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Molecular Biology, Epidemiology and Radiation Protection

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Introduction

Low doses of ionizing radiation induce damage and signaling to cells and tissues and subsequent stimulatory responses. In the intact organism these responses are expressions of complex adaptive systems that maintain homeostatic control essential for survival. The antimutagenic DNA damage-control system is the central component of this homeostatic control. The subject of this article is the effect of ionizing radiation on this system with its consequences to the organism.

Antimutagenic System of Metabolic DNA Damage Control

Over eons of time a complex DNA damage-control biosystem evolved in aerobic organisms to control the vast number of DNA alterations (oxidative adducts) produced by reactive oxygen species (ROS). Aging, mortality, and cancer mortality are generally accepted to be associated with stem cell accumulation of permanent DNA alterations (mutations)¹⁻³. These alterations are principally the result of DNA interactions with reactive oxygen species (ROS) produced by leakage of free radicals from mitochondrial metabolism of oxygen⁴. In humans about 10^9 free radicals/cell/d are derived from about 0.25% of all metabolized oxygen. In a low background gamma radiation area of 1 mGy/y these are reduced by antioxidants and other intermediate reactions to about 10^6 DNA alterations/cell/d, including about 10^{-1} double strand breaks (DSB)/cell/d, calculated⁵ from measurements of steady state alterations⁶ and their repair rates⁷. A complex system of specific enzyme repair mechanisms⁸⁻¹³ with an error rate of 10^{-4-14} except for DSB repair error rate of about 10^{-1-15} reduce these to about 10^2 persistent DNA alterations. These remaining alterations are subsequently removed with an error rate of nearly 10^{-2} by apoptosis¹⁶⁻²¹ (programmed self destruction) and immune system surveillance,²²⁻²⁶ leaving about 1 mutation/cell/d (Figure 1).

The estimate of 10^6 endogenous DNA alterations/cell/d is conservative for it is calculated from ROS DNA damage produced by oxygen metabolism without considering significant contributions from micronutrient deficiencies²⁷⁻³⁰ and environmental toxins. In comparison, 1 mGy/y background radiation produces 2

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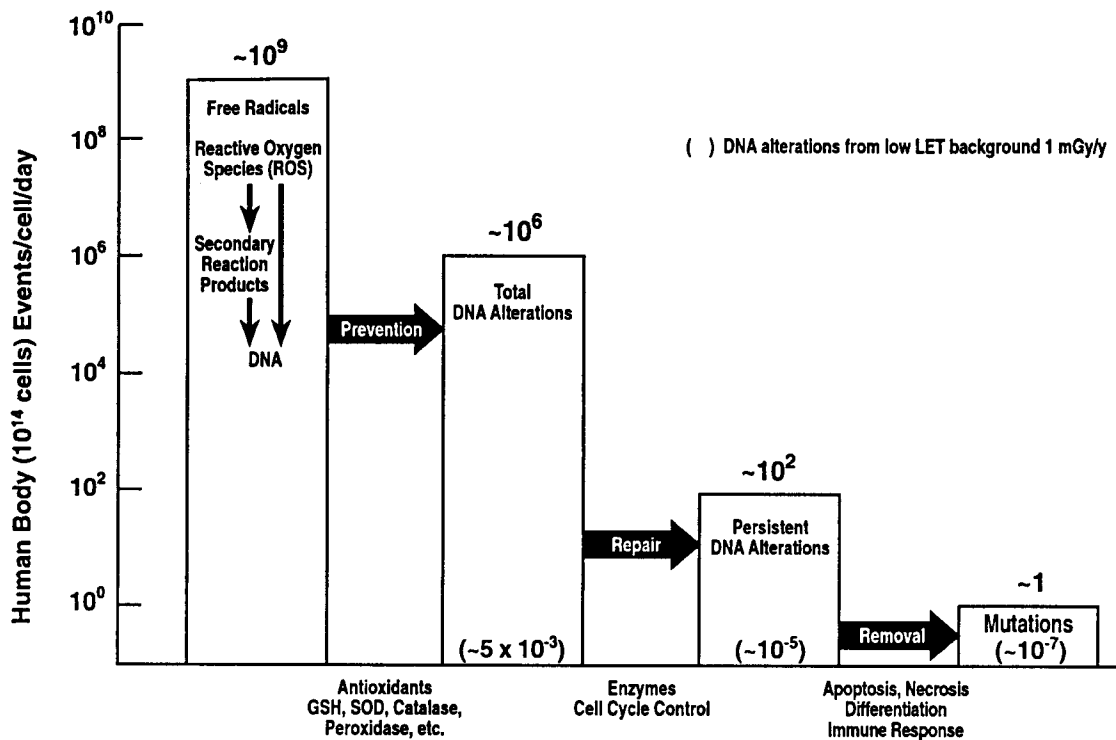


Figure 1. The antimutagenic DNA damage-control biosystem. Estimates based on data in literature. Polycove M and Feinendegen LE.

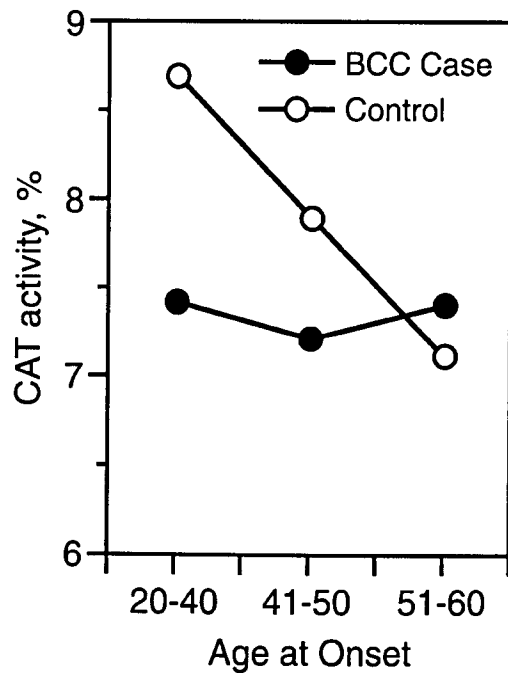


Figure 2. CAT (chloramphenicol acetyl transferase) activity, a measure of cellular DNA repair capacity, progressively declines with age and correlates inversely with carcinoma. Rare young patients with genetic defective DNA repair capacity also develop basal cell cancer (BCC), which is common in the elderly. Wei Q, et al. (1993)

DNA alterations/cell/y, 5×10^{-3} /cell/d including 10^{-4} DSB/cell/d³¹. Enzymatic repair of these DNA alterations, determined by DSB, leaves about 10^{-5} persistent DNA alterations that are reduced by apoptosis and immune system removal to about 10^{-7} radiation induced mutations/cell/d (Figure 1).

DNA alterations which are not eliminated by this biosystem are residual mutations that gradually accumulate during a lifetime in stem cells, at least 30,000 metabolic mutations/stem cell/70y. This accumulation of residual mutations is associated with decreased DNA damage-control efficiency (Figures 2,3), aging (Figure 4), and the associated development of cancer to the 3rd-5th power of age.³²⁻⁴¹ Cancer is the cause of death in approximately 25% of the U.S. population. Mutations produced by background ionizing radiation, also generated largely by oxygen free radicals, is quantitatively negligible.

