MOLECULAR BIOLOGY, EPIDEMIOLOGY, AND THE DEMISE OF THE LINEAR NO-THRESHOLD HYPOTHESIS

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ABSTRACT

The LNT hypothesis is the basic principle of all radiation protection policy. This theory assumes that all radiation doses, even those close to zero, are harmful in linear proportion to dose and that all doses produce a proportionate number of harmful mutations, i.e., mis- or unrepaired DNA alterations. The LNT theory is used to generate collective dose calculations of the number of deaths produced by minute fractions of background radiation.

Current molecular biology reveals an enormous amount of relentless *metabolic* oxidative free radical damage with mis/unrepaired alterations of DNA. The corresponding mis/unrepaired DNA alterations produced by background radiation are negligible. These DNA alterations are effectively disposed of by the DNA damage-control biosystem of antioxidant *prevention*, enzymatic *repair*, and mutation *removal*.

High-dose radiation *injures* this biosystem with associated risk *increments* of mortality and cancer mortality. Low-dose radiation *stimulates* DNA damage-control with associated epidemiologic observations of risk *decrements* of mortality and cancer mortality, i.e., hormesis.

How can this 40-year-old LNT paradigm continue to be the operative principle of radiation protection policy despite the contradictory scientific observations of both molecular biology and epidemiology and the lack of any supportive human data? The increase of public fear through repeated statements of deaths caused by "deadly" radiation has engendered an enormous increase in expenditures now required to "protect" the public from all applications of nuclear technology: medical, research, energy, disposal, and cleanup remediation. Government funds are allocated to appointed committees, the research they support, and to multiple environmental and regulatory agencies. The LNT theory and multibillion dollar radiation activities have now become a symbiotic self-sustaining powerful political and economic force.

BACKGROUND

The best scientific evidence of human radiation effects initially came from epidemiologic studies of atomic bomb survivors in Hiroshima and Nagasaki. While no evidence of genetic effects has been found, these studies showed a roughly linear relationship between the induction of cancer and extremely high dose-rate, single high doses of atomic bomb radiation. This was consistent with the knowledge that ionizing radiation can damage DNA in linear proportion to high-dose exposures and so produce gene mutations known to be associated with cancer. In the absence of comparable low dose effects it was prudent to propose tentatively the no threshold hypothesis that extrapolates linearly from effects observed at very high doses to the same effects at very low doses. It was accepted in 1959 by the International Commission on Radiological Protection (ICRP) (ICRP, 1959) and afterwards adopted by national radiation protection organizations to guide regulations for the protection of occupationally exposed workers and the public (ICRP, 1984).

This hypothesis that all radiation is harmful in linear proportion to the dose, is the principle used for collective dose calculations of the number of deaths produced by any radiation, natural or generated, no matter how small. The National Council of Radiation Protection and Measurements Report 121, "Principles and Application of Collective Dose in Radiation Protection," summarizes the basis for adherence to linearity of radiation health effects (NCRP, 1995):

> "Taken as a whole, the body of evidence from both laboratory animals and human studies allows a presumption [sic] of a linear no threshold response at low doses and low-dose rates, for both mutations and carcinogenesis. Therefore, from the point of view of the scientific bases of collective doses for radiation protection purposes, it is prudent to assume the effect per unit dose in the low-dose region following single acute exposures or low-dose fractions is a linear response. There are exceptions to this general rule of no threshold, including the induction of bone tumors in both laboratory animals and in some human studies due to incorporated radionuclides, where there is clearly evidence for an apparent threshold.
>
> However, few experimental studies, and essentially no human data, can be said to prove or even to provide direct support for the concept of collective dose with its implicit uncertainties of nonthreshold linearity and dose-rate independence with respect to risk. The best that can be said is that most [sic] studies do not provide quantitative data that, with statistical significance, contradict the concept of collective dose.
>
> Ultimately, confidence in the linear no threshold dose-response relationship at low doses is based on our understanding of the basic mechanisms involved. Genetic effects may result from a gene mutation, or a chromosome aberration. The activation of a dominant acting oncogene is frequently associated with leukemias and lymphomas, while the loss of suppressor genes appears to be more frequently associated with solid tumors. It is conceptually possible, but with a vanishing small probability, that any of these effects could result from the passage of a single charged particle, causing damage to DNA that could be expressed as a mutation or small deletion. It is a result of this type of reasoning that a linear nonthreshold dose-response relationship cannot be excluded. It is this presumption [sic], based on biophysical [sic] concepts, which provides a basis for the use of collective dose in radiation protection activities."

NCRP Report 121 summarizes that while some studies "provide quantitative data that, with statistical significance, contradict the concept of collective dose," "ultimately, confidence in the linear no threshold dose-response relationship at low doses [LNT hypothesis] is based on our understanding of the basic mechanisms involved." What are the current data and understanding of the basic molecular biological mechanisms involved?

METABOLIC AND RADIATION DNA DAMAGE CONTROL

During the past decade rapid advances in our knowledge of molecular biology and cell function enable us to understand why low-dose, low-dose-rate radiation is associated with positive health effects, despite the carcinogenic effect of high-dose, high-dose-rate radiation. Our understanding is based upon current cellular molecular biology observations. Estimates are based on published data and recent personal communications:

- Two to three percent of all metabolized oxygen is converted to free radicals (Sohal and Weindruch, 1996), 10^{10} free radicals/cell/d, that produce about 10^{6} DNA alterations (oxidative adducts)/cell/d (Pollycove and Feinendegen, 1998, Beckman, 1997). A relatively small number of additional metabolic DNA alterations are produced by DNA replication and thermal instability (Bishop, et.al., 1989). By comparison, 1 cGy low LET radiation produces 20 DNA

alterations/cell that include an average of 0.4 double strand breaks/cell (Billen, 1990, Ward, 1987).

