the same (a single radiation track passing through a cell), but what changes is the number of cells that are subjected to this same damage, which decreases linearly as the dose decreases. This is the argument for a linear no-threshold (LNT) model. It is important to emphasize that this LNT argument only applies to the extrapolation from low doses to very low doses, not from high to low doses. Of course there are caveats to this argument, such as the potential effects of phenomena such as inter-cellular communication and immunosurveillance, and the possibility of different radiobiological processes at very low doses, compared to low doses. However, there is little conclusive experimental evidence about the significance of these phenomena at very low doses, and comparative mechanistic studies at high doses vs. low doses will not be informative in this context. At present, we do not know whether such radiobiological phenomena would produce small or large perturbations, or even whether they would increase or decrease cancer risks at very low doses, compared with the prediction of a linear extrapolation from low doses.
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INTRODUCTION

THERE IS considerable uncertainty as to the extent to which low or very low doses of radiation affect cancer risks (NCRP 2001; Tubiana 2005; NRC 2006; UNSCEAR 2008). This is an important issue in a variety of contexts,

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such as diagnostic radiology, nuclear power production, and responses to a large-scale radiological event. There exists a range of high radiation doses which demonstrably increase cancer risks, and a lower dose range where there is plausible (but controversial) evidence for an increase in cancer risk; but almost by definition there is a very low-dose range where there is no direct epidemiological evidence, nor is there likely to be any in the foreseeable future. This is because of the high "natural" cancer rate in the general population of $\sim 40\%$, which essentially precludes practical epidemiological studies to assess potential small radiation-induced changes in cancer risk. Without the possibility of direct measurements of cancer risks at very low doses, and lacking a complete mechanistic understanding of the processes involved in radiation-induced cancer, or any other cancer process for that matter, the only current option is to extrapolate radiation-induced cancer risks from higher doses, where the risks can be assessed epidemiologically, to lower doses. Thus a key question becomes the most plausible methodology of extrapolating cancer risks from low doses, where there is some evidence of an increased cancer risk, to very low doses.

METHODS AND RESULTS

The epidemiological data will not be discussed here *per se*, but rather the focus will be on risk extrapolations between dose regions. It will be convenient to divide the relevant dose range into three regions: at high doses (e.g., ≥ 1 Gy) there is strong epidemiological evidence that ionizing radiation increases cancer risks (Preston et al. 2007); at lower doses of the order of 10 mGy, there is persuasive, if less definitive, epidemiological evidence that cancer risks are increased (Doll and Wakeford 1997; Cardis et al. 2007); at very low doses, however, epidemiological studies cannot provide statistically useful information. Discussed here are the issues relating to extrapolating radiation risks from low doses (~ 10 mGy) to very low doses (≤ 1 mGy) — for which purpose we are forced to rely on radiobiological evidence and biophysical arguments.

Energy deposition patterns in cells in the three dose regions

As well as being associated with different levels of confidence as to the associated cancer risks, the three dose regions discussed above also correspond to different patterns of energy deposition in individual cells, as illustrated in Fig. 1. It will be argued, with caveats, that these energy deposition patterns allow significant insights into risk extrapolation approaches among the three different dose ranges illustrated here.

As schematized in Fig. 1, at high doses (≥1 Gy, Fig. 1A), mammalian cell nuclei are hit by multiple tracks of radiation; for example, in an x-ray field, they would be traversed by many incident x rays. By contrast, at low doses (e.g., 10 mGy, Fig. 1B), cell nuclei are on average hit by a *single* track of radiation [it is pertinent to note that these generalizations actually depend both on the x-ray energy and on the biological target size (ICRU 1983); here we have considered 80-kVp x rays, a typical peak energy used in radiology, and have assumed the target to be a typical human epithelial cell nucleus (Altman and Katz 1976)]. At still lower doses (e.g., 1 mGy, Fig. 1C), the type of energy deposition to any given hit cell does not change, still being a single radiation track — but rather the number of hit nuclei decreases, proportionately to the dose.

