

# CT Scans May Reduce Rather than Increase the Risk of Cancer

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## ABSTRACT

Extrapolating from data on atomic bomb survivors on the basis of the linear no-threshold (LNT) model as applied to radiation exposure, a recent paper concludes that within a few decades 1.5–2 percent of all cancers in the U.S. population could be caused by current rates of use of computed tomography (CT). This paper ignores the other war-related exposures of the Japanese population, which would be expected to shift the dose-response relationship for cancer induction to the left. Moreover, the LNT model is shown to fail in four tests involving low-dose radiation exposures. Considering the available information, we conclude that CT scans may reduce rather than increase lifetime cancer risk.

## Introduction

In a Nov 29, 2007, article in the *New England Journal of Medicine*<sup>1</sup> Brenner and Hall argue that the potential carcinogenic effects from using computed tomography (CT) may be underestimated and that one-third of all CT scans performed in the United States may not be medically necessary. They estimated that more than 62 million CT scans per year are currently done in the United States as compared to 3 million in 1980.<sup>1</sup> With such an increased rate Brenner and Hall speculate, based on extrapolations from cancer data derived from survivors of the atomic bombings in Hiroshima and Nagasaki, that in a few decades about 1.5–2 percent of all cancers in the United States may be the result of current CT scan usage. Their calculation uses the linear-no-threshold (LNT) method of adding up small, hypothetical individual risks (none of which may be real) over a large irradiated population.

Such speculation aggravates the widespread worry about undergoing routine CT scans, which is unfortunate given that many lives have been saved because of medical problems revealed by these scans.

Brenner and Hall<sup>1</sup> correctly point out that x-ray doses from CT scans are much higher than those from dental and chest radiography. In discussing the biologic effects of low doses of ionizing radiation, the authors, while mentioning the potential cancer-inducing implications of DNA double-strand breaks and their misrepair, do not consider the adaptive response of humans to ionizing radiation. Low doses and low dose-rates of some forms of radiation (e.g., x-rays and gamma rays) stimulate the body's natural

defenses. This effect has been called radiation activated natural protection (ANP).<sup>2</sup> Radiation ANP includes selective removal of aberrant cells (e.g., precancerous cells) via apoptosis and stimulated immunity against cancer cells. Thus, radiation ANP can prevent some cancers (sporadic and hereditary) that would otherwise occur in the absence of radiation exposure.<sup>3</sup>

Recent papers by Bauer<sup>4</sup> and by Portess et al.<sup>5</sup> describe how low-dose radiation activates the selective removal of precancerous cells via apoptosis. The selective removal is mediated via intercellular signaling involving reactive oxygen and nitrogen species and specific cytokines (e.g., transforming growth factor  $\beta$ ).

Numerous papers have been published related to low-dose radiation stimulating immunity against cancer cells.<sup>6-8</sup> Because of radiation ANP, low doses and low dose-rates of x-rays and gamma rays can actually reduce rather than increase cancer occurrences.<sup>3</sup> Conversely, high radiation doses suppress immunity and inhibit selective removal of aberrant cells via apoptosis, leading to an increase in the number of cancer cases to a rate greater than the spontaneous level.<sup>3,6-8</sup>

## Extrapolating Observed Radiation Effects from High to Low Doses

In order to obtain lifetime cancer risk predictions from small radiation doses such as those received from CT scans, many researchers extrapolate the risk from observed effects after moderate and high radiation doses using the LNT model. With this model, any amount of radiation is considered to cause some cancer fatalities in any large irradiated population. Doubling the radiation dose doubles the number of cancer fatalities.

When the lifetime attributable risk estimates of radiation-induced cancer after high doses fall around an LNT function with slope  $\alpha$ , a hypothetical risk  $R$  at a low dose  $D$  can be calculated with the LNT model as:

$$R = \alpha D.$$

Only the radiation-associated risk (i.e., attributable risk) is counted in this equation, which can be applied to both cancer incidence and cancer mortality. To obtain the total risk, the spontaneous risk  $R_0$  must also be accounted for. Here, the focus is on attributable risk as defined by the equation above, which differs from attributable risk as used in addressing multiple risk factors. Brenner and Hall<sup>1</sup> evaluated what corresponds to  $R$  by using age-specific values for cancer mortality based on A-bomb survivor data.

To assess risk, Brenner and Hall used special dose units (valid only for LNT-type responses and based on dose weighting for different radiation types) that supposedly allow for converting the

effects of mixed neutron and gamma irradiation (as occurred for the A-bomb survivors) to equivalent harm from x-rays from CT scans. One such unit is the millisievert (mSv).<sup>1</sup> For radiation such as x-rays and gamma rays, a mSv is the same as a milligray (mGy). Further, 1 mSv received from combined exposure to neutrons and gamma rays can be hypothetically equated to 1 mSv of x-ray exposure from CT scans.