- Over eons of time, as multicellular animals developed and metabolized oxygen, a complex DNA damage-control biosystem evolved (Figure 1) (Pollycove and Feinendegen, 1998). The damage corresponding to 10^{10} free radicals/cell/d, of which about 10^{8} surround DNA, is largely prevented by antioxidants that scavenge approximately 99% of these free radicals. The resultant ~10^{6} DNA alterations/cell/d are reduced by enzymatic repair to about 10^{2} mis/unrepaired DNA alterations. Apoptosis, differentiation, necrosis, and the immune system remove approximately 99% of these mis/unrepaired DNA alterations so that an average of about 1 mutation/cell/d accumulates during a lifetime of a stem cell to decrease DNA damage-control capability with associated aging and malignant growth (Figure 1). 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 (UNSCEAR, 1994, Sohal and Weindruch, 1996, Pollycove and Feinendegen, 1998, Beckman, 1997, Bishop, et.al., 1989, Feinendegen, et.al., 1995, Feinendegen, et.al., 1996, Varmus and Weinberg, 1993, Ames, et.al., 1996, Yamaoka, 1991, Makinodan and James, 1990, Anderson, 1992, Lithgow and Kirkwood, 1996, Wei, et.al., 1993, Miller, 1996, Ross, 1996, Duke, et.al., 1996).
- 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 ($2x10^{-2}$ versus $5x10^{-7}$). 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 0.1 cGy/y ($5x10^{-3}$/cell/d), that an average of 10^{-7} radiation mutations/cell/d are added to ~1 metabolic mutations/cell/d (Pollycove and Feinendegen, 1998). (Figure 1).

RESPONSE TO LOW-DOSE RADIATION

The activity of the DNA damage control biosystem is decreased by high-dose radiation (e.g., >30 cGy) radiation, but adaptively responds with increased activity to low-dose radiation (e.g., ≤30 cGy) (UNSCEAR, 1994, Feinendegen, et.al., 1995, Feinendegen, et.al., 1996, Yamaoka, 1991, Makinodan and James, 1990, Anderson, 1992, Lithgow and Kirkwood, 1996, Wei, et.al., 1996, Miller, 1996, Ross, 1996, Duke, et.al., 1996).

The efficiency of this biosystem is increased by the adaptive responses to low-dose ionizing radiation (Figure 2). 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 reduction of the relatively negligible number of mutations produced by low-dose radiation. This critical factor must be considered in order, "to judge the balance between stimulated cellular repair and residual damage."

Assuming a 20% increased efficiency of biosystem control in response to a tenfold increase of annual radiation from 0.1 cGy/y to 1 cGy/y, *radiation* mutations would indeed increase from $1x10^{-7}$/cell/d to $8x10^{-7}$/cell/d, but *metabolic* mutations would *decrease* from ~1/cell/d to ~0.8/cell/d. "The balance between stimulated cellular repair and residual damage" is a 20% *decrease* of mutations from an average of ~1 mutation/cell/d (Figure 1) to ~0.8 mutation/cell/d (Figure 3).

UNSCEAR did not consider that the 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 biologic effect of radiation is not determined by the number of DNA mutations it creates, but by its effect on the biosystem that controls the relentless enormous burden of oxidative DNA damage*. High-dose radiation *impairs* this biosystem with consequent significant *increase* of *metabolic* mutations and corresponding *risk increments.* Low-dose radiation *stimulates* the DNA damage-control biosystem with consequent significant *decrease* of *metabolic* mutations and corresponding *risk decrements* (Figures 2, 3). (Azzam, et.al., 1996)

This reduction of gene mutations in response to low-dose radiation provides a *biological* explanation of the statistically significant observations of low-dose mortality and cancer mortality risk *decrements*, and contradicts the *biophysical* understanding of the basic mechanisms upon which, ultimately, the NCRP's confidence in the LNT hypothesis is based.

EPIDEMIOLOGIC STUDIES

What are some of the statistically significant epidemiologic studies that demonstrate risk *decrements* (hormesis) as predicted by the adaptive responses to low-dose radiation of the DNA damage-control biosystem? For several decades increased longevity and decreased cancer mortality have been reported in populations exposed to high background radiation. Established radiation protection authorities consider such observations to be spurious or inconclusive because of unreliable public health data or undetermined confounding factors such as pollution of air, water and food, smoking, income, education, medical care, population density, and other socioeconomic variables. Recently, however, several epidemiologic, statistically significant, controlled studies have demonstrated that exposure to low or intermediate levels of radiation are associated with positive health effects.

Dr. Zbigniew Jaworowski, past chairman of UNSCEAR, in his current review of hormesis cites recent data showing hormetic effects in humans from the former Soviet Union (Jaworowski, 1995). After high radiation exposure from a thermal explosion in 1957, 7852 persons living in 22 villages in the Eastern Urals were divided into three exposure groups averaging 49.6 cGy, 12.0 cGy, and 4.0 cGy and followed for 30 years. Tumor-related mortality was 28%, 30%, and 27% *lower* in the 49.6 cGy, 12.00 cGy, and 4.0 cGy groups, respectively, than in the nonirradiated control population in the same region. In the 49.6 cGy and 12.0 cGy groups the difference from the controls was statistically significant (Figure 4). Epidemiologic studies showing beneficial effects of low doses of radiation in atomic bomb survivors (Figure 5) and other populations were reviewed by Sohei Kondo, Professor of Radiation Biology, Atomic Energy Research Institute, Kinki University, Osaka, Japan (Kondo, 1993). Included are the apparently beneficial effects of low doses of external gamma rays on the life span of radium-dial painters and the significantly lower mortality from cancers at all sites of residents of Misasa, an urban area with radon spas, than residents of the suburbs of Misasa (Figure 7).