Biphasic Response to Radiation of the Antimutagenic System

Nevertheless, ionizing radiation has a very significant effect on DNA damage-control as a result of spatial and temporal differences in the DNA alterations it produces. High-dose, high-dose rate radiation suppresses the activity of this biosystem with consequent increased mutations and cancer mortality. Low-dose radiation, on the other hand, stimulates increased antimutagenic biosystem activity that decreases metabolic mutations (Figure 5), thus lowering cancer mortality and increasing longevity.^{25,26,42-46} The efficiency of the DNA damage-control biosystem is increased by homeostatic adaptive responses of increased prevention, repair, and removal of DNA damage. This is well documented in UNSCEAR 1994.⁴⁷ Increased preventive antioxidant activity is associated with increased life span (Figures 4,6)^{35,48} and its response to radiation is biphasic (Figure 3).⁴⁴ Enzymatic repair of damaged DNA is tripled by exposure to 25 cGy (Figure 7).⁴⁵ Response of immune system removal to radiation is biphasic (Figure 8).^{25,26} Review of several decades of significant data confirming prevention and removal of cancer and cancer metastases in mice, rats, and humans by low-dose stimulation of the immune system is beyond the scope of this article.^{22-24,26a-26f} The biphasic reaction of antimutagenic adaptive responses to radiation, often referred to as radiation hormesis, predictably precludes a linear dose-response relation of radiation and health effects.^{49,50}

A tenfold increase of background radiation from 1mGy/y to 10 mGy/y stimulates overall DNA damage-control activity by about 20%, producing a corresponding decrease in the production of metabolic mutations and associated decreases of cancer mortality and mortality from all causes (Figures 5,9,10).^{45-51,51a} Radiation hormesis provides the biological basis for statistically significant epidemiologic observations of low-dose radiation induced decreased human mortality and cancer mortality.

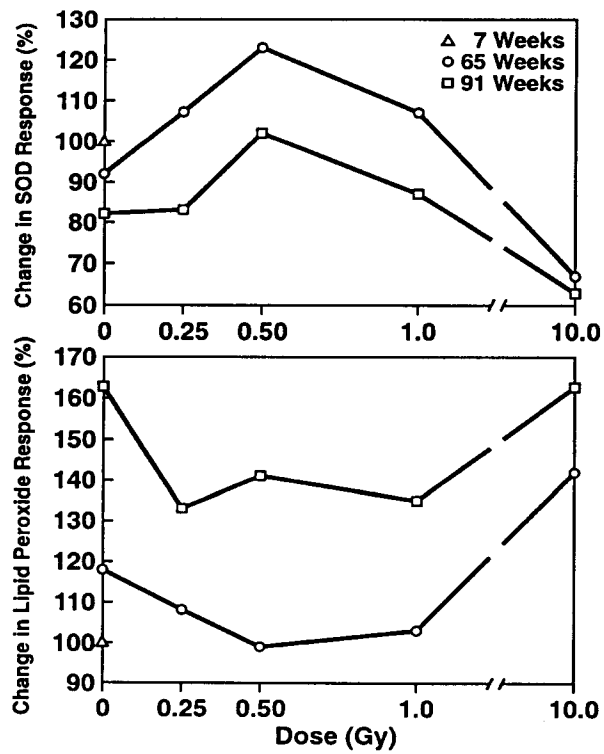


Figure 3. Antioxidant SOD and lipid peroxide response to age and radiation of rat brain cortex. Yamaoka K. (1991)

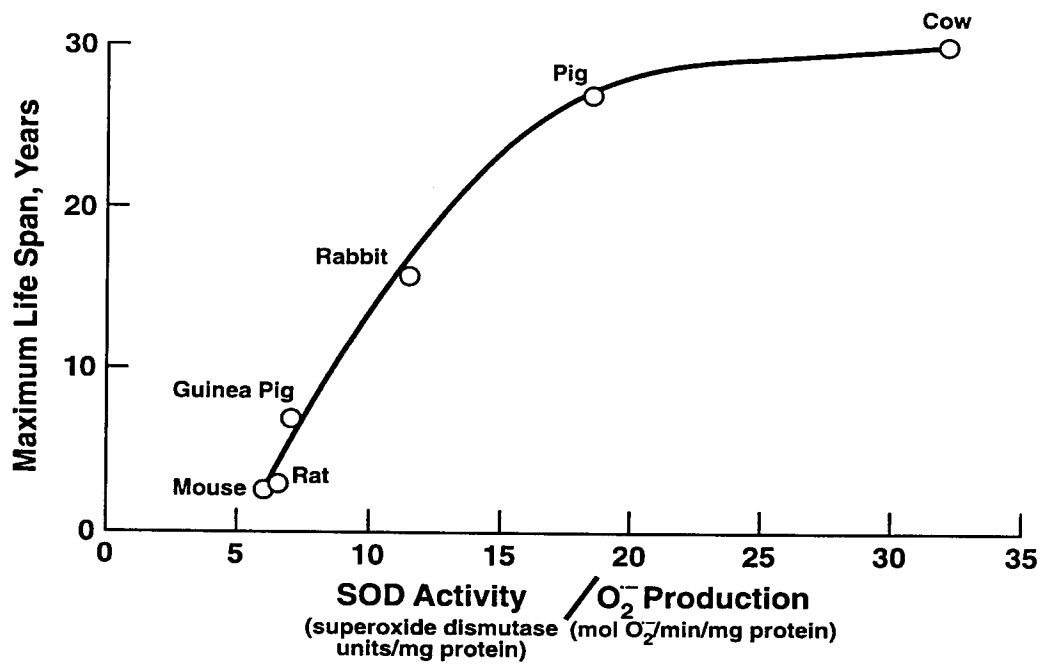


Figure 4. Antioxidant activity, oxygen radicals and maximum life span. Adapted from Sohal RS and Weindruch R. (1996)

