LNT RIP: It is time to bury the linear no threshold hypothesis

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The potential health effects of low doses of ionizing radiation (IR) have long been a concern as well as a source of controversy. Many have felt that the scientific questions were definitively answered by the Life Span Study (LSS) and that the effects of radiation can be modeled with a linear no threshold (LNT) model. We must remember that science—true science—is never static. Science is never settled; it is an iterative process. When a theory fails to explain new data, it must be adapted or rejected in a never-ending process of evolution. Newer insights into the cellular defenses with respect to IR have come from recent clinical and molecular studies and were recently summarized elegantly in these pages.[1] We believe it is important to extend these observations since, as we will demonstrate, the existence of effective cellular defense mechanisms against IR make the LNT hypothesis untenable.

The appeal of LNT is its simplicity, both conceptually and predictively. The idea is that a single photon can create a double-stranded DNA break (DSB) that leads to a permanent mutation and a consequent malignancy. Thus, the greater the number of photons, the greater the number of DSBs, and the risk of cancer increases in a linear fashion. Likewise, the predictive effects are quite simple with this model. It predicts the risk of a single 100 mSv exposure to be precisely 10 times that of a single 10 mSv exposure, equal to 10 exposures of 10 mSv or 100 exposures of 1 mSv, and so on. However, there are many issues that need to be addressed.

DNA is a fragile molecule; it is subject to constant injury through multiple mechanisms. Life on this planet began in an environment hostile to DNA. It had to adapt first to radiation, both ionizing and ultraviolet as well as thermal and chemical insults. Some billion or so years later with the appearance of oxygen in significant quantities came the potential for damage from reactive oxygen species (ROS). Life adapted by developing a three-pronged response DNA damage: repair, apoptosis, and immune-mediated destruction of damaged cells. We will focus on the first of these.

The magnitude of ongoing DNA damage is staggering. As early as 1930, Müller and Mott-Smith concluded that most mutations in the genome occur due to causes other than radiation.[2] It has been estimated that there are approximately 8000 spontaneous DNA-damaging events per hour in each cell.[3] Clearly, life could not continue without effective repair mechanisms.

Most DNA damage produced by low energy transfer (LET) photons is not caused by direct damage of DNA but rather mediated through the generation of OH radicals through radiogenic hydrolysis and the production of other ROS.[3–5] This is supported by the effect the availability of oxygen has on the radiosensitivity of cells, a fact that has been recognized for decades. Anoxic cells are reported to be roughly three times more resistant to radiation than non-hypoxic cells.[6] If most of the damage was caused directly to DNA, the substrate for ROS generation would not be as important. It is estimated that, at most, 100 DNA alterations will occur per cGy of low LET radiation, an amount which is only 1-2% of spontaneous damage.[3] Thus, the damage produced by low doses of IR is manifested through a common pathway and, at lower doses, is only a fraction of the total number of insults to the genome.

The genetic damage caused by IR was originally studied by visual assessment of chromosomal damage. This is a painstaking process, and it is difficult to measure any effect at doses less than 0.5 Gray.[7] An enormous project sponsored by the IAEA to determine the effects of low-dose IR involved the analysis of more than 60,000 metaphases, which was standardized; the analysis was so laborious that the work had to be divided among 10 labs. At this scale, chromosomal damage to

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human lymphocytes from doses of IR ranging from 4 to 300 mGy could be evaluated.[8] No statistically significant increase in damage above controls could be identified below doses of 20-50 mGy. Interestingly, there was statistically significant decrease in chromosomal damage with a dose of 4 mGy.

Recently, more automatable techniques to track the induction of cellular DNA repair enzymes to IR have been introduced. A common technique uses immunofluorescence to identify the activation of the histone H2AX to γ-H2AX as part of a DNA repair-related complex, which has been shown to be a reliable marker for DSBs.[9] Using this technique, Vilenchik et al, estimated that it takes about 1.5 Gy of IR to equal the background rate of DSBs in a mammalian cell.[10] Neumaier et al, used immunofluorescence and time-lapse imaging to identify the spatial and temporal extent of p53-binding protein in radiation-induced foci (RIF) as DNA repair centers in human mammary epithelial cells exposed to IR.[11] Both the RIF induction rate and the duration of the foci increased as the radiation dose increased in a highly nonlinear fashion.

Separate studies by Lee and Nguyen from Joseph Wu's lab used similar techniques to evaluate the human cellular response to IR from clinically performed SPECT MPI and CTA studies.[12,13] Lee's study revealed that most patients undergoing SPECT MPI showed no overall increase in induction of repair enzymes compared to control. They speculated that the minority of patients who demonstrated an increase might represent a group at increased risk. However, if this represents a different response in this subgroup, it would require a counterintuitive explanation that there was a counterbalancing mechanism where exposure to radiation would cause a decrease in repair enzymes in the remaining patients.