These beneficial effects are consistent with the findings of B. L. Cohen, Professor of Physics, University of Pittsburgh, that relate the incidence of lung cancer to radon exposure in nearly 90% of the population of the United States (Cohen, 1995). The 1601 counties selected for adequate permanence of residence provide extremely high-power statistical analysis. After applying the National Academy of Sciences BEIR IV correction for variations in smoking frequency (NAS 1988), the study shows a very strong tendency for lung cancer mortality to decrease with increasing mean radon level in homes, in sharp contrast to the BEIR IV theoretical increased mortality derived by linear no threshold extrapolation of effects in uranium miners exposed to very high radon concentrations. The discrepancy between theoretical and measured slopes is 20 standard deviations (Figure 6). Rigorous statistical analysis of 54 socioeconomic, seven altitude and weather, and multiple geographic variables as possible confounding factors, both single and in combination, demonstrates no significant decrease in the discrepancy. The multiple independent requirements that a possible unknown confounding factor must meet, make its existence highly improbable. A reasonable explanation is that stimulated biological mechanisms more than compensate for the radiation "insult" and are protective against cancer in a low-dose, low-dose-rate range.

The thirteen-year U.S. Nuclear Shipyard Workers study of the health effects of low-dose radiation was performed by the Johns Hopkins Department of Epidemiology, School of Public Health and Hygiene, reported to the Department of Energy in 1991 (Matanoski, 1991) and reported in UNSCEAR 1994. Arthur C. Upton, who concurrently chaired the National Academy of Sciences BEIR V Committee on "Health Effects of Exposure to Low Levels of Ionizing Radiation" (NAS 1990), chaired the Technical Advisory Panel that advised on the research and reviewed the results.

The results of this study contradict the conclusions of the BEIR V report that small amounts of radiation have risk - the LNT hypothesis. From the database of almost 700,000 shipyard workers, including about 108,000 nuclear workers, three study groups were selected, consisting of 28,542 nuclear workers with working lifetime doses ≥5 mSv (many received doses well in excess of 50 mSv), 10,462 nuclear workers with doses <5 mSv and 33,352 non-nuclear workers. Deaths in each of the groups were classified as due to: all causes, leukemia, lymphatic and hematopoietic cancers, mesothelioma, and lung cancer. The results demonstrated a statistically significant decrease in the standardized mortality ratio for the two groups of nuclear workers for 'death from all causes' compared with the non-nuclear workers. For the ≥5 mSv group of nuclear workers, the highly significant risk decrement to 0.76, 16 standard deviations below 1.00, of the standard mortality ratio for death from all causes is inconsistent with and does not appear to be explainable by the healthy worker effect (Figure 8) (UNSCEAR, 1994). The non-nuclear workers and the nuclear workers were similarly selected for employment, were afforded the same health care thereafter, and performed the identical type of work, except for exposure to ^{60}Co gamma radiation, with a similar median age of entry into employment of about 34 years. This provides evidence with extremely high statistical power that low levels of ionizing radiation are associated with risk *decrements*.

Arthur C. Upton (Upton, 1996) and others in Europe, United States, and Canada consider the three-country low-dose radiation and cancer study of Cardis, et al., to be the best occupational study of nuclear workers (Figure 9) (Cardis, et al., 1995). This study also demonstrated no healthy worker effect and concluded, "There was no evidence of an association between radiation dose and mortality from all causes or from all cancers. Mortality from leukemia, excluding chronic, lymphocytic leukemia (CLL) ... was significantly associated with cumulative external radiation dose (one-sided P value = 0.046: 119 deaths)." The statistical methods used state, "As there was no reason to suspect that exposure toradiation would be associated with a decrease in risk of any specific type of cancer, one-sided tests are presented throughout." The authors' analysis of the 119 deaths from all leukemias except CLL *excluded* 86 deaths in dose categories 1, 3, 4 and 6 in which there were *fewer* deaths than expected. Trend analysis of the remaining 33 deaths in dose categories 2, 5, and 7 for estimated P=0.046 was obtained "using computer simulations based on 5000 samples, rather than the normal approximation."

The Canadian Breast Cancer Fluoroscopy Study (Miller, et al., 1989) reports the observations of the mortality from breast cancer in a cohort of 31,710 women who had been examined by multiple fluoroscopy between 1930 and 1952. The observed rates of mortality are related to breast radiation doses and presented only in tabular form. The authors compare linear and linear-quadratic dose-response models fit to the data and conclude, "that the most appropriate form of dose-response relations is a simple linear one, with different slopes for Nova Scotia and the other provinces." On the basis of this linear model, that includes only non-significant data and excludes the data with the highest confidence limits (Figure 10), the authors predict the lifetime excess risk of death from breast cancer after a single radiation exposure at age 30 to 1 cGy (1 r) to be approximately 60 per million women or 900 per million women exposed to 15 cGy. The observed data, however, demonstrates with high statistical confidence, a *reduction* of the relative risk of breast cancer to 0.66 (P = 0.05) at 15 cGy and 0.85 (P = 0.32) at 25 cGy. The study actually predicts that a dose of 15 cGy would be associated with 7,000 *fewer* deaths in these million women. Lauriston S. Taylor, past president of the NCRP, considered application of LNT theory for calculations of collective dose as, "deeply immoral uses of our scientific heritage" (Taylor, 1980).

NON-SCIENTIFIC INFLUENCES ON RADIATION PROTECTION

Contrary to the increased risks associated with injury of the DNA damage-control biosystem by high-dose radiation, this biosystem is stimulated by low-dose radiation to control even more effectively the relentless metabolic DNA damage and *so decrease* the risks of mortality and cancer. These observations of fundamental *biologic* cellular functions and corresponding statistically significant epidemiologic studies both contradict the theoretical assumptions based on *biophysical* concepts and *exclude* a LNT dose-response relationship.

Nobel Prize laureate, Richard Feynman states, "In general we look for a new law by the following process: First we guess it. Then we compute the consequences of the guess to see what would be implied if this law we guessed is right. Then we compare the result of the computation with nature, with experiment or experience, compare it directly with observation, to see if it works. If it disagrees with experiment it is wrong. In that simple statement is the key to science. It does not make any difference how beautiful your guess is. It does not make any difference how smart you are, who made the guess, or what his name is -- if it disagrees with experiment it is wrong. That is all there is to it." (Feynman, 1965).

