

Invited Perspective

on

Subjecting Radiological Imaging to the Linear No-Threshold Hypothesis:

A Non Sequitur of Non-Trivial Proportion

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Estimation of the risk of radiation-induction of cancer in the low (eg diagnostic)-dose range remains one of the most contentious issues in modern science and has engendered often strident debate (1, 2), particularly with respect to the linear no-threshold (or LNT) dose-response model. As John Boice, President of the National Council on Radiation Protection and Measurement (NCRP), has aptly stated (3), “LNT is not TNT, but differences in opinions sometimes appear explosive!” A critical assessment of the LNT model and a consideration of alternative dose-response models are presented in the article by Siegel, Pennington, and Sacks. The article highlights the uncertainty associated with the LNT model and LNT model-based risk factors.

In this Invited Perspective, some background is provided for the controversy regarding the validity of the LNT model and specifically its application in medicine. Fundamentally, the LNT model implies a uniform cancer risk per unit dose from higher to lower doses, meaning that, for example, a radiation dose of 10 mSv is associated with one one-hundredth of the risk of a radiation dose of 1,000 mSv. Since the LNT model assumes that there is no threshold dose for radiation-induced cancer, even a radiation dose as low as 0.1 mSv is associated with a non-zero excess risk (ie 1/100 of the risk from 10 mSv).

The excess number of fatal cancers in an irradiated population using the LNT model is calculated in a deceptively simply manner: as the number of persons exposed • effective dose (rem or mSv) per person • excess relative risk (/rem or /mSv). A widely cited excess relative risk (ERR) value is that recommended by the NCRP Report No 115 (4), 5×10^{-5} per person per mSv (or 5×10^{-4} per person per rem). Thus, if a population of a million people each received an effective dose of 10 mSv (1 rem), the expected number of excess fatal cancers observed in this population over the balance of the lifetimes of the irradiated individuals would be 1×10^6 persons

• $10 \text{ mSv} \bullet 5 \times 10^{-5} \text{ person/mSv} = 500$. This compares to the spontaneous, or background, lifetime incidence of $\sim 300,000$ (or 30%) otherwise occurring in such a population; this corresponds to an increase in overall incidence of only $(500/300,000) \bullet 100\% = 0.17\%$.

Siegel et al provide a detailed discussion of why the assumptions of the LNT model are counterintuitive and difficult to reconcile with the biology of DNA repair and the well-established decrease of radiation toxicity by dose fractionation in clinical radiation oncology. Nevertheless, the LNT model is currently recommended by advisory bodies such as the NCRP (5, 6), the International Council on Radiation Protection (ICRP) (7), and the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) (8) and adopted by regulatory agencies such as the Nuclear Regulatory Commission (NRC) (9).

The main reasons for the acceptance of the LNT model are that it is simple, fits data from several observational studies on radiation exposure and the development of cancer fairly well (6) and no alternative model has convincingly been shown to provide a better fit to these data. Importantly, however, “consistency” of a model’s mathematical fit to available dose-response data should *not* be construed as validation of such a model. Among many others, Siegel et al argue that the data and associated analyses supporting the LNT model are actually refuted by some epidemiologic and experimental studies and that this model over-states the risk of radiation carcinogenesis at doses of the order of 100 mSv (10 rem) and less and does not account for creditable evidence for a threshold for cancer induction, that is, a non-zero radiation dose below which there is no increased risk of cancer (2, 10, 11). The validity, applicability, and utility of the LNT model and of alternative models thus remain highly controversial (1, 2).