Extrapolating risks between the three dose regions

As can be intuitively seen from Figs. 1A and 1B, there is unlikely to be a simple biophysically-based argument to describe the extrapolation of risks from high doses to low doses, because the basic type of cellular damage to cells changes drastically, from many hits to single hits — and indeed, as one might expect, there is persuasive evidence of different types of radiobiological
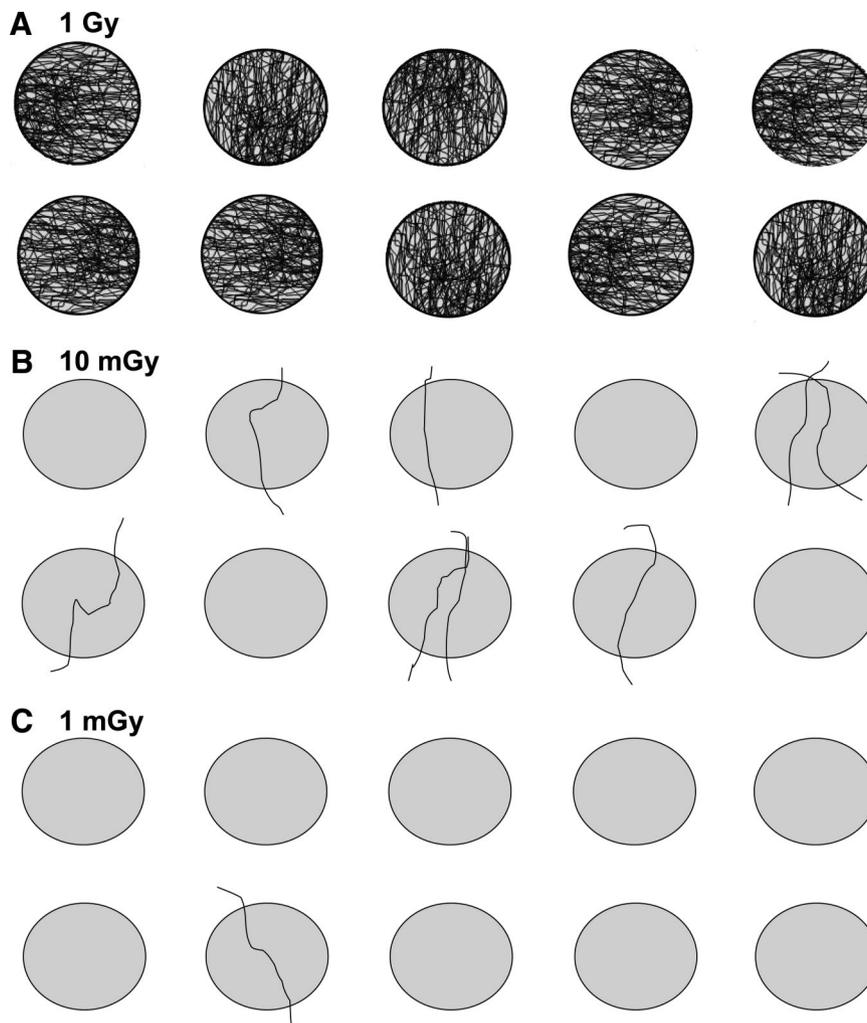

Fig. 1. Schematic illustrations of radiation tracks in 10 typical human epithelial cell nuclei exposed to 80-kVp x rays, at doses of 1 Gy, 10 mGy, and 1 mGy, respectively. It can be seen that there is unlikely to be a simple methodology for extrapolating risks from high to low doses (A to B), but extrapolating risks from low to very low doses (B to C) may be more feasible.

damage when comparing high and low radiation doses (e.g., Yin et al. 2003; Portess et al. 2007).

By contrast, comparing low doses (e.g., 10 mGy, Fig. 1C) with very low doses (≤1 mGy), the energy deposition to the hit cells remains essentially the same (essentially a single radiation track passing through a cell), but what changes is the proportion of cells that are subjected to this same damage, which decreases linearly as the dose decreases. In principle, therefore, extrapolating from low to very low doses is expected to be easier than extrapolating from high to low doses, because the type of damage does not change, merely the proportion of cells subject to that damage.

The linear no-threshold (LNT) extrapolation from low doses to very low doses

These considerations suggest a biophysically-based rationale for an LNT extrapolation of risks from low doses to very low doses, summarized as follows:

1. At low to very low doses, if a cell nucleus is traversed by an x ray, it will be traversed by one or, at most, a few physically-distant radiation tracks; and
2. Thus at low to very low doses, given that the type of physical damage to cells does not change, the main effect of a decrease in dose will be a proportionate decrease in the number of cells subject to this same type of physical damage, and thus a proportionate, i.e., linear, decrease in risk.