Nevertheless, since 1959 the LNT hypothesis has remained the basic principle of all radiation protection policy. This "presumption, based on biophysical concepts," is used to generate collective dose calculations of the number of deaths produced by background radiation. The increase of public fear by repeated statements of deaths caused by "deadly" radiation has engendered an enormous increase in expenditures now required to protect the public from all applications of nuclear technology: medical, research, energy, disposal, and cleanup remediation. Government funds are allocated to appointed committees, the research they support, and to multiple environmental and regulatory agencies. The LNT hypothesis and multibillion dollar radiation protection activities have now become a symbiotic self-sustaining powerful political and economic force.

Scientific understanding of the positive health effects produced by adaptive responses to low-level radiation would result in a realistic assessment of the environmental risk of radiation. Instead of adhering to non-scientific influences on radiation protection standards and practice (Taylor, 1980) that impair health care, research, and other benefits of nuclear technology, and waste many billions of dollars annually for protection against theoretical risks, these resources could be used productively for effective health measures and many other benefits to society.

This paper represents the views of the author and not necessarily those of the U.S. Nuclear Regulatory Commission.

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KEY WORDS

Radiation, Health Effect, Mortality, Cancer, DNA Alteration, Mutation, Molecular Biology, Epidemiology, Linearity, Hormesis.

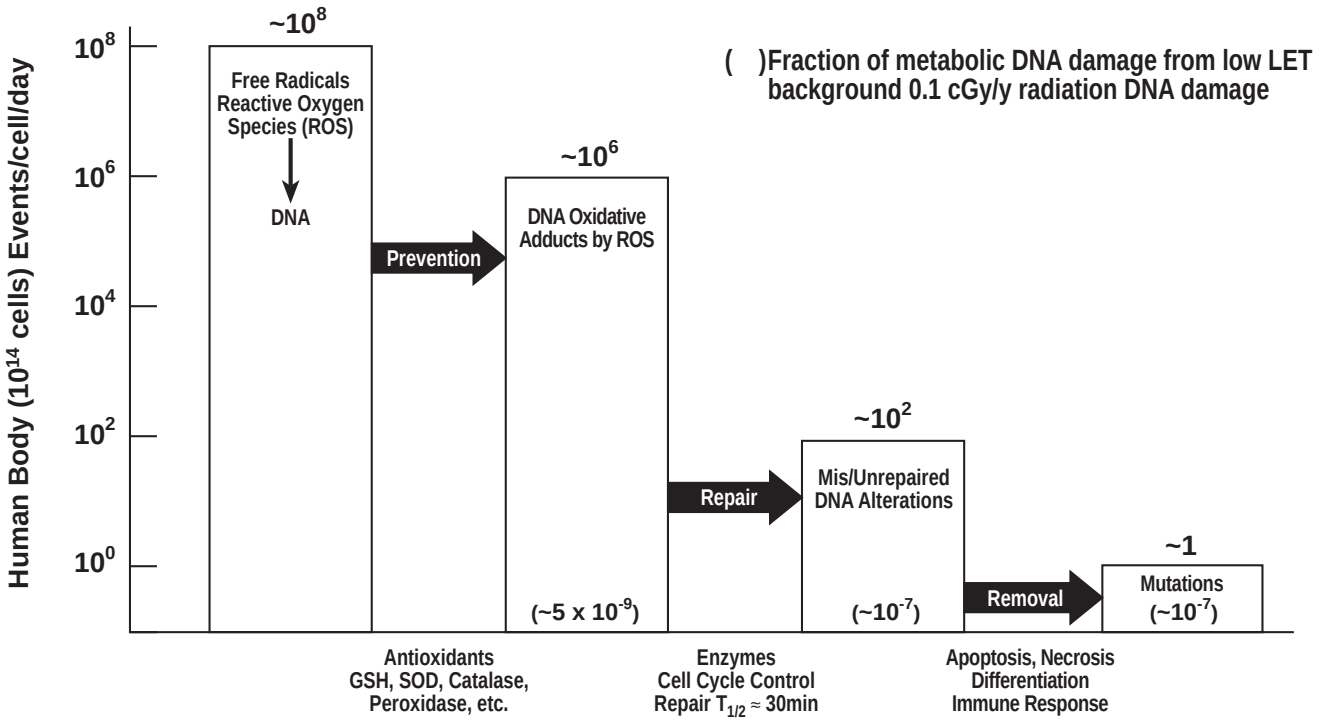

Figure 1. The DNA damage-control biosystem. Estimates based on data in literature. Pollycove M and Feinendegen LE.