Brenner and Hall first extrapolated from A-bomb survivor data based on dose in mSv for combined neutron and gamma irradiation. The dose in mSv was then equated to the dose in mGy of CT scan x-rays. This is how they arrived at their Figure 4, which presents hypothetical lifetime attributable risk of death from lung or colon cancer per million patients exposed to 10 mGy of x-rays from a CT scan. Hypothetical results are presented for exposure at different ages from birth to 80 years.

No adjustments were made by Brenner and Hall<sup>1</sup> to account for the influences of combined injuries suffered by survivors in Hiroshima and Nagasaki or for differing genetic susceptibilities to radiation in the Japanese and U.S. populations. When an atomic bomb is detonated on a city, there are blast-propelled projectiles and thermal waves in addition to radiation. The mode of damage is one of combined injuries (radiation + toxins + wounds + burns + infection) to those people in demolished cities (a highly stressful and unsanitary environment). Such combined injuries are known to shift the radiation effect dose-response curve to the left, with higher risks coming from combined injuries than from radiation exposure alone.<sup>9-11</sup> Further, some genetic risk factors, such as defects in DNA repair mechanisms, are known to influence susceptibility to cancer.<sup>12-16</sup> The LNT model does not address combined injuries under stressful environments or population variability in genetic risk factors. These issues were also not addressed by Brenner and Hall<sup>1</sup> in their extrapolation of cancer risk from A-bomb victims in Japan (moderate- and high-dose data) to CT scan exposures (low doses) in clinical settings in the United States.

Brenner and Hall<sup>1</sup> recognized that radiation dose distribution over the body is quite different for A-bomb survivors, who received total-body irradiation, than for persons receiving CT scans. They simply assert, without evidence, that the cancer risk for one organ is not substantially influenced by the radiation exposure to other organs. Significant damage to the immune system is known to increase the risk of cancer.<sup>7</sup> Wounds and thermal (or radiation) burns would be expected to adversely affect the immune system.

### **Tests of the LNT Model**

Four plausible tests of the LNT model are summarized below. They are based on recent studies of brief exposures to low doses ( $\leq 100$  mGy) of x-rays or gamma rays, or of protracted exposures to similar or higher doses of gamma rays over extended periods at low rates. Chemical carcinogen exposure in combination with low-rate gamma-ray exposure is also considered. Endpoints are neoplastic transformations and cancer. For the brief exposures, the dose can be presumed to be essentially instantaneous. For the protracted

exposures, a small dose was added each hour or each day. With the LNT model any small dose increases the hypothetical risk of cancer. Each hourly or daily additional dose increases the hypothetical risk so that the risk of cancer is postulated to continue to increase under conditions of chronic, low-rate exposure.

### **Neoplastic Transformation and Low Doses**

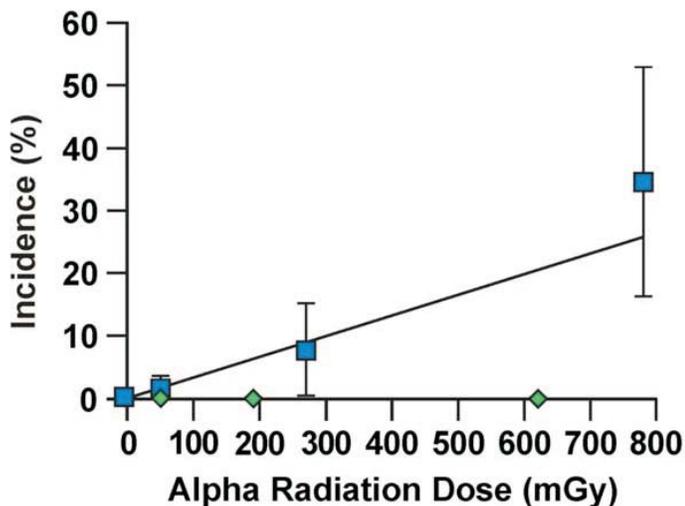
According to the LNT model, a low dose of x-rays or gamma rays is predicted to increase the risk of neoplastic transformation. The predicted increase was not supported by studies conducted by Redpath et al.<sup>17</sup> and by Azzam et al.,<sup>18</sup> who showed that for doses  $\leq 100$  mGy (100 mGy being the equivalent of several CT scans), the frequency of neoplastic transformation was reduced below the spontaneous level, presumably because of gamma-ray ANP with selective removal of aberrant cells via apoptosis.<sup>3,5</sup> Recall that high doses and high dose rates are considered to inhibit ANP.<sup>3,7</sup> Redpath et al.,<sup>17</sup> when expressing their transformation frequency data as relative risk (RR), found the dose-response curves for neoplastic transformation were similar to and overlapped those for breast cancer and leukemia induction in humans, supporting the occurrence of radiation ANP against human cancers.