Again it is emphasized that:

 I. The rationale for the LNT model relates to extrapolating risks from low doses (e.g., 5 to 20 mGy) to still lower doses, not for extrapolating risks from high doses to low doses; and
II. The LNT argument does not address the issue of whether there are, in fact, increased cancer risks in the low-dose range from 5 to 20 mGy, although there are large-scale epidemiological studies suggesting that this is indeed the case, such as the Oxford Survey of Childhood Cancers, a case control study of 15,000 childhood cancers (Doll and Wakeford 1997), and initial reports from the 15-country study of nuclear industry workers (Cardis et al. 2007).

Potential confounders of the biophysical argument

There are several potential weaknesses to this biophysical argument for linearity, the most commonly considered being:

1. Possible confounding effects of inter-cellular communication;
2. Potential differential effects of immunosurveillance when the number of (pre) malignant cells is low; and

3. The possibility of different types of biological damage, and damage responses, dominating at very low doses, compared to low doses.

Each of these potential confounders will be briefly discussed.

Intercellular communication. As described above, the biophysical argument for linearity refers to the development of monoclonal tumors by autonomous (independently developing) cells (Rossi and Kellerer 1972; Brenner et al. 2003). By contrast, it is well known that, while most tumors are monoclonal in origin (Fearon et al. 1987), cell-to-cell communication is a central component of the process of carcinogenesis (Bhowmick and Moses 2005; Trosko et al. 2005).

Not all types of cell-to-cell communications would invalidate the biophysical argument for linearity. For example, if the interactions are between unirradiated tissue and radiation-damaged cells, the argument for linearity remains valid. However, the argument would potentially not hold if other irradiated cells could significantly change the probability that a radiation-damaged cell develops into a cancer in a way which is non-linear with dose. But it would still then remain to be determined whether such intercellular communication would decrease the cancer risk [suggested, for example, by Barcellos-Hoff (2001)], or increase it [suggested, for example, by Tubiana (2005) and colleagues], or indeed would make any appreciable difference. One may note here that the most studied intercellular communication phenomenon in the field of radiobiology is the so-called bystander effect (Nagasawa and Little 1992; Brenner et al. 2001; Ballarini et al. 2006), which generally results in risks per unit dose that are higher at very low doses compared to low doses (Sawant et al. 2001; Zhou et al. 2001).

Overall, our current understanding of the relevance of intercellular communication to the biophysical argument for LNT was well summarized by Trosko et al. (2005): "*At present, one cannot predict whether the [intercellular communication] response is biologically relevant to any health effect or even whether the effect on the affected cells could be considered positive or negative.*"

Immune surveillance. It has been suggested (Tubiana 2005) that immune surveillance and other systems are able to eliminate small numbers of radiation-induced premalignant cells, but would be overwhelmed by larger numbers of such cells—which would lead to cancer risks per unit doses which are lower at very low doses than at higher doses. It is certainly true that innate and adaptive immune effector cells and molecules can recognize and destroy tumors (Gasser and Raulet 2006). However, it is also clear that small numbers of pre-malignant cells can

survive immune surveillance (Willimsky et al. 2008), and there is no evidence to suggest that the immune surveillance system is more efficient when the number of pre-malignant or malignant cells is low. To the contrary, there is considerable evidence that small numbers of tumor cells can escape immune surveillance *more* efficiently than larger numbers, a phenomenon referred to as "sneaking through" (Old et al. 1962) or "dilution escape" (Bonmassar et al. 1974), and which has been demonstrated for many different syngeneic and allogeneic tumors (Hewitt 1953; Old et al. 1962; Kölsch et al. 1973; Bonmassar et al. 1974; Mengersen et al. 1975).

An example of "sneaking through" is illustrated in Fig. 2, which shows the incidence of BALB/c mastocytoma tumors in BALB/c mice injected with various numbers of BALB/c mastocytoma tumor cells (Kölsch et al. 1973); there is a very high tumor incidence when large numbers (>500,000) of tumor cells are injected, and this incidence decreases as the number of injected tumor cells is reduced. But as the number of injected tumor cells is reduced from 5,000 down to, in this case, 20 tumor cells, there is no further decrease in the induced tumor incidence.

