Low-Level Radiation Improvement of Health and Therapy of Cancer

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INTRODUCTION
Observations of mice, rats, and human clinical trials demonstrate the efficacy of low-dose radiation immunotherapy. The immune system is an essential component of effective antimutagenic control of the enormous burden of relentless metabolic DNA alterations produced by reactive oxygen species (ROS) leaked from mitochondria. Our modeling of the human antimutagenic biosystem includes antioxidant prevention, enzymatic repair of DNA alterations and removal of persistent DNA alterations by apoptosis and the immune system that reduce DNA damage from ~10^6 DNA alterations/cell/d to ~1 “mutation”/cell/d. In comparison, only ~5x10^7 DNA alterations/cell/d and ~10^-7 “mutations”/cell/d are produced by 0.1 cGy/y background low LET radiation (Figure 1).

The accumulation of gene mutations with aging gradually impairs DNA damage-control. This in turn increases the rate of accumulation that is associated with increased risk of cancer with the 3rd to the 5th power of age. Death from cancer at an early age is usually the result of severe genetic impairment of DNA damage-control. Similarly, high-dose, high dose rate radiation also increases the risk of cancer by exceeding the homeostatic capacity of the antimutagenic system.

MOLECULAR AND CELLULAR BIOLOGY
While high-dose radiation overwhelms the antimutagenic system, low doses are stimulatory. The UNSCEAR 1994 Report and recent studies provide extensive documentation of low-dose stimulation of many cellular functions, including antioxidant prevention (Figure 2), enzymatic repair (Figure 3), and apoptotic and immunologic removal (Figure 4) of DNA damage. This biphasic reaction of antimutagenic adaptive responses predictably precludes a linear dose-response relation of radiation and health effects. The quantitative damage produced by background radiation ROS is comparatively negligible and is controlled by the same antimutagenic system, a homeostatic system that is stimulated by a ten, or even a hundredfold increase in background radiation. This enhanced prevention of gene mutations by spatial and temporal differences of ionizing radiation ROS is associated with decreased mortality and decreased cancer mortality observed in populations exposed to low-dose radiation.

EPIDEMIOLOGY
All epidemiologic surveys of populations with high background radiation in the United States, Brazil, China, India, and Iran have observed no increased mortality or cancer mortality than in control populations with low background radiation. During the past decade decreased mortality and decreased cancer in human populations exposed to low-dose radiation have been observed with high statistical power in large populations and with careful consideration of controls: US-Japan Atomic Radiation Effect Research Foundation (RERF) (Figure 5), East Urals Population Study (Figure 6), U.S. Nuclear Shipyard Worker Study (Figure 7), University of Pittsburgh Residential Radon Study (Figure 8), and the Canadian Breast Cancer Fluoroscopy Study (Figure 9).

These epidemiologic observations of decreased cancer mortality and increased longevity of public, occupational, and medical cohort populations exposed to increased low-dose radiation are consistent with 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).

IMMUNE SYSTEM RESPONSE TO RADIATION
Low-dose total body irradiation (TBI) and chronic TBI (LDR) stimulate immune system prevention and removal of cancer metastases in mice, rats, and humans. This has been shown in mice for almost 40 years and more recently in rats and humans. The maximal immune response of mouse splenic cells to sheep red blood cells, both in vitro and in vivo, occurs after a single dose of 0.25 Gy (25 r) (Figure 11). The maximal response is 180% in vitro and 145% in vivo compared to 100% response in control sham-irradiated mice. Though the in vivo maximum response is less, it is much more resistant to suppression by high doses; more than 260 r is required for suppression to 50% of control compared to 100 r suppressing in vitro response to 50% of control.
TBI with subimmunogenic tumor antigen induce tumor immunization (Figure 12).\textsuperscript{15} Sham irradiated controls inoculated subcutaneously with 100 non-viable tumor cells did not suppress growth of 10,000 viable tumor cells inoculated subcutaneously 21 days later. However, 15 r TBI given simultaneously with 100 non-viable tumor cells induced marked suppression of tumor cell growth exceeding that induced by 100,000 non-viable tumor cells without TBI.

TBI stimulates immune suppression of tumor metastasis to lung (Figure 13).\textsuperscript{20} Lung colonies counted 20 days after TBI which was given 12 days after tumor cell transplantation into axilla of mice, were decreased by TBI doses less than 50 r; 15 r TBI induced the maximal decrease of 60%. High doses of 50-100 r suppressed the immune system with increased metastases to lung.

Chronic TBI (a course of total body low dose radiation [LDR]) stimulates immune system response of splenic T lymphocyte proliferation in mice (Figure 14).\textsuperscript{16} Mice irradiated 5 days/week for 4 weeks with LDR courses of 10 r (0.5 r/d), 20 r (1.0 r/d) and 80 r (4.0 r/d) showed proliferative responses of 115%, 140%, and 160%, respectively, relative to the 0 r control group as 100%.