### **Neoplastic Transformation and Protracted Exposure**

According to the LNT model, each small increment in radiation dose increases the risk of neoplastic transformation under circumstances of protracted exposure at a low rate. The predicted increase was, however, not supported by studies conducted by Elmore et al.<sup>19</sup> Low-rate exposure for doses up to at least 1,000 mGy (equivalent to multiple CT scans separated in time) suppresses rather than increases neoplastic transformation risk. The indicated suppression and extension of the protective dose range is considered to relate to the repeated activation of transient gamma-ray ANP during protracted exposure.<sup>3</sup> Similar gamma-ray ANP has also been reported against lymphomas in cancer-prone mice.<sup>20</sup> Low, single gamma doses of 10 or 100 mGy administered at a low rate extended the lifespan of the cancer-prone mice and reduced the cancer incidence at given follow-up times.<sup>20</sup> Similar studies with repeated exposures to low-dose x-rays, now being carried out by Boreham, will have implications for assessing risk from multiple CT scans. Because the biological processes that contribute to radiation ANP are transient, appropriate time intervals between exposures should also be determined.

### **Combined Exposure of Lung to Low-dose-rate Alpha and Gamma Radiation**

According to the LNT model, adding a low-rate, low-dose gamma-ray exposure on top of a low-rate alpha-radiation exposure increases the risk of lung cancer. The predicted increase was not supported by the study by Sanders.<sup>21</sup> Adding a very small (1-2 mGy) gamma-ray dose to the protracted alpha radiation dose prevented alpha-radiation-induced lung cancers in rats that inhaled the alpha-emitting radionuclide plutonium-239 in an insoluble dioxide form,



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**Figure 1.** Lung Cancer Incidence in Wistar Rats: after inhalation exposure to the alpha radiation source  $^{239}\text{PuO}_2$  (squares) or  $^{239}\text{PuO}_2$  labeled with a ytterbium-169 gamma-emitting tag (diamonds). The added gamma exposure (1-2 mGy) prevented alpha-radiation-induced lung cancers, presumably via gamma-ray ANP. None of the 1877 animals receiving gamma rays (diamonds) in addition to their alpha radiation exposure developed lung cancer for the indicated dose range. The data are from Sanders,<sup>21</sup> and for the indicated dose range a total of 3793 animals were used. Error bars are 95% CI, assuming a binomial distribution of cancer cases.

$^{239}\text{PuO}_2$  (Figure 1). The plutonium aerosols were labeled with a gamma-emitting ytterbium-169 tag. Complete cancer prevention occurred even for alpha radiation doses up to about 600 mGy. The prevention is thought to relate to gamma-ray ANP, which includes selective apoptosis of precancerous cells<sup>3-5</sup> and enhanced immunity to cancer cells.<sup>6-8</sup> Gamma-ray ANP against  $^{239}\text{Pu}$  alpha-radiation-induced lung cancer has also been reported for humans.<sup>3</sup> An average of 86 percent of lung cancer cases were estimated to be avoided by chronic-gamma-irradiation ANP.<sup>3</sup>

### **Combined Exposure to Chemical Carcinogens and Low-dose-rate Gamma Rays**

According to the LNT model, adding low-rate gamma rays to a chemical carcinogen exposure increases the cancer risk as the radiation dose increases. The predicted increase was not supported in the study by Sakai et al.<sup>22</sup> The protracted low-dose-rate gamma-ray exposure reduced rather than increased the risk of skin cancers from methylcholanthrene injected into mice.<sup>22</sup>

In many additional published tests of the LNT model, reduced rather than increased harm was found to be associated with doses similar to those from CT scans.<sup>3,23</sup>

### **Failure to Report Radiation-ANP-related Suppression of Cancer**

Most epidemiologic studies of radiation-induced cancer do not report radiation-related ANP. The designs of epidemiologic studies of radiation-induced cancer are largely influenced by the

presumption that the LNT model is valid. Some approaches used in such epidemiologic studies that make it difficult to demonstrate or recognize radiation adaptive response and thresholds for excess cancers are as follows:

1. Dose lagging (ignoring some of the radiation dose), which shifts the dose-response curve to the left,<sup>24</sup> as was done in the analyses of Cardis and colleagues discussed by Brenner and Hall<sup>1</sup> as supporting evidence for increased cancer risk at low doses;

2. Averaging risk over wide dose intervals in cohort studies,<sup>24,25</sup> as was done for A-bomb survivor cancer data cited by Brenner and Hall<sup>1</sup> to infer increased risk for the entire weighted dose interval 10–150 mSv;