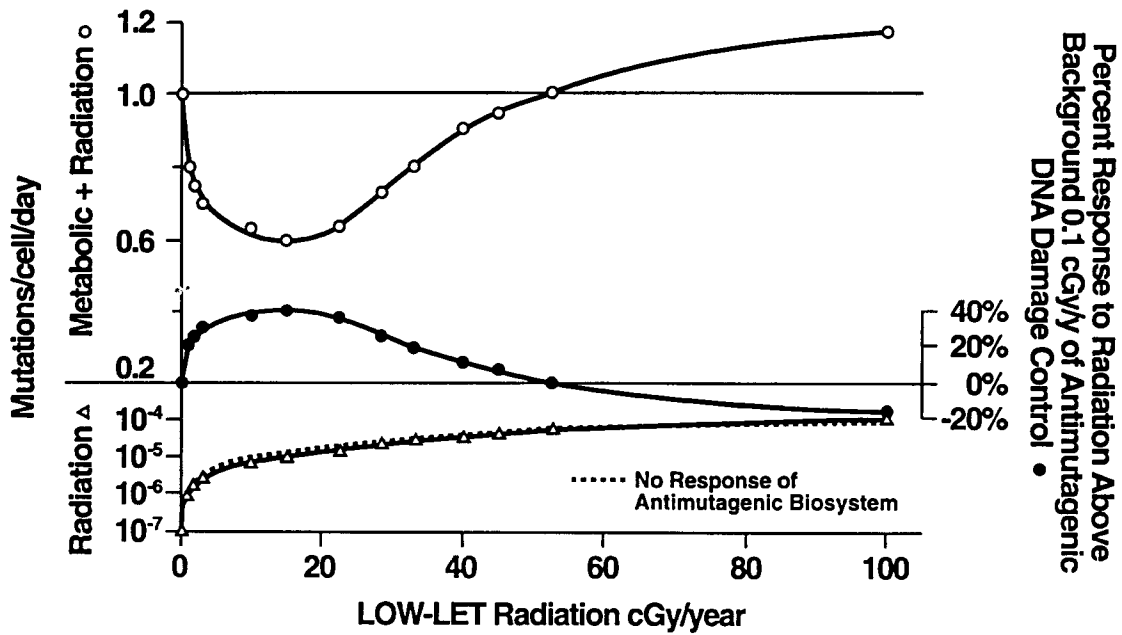


Figure 5. Response of antimutagenic DNA damage-control biosystem and mutations to low-LET ionizing radiation. Polycove M and Feinendegen LE.

EXTENSION OF LIFE SPAN BY INCREASED ANTIOXIDANT ACTIVITY AUGMENTATION OF NATURAL ANTIOXIDANT SYSTEMS OF CAENORHABDITIS ELEGANS WITH SYNTHETIC SUPEROXIDE DISMUTASE/CATALASE MIMETIC EUK-134

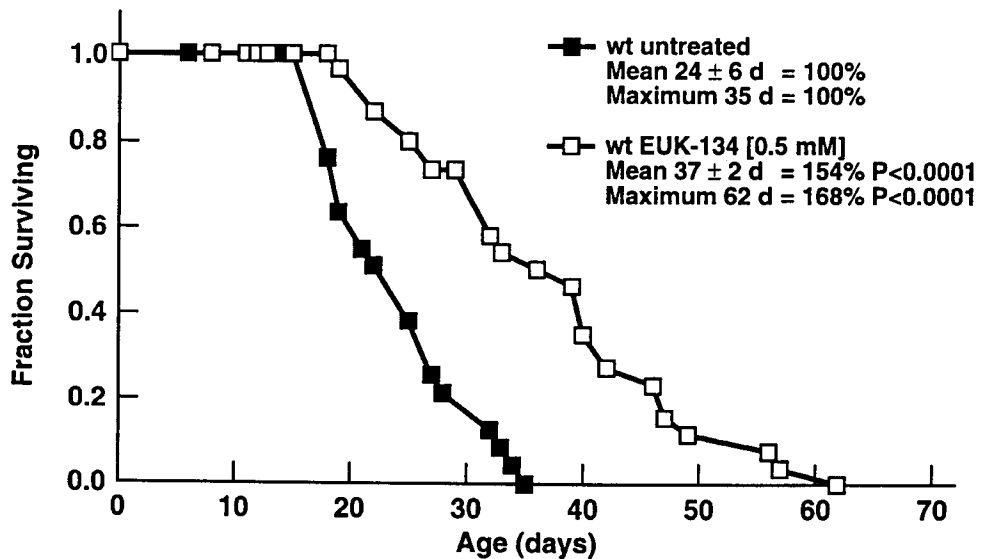


Figure 6. Survival of wild-type (wt) adult worms with and without SOD/catalase mimetic EUK-134 in S medium during culture with *E. Coli* as a food source. Shortened 15 d mean survival of mutant *C. Elegans* with increased free radical oxidants was increased to normal 25 d mean survival with 0.5 mM EUK-134 in S medium culture. Melov S, et al. Extension of life span with superoxide dismutase/catalase mimetics. *Science* 289:1567-1569 (2000)

A 549 Human Lung Cancer Cell
Removal of Thymine Glycol After 2 Gy Dose

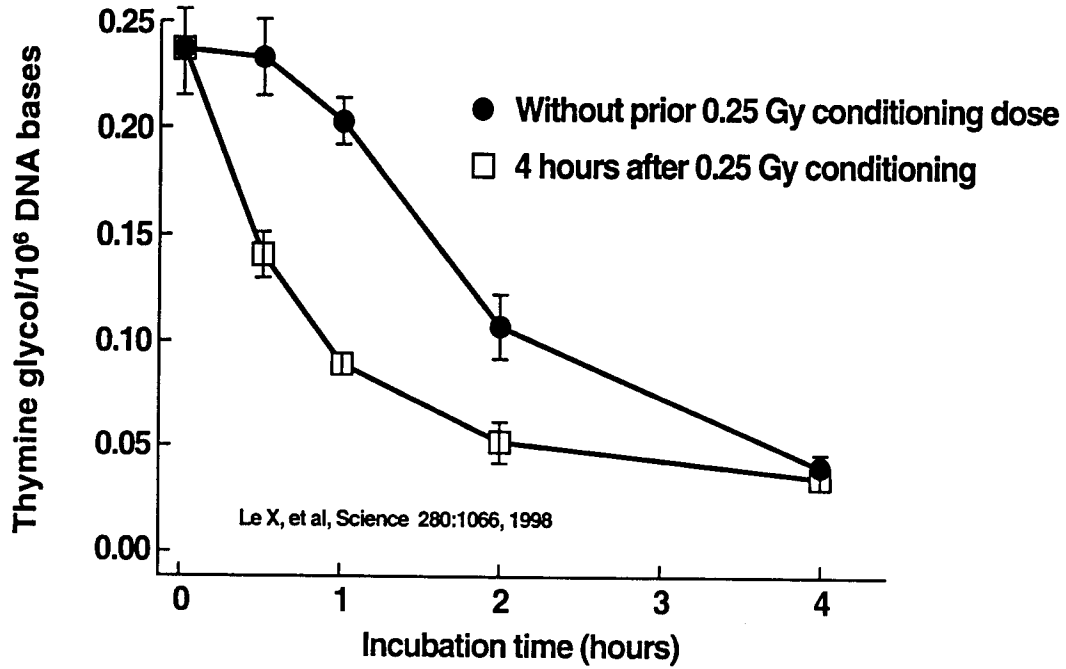


Figure 7. Low dose induced DNA repair. Le X, et al. Science 280:1066 (1998)