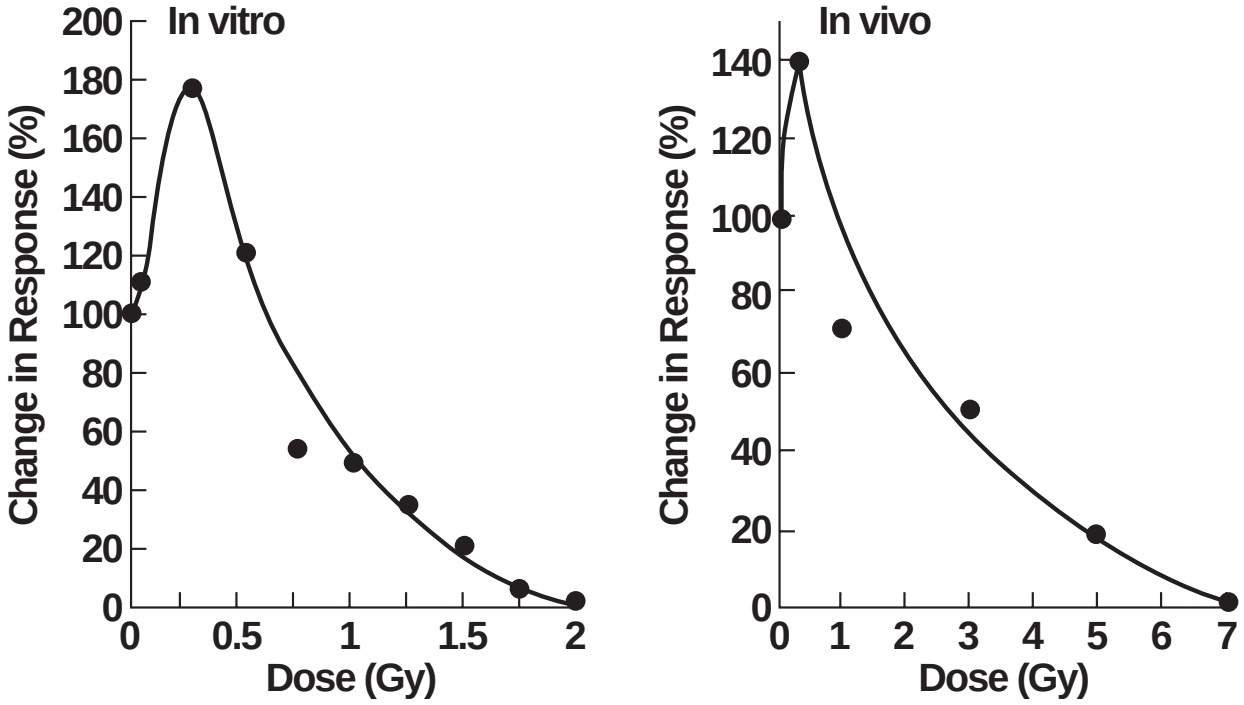

**Figure 2. Immune system response to radiation. Mouse splenic cells primed with antigenic sheep red blood cells.
Makinodan T, James SJ, 1990.**

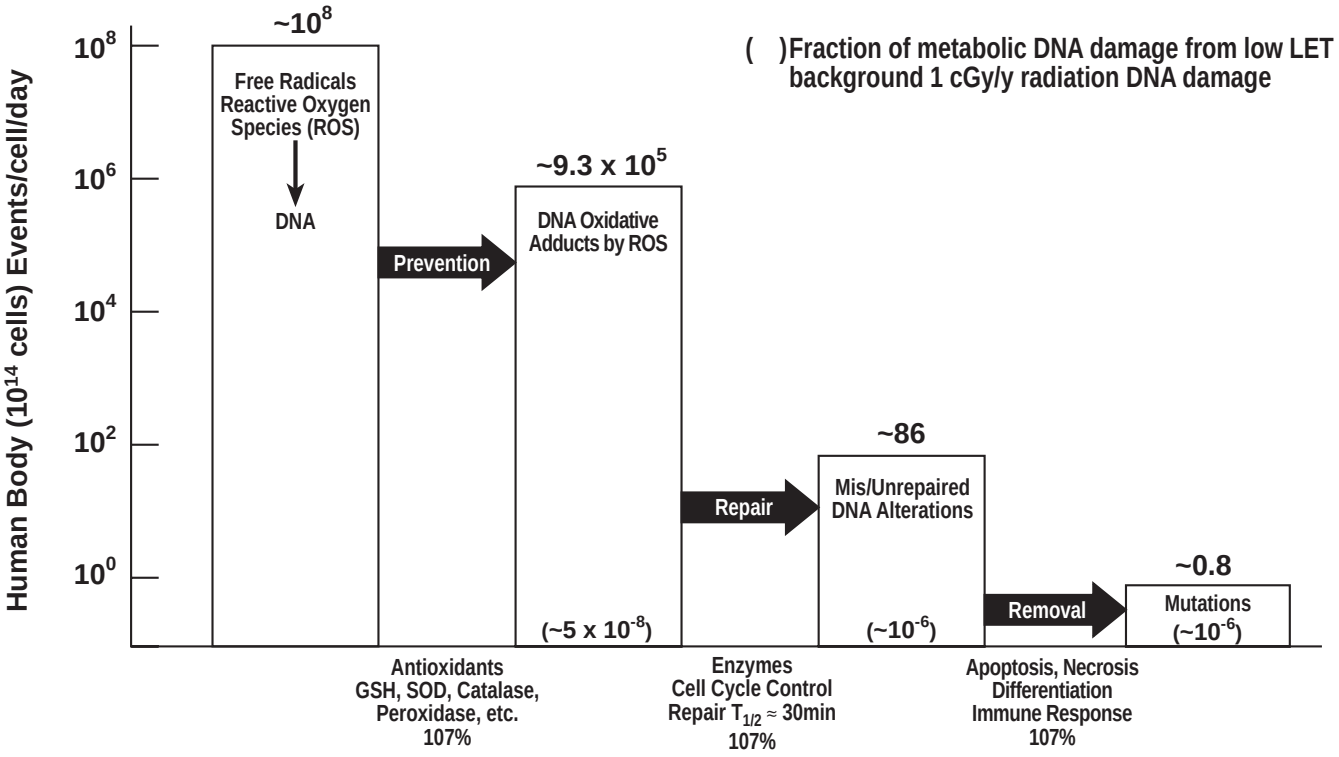

Figure 3. The DNA damage-control biosystem response to high background radiation = 120% Estimates based on data in literature. Pollycove M and Feinendegen LE.

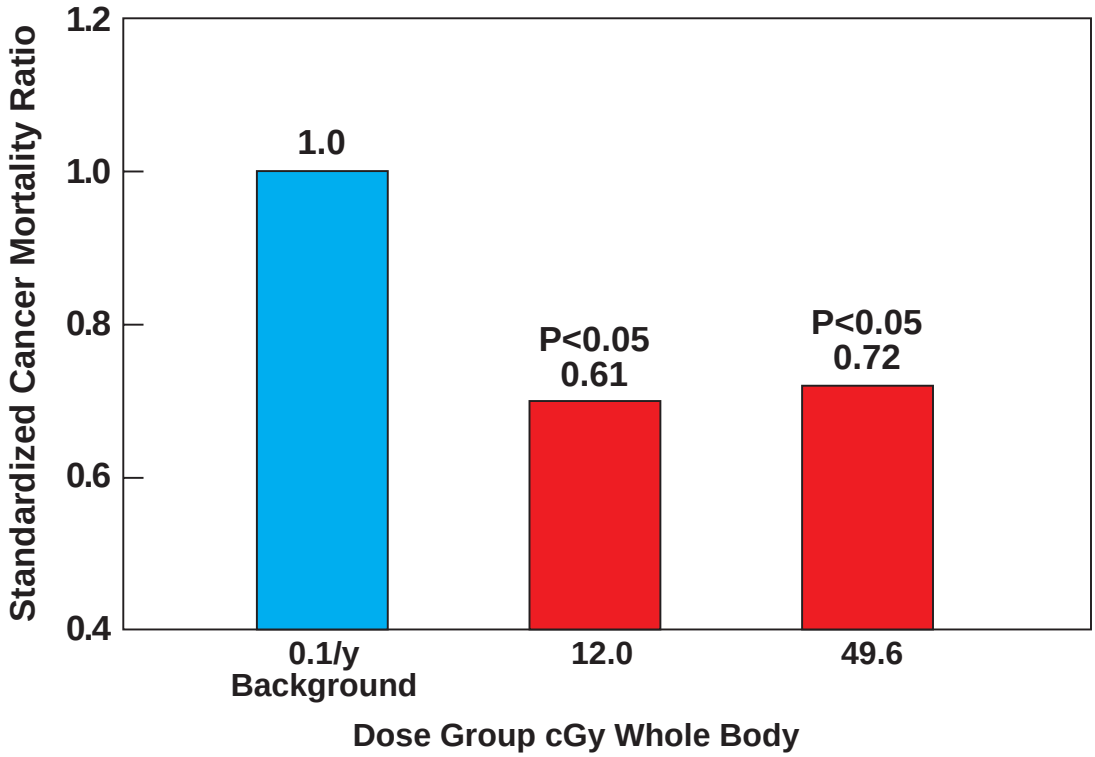

Figure 4. Standardized cancer mortality ratio in 3 exposure groups followed for 30 years after a thermal explosion. Jaworowski Z, 1995.

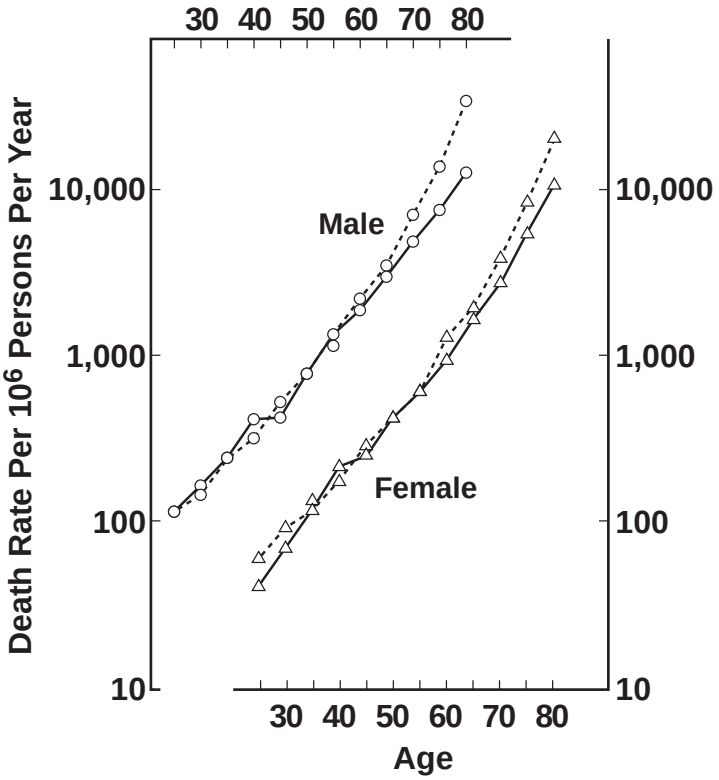

Figure 5. The higher death rate after 55 years old (dotted line) corresponds to the people living in Nagasaki, who were *not* exposed to A. Bomb. Lower death rate after 55 years old (solid line) corresponds to A. Bomb survivors. Mine, et al, 1981.

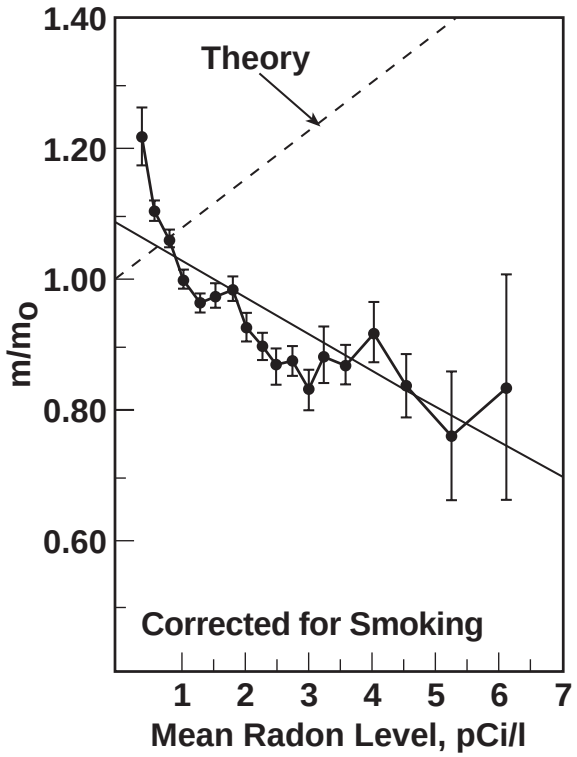

Figure 6. Lung cancer mortality rates compared with mean home radon levels by U.S. county and comparison with linear model by BEIR IV. m/m_o = ratio of lung cancer mortality rate for residential radon levels to that at 0 level (theoretical), or to that at average residential level, 1.7 pCi/l. Cohen B, 1995.

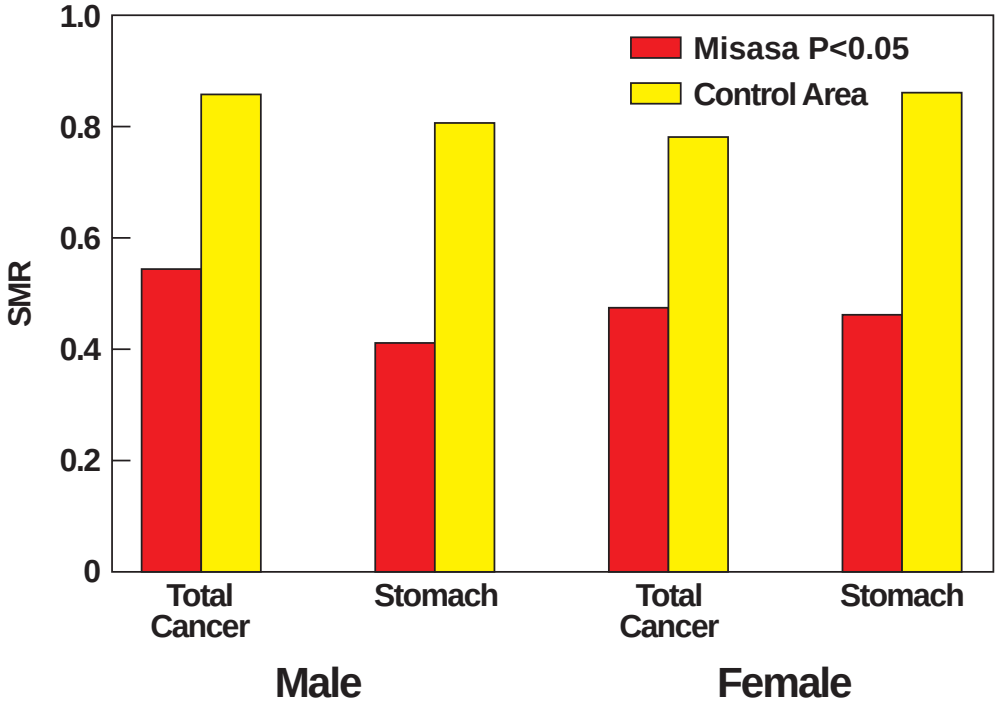

Figure 7. Standardized mortality ratios of populations continually exposed to high, Misasa radium springs, and low air concentrations of radon. Kondo S, 1993.

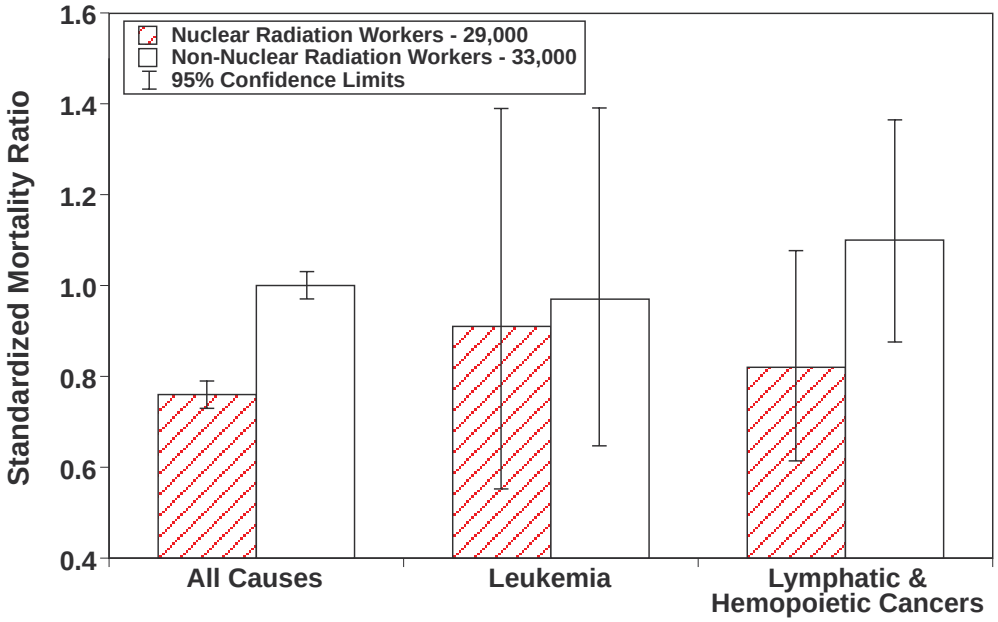

Figure 8. Standardized mortality ratios for selected causes of death among shipyard workers in the U.S. Nuclear worker cumulative dose: 0.5 – >40 cSv (rem). Matanoski GM, 1991.