3. Averaging odds of cancer over very wide dose intervals before calculating the odds ratio in case-control studies;<sup>24</sup>

4. Including individuals who received low-dose radiation in the unexposed group in cohort and case-control studies;<sup>24</sup>

5. Employing linear extrapolation from high to low doses after dose lagging and risk or odds averaging over wide dose intervals;

6. Not adjusting for the impact of combined injuries and differences in genetic susceptibilities when using A-bomb survivor data to assess cancer risk for another population; and

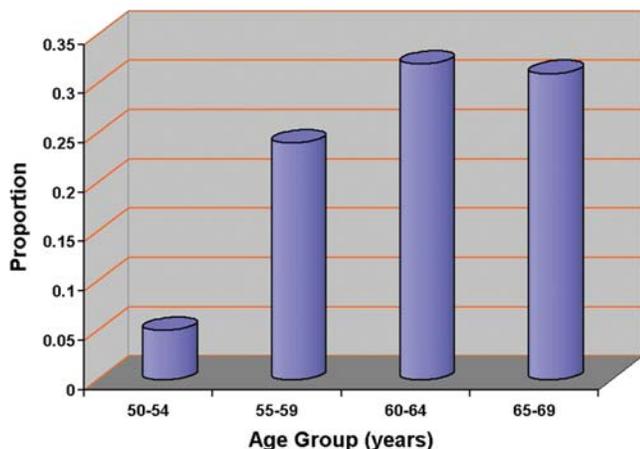
7. Ignoring radiation ANP (which is supported by low-dose data) for no apparent reasons other than it does not fit the LNT model.

Employing such approaches can cause one to conclude that an LNT-type dose-response curve is real when actually there is a reduced risk at low doses and dose rates and/or a threshold dose for excess risk.<sup>26,27</sup>

Dose lagging, a potential flaw in epidemiologic study design, is based on the assumption that some radiation dose is wasted. Assuming an LNT dose-response curve and using dose lagging is a contradiction because with the LNT model each unit-dose increment (e.g., each 1 mGy increment) is presumed equally effective in adding to the cancer risk. Actually, no wasting occurs when each fixed increment in dose (e.g., each 100 mGy increment) shortens the latency period for cancer occurrence as is implied by existing data for the cumulative incidence of cancer vs. time for different radiation dose groups.<sup>20</sup> Additionally, no dose is wasted when added dose increments contribute to suppression of neoplastic transformation and cancer as was demonstrated for extended low-rate protracted exposure.<sup>19, 22</sup> No evidence of dose wasting has been reported for inducing DNA double-strand breaks, mutations, or neoplastic transformations. Discarding radiation dose under the presumption of dose wasting could mistakenly support an LNT-type dose response for cancer induction with a corresponding slope parameter ( $\alpha$  in the equation above).

### **Influence of Age at Exposure**

Brenner and Hall<sup>1</sup> point out that children are at higher risk than are adults for cancer induction by radiation. Based on the published data of Nystöm et al.<sup>28</sup> from Swedish randomized controlled trials of breast cancer mortality after multiple mammography-related x-



**Figure 2.** Radiation ANP and Age. Bars show upper-bound estimates of the proportion of breast cancer cases prevented by radiation ANP as a function of age at exposure to diagnostic x-rays (multiple mammograms), based on breast cancer mortality data of Nyström et al.<sup>26</sup>

rays, the level of x-ray ANP appears to be age dependent (Figure 2). Figure 2 presents upper-bound estimates of the proportions of breast cancer cases among those that would occur normally that are calculated *not* to occur as a result of radiation ANP. With such age dependencies, children may benefit much less from low-dose x-ray ANP than adults. However, radiation ANP benefits are known to vary for different body organs; thus, age dependencies for radiation ANP may vary with cancer sites.<sup>20</sup> New adaptive-response research is needed to address such issues.

## Conclusions

There is no credible evidence to support the contention that current routine usage of CT scans in clinical settings in the United States will cause future cancers. Rather, the available data indicate that occasional exposure to diagnostic x-rays could possibly reduce the risk of future cancers among irradiated adults. The impact of CT scans on future cancers among persons irradiated as children is less clear. However, LNT-model-based risk estimates derived for children by extrapolating from A-bomb survivors cannot be considered valid, especially when no adjustment is made to remove the influence of combined injuries or to account for differing genetic susceptibilities of Japanese and U.S. populations, or when radiation adaptive response is not addressed.

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**Potential Conflict of Interest:** Authors report no conflict of interest related to the contents of this paper.

**Acknowledgments:** The preparation of this commentary was supported by Lovelace Respiratory Research Institute. We are grateful to Dr. J.L. Redpath for reviewing the initial version of this paper, to V. Fisher and J. Orient for editorial assistance, and to journal reviewers for their comments.

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