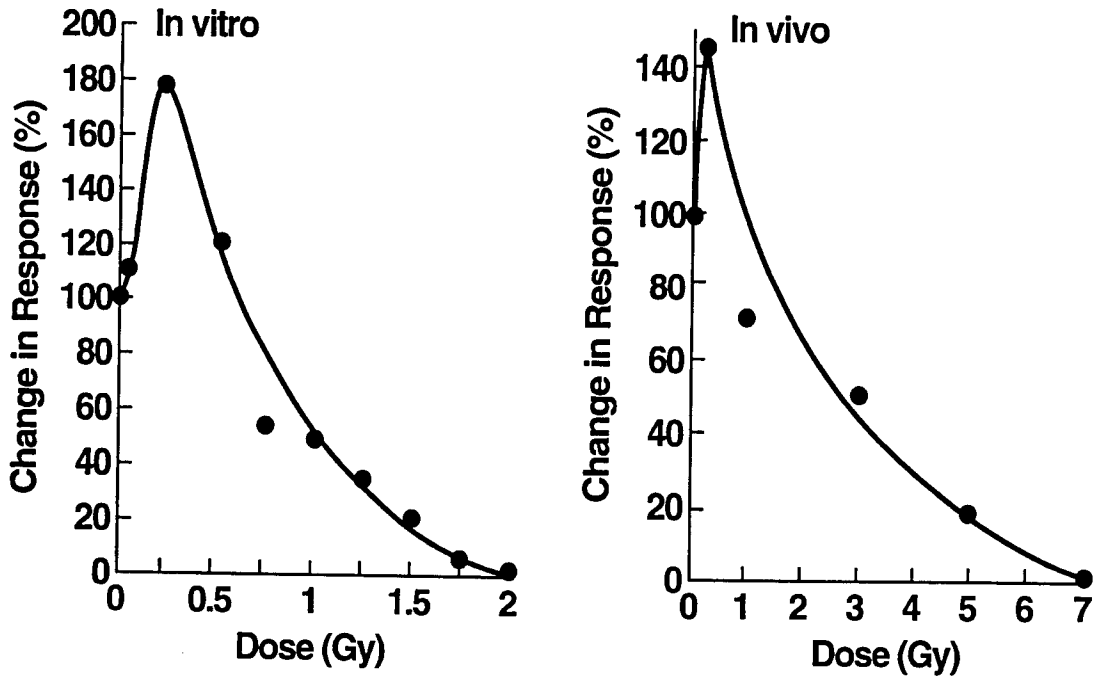


Figure 8. Immune system response to radiation. Mouse splenic cells primed with antigenic sheep red blood cells. Makinodan T and James SJ. (1990)

Spontaneous Transformation Frequency

C3H 10 T1/2 Cells

Unirradiated and after ^{60}Co - γ irradiation with 0.1, 1.0, 10 cGy

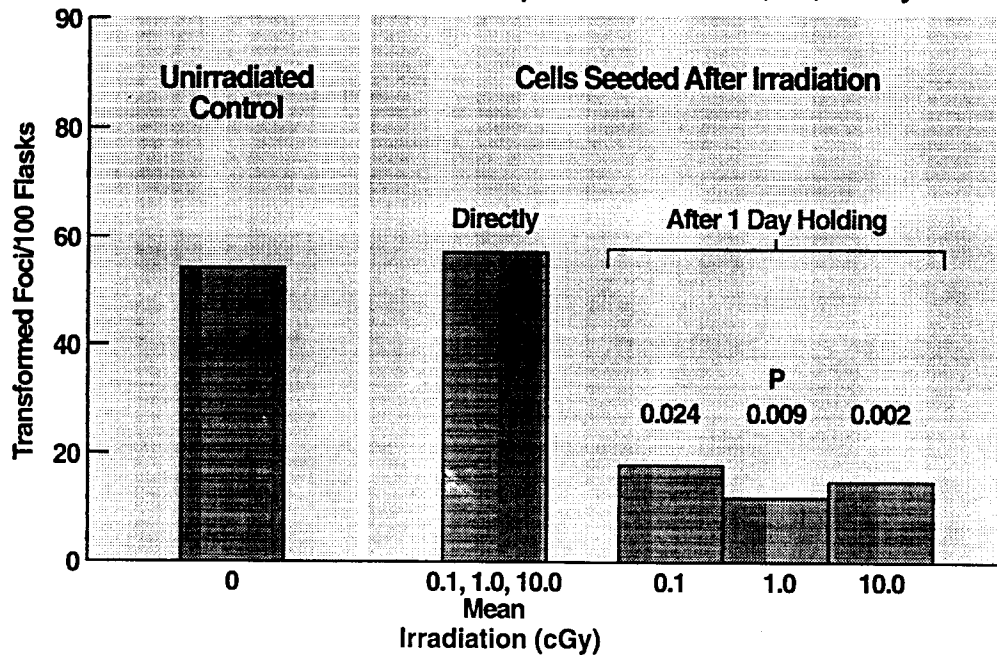


Figure 9. Spontaneous malignant transformation of cells is decreased by 78% after low dose gamma irradiation. Azzam El et al. Radiation Research 146: 369-373 (1996)

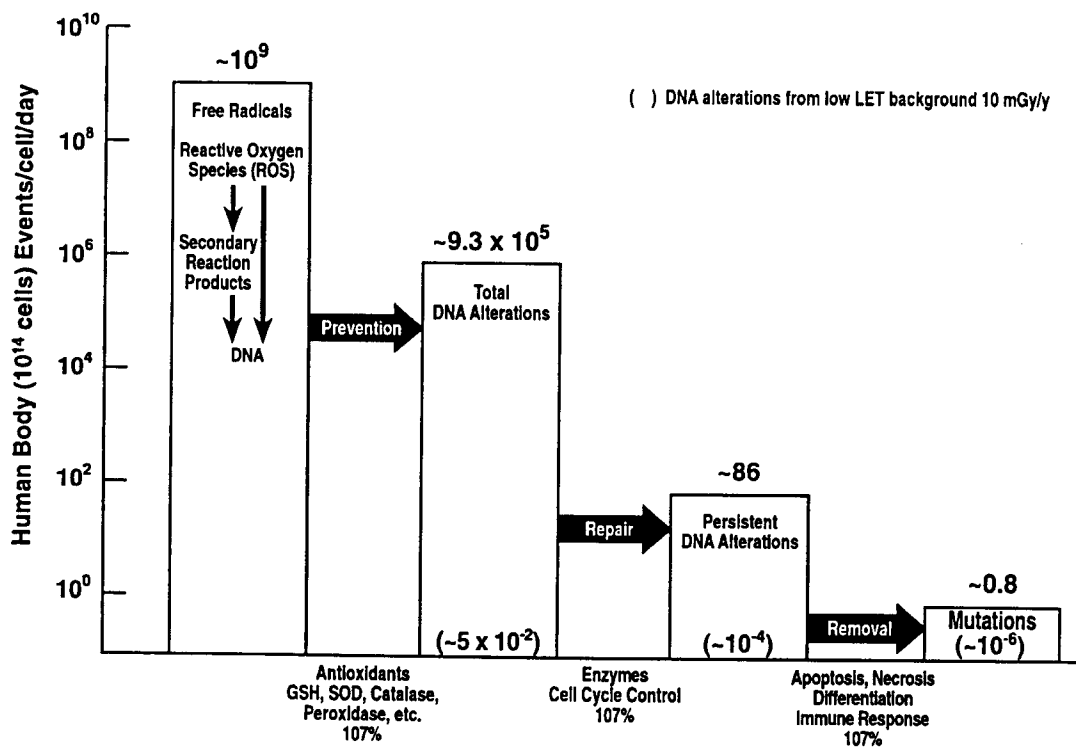


Figure 10. The antimutagenic DNA damage-control biosystem response to high background radiation = 120% Estimates based on data in literature. Polycove M and Feinendegen LE.