On the other hand, Nguyen's study of patients undergoing CTA showed a vigorous response. Part of this difference is likely due to the higher radiation doses with CTA (29.8 mSv for CTA vs 10.7 mSv for SPECT) but part is also likely due to the dose-rate effect of where a CT scan is performed over several seconds vs two divided doses of radioisotopes for MPI that would have a weaker effect that is spread over dozens of hours. This difference in response strongly suggests that the amount of DNA damage produced by SPECT MPI is far enough below the background level of damage (and associated ongoing repair) so that the upregulation of repair enzymes is not necessary. Of note, Nguyen et al reported the patients undergoing CTA who received < 7.5 mSv (number was not given) showed no increased activity of repair enzymes. Other studies have shown DNA damage occurring after cardiac MRI without any exposure to IR.[14,15] This is an effect that is felt to be mediated through free radical formation.[16]

Further appreciation of both the existence and effectiveness of cellular DNA repair mechanisms can be appreciated by investigating disease states characterized by their absence. There are several congenital diseases where given repair pathways are defective or absent. Ataxia telangiectasia and its variants (such as Nijmegan Breakage Syndrome and Berlin Breakage Syndrome), Fanconi's Anemia, and Bloom's syndrome, among others, are characterized by increased risk of malignancies (a 100-fold increase in lymphoid tumors in Ataxia Telangiectasia[17]) and a heightened sensitivity to IR given as radiotherapy.[18,19] The effects of weakened repair systems prove two things. First, there is a substantial risk of malignancy resulting from unrepaired background DNA damage in these patients, which is not caused by IR. Second, healthy subjects must have very effective mechanisms for repairing DNA damage from IR. There is no other way to explain the increased toxicity of IR in these patients.

Initial DNA damage most likely does follow LNT but clearly the response, hence repair, does not. For the risk of cancer to follow LNT, the permanent, unchecked damage would have to exactly mirror the inverse of the nonlinear repair response to IR. It is extremely unlikely that the defenses would be designed to let malignancies ''trickle'' through at a steady linear rate. Also, to maintain the linearity of LNT would also require that the cellular defenses be unlimited. That is, there cannot be a point where the defenses are overwhelmed and further insult goes unrepaired; this is clearly impossible. It is here where LNT irrefutably breaks down since the model requires the risk of a single, overwhelming exposure to have the same risk as 100 exposures, each 1/100th of the exposure distributed over an indefinite period.

Since the radiation suffered by the atomic bomb survivors was an intense exposure for only a brief amount of time, the data from the LSS can only be considered relevant if one assumes the veracity of LNT. In this way, the logic behind the argument becomes circular and therefore questionable. Furthermore, the validity of the conclusion that the LSS data support LNT has been credibly challenged by multiple investigators.[4,20–22] Also, the conditions in Japan in 1945 were dire. Due to the US Naval blockade and diversion of the available foodstuffs by the Imperial Government to the military and workers in essential industries, starvation was widespread. The effects this had on general health and infectious diseases has been documented.[23] To our knowledge, the effects this would have on cellular DNA defense mechanisms is not known but should be considered before generalizing the LSS to other populations.

Finally, it should be noted that most of the doses evaluated for induction of RIFs were in the range of cGy to Gy—a much higher amount than that received during diagnostic testing. Similarly, most of the experience in radiosensitivity in patients with the absence of repair enzymes has been with therapeutic, not diagnostic radiation.

In conclusion, we have seen that there is a high baseline level of ongoing DNA damage manifested mainly through ROS which are constantly generated from multiple sources independent of IR. The damage to DNA from low LET radiation is effected mainly through ROS. As life has evolved, multiple, very effective mechanisms for DNA repair have emerged. The effectiveness of these mechanisms is highlighted by the marked increase in cancer and radiosensitivity in patients who lack them. The understanding that these defense mechanisms, like any defense mechanism can be overwhelmed alone invalidates LNT since it requires that a single, overwhelming dose of radiation has the same risk as the same total dose administered in fractions over a prolonged period. Many of these defense mechanisms can now be tracked in vivo and have been shown to be highly nonlinear. These techniques now allow the assessment of patient response to routine clinical tests both those that employ IR (nuclear and CT) and even one that doesn't (MRI). The response to nuclear was not significantly different from baseline, suggesting that in most patients, background repair activity is sufficient to deal with the insult.

When science becomes ''settled,'' it ceases to be science and becomes dogma. When a hypothesis is inconsistent with new data, it must be modified or rejected. LNT, though simple to apply, clearly cannot stand up to scientific or even logical scrutiny.

LNT is no longer tenable. Using it to predict the health risks of IR in low doses is indefensible and should be abandoned.

Disclosure

The authors have nothing to disclose.

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