LDR with chronically restricted diet (CRD), calorically 70% of ad libitum diet, prevent and remove spontaneous breast cancer tumors in mice (Figure 4).\textsuperscript{7} Eight month old, breast tumor susceptible female mice, after 3-week adjustment to CRD, were exposed to a 4-week course of LDR 48 r (4 r 3d/week x 4 weeks) and then observed for 35 weeks. While 73% of the ad libitum diet mice and 27% of the CRD mice developed breast cancer, only 16% of the CRD+LDR mice developed breast cancer. Most impressive was the very rapid 80% tumor regression of the CRD+LDR mice compared to 20% and 4% regression in the CRD and control mice, respectively. Large numbers of cytotoxic CD8\textsuperscript{+} T cells were observed infiltrating the regressing tumors of CDR+LDR mice, but not in control and CRD mice.

Metastasis is also suppressed by TBI tumor-bearing rats (Figure 15).\textsuperscript{17} TBI, or localized irradiation to implanted tumor with 20 r, or control sham-irradiation were given 14 days after tumor implantation into the leg. The number of visible metastatic colonies in the lung and the incidence of metastasis in mediastinal and axillary lymph nodes were obtained 50 days after implantation. The number of tumor-tissue infiltrating lymphocytes/microscopic field was observed 21 days after implantation. Metastases to the lung and mediastinal and axillary nodes in TBI rats were reduced by more than 70% of those in control and locally irradiated rats. Tumor tissue infiltration by lymphocytes in TBI rats was more than 900% of that in control and locally irradiated rats. Cytotoxic CD8\textsuperscript{+} T cells in the spleen of TBI rats were increased to 176% of those in control and locally irradiated rats.

HUMAN LOW DOSE RADIATION (LDR) CANCER IMMUNOTHERAPY

Two Harvard University clinical trials of LDR therapy of patients with non-Hodgkins lymphoma were published in 1976 (Figure 16)\textsuperscript{15} and 1979 (Figure 17).\textsuperscript{19} The protocols were very similar. The Chaffey et al. (1976) trial used a LDR course of 150 r given in fractionated TBI doses of 15 r 2x/week for 5 weeks. The Choi et al. (1979) trial also used a course of 150 r given in TBI doses of either 15 r 2x/week or 10 r 3x/week for 5 weeks. In both studies transient low platelets requiring temporary interruption of scheduled therapy occurred in 35-40% of patients, irrespective of 10 r or 15 r dose schedule. Both control and LDR patients received chemotherapy and localized tumor high dose radiation. Histologic grades of LDR and control patient tumors were similar. COP chemotherapy used in the 1976 trial was replaced in the 1979 trial by more effective CHOP chemotherapy.

Both studies present 4 year survival data. Four year survival in the 1976 study of 25 LDR patients is 70% compared with 40% survival of 25 matched control patients treated with COP (Figure 16).\textsuperscript{18} The 1979 study shows 74% 4 year survival of 39 LDR patients compared with 52% survival of 225 patients treated with CHOP (Figure 17).\textsuperscript{19}

Sakamoto et al. (1997)\textsuperscript{20} at Tohoku University, Sendai, Japan, published a review of their experimental studies in mice and a clinical trial of LDR in humans. In mice, 15 r TBI induced the maximal suppression of tumor metastasis (Figure 13).\textsuperscript{21} TBI given 6-12 hours before localized high dose tumor therapy increased effectiveness of tumor therapy. TBI, upper half body irradiation (HBI), and localized splenic irradiation were equally effective in stimulating the immune system.

Their 1997 study of LDR therapy of patients with non-Hodgkin’s lymphoma is similar to the 1979 study by Choi et al. Both used a LDR course of 150 r with equally effective doses of either 15 r 2x/week or 10 r 3x/week for 5 weeks and CHOP chemotherapy. Choi et al. used TBI while Sakamoto et al. used either TBI or HBI (Figure 18) with equal effectiveness and without interruption of scheduled therapy because of low platelets.

Sakamoto et al. present 9 year survival data of 23 LDR patients and 94 control patients with similar histological tumor grades; approximately 75% of each group showing intermediate and high grade non-Hodgkin’s lymphoma (Figure 19).\textsuperscript{20} Tumors outside the HBI field were shown to regress completely in response to LDR (Figure 20).\textsuperscript{21} The 9 year survival of LDR patients is 84% compared with 50% survival of CHOP.
control patients. The 12 year survival of LDR patients remains 84% (personal communication).

Comparison of 4 year survival in the Harvard and Tohoku studies are consistent in showing about a 20% better survival of LDR patients compared with control CHOP patients. In the Japanese study, however, the moderate decrease of platelets did not require schedule interruption and the 4 year survival of both LDR and control CHOP patients is increased about 10% above those of the United States study. This may be related to the well established benefits of lower caloric dietary intake and more exercise in the Japanese population. Though racial differences may be a factor, this has not been demonstrated in Japanese living in the United States. In general, the population of Japan is lean and physically active with a diet low in calories and fat, high in vegetables - particularly soy and seaweed products, with some fruit, little fish and very little meat. Sound nutrition and regular exercise stimulate the immune system. LDR therapy is more effective when administered to patients with better initial immune system activity.

