Replacing LNT: The Integrated LNT-Hormesis Model

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Abstract
Many scientists and regulators utilize the linear no-threshold (LNT) relationship to estimate the likelihood of carcinogenesis. The LNT model is incorrect and was adopted based upon false pretenses. The use of the model has been corrupted by many to claim that even the smallest ionizing radiation dose may initiate carcinogenesis. This claim has resulted in societal harm.

Keywords
cancer, dose response, hormesis, radiation, risk assessment, LNT

Introduction
The linear no-threshold (LNT) model is based upon the proportionality of radiation dose and cancer risk. This model is supported by flawed scientific and epidemiological data. For example, the scientific data, based upon γH2AX foci as a marker for DNA double-strand breakage, demonstrate linearity between dose and DNA damage from 1 mGy to 100 Gy. The hypotheses follow: (1) Each double-strand break has an equal probability at inducing transformation irrespective of the number of double-strand breaks simultaneously within the cell and (2) each transformed cell has the same probability of developing into a cancer irrespective of the tissue environment and/or health of the organism. However, γH2AX is a nonspecific marker and may result from single-strand breaks.

From the scientific data, one must conclude that dose and carcinogenic risk is nonlinear if one views the organism in a hierarchical approach. Organisms are made up of systems, systems are made up of tissues, tissues are made up of cells, and cells are made up of their constituents. At each level mechanisms exist to prevent and/or mitigate damage.

Cellular Defenses
Three types of defenses that immediately combat DNA damage have been identified. (1) Defenses against reactive oxygen species (ROS)—Oxygen metabolism, infection, physical exercise, ionizing radiation, ultraviolet light, chemicals, and others result in ROS. Potential damage is mitigated by scavengers and antioxidant molecules within cells. (2) DNA repair—There are cellular sensor molecules that detect DNA damage which eventually result in cell cycle arrest, DNA repair, and upregulation of defense mechanisms. DNA repair is dependent upon the dose and dose rate. (3) Elimination of damaged cells—Cells are eliminated through apoptotic, mitotic, and senescent cell death.

Adaptive responses. When cells undergo radiogenic or nonradiogenic genotoxic damage, an increase in protective mechanisms are observed in the cells and nearby cells (bystander effects). These defenses include ROS scavengers, damaged cell removal, and DNA repair. The upregulation of these factors can last for hours to months.

Tissue Defenses
The surrounding environment protects and controls cellular proliferation when functional. If the microenvironment is impaired through physical, chemical agents, or disease, the cells are more likely to undergo DNA alterations with subsequent neoplastic transformation. Tissue disorganization also facilitates escape of preneoplastic subclones from microenvironmental barriers. For example, fibrosis increases the risk for cancer of the lung, liver, and skin. Immune mechanisms are...
also potent regulators in the prevention of cancer. Currently, there are many therapies that modulate the immune system for the treatment of cancer.

Although an imperfect system, life has evolved to protect itself from genotoxic damage. When cellular and/or tissue repair mechanisms are damaged, the risk of cancer increases. Organisms are constantly undergoing genotoxic stresses. Small insults are fairly well addressed and may be beneficial; however, with large insults, the cell, the tissue, the system, and the body are unable to compensate appropriately and the risk of cancer exceeds a threshold above which cancer risk increases.

Too often, epidemiological evidence is used inappropriately to support the LNT model. For example, the atomic bomb data have been frequently used to demonstrate the concept of the LNT model. However, the atomic bomb survivors were exposed to other carcinogenic agents including trauma from nonradioactive insults such as burns, nonradioactive toxins from the explosion, and subsequent fires, which contaminated the food, water, and air. Environmental stressors unrelated to ionizing radiation increase the risk for carcinogenesis or other adverse health effects. For example, the World Trade Center Disaster on September 11, 2001, released a number of toxins into the environment possibly resulting in an increased risk of certain cancers. Also, the incidence of all cancers was higher among Israeli Jews who were exposed to the extreme stressors of the Holocaust than among those who were not. These nonradioactive stressors should be considered by those claiming that low doses of radiation are carcinogenic. Furthermore, the stigma associated with the radioactive exposure may have resulted in many atomic bomb survivors who were exposed to higher doses to claim that they were further away from the explosion, resulting in incorrect dose estimates. To further complicate the matter, the estimated doses do not include that from residual radiation thereby underestimating those (including the “not in the city” control population) who were thought to have received, for example, less than 100 mGy. Furthermore, the atomic bomb survivors and the “not in the city” controls have a longer life span and reduced cancer mortality relative to unirradiated Japanese. There are many good reviews that provide critiques of the epidemiological studies.

Hormesis

Compelling scientific and epidemiological data for hormesis exist. Small insults, whether from radiation or other genotoxic stressors, result in upregulation of protective mechanism at the cell and tissue level. These defenses more than compensate for any potential (or real) damage that the organism incurred from the original insult; thereby decreasing the risk of carcinogenesis from future genotoxic insults.

Conclusion

Data for ionizing radiation induced carcinogenesis support the existence of a hormetic response at low doses with a threshold. The dose from current diagnostic studies (eg, 10 mGy) is well below the threshold. Those who estimate radiation induced cancer risks should consider confounding effects of coexisting nonradiation carcinogenic risks. The fear of carcinogenesis that has been propagated due to those grossly overestimating the cancer risks from low doses of ionizing radiation is unethical and has resulted in medical, economic, and other societal harm. The LNT model should not be applied for cancer risks in the low-dose range. The regulatory bodies including the Nuclear Regulatory Commission should change from an LNT-model based risk assessment to the integrated LNT-Hormesis model as Calabrese describes.
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