Epidemiology

All epidemiologic surveys of populations with high background radiation in the United States, China, India, and Iran have observed no increased mortality or cancer mortality compared to control populations with low background radiation.⁵²⁻⁶³ NCRP 136, p.6 reports, "...it is important to note that the rates of cancer in most populations exposed to low-level radiation have not been found to be detectably increased, and that in most cases the rates have appeared to be decreased."^{63a}

During the past decade decreased mortality and decreased cancer mortality in human populations exposed to low-dose radiation have been observed with high statistical power in large populations with careful consideration of controls:

- Kostyuchenko and Kristina⁶⁴ reported cancer mortality in 7852 Eastern Urals villagers following radiation exposure produced by the 1957 Mayak thermal explosion. Tumor-related mortality was 28%($P<0.05$), 39%($P<0.05$), and 27% *lower* in the 496 mGy, 120 mGy and 40 mGy groups, respectively, than in the unexposed villagers (Figure 11).
- Kondo²⁰ reviewed beneficial effects of low-dose radiation in atomic bomb survivors, radium-dial painters, and residents of Misasa, an urban area with radon spas (Figure 12).
- Rossi and Zaider⁶⁵ meta-analysis of human relative risk(RR) of lung cancer following exposure to low LET radiation shows that "doses < 2 Gy do not appear to cause lung cancer, but in fact, indicate reduction of the natural incidence" (Figure 13).
- Cohen⁶⁶ relates lung cancer mortality to residential radon exposure in nearly 90% of the US population. After correction for smoking, lung cancer mortality *decreases* with increasing mean residential radon levels, in sharp contrast (20 standard deviations[SD]) to BEIR IV increasing mortality calculated by linear extrapolation of effects in uranium miners exposed to very high radon concentrations (Figure 14).
- Miller et al.⁶⁷ Canadian Breast Fluoroscopy Study reports breast cancer mortality in 31,710 women examined by multiple fluoroscopy between 1930 and 1952. Standardized mortality rates show breast cancer RR *reduced* to 0.66($P<0.05$) at 150 mGy and 0.85 at 250 mGy cumulative 2 mGy fluoroscopy doses (Figure 15).
- Matanoski,⁶⁸ UNSCEAR 1994⁴⁷ US Nuclear Shipyard Worker Study reports cancer mortality and mortality from all causes among almost 700,000 workers including about 108,000 nuclear workers(NW). "The healthy worker effect" was excluded by including an internal control of 33,352 non-nuclear workers(NNW) scrupulously matched with 28,542 NW having lifetime doses > 5 mSv. *Decreased* standardized mortality ratios for NW of death from "all causes" are 0.76 vs.1.02 for NNW, decreased 16 SD, and from "all malignant neoplasms" 0.95 vs.1.12 for NNW($P<0.001$), decreased > 4 SD (Figure 16).

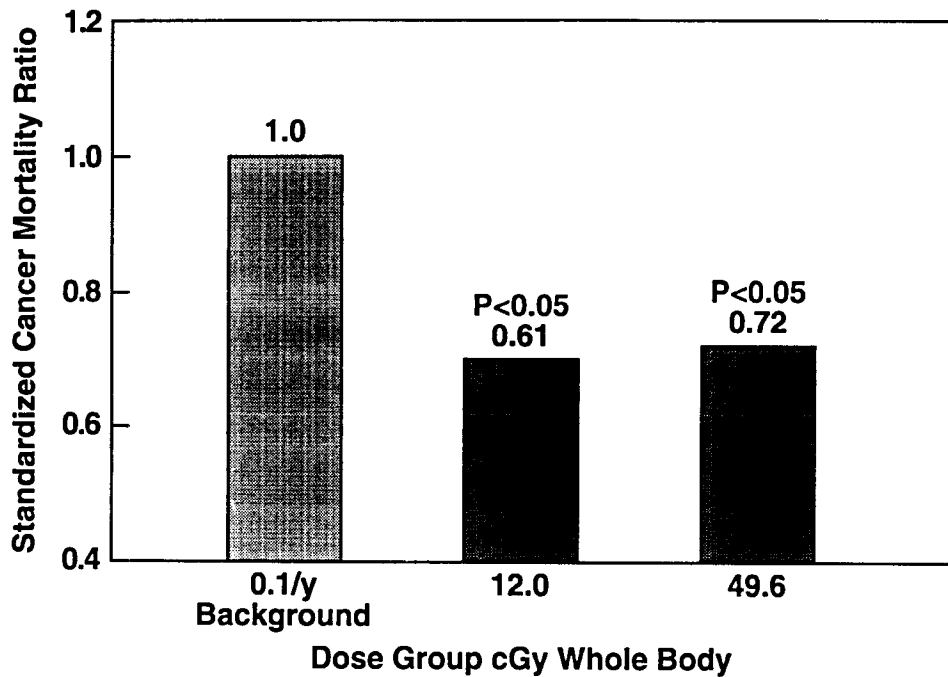


Figure 11. Standardized cancer mortality ratio in 3 exposure groups of Eastern Urals villagers followed for 30 years after a thermal explosion September 1957 in the Mayak USSR reprocessing facility. Kostyuchenko VA, Krestina L Yu. Long-term irradiation effects in the population evacuated from the East-Urals radioactive trace area. The Sci Total Environ 142:119-125 (1994)

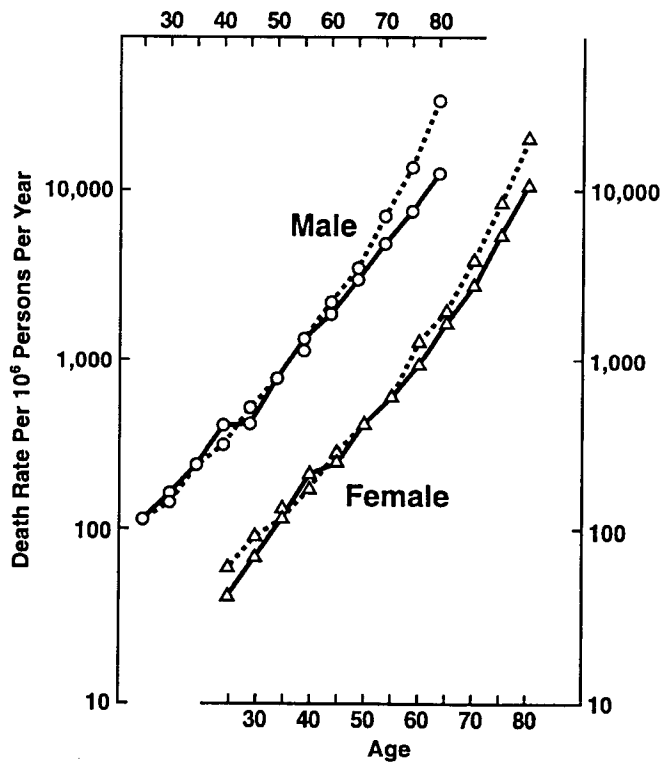


Figure 12. The higher death rate after 55 years old (dotted line) corresponds to the people living in Nagasaki, who were exposed to A. Bomb. Lower death rate after 55 years old (solid line) corresponds to A. Bomb survivors. Mine M, et al. (1981)

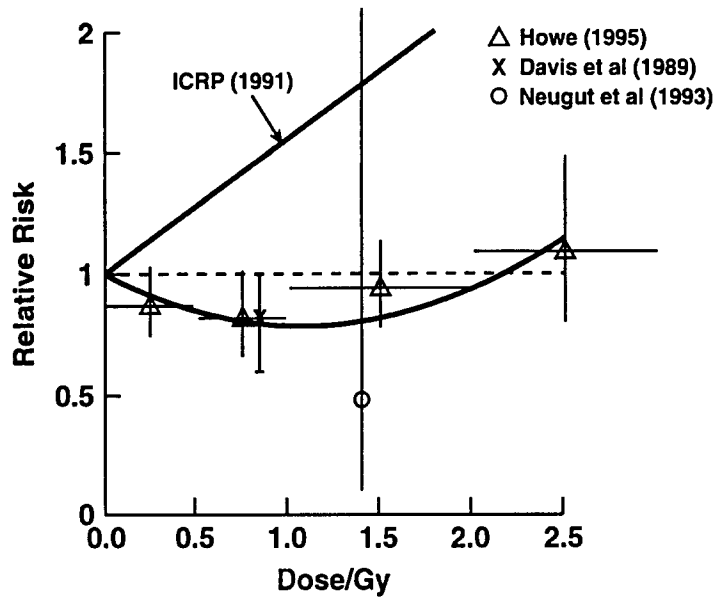


Figure 13. Relative risk of lung cancer following exposure to low-linear energy transfer (LET) radiation. The data by Howe are given together with horizontal bars that indicate the dose bins he used. The data point from Neugut et al. (1993) represents the relative risk in the contralateral lung 10 years or more after diagnosis of breast cancer: it is shown at the average of the two doses reported. The 95% confidence intervals, indicated by vertical bars, were taken from the original publications, for the data from Neugut et al. (1993) the confidence interval was estimated (data from Rossi and Zaider, 1997).

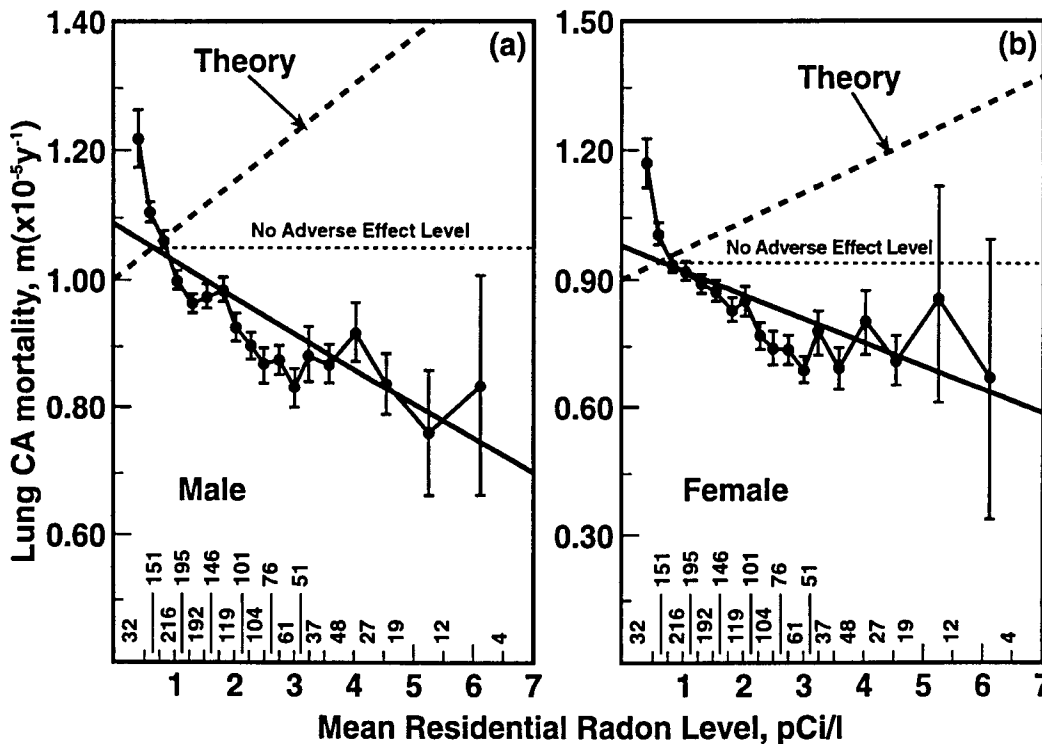


Figure 14. Lung cancer mortality rates corrected for smoking vs. mean residential radon level for 1,601 U.S. counties. Data points shown are the mean of the number of counties within the range of radon concentrations shown on the base line. Error bars are standard deviation of the mean. Theory lines (NAS BEIR IV and BEIR VI) are obtained by linear extrapolation of lung cancer mortality in uranium miners exposed to prolonged very high radon concentrations (data from Cohen, 1995).

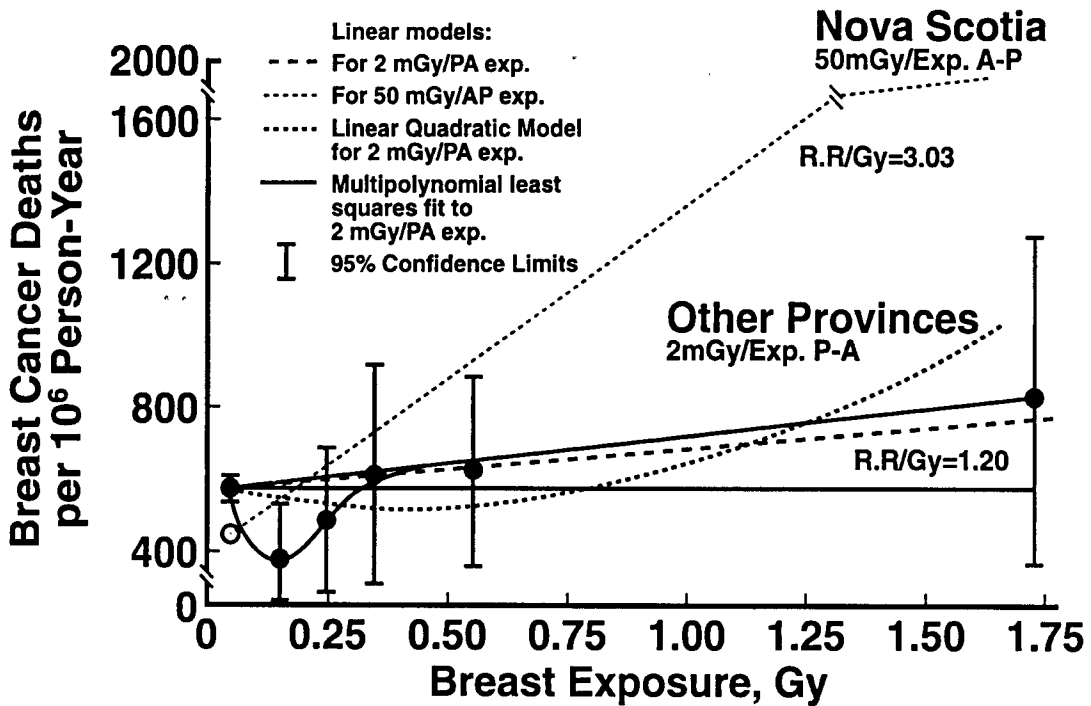


Figure 15. Canadian breast fluoroscopy study. Adapted from Miller AB, et al. (1989)

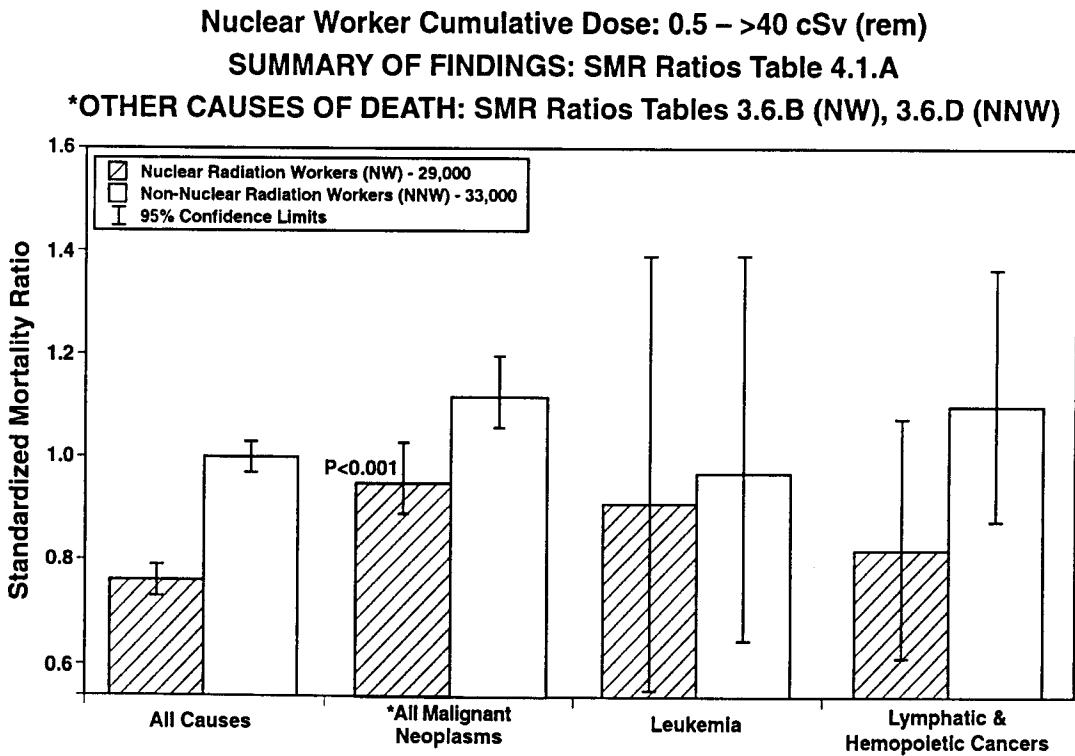


Figure 16. Standardized mortality ratios for selected causes of death among shipyard workers in the U.S. Matanoski GM. (1991)

- Cardis et al. report cancer mortality among 95,673 nuclear industry workers in three countries: Canada 1 facility, UK 3 facilities, US 3 facilities.⁶⁹ Omitted are 8 US facilities with 108,000 NW reported 4 years earlier in the Matanoski NSWS. For all cancers excluding leukemia RR was 0.93. For "leukemia excluding CLL" reported RR of 2.18 with trend of 1.85 is invalidated by the statistical methods used: "As there was no reason to suspect that exposure to radiation would be associated with a decrease in risk of any specific type of cancer,..one-sided tests are presented throughout... For..leukemia excluding CLL,..the number of deaths was less than 30,..P value presented was estimated using computer simulations based on 5000 samples, rather than the normal approximation" (Figure 17).
- Tokarskaya et al.⁷⁰ reported cancer incidence induced in 500 Mayak nuclear workers following chronic inhalation of Pu-239. Compared to internal controls, lung cancer incidence, corrected for smoking, at body burdens of 0.343 kBq, 1.18 kBq and 4.2 kBq was significantly *reduced* to 0.56, 0.59 and 0.83, respectively (Figure 18). *Decreased* lung cancer incidence at low body burdens of plutonium is also reported by Voelz et al.⁷¹, Tietjen⁷², and Gilbert et al.⁷³.
- Mortazavi et al.⁷⁴ measured lymphocyte chromosome aberrations following a challenge dose of 1.5 Gy to lymphocytes of residents in high(H)(10 mGy/y) and normal(N)(1 mGy/y) background radiation areas (BRAs) of Ramsar, Iran. Chromosome aberrations are formed during mitosis of cells with damaged DNA. These aberrations are decreased about 50% if enzymatic repair of DNA damage is increased by lymphocyte exposure to an acute conditioning dose of 10-100 mGy 4 hours before exposure to the high-dose, high-dose rate challenge dose^{45, 75, 76}. Following the challenge dose, lymphocytes of HBRA residents have 55% of the chromosomal aberrations of NBRA residents (P<0.001) (Figure 19). These findings suggest that chronic low-dose radiation may not only reduce mortality from all causes and cancer mortality, but may also be protective against accidental high-dose, high-dose rate radiation.

These epidemiologic observations of decreased cancer mortality and increased longevity of public, medical cohort and occupational populations exposed to increased low-dose radiation are consistent with the antimutagenic biosystem model prediction of radiation hormesis: a high background of 1.0 cGy/y decreases metabolic mutations occurring at 0.1 cGy/y low background from ~1 to ~0.8 mutations/cell/d with corresponding decreases of mortality and cancer mortality (Figure 10).⁴⁹

Summary

The genes in every cell continuously undergo a vast number of intrinsic metabolic alterations by reactive oxygen species (ROS) which are prevented, repaired, and removed by a complex antimutagenic system. Recent studies document low dose radiation stimulation of many cellular functions, including antioxidant prevention, enzymatic repair, and apoptotic and immunologic removal of persistent DNA damage. This homeostatic DNA damage-control system is stimulated by a ten, or even a hundredfold increase in background radiation.

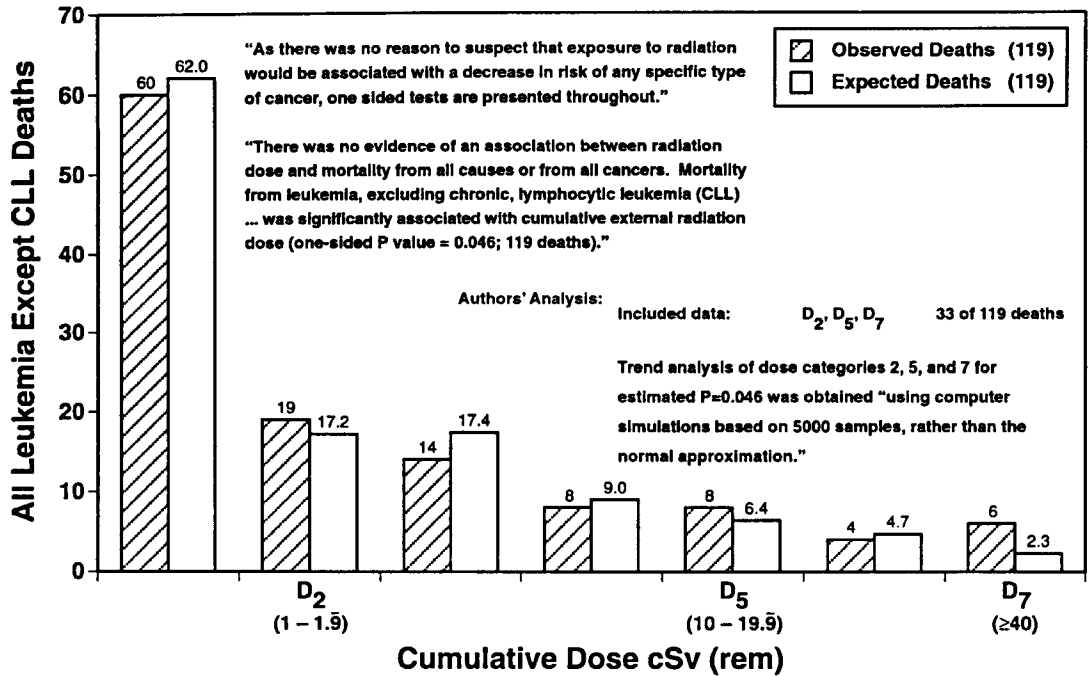


Figure 17. Cancer mortality among nuclear industry workers in three countries. Cardis E, et al 1995.

Dependence of Lung Cancer Relative Risk On ^{239}Pu Body Burden (kBq) and Smoking (cig/d-year)

Mean (kBq)	OR adjusted		Trend	
	RR	95% confidence interval	χ^2	P
0.010	1.0			
0.34	0.56	0.28-1.12	4.9	<0.05
1.18	0.59	0.32-1.04		
4.2	0.83	0.45-1.57	16.1	<0.001
16.5	2.48	1.28-4.82		
54.2	59.3	11.2-314		

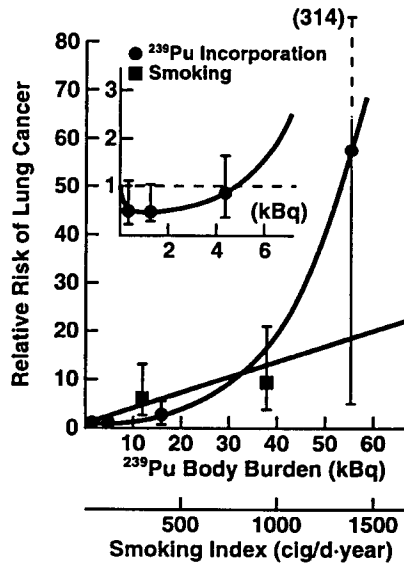


Figure 18. Relative risk of lung cancer and 95% confidence interval, depending on incorporation ^{239}Pu and smoking (data from Tokarskaya, et al., 1997).

	1 r/y HBRA \pm SE	0.1 r/y NBRA \pm SE	P-value
MCAPC (0 Gy)	0.013 \pm 0.003	0.016 \pm 0.004	Not Significant
MCAPC (1.5 Gy)	0.098 \pm 0.012	0.176 \pm 0.017	P < 0.001

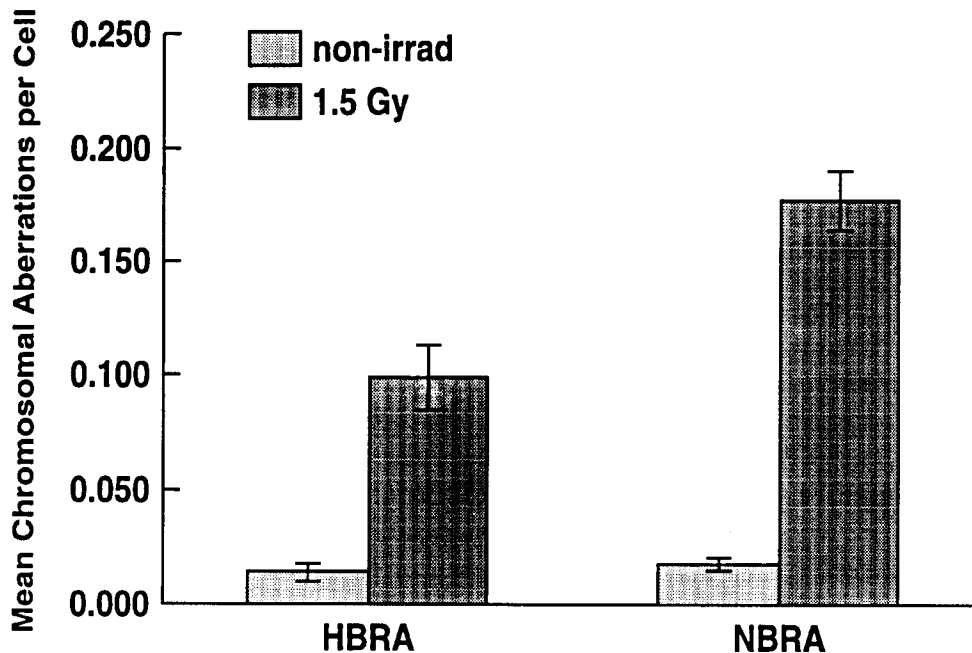


Figure 19. Mean chromosomal aberrations per cell (MCAPC) were measured in lymphocytes before and after exposure to 150 rad. Lymphocytes were obtained from Ramsar, Iran residents in a high background gamma radiation area (HBRA) of about 10 mGy per year and residents in a normal background gamma radiation area (NBRA) of about 1 mGy per year. The MCAPC results based on analysis of about 200 cells per person, obtained during two sampling events, indicate a radioadaptive response to high background radiation levels (data from Mortazavi, et al., 2001).

Enhanced prevention of gene mutations by the spatial and temporal differences of low dose ionizing radiation ROS is associated with radiation hormesis: decreased mortality and decreased cancer mortality observed in populations exposed to low dose radiation. Stimulation of the immune system by therapeutic low-dose body irradiation removes cancer and cancer metastases in mice, rats, and humans.

Widespread recognition of the health benefits of radiation hormesis would lead to development of new radiation protection standards; standards set marginally below the upper limits of the hormetic low dose range determined in cells, tissues, and organisms, including epidemiologic studies of man. Application of these new radiation protection standards would produce far reaching health, economic, environmental, and societal benefits.

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