The possibility of different biological damage-response processes dominating at very low doses, compared to low doses. There has been considerable recent interest in comparing biological damage-response mechanisms in different dose ranges, specifically as a test of the validity of the LNT extrapolation. As discussed above (see Fig. 1), one would expect different types of biological damage in the Gy dose range as compared with mGy doses, and thus different types of biological responses — and indeed such has been reported by several investigators [e.g., Yin et al. (2003), Portess et al. (2007)]. It follows that
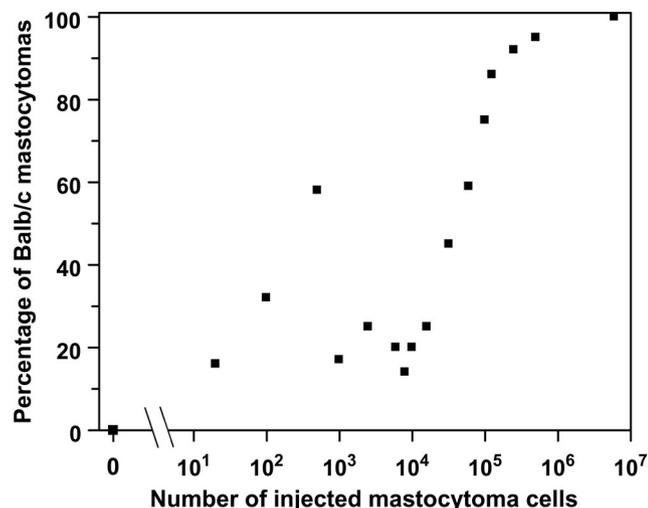

Fig. 2. Incidence of BALB/c mastocytoma tumors in BALB/c mice injected with a single dose of different numbers of BALB/c mastocytoma tumor cells (based on Kölsch et al. 1973).

comparisons of mechanisms in the mGy vs. the Gy dose range will not be informative regarding the validity of the LNT approach, which is concerned with extrapolating from risks at ~10 mGy to risks at doses of less than 1 mGy.

It is pertinent to point out here, in regard to radiobiological experiments in the sub-mGy dose range, that they are extraordinarily difficult to perform and interpret, particularly in light of the requirements that they be pertinent to carcinogenesis and, ideally, in vivo. As an example, initial studies by Rothkamm and Löbrich (2003) on DNA double strand break (DSB) repair kinetics in the mGy dose range initially suggested very different DNA repair kinetics at 1.2 mGy compared to 5 or 20 mGy. Such a result might argue against LNT in that the initial energy deposition in hit cells would be expected to be essentially the same for each of these doses (see Figs. 1B and 1C), and thus the repair kinetics would be expected to be the same. However, when the experiments were repeated in vivo (Löbrich et al. 2005), no such differences in repair kinetics were observed over the mGy dose range.

DISCUSSION

The LNT approach is a plausible mechanistically-based approach for extrapolating radiation-induced cancer risks from low doses (e.g., 5 to 20 mGy) down to very low doses (e.g., ≤1 mGy). Two things it cannot do are (1) extrapolate cancer risks from high doses (≥1 Gy) to low doses; or (2) establish whether there are, in fact, increased cancer risks at doses in the range of, say, 5 to 20 mGy.

There are, of course, several key assumptions that underlie the LNT approach. Three of the most commonly discussed issues are the possible confounding effects of intercellular communication; the potential differential effects of immune surveillance when the number of premalignant cells is low; and the possibility of different radiobiological processes dominating at very low doses, compared to low doses. As discussed here, there is currently no strong evidence that any of these three phenomena significantly affect the LNT argument, though this may be in large part because essentially no decisive experiments have been reported — in turn a consequence of the difficulties of undertaking quantitative radiobiological studies in the mGy dose range.

Finally, at least two different experimental approaches are possible to assess the validity of the LNT approach. First, the LNT argument makes clear predictions that the same types of biological damage and damage responses should be dominant at doses ≤1 mGy, compared to doses in the range of 5 to 20 mGy. This is clearly testable, though the technical difficulties involved are formidable. It is emphasized that comparisons of mechanisms at mGy vs. Gy doses will not be informative in this context — the mechanisms would be expected to be very different (Fig. 1).

Second, the LNT argument relies on an assumption about single cells acting autonomously during carcinogenesis, which is clearly not correct. However, we do not currently know if deviations from the predictions of LNT that are associated with intercellular communication will be large or small, nor even whether they will increase or decrease low-dose cancer risk estimates. This is likely to be a central theme of future research in the field (Trosko 2005; Barcellos-Hoff 2008).

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