SUMMARY

Recent research has led to recognition of the importance of the immune system in controlling cancer as well as infectious disease. LDR cancer immunotherapy has been shown to be effective in rodents and man. Optimal protocols need to be developed, including the efficacy of LDR localized to the spleen. Published results justify support of well designed clinical trials of LDR therapy in patients with prostate, breast, colon, ovarian cancer, and lymphomas. Clinical trials are also indicated to determine the efficacy of LDR immune stimulation in patients with early HIV disease and in vaccine potentiation for prevention of HIV and other diseases. LDR therapy is a rational and very promising way of using our antimutagenic system to control cancer and infection.

REFERENCES:


A 549 Human Lung Cancer Cell

Removal of Thymine Glycol After 2 Gy Dose

![Graph showing the removal of thymine glycol after 2 Gy dose.](image)


Figure 3. Low dose induced DNA repair. Le X. et al. Science 280:1066 (1998)

![Graph showing the change in SO2 response with dose.](image)

Figure 2. Antioxidant SO2 and lipid peroxide response to age and radiation of rat brain cortex. Yamazaki K, (1991)

Figure 4. Eight month old, mammary tumor-susceptible, female C3H/He mice were first adjusted in a stepwise manner to chronic restrictive diet (calorically 70% ad libitum diet) (CRD) over a period of 3 weeks. The mice were maintained on CRD until completion of the study. After their diet was adjusted, the mice were exposed to TBI (0.04 Gy, 5 alternating days/weeks, 4 weeks) and were observed for 35 weeks. Tumor regression of the CRD + TBI group was very rapid and large numbers of C3H-7 cells were found infiltrating the regressing tumors, which were not seen in mice of the untreated control, LDR and CRD groups. Adapted from Malmudin (1990).
Figure 3. 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. Silver M. et al. (1983)

Nuclear Worker Cumulative Dose: 0.5 – >40 cSv (rem)

SUMMARY OF FINDINGS: SMR Ratios Table 4.1.A


Figure 5. Standardized mortality ratios for selected causes of death among shipyard workers in the U.S. Marine Corps (1991)

Figure 6. Lung cancer mortality rates compared with mean home radon levels by U.S. county and comparison with linear model by BSR IV

Figure 9. Canadian breast fluoroscopy study. Adapted from Miller AB, et al. (1989)

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

Figure 11. Immune system response to radiation. Mouse splenic cells primed with antigenic sheep red blood cells. Makinohana T and James SJ. (1990)

Figure 12. Effect of 0.15 Gy upon response of AJ mice to subimmunogenic and immunogenic numbers of non-viable mitomycin-C-treated fibrosarcoma (SW) tumor cells. Groups of 80 mice were exposed to whole-body irradiation or sham-irradiated and inoculated subcutaneously with the indicated numbers of mitomycin-treated tumor cells. Twenty-one days later, all animals received 10^6 untreated SW cells and were followed for tumor size. A control group did not receive mitomycin-treated cells. Adapted from Anderson, et al. (1989).
Figure 13. TBI given 12 days after tumor cell transplantation into axilla. Lung colonies counted 20 days after TBI. Low dose TBI ineffective with spleen blocked. Low dose splenic irradiation, half-body irradiation (HBI) and TBI equally effective. Adapted from Sakamoto, et al. J. Appl. Soc. Thor. Radiol. Oncol. 9:169-175, 1977.

Figure 14. Dose-response analysis of splenic T cell proliferative response 3-5 d after the last radiation exposure of immunologically normal, long-lived C57Bl/6 J +/- mice. Results are expressed as the mean percent increase in thymidine uptake relative to 0 Gy control group as 100%. The vertical bars = ± SEM. Makinodan and James (1999); adapted from James and Makinodan (1988).

Figure 15. The number and incidence of metastases in lung and lymph nodes of mediastinum and axilla 50 days after intramuscular (leg) tumor implantation. In rats, and the number of tumor infiltrating lymphocytes 21 days after implantation. Total body or localized tumor irradiation, with 0.2 Gy was given 14 days after implantation for 10% allogenic hepatoma cells. Hashimoto et al. Radiation Res. 151:717-728 (1999).

Figure 16. Comparison of TBI with COP Chemotherapy (Cytoscan, Oncovin, Prednisone) in matched groups of 25 patients.

4 year survival: TBI-HBI 84%  Chemotherapy 66%  (79% of TBI-HBI Survival)
9 year survival: TBI-HBI 84%  Chemotherapy 50%  (60% of TBI-HBI Survival)

Figure 19. Comparison of low-dose irradiation of half body (HBI) or Total Body (TBI) of patients with Non-Hodgkin's Lymphoma. Patients in both groups received chemotherapy and localized tumor high-dose irradiation. Adapted from Sakamoto et al. J Jpn Soc Ther Radiol Oncol 9:161-175, 1997.

Figure 18. Treatment of patients with Non-Hodgkin's Lymphoma with half (HBI) or total (TBI) body irradiation. Adapted from Sakamoto K, et al. J Jpn Soc Ther Radiol Oncol 9:161-175 (1997).