Small Radiation Doses Enhance Natural Barriers to Cancer

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http://www.jpands.org/vol22no4/scott.pdf

ABSTRACT

Natural barriers to cancer exist at the molecular, cellular, tissue, organ, and whole-body levels. The cancer barriers are diminished by high radiation doses, facilitating cancer occurrence. In contrast, low radiation doses enhance these cancer barriers, which can lead to threshold and hormetic dose-response relationships for cancer induction. These facts render the linear-no-threshold (LNT) model for cancer induction implausible.

In earlier eras in geologic time, the level of natural background radiation is estimated to have been about five-fold larger than in recent times.[1] Mammals likely could not have survived in this harsher radiation environment without the ability to enhance natural protection (barriers) against cancer and other life-threatening diseases.[2]

Molecular-Level Cancer Barriers

Protection against Cancer-Facilitating Oxidative Damage

Reactive oxygen species (ROS) are generated in cells through natural metabolic processes. These processes include respiration, ischemia/reperfusion, and oxidation of fatty acids. High concentrations of ROS can overwhelm cellular defenses, resulting in unrepaired damage to DNA, lipids, and enzymes, which can lead to diseases including cancer.[3] Cells have, however, sophisticated molecular defenses (i.e., natural barriers) that protect them from ROS attack. These include enzymatic mechanisms (e.g., superoxide dismutase, catalase, and glutathione peroxidase), as well as non-enzymatic mechanisms that involve the reduced forms of molecules such as glutathione (GSH), thioredoxin-1 (Trx-1), vitamin C, and vitamin E.[3-8]

A small whole-body x-ray dose (0.2 Gy) increased the antioxidants superoxide dismutase (SOD), glutathione peroxidase (GPx), and GPx messenger RNA in spleens of C57BL/6NJcl and BALB/c mice;[8] however, a large dose (4 Gy) did not.[8] Radiation enhancement of natural molecular barriers against oxidative damage was also observed in an earlier mouse study,[5] which showed that the levels of reduced GSH, glutathione reductase (GR), γ-glutamylcysteine synthetase (γ-GCS), and Trx (thioredoxin) increased in liver shortly after whole-body gamma-ray exposure to a moderate dose (0.5 Gy). In addition, the levels of GSH, GR, γ-GCS, and Trx increased in the brain.[6] These findings support the claim that exposure to low and moderate radiation doses enhances natural molecular barriers (antioxidants) to oxidative damage, thereby helping to protect from sporadic cancer.

Cancer Barrier Regulation by Rapid Epigenetic Changes

Research on the biological effects of exposure of human cells to low radiation doses demonstrated that the molecular and cellular processes observed are often related to adaptive responses associated with enhancing natural protection against cancer.[9] The adaptation appears to be epigenetically regulated via changes in gene expression that involve messenger RNA (mRNA) and microRNA (miRNA). Such protective epi-regulated changes are much more likely than are gene mutations after exposure to low radiation doses.[10-11] At the cellular level, mild stress from low-dose radiation elicits adaptive responses.[12]

Epigenetic alterations are heritable changes that control gene expression. The changes are important for regulating the structure and function of the genome without any changes in the DNA sequence. The alterations include remodeling of chromatin, genetic imprinting, DNA methylation, histone modifications, random X chromosome inactivation, and noncoding-RNA-regulated gene expression. The main mechanisms of epigenetic changes are via modifications in DNA methylation and changes in how DNA is packaged around the core histones. Both mechanisms can result in rapid gene activation or silencing.[10]

Radiation-induced rapid epigenetic changes include miRNA expression.[13] At low radiation doses, miRNA changes that occur are involved in stimulating DNA repair, suppressing cell lethality, and suppressing cancer progression.[13]

Enhancement of DNA Damage Repair and Related Molecular Changes

DNA double-strand breaks are the most serious type of genomic damage and are induced as a linear-no-threshold (LNT) function of dose.[14] This LNT relationship led to the false belief that cancer induction is also an LNT function of radiation dose. DNA double-strand break repair is activated by low radiation doses and may involve intercellular communications arising as what has been called an epi-regulated cell-community-wide (epicellcom) process.[15] With an epicellcom process, damage to a small number of cells leads to signaling between a large number of cells (a mild stress response), thus bringing about a cell-community-wide rather than an individual cell response.

Useful information related to DNA damage repair activation by low radiation doses has been derived from studies of radiation-induced mutations. A sex-linked recessive lethal mutation assay was performed[16] in *Drosophila melanogaster* using immature spermatocytes and spermatogonia that were exposed to x-rays at a high (0.5 Gy/min) or low (0.05 Gy/min) rate. The mutation frequency in the sperm irradiated with a low dose given at a low rate was significantly lower than that for controls. In contrast, irradiation with a high dose and dose rate resulted in a significant increase in the mutation frequency. This is a hormetic response: low-dose enhancement of natural mutation barriers and high-dose/high-rate suppression of the barriers. When cells deficient in DNA excision repair were used instead of wild-type cells, low-dose irradiation at a low rate did not reduce the mutation frequency. There was no evidence for mutation barrier enhancement. These findings are consistent with the possibility that error-free DNA repair was

activated (enhanced) by low-dose/low-dose-rate irradiation as an epicellcom process and that this repaired spontaneous DNA damage throughout the target cell population as well as radiation-related damage, thus producing a protective natural barrier for mutation-related harm (e.g., mutation-facilitated cancer). The findings contradict the LNT hypothesis as it relates to mutation and cancer induction, as a dose threshold would be expected to overcome the protective barrier. With the LNT hypothesis, a low dose benefits nobody and always harms someone (e.g., causes cancer) in a large population.

The LNT hypothesis was initially justified on the basis of the dose-response function for mutation induction in germ cells of *Drosophila melanogaster* interpreted to be of the LNT type, based on the very high x-ray doses employed by Muller;[17] however, a more recent, better designed, and more reliable study[18] using gamma rays that included much smaller radiation doses (delivered at the low rate 0.0224 Gy/h) demonstrated that a strong adaptive response (enhanced barriers to mutations) occurs at low doses with a significant reduction ($p < 0.01$) in the mutation frequency to well below the spontaneous (background) level. This was observed for a dose of only 0.0005 Gy (0.5 mGy).

Because there is on average less than 1 radiation hit (electron track from ionizations) to a given cell at the indicated radiation dose, this is likely a protective bystander effect that relates to rapid epigenetic activation (epiactivation) of adaptive-response genes.[15] Thus, the induced-mutations basis for use of the LNT risk model for cancer induction is implausible.[19] Interestingly, the 0.0005 Gy dose up-regulated protective mild-stress-response genes; however, DNA repair-related genes were not up-regulated at this very low dose.[18] Somewhat higher doses appear to be needed for up-regulation of DNA repair genes.[20] Rather than relying only on DNA damage repair for mutation and cancer avoidance, aberrant cells can be eliminated via selective apoptosis (another natural cancer barrier) as a mild-stress response when signaled to divide.[20] These adaptive responses are probably regulated epigenetically and likely involve intra- and intercellular signaling.

ATP signaling is emerging as having an important role in radiation adaptive responses. This includes DNA damage repair, stimulating the production of endogenous antioxidants, cell-mediated immune responses, and differentiation of regulatory T (Treg) cells.[21]

Cancer Barriers at Cellular, Tissue, and Organ Levels

Humans and other species also have natural barriers against cancer at the cellular, tissue, and organ levels that are enhanced by low-dose radiation.

Cellular Senescence

Cellular senescence, a metabolically active form of irreversible growth arrest, can provide a barrier to cancer occurrence.[22-23] The senescence occurs in response to a variety of intrinsic and extrinsic stimuli (e.g., low-dose radiation)[24-27] and is mediated through tumor suppressor signals.[28,29] Importantly, senescence can halt the division of unstable cells, thereby preventing the transmission of cancer-facilitating instability to daughter cells. Cellular senescence thus represents a natural cellular barrier to tumor formation,[30] and the barrier can be enhanced by low-dose radiation.

Selective Removal of Aberrant Cells

Selective death of aberrant cells via apoptosis without harming normal cells is also an important barrier to cancer,[31-37] and in some cases is p53-independent (e.g., for neoplastically transformed cells).[35] Cell death via apoptosis, autophagy, or necrosis is a fundamental cellular response to stress. Apoptosis (which can selectively eliminate aberrant cells) is a regulated cell death process in response to signals from the cellular environment and is carried out by machinery within cells.[34, 38-40] In contrast, necrosis is uncontrolled cell death brought on by massive stress (e.g., from high-dose radiation). Autophagy involves self-destruction starting with engulfment of cytoplasmic material by the phagophore and sequestration of material to the autophagic vacuoles, where they are eventually destroyed.[41] The type and intensity of stimuli, type of tissue, developmental stage of the tissue, and the physiologic cellular micro-environment determines the cell death process.[39]

The ability of a pre-cancerous cell to escape natural anti-cancer signals from neighboring cells and the micro-environment is an important step towards tumor formation.[42] Researchers have characterized a system of intercellular induction of apoptosis whereby non-transformed cells communicate (via intercellular signaling) with and stimulate selective removal of neoplastically transformed cells from cell cultures that include both cell types. The communication is carried out via cytokine, reactive oxygen species (ROS), and reactive nitrogen species (RNS) signaling. This p53-independent phenomenon has been called a protective apoptosis-mediated (PAM) process.[43,44] The researchers[42] demonstrated that irradiation of non-transformed cells with low doses of alpha particles or gamma rays led to intercellular induction of apoptosis (i.e., the PAM process). By using specific scavengers and inhibitors, they confirmed the involvement of ROS/RNS signaling and the importance of transformed-cell-secreted nicotinamide adenine dinucleotide phosphate (NADPH) oxidase in the selective removal of transformed cells. By applying a neutralizing antibody assay, the researchers confirmed an important role for transforming growth factor β (TGF-β) in the radiation-induced intercellular signaling. The indicated protective system appears to represent natural anti-cancer mechanisms (i.e., cancer barrier) that protected organisms even when background radiation levels on earth were much higher than they are today.

Researchers studying the PAM process using cell cultures have also found that low-dose gamma rays substantially increased superoxide anion production in both oncogenically transformed cells and tumor cells, but not in non-transformed cells.[45] The level of increase did not depend on the radiation dose over the range 0.02 to 0.2 Gy (20 to 200 mGy). This observation supports the concept of an epicellcom response to mild stress.

Other researchers demonstrated using cell cultures that low doses of ionizing photon radiation (x-rays, gamma rays) can lead to a reduction in the neoplastic transformation frequency to below the spontaneous level,[46-49] while high doses led to elevated transformation frequencies that increase as the radiation dose increases (i.e., a hormetic response). The reduction in the spontaneous frequency (hormetic benefit) may relate to intercellular signaling between transformed and non-transformed cells leading to selective removal of the transformed cells.

Tissue Interactions

Tissue-level interactions (contact inhibition of cell proliferation, exchange of signaling and regulatory molecules via intercellular junctions, and secretion of regulatory factors by neighboring cells and stroma) are important in tumor suppression and control.[50,51] Thus, these interactions can serve as barriers to the carcinogenic process.

Suppression of Cancer-Facilitating Inflammation

Large radiation doses to the total body exceeding 1 Gy may initiate inflammatory reactions, and if so can facilitate cancer development.[52] A large amount of experimental evidence indicates that small radiation doses can suppress several inflammatory processes.[52-54] The suppression involves hindered leukocyte adhesion to endothelial cells, reduced activity of inducible nitric oxide synthase, and reduced oxidative burst in macrophages.[53]

Cigarette smoke contains the chemical benzo[a]pyrene (BaP) that when metabolized in the body produces the inflammation-promoting carcinogen BaP diol epoxide (BPDE). The metabolite induces lung tumors (often multiple) in animal models when given at high immunosuppressive levels.[55] Further, cigarette smoke constituents cause inflammation and related lung cancer in humans. Importantly, lung cancer (including smoking-related cancer) in humans has been found to be suppressed by long-term, low-to-moderate-level exposure to radon in the home,[56,57] and also demonstrated to be suppressed in animal studies.[8]

Because BPDE modifies the microenvironment (e.g., stromal cells) of potential cancer-causing lung epithelial cells (if neoplastically transformed), researchers investigated whether low-dose-gamma rays could modify the in vitro response of stromal cells to BPDE exposure.[58] The strategy was based on neoplastic transformation of human bronchial epithelial cells (HBEC) being an essential step in the lung cancer development in cigarette smokers. Researchers used a cell-culture/media-transfer approach in their neoplastic transformation work. Results indicated that BPDE induces secretion of the pro-inflammatory cytokines (interleukin-6 (IL-6) and others) from human lung fibroblast, which facilitates neoplastic transformation of the HBEC. More importantly, a single low-dose 0.09 Gy (90 mGy) of gamma rays inhibited the IL-6 secretion, thereby enhancing the barrier to neoplastic transformation of HBEC. This implied protective effect of low-dose radiation against lung cancer among smokers does not support the LNT risk model for cancer induction, since with the LNT model radiation exposure should add to the smoking-related harm rather than reducing it.

Whole-Body Level Cancer Barriers

Some natural barriers against cancer operate at the whole-body level, and they are also enhanced by low-dose radiation.

Anti-Cancer Immunity

At the whole-body level, anti-cancer immunity can eliminate cancer cells via a coordinated cellular and humoral biological system. Unfortunately, tumors can locally suppress the body's immune system by creating a microenvironment that allows unchallenged tumor growth. One way they do this is by recruiting high numbers of regulatory T cells (Tregs), which can be immunosuppressive.

It is now recognized that while high radiation doses suppress anti-cancer immunity and thus facilitate cancer development, low doses and dose rates can enhance anti-cancer immunological barriers.[59-64] Ecological studies that support this view have shown that people living in elevated-natural-background radiation areas in Brazil, China, India (Kerala), the U.S., the Misasa Radon spa area of Japan, and elsewhere, have lower cancer mortality than those living in areas with lower background radiation.[65-68] In addition, a significantly lower rate of cancer mortality among the population residing in the Guangdong area of China with elevated background radiation correlates with enhancement of the immune system.[59,69] Similar results have been reported for other human populations and for experimental studies with laboratory animals.[59,70-72]

Activation of several immune system-related cells such as natural killer (NK) cells, dendritic cells, macrophages, and T cells, as well as an increase in mast cell activity, was observed after use of low-dose radiation to treat tumors.[62,73] A decrease in tumor-growth-promoting Tregs, altered cytokine responses (e.g., an increase in IL-2 and IFN-γ secretion, and a decrease in TGF-β levels),[63,74] and antibody production have also been observed.[64]

Experimental studies using low-dose x-rays or gamma rays in different strains of mice demonstrated a decrease in the growth rate of tumors as well as inhibition of metastasis, and these findings correlated with enhancement of anti-cancer immunity.[64,75,76] Low-dose radiation-induced enhancement is reported to occur at least in part through induction of both antigen-presenting cells (APCs) and T lymphocytes, facilitating intercellular reactions within the immunological synapse.[61] Expression of molecules that are involved in immunosuppression, such as CTLA-4, cytokines (such as IL-10 and IL-4), c-AMP, and protein kinase A, decreases after low-dose irradiation, leading to enhancement of anti-cancer immunological barriers.[61] Low-dose irradiation also up-regulates several other anti-cancer factors such as the NK-cell activity, antibody-dependent cellular cytotoxicity (ADCC) activity of splenocytes, cell surface molecules such as CD25 (IL-2 receptor), and immune system signaling molecules.[61] However, the immune system response to low-dose irradiation varies with cell type, dose range, dose rate, and how the dose is spread over time.[59]

Researchers examined whether the increase of glutathione levels induced by low-dose gamma rays is involved in the appearance of enhanced NK (natural killer) cell activity and ADCC (antibody-dependent cellular cytotoxicity), and leads to a suppression of tumor growth in Ehrlich solid tumor-bearing mice.[77] NK cell activity in ICR mouse splenocytes increased from 4 to 6 hours after whole-body exposure to 0.5 Gy (500 mGy) of gamma rays, and thereafter decreased to near the baseline level by 24 hours after exposure. The ADCC pattern over time was similar.

Adding reduced glutathione to splenocytes in culture (obtained from normal mice) enhanced both NK activity and ADCC in a dose-related manner. Tumor growth was also examined in mice with inoculated tumors and the growth rate after inoculation was significantly reduced by low-dose gamma rays. The results support the view that low-dose irradiation can activate anti-cancer immune functions in the body through induction of glutathione.

Researchers also investigated the influence of repeated (fractionated) 0.5 Gy (500 mGy) gamma-ray doses on the Th1/

Th2 immunity balance in mice with Ehrlich solid tumors.[78] Fractionating the dose helps reduce severe damage to normal tissue. The radiation exposure delayed the growth of the tumors. In addition, the cytotoxic activities of natural killer cells and cytotoxic T lymphocytes were enhanced. Radiation exposure also increased the production of IFN-γ by splenocytes of tumor-bearing mice, but their Interleukin 4 (IL-4) was not altered, resulting in an increased IFN-γ/IL-4 ratio, an indication of a shift to a Th1 phenotype. The radiation exposure also increased IL-12 production and levels of reduced glutathione in macrophages. These findings reflect fractionated radiation exposure with moderate-size fractions enhancing natural cancer barriers.

It has also been demonstrated [79] that low-dose irradiation causes macrophage differentiation to a phenotype (called iNOS+/M1) that coordinates effective T cell immunity. The researchers showed that local low-dose gamma irradiation causes normalization of aberrant vasculature and efficient recruitment of tumor-specific T cells in human pancreatic carcinomas and also T-cell-mediated tumor rejection in spontaneous and xenotransplant (foreign tissue transplant) mouse models for tumor research.

Using an artificial tumor metastasis model, in which tumor cells were injected into mice, researchers conducted studies of metastasis suppression by low-dose radiation by enhancing anti-cancer barriers.[80,81] They demonstrated that single, total-body exposure of mice to 0.1 or 0.2 Gy (100 or 200 mGy) of x-rays inhibited development of artificial tumor metastases in the lungs, and that the effect related in part to the enhanced activity of NK cells. The same research group also demonstrated in another study[82] that inhibition of the tumor metastases by single exposure of mice to 0.1 or 0.2 Gy (100 or 200 mGy) of x-rays results largely from stimulation of the cytocidal activity of macrophages that secrete increased amounts of nitric oxide.

Ingested and Inhaled Radon

An increasing number of research findings support the view that radon suppresses inflammation and stimulates the immune system. Suppressing inflammation can indirectly be inferred from the suppression of inflammation-related diseases. Stimulation of anti-cancer immunity can be inferred from a reduction of metastatic cancer. Researchers examined the effect of ingested radon (an alpha radiation source) in suppressing metastatic cancer by enhancing natural cancer barriers.[83] The number of pulmonary metastatic foci in six-week-old male C57BL/6 mice inoculated with B16 melanoma cells two weeks after the start of radon ingestion (in drinking water) was reduced significantly by the ingested radon. In addition, the IFN-γ/IL-4 ratio in splenocytes from BALB/c mice immunized with DNP-Ascaris was significantly increased by ingested water that contained elevated radon. Researchers interpreted the results to indicate beneficial modulation of the immune system (anti-cancer immunity) by the ingested radon.

We are all exposed by inhalation to residential radon. In fact, residential radon levels are tightly regulated, and this impacts new home purchases. Researchers[56] in an epidemiological study of lung cancer in association with residential radon exposure found a reduction in lung cancer cases for persons in homes with radon levels near and at the U.S. Environmental Protection Agency's action level of 4 pCi/L for home remediation (i.e., removal of radon). The exposure-response relationship was hormetic, indicating that reducing radon in the home could in some cases increase lung cancer risk, especially for smokers.[15]

Discussion

This paper reviews the currently known hierarchy (molecular, cellular, tissue, organ, and whole-body levels) of natural cancer barriers that are enhanced by low-dose radiation-related mild stress. The indicated beneficial effects of low-dose radiation are linked to the currently known hallmarks of cancer suppression (Table 1) that include epiregulated (i.e., epigenetically regulated) DNA repair and antioxidant production, selective p-53-independent apoptosis of aberrant cells (e.g., neoplastically transformed cells), suppression of inflammation, and anti-cancer immunity along with diminution of tumor growth signaling. All these hallmarks of cancer suppression (and possibly other unknown hallmarks) are stimulated by low doses of ionizing radiation and may also be stimulated by other forms of mild stress including some chemical stresses and exercise. The cancer suppression mechanisms and their boosting by low-dose radiation are consistent with the previous conclusion by others[84-86] that the LNT risk model for radiation-induced cancer has no scientific basis.

Suppression of inflammation by low- and moderate-dose radiation could possibly reduