HEALTH EFFECTS OF LOW-DOSE RADIATION: MOLECULAR, CELLULAR, AND BIOSYSTEM RESPONSE

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Abstract **- Since the fifties, the prime concern of radiation protection has been protecting DNA from damage. UNSCEAR initiated a focus on *biosystem response* to damage with its 1994 report, "Adaptive Responses to Radiation of Cells and Organisms." The DNA damage-control biosystem is physiologically operative on both metabolic and radiation induced damage, both effected predominantly by free radicals. These adaptive responses are suppressed by high-dose and stimulated by low dose radiation. Increased biosystem efficiency reduces the number of mutations that accumulate during a lifetime and decrease DNA damage-control with resultant aging and malignancy. Several statistically significant epidemiologic studies have shown risk decrements of cancer mortality and mortality from all causes in populations exposed to low-dose radiation. Further biologic and epidemiologic research is needed to establish a valid threshold below which risk decrements occur.**

For more than 40 years radiation protection has been primarily concerned with protecting DNA against radiation damage. This predominant concern was the logical consequence of new data in the fifties on the molecular structure of DNA and its damage in linear proportion to radiation dose, and the newly observed roughly linear increase of leukemia and cancer in atomic bomb survivors in proportion to high-doses of radiation. In 1994, after two decades of epidemiologic and biologic research at molecular, microdosimetric, cellular, organ, and intact organism levels, UNSCEAR focused upon *biosystem response* to damage and in 1994 published its watershed report, "Adaptive Responses to Radiation in Cells and Organisms." [1]

Over eons of time, as multicellular animals developed and metabolized oxygen, a complex DNA damage-control biosystem evolved (Fig. 1) [2]. In this attempt to place metabolic DNA damage into perspective, estimates are based on the literature. Human metabolism produces about 10^6 metabolic DNA alterations per cell per day from thermal instability, DNA replication, and, predominantly, from free radicals that are derived from 2-3 % of all metabolized oxygen. Corresponding cellular and DNA damage is largely prevented by antioxidants that scavenge approximately 99% of these free radicals. The resultant ~10^6 DNA alterations/cell/d are then efficiently repaired enzymatically so that only ~1 in ten thousand is mis-or unrepaired. These are defined as mutations. Most of these remaining ~10^2 mutations/cell/d are eventually removed by apoptosis, induced differentiation, immune response, and tissue necrosis. Relatively few persist, ~1/cell/d, accumulating during a lifetime to decrease DNA damage-control with resultant aging and malignant growth, still removable by the immune system [2]. This remarkably efficient biosystem prevents precocious aging and malignancy unless impaired by genetic defects, or damaged by high doses of radiation or other toxic agents.

How does background radiation add to this metabolic accumulation of mutations? A much larger fraction of double strand breaks within 5 base positions occurs in DNA alterations produced by radiation than in those produced by metabolism ($2x10^{-2}$ vs $2.5x10^{-5}$). The mis-unrepaired fraction of these double strand breaks is also much larger than that of other metabolic DNA alterations (~10^{-1} vs ~10^{-4}). Nevertheless, the number of metabolic DNA alterations (~10^6/cell/d) is so much greater than the number of alterations from low LET background of 100 mr/y ($5x10^{-4}$/cell/d), that just ~10^{-5} radiation mutations/cell/d are added to ~10^2 metabolic mutations/cell/d [2]. These relatively few radiation induced mutations also are almost all removed by the DNA damage-control biosystem (Fig.1).

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The efficiency of this biosystem is increased by the adaptive responses to low-dose ionizing radiation. This is well documented in UNSCEAR 1994:

> "There is substantial evidence that the number of radiation-induced chromosomal aberrations and mutations can be reduced by a small prior conditioning dose in proliferating mammalian cells *in vitro* and *in vivo*."
>
> "There is increasing evidence that cellular repair mechanisms are stimulated after radiation-induced damage... Whatever the mechanisms, they seem able to act not only on the lesions induced by ionizing radiation but also on at least a portion of the lesions induced by some other toxic agents."
>
> "As to the biological plausibility of a radiation-induced adaptive response, it is recognized that the effectiveness of DNA repair in mammalian cells is not absolute... An important question, therefore, is to judge the balance between stimulated cellular repair and residual damage."

This statement applies not only to the mutations produced by radiation and other toxic agents, but also to the unmentioned *enormous number of daily metabolic mutations. The operative effect of reducing metabolic mutations by the adaptive response of the DNA damage-control biosystem to low-dose radiation is the critical factor*, not the insignificant number of mutations produced by low-dose radiation. This factor must be considered, "to judge the balance between stimulated cellular repair and residual damage."

Assuming a 10% increased efficiency of biosystem control in response to an increase of annual background radiation from 1mGy/y, to 1cG/y, radiation mutations would indeed increase from $1/10^5$cells/d to $9/10^5$cells/d but *metabolic* mutations would *decrease* from $\sim 10^7/10^5$cells/d to $\sim 9x10^6/10^5$cells/d. "The balance between stimulated cellular repair and residual damage" is a *decrease* of total mutations from $\sim 10^7/10^5$cells/d to $\sim 9.00009x10^6/10^5$cells/d, a net reduction of $\sim 10^6$ mutations/10^5cells/d, every day.

UNSCEAR did not consider that the non-linear increase of radiation mutations is negligible compared to the operative effect of the adaptive response to low-dose radiation upon the very high background of metabolic mutations. *The biological effect of radiation is not determined by the number of DNA mutations it creates, but by its effect on the body's protective processes.* At high levels, radiation suppresses them; at low levels, it stimulates the DNA damage-control biosystem.

These biologic findings predict that exposure to low-dose radiation would decrease mortality from aging and malignancy, and these predictions are confirmed by many epidemiologic studies. Decreased mortality and decreased cancer mortality have been observed in populations exposed to high natural background radiation in the U.S., China, Japan, India, Austria, and the U.K., and with *high statistical significance* in the following studies:

- U.S. Nuclear Shipyard Worker Study (1991). Mortality of exposed workers is decreased 24% below unexposed workers (Fig. 2) [1].
- Atom Bomb Survivor Mortality (1993). Mortality is decreased in the exposed survivors [3].
- Irradiated Eastern Urals Population (1994). Cancer mortality of the groups exposed to 120mSv and 500mSv is decreased by 39% and 28%, respectively [4].

- University of Pittsburgh Radon Study (1995). Lung cancer mortality decreases progressively as residential radon increases from 1 to 7pCi/L (Fig. 3) [5]. Similar findings in Japan and China.

- Canadian Fluoroscopy Breast Cancer Study (1989). Breast cancer mortality of the groups exposed to 150mSv and 250mSv is decreased by 34% and 16%, respectively (Fig. 4) [6].

Similar carefully controlled epidemiologic studies are needed for other malignancies and for mortality from all causes. In this way, a valid threshold can be established for the general public.

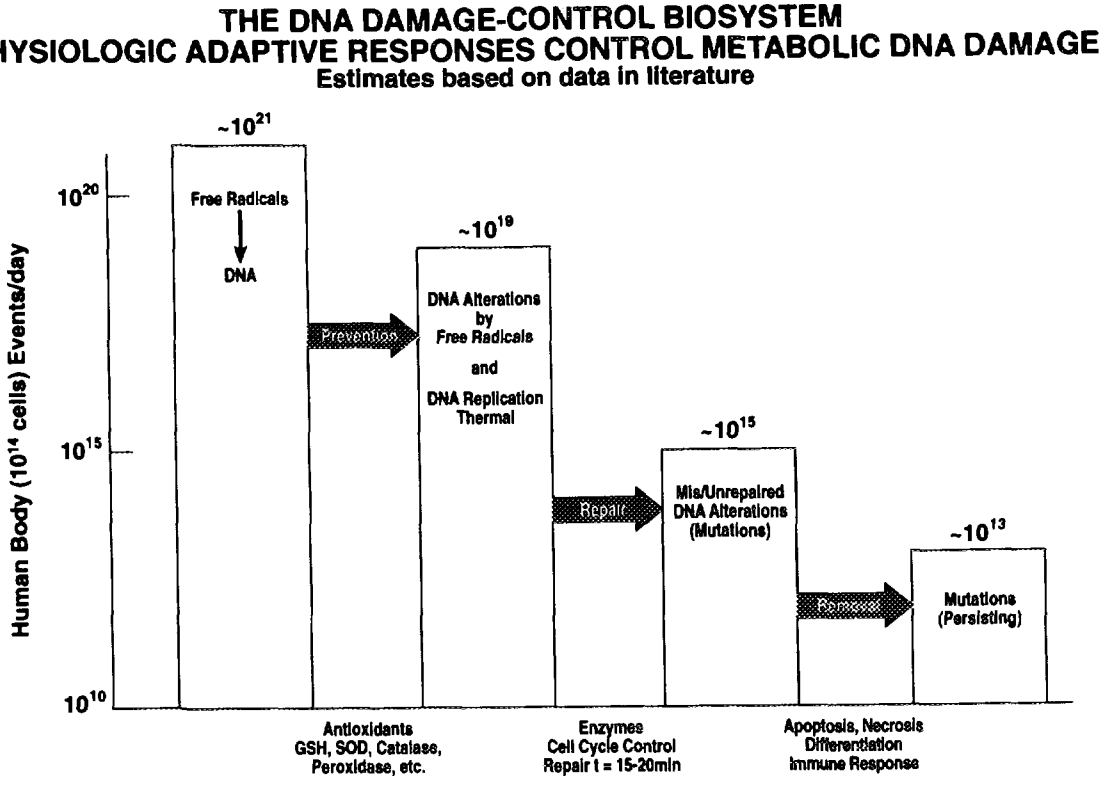
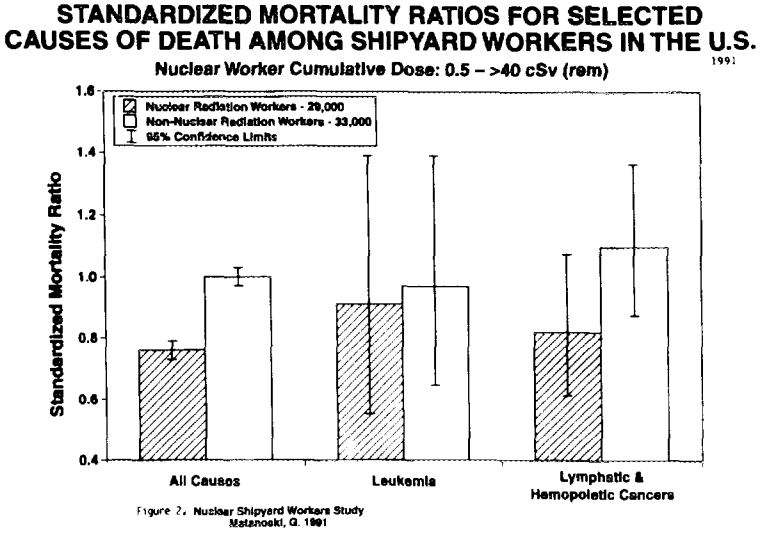


Figure 1. The DNA Damage-Control Biosystem. Pollycove, M and Feinendegen, LE [2].



U.S. Residential Radon Study, Cohen B. 1995

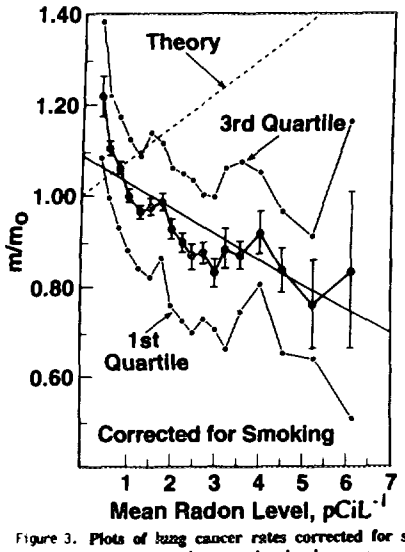
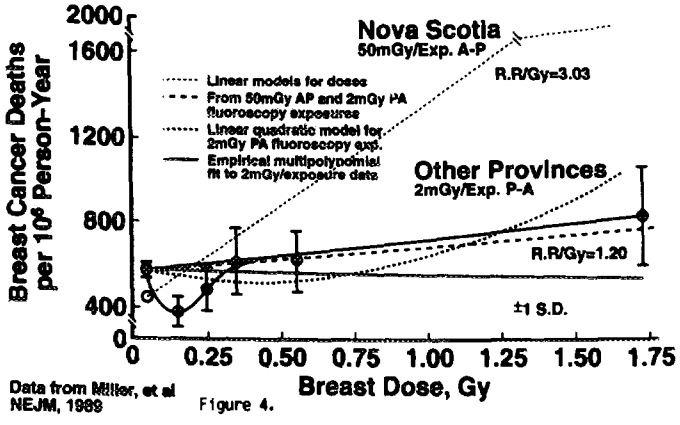


Figure 3. Plots of lung cancer rates corrected for smoking prevalence vs. average home radon levels are presented for U.S. counties with a wide variety of socioeconomic characteristics.

Canadian Breast Fluoroscopy Study



Data from Miller, et al NEJM, 1989

Figure 4.

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Additional references available upon request.

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