The specific challenge in assessing the risk of cancer induction among patients undergoing diagnostic imaging studies is that there are actually very few reliable data in humans quantifying an increased cancer incidence, if any, following diagnostic radiation doses (ie less than ~100 mSv (10 rem)). The risk for low radiation doses are therefore extrapolated by some from the apparently linear relationship between cancer incidence and radiation exposure observed at markedly higher doses. The confidence intervals for these extrapolated risks are typically broad, however, and critically depend on the model used to extrapolate the data (as discussed by Siegel et al.) Because of these uncertainties, typical radiation doses from medical imaging have therefore been interpreted as “completely safe” by some or “potentially dangerous” by others. No prospective epidemiologic studies with appropriate non-irradiated controls have definitively demonstrated either the adverse or hormetic (ie beneficial) effects of radiation doses less than 100 mSv (10 rem) in man, and current estimates of the risks of low-dose radiation indicate that very large-scale epidemiological studies with long-term follow-up would be needed to actually quantify any such risk or benefit; such studies may be logistically and financially prohibitive.

The most creditable dose-response data for radiation carcinogenesis in man mainly involve doses one to two orders of magnitude greater than those encountered in diagnostic imaging studies - of the order of 1 Sv (100 rem) and greater - including, most notably, the A-bomb survivor follow-up data. Pierce and Preston (12), for example, published an analysis of the A-bomb Radiation Effects Research Foundation (RERF) data on cancer risks among survivors receiving doses less than 500 mSv (50 rem), with ~7,000 cancer cases among ~50,000 low-dose survivors. They concluded that cancer risks are not overestimated by linear risk estimates computed over the dose range 50-100 mSv, with a statistically significant non-zero risk in the

range 0-100 mSv (0-10 rem) and an upper confidence limit on any possible threshold of 60 mSv (6 rem).

A handful of high-profile studies have, however, reported cancer risks derived from relatively low-dose exposures. The United Kingdom CT study (13), a record-linkage study of leukemia and myelodysplastic syndrome (MDS) and of brain cancer incidence following CT scans of 178,000 pediatric patients (0-21 years of age), reported ERRs of 36 /Gy (0.36 /rad) for leukemia and MDS and of 23 /Gy (0.23 /rad) for brain cancer. Even allowing for the higher cancer risk associated with irradiation in childhood, these values are high when compared to the overall cancer ERR for the general population (0.05 /Gy) recommended by the NCRP (4), and critical evaluation of this study cited absence of the scan parameters and therefore organ doses for individual patients. Another potentially confounding factor in the results observed is reverse causation (14): because the children in this study were referred for imaging for some medical problem, they may have been at a naturally increased risk for cancer due to their underlying medical condition rather than as a result of any diagnostic irradiation.

In the International Nuclear Workers Study (INWORKS) (15), a cohort study of over 300,000 workers (over 8.2 million person-years) in the nuclear industry with detailed external dose data (mean dose: 21 mGy (2.1 rad)), the ERR for all cancers was 0.51 /Gy (95% CI: 0.23-0.82 /Gy) (0.0051 /rad (95% CI: 0.0023-0.0082 /rad)). In addition to possible uncertainty in personnel dose estimates, smoking and occupational asbestos exposure were identified as potential confounding factors; however, exclusion of deaths from lung cancer and pleural cancer did not affect the association of cancer risk and occupational radiation exposure. Although the ERR estimate for solid cancers in the INWORKS, 0.47 /Gy (0.0047 /rad), was higher than that

for adults in the study of A-bomb survivors by Preston et al (16), 0.32 /Gy (0.0032 /rad), these estimates were judged to be statistically compatible.

Importantly, even if one concedes the validity of the LNT model, it cannot be applied reliably to individuals but only to large populations (7), that is, populations sufficiently large that differences among individuals in radiation sensitivity related to gender, age, diet and other lifestyle factors, and intrinsic biology are effectively averaged out. Clinical care is clearly the least forgiving of the large uncertainty in risk factors, regardless of the model from which they were derived, and application with certitude of population-derived risk factors to individual patients or even defined patient populations is simply not justified. While the debate over LNT will not be resolved anytime soon, and as reinforced by the article by Siegel et al, one point should be abundantly clear: the scale of the associated uncertainties is such that it is not appropriate to utilize such risk factors for clinical decision-making and the management of individual patients.

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