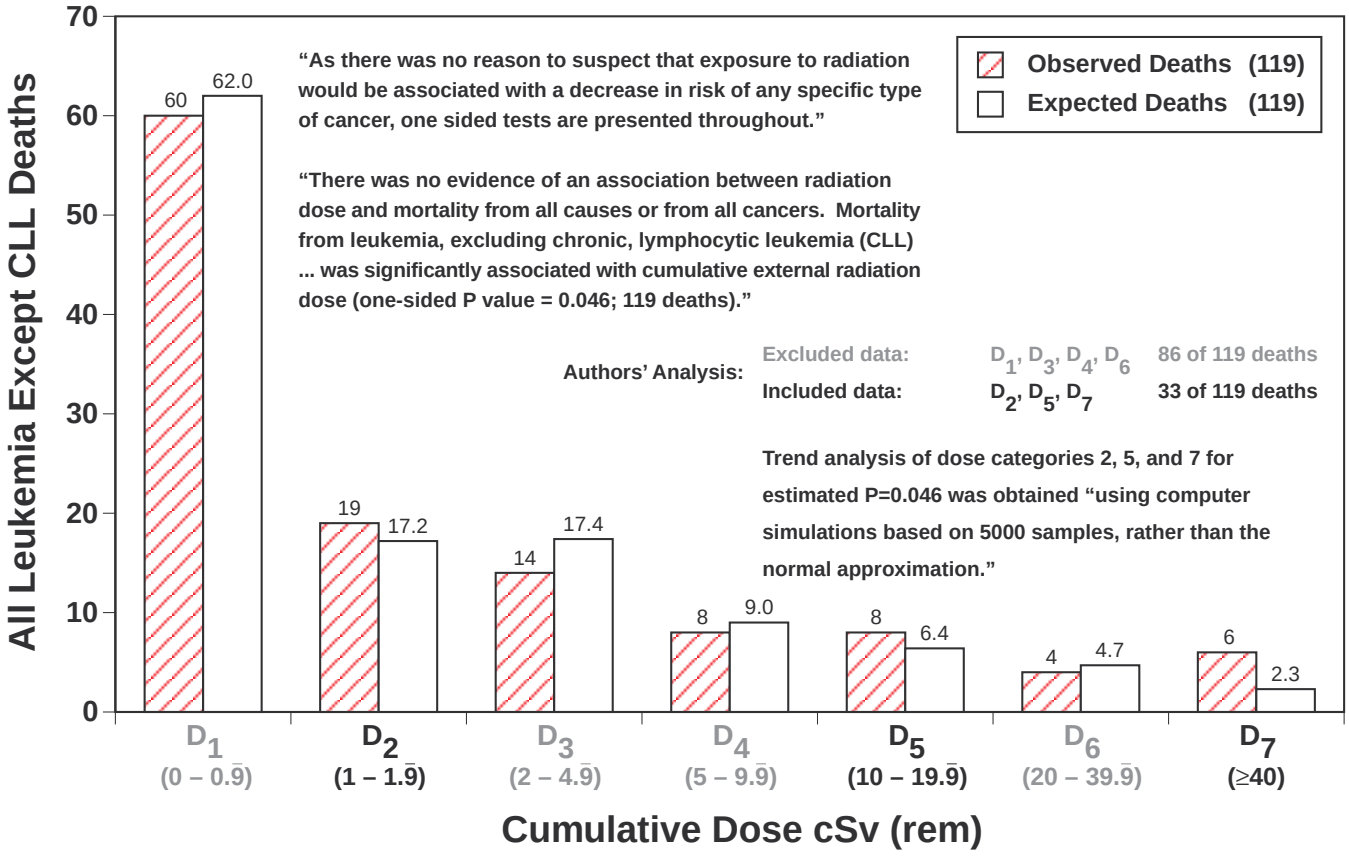

Figure 9. Cancer mortality among nuclear industry workers in three countries. Cardis E, et al 1995.

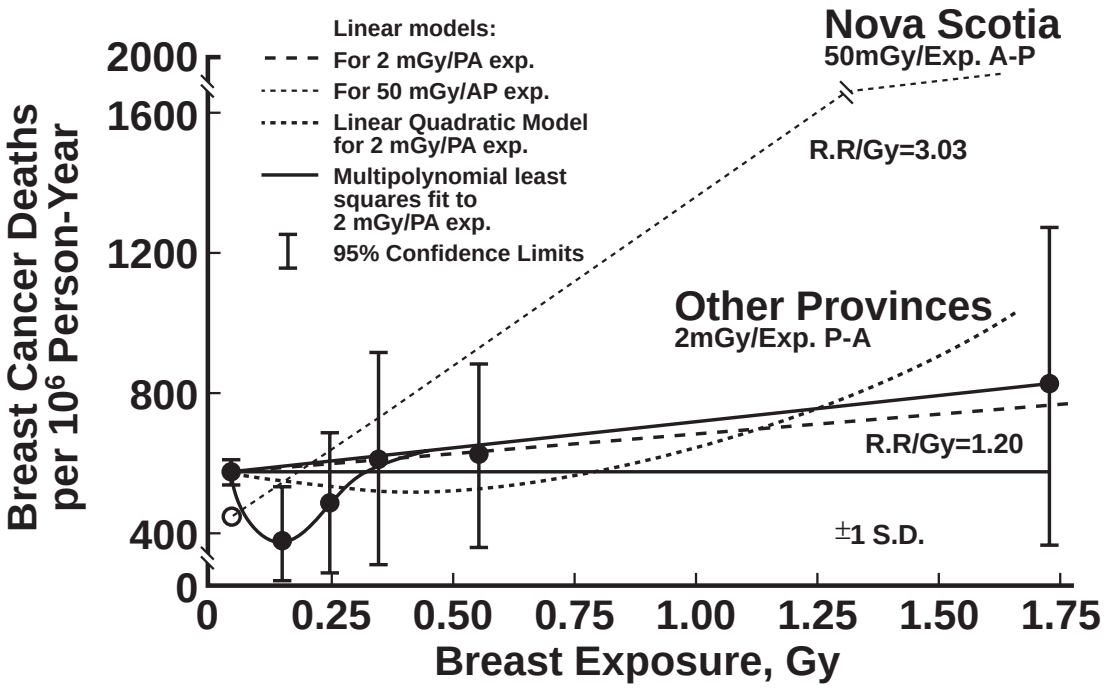

Figure 10. Canadian breast fluoroscopy study. Miller AB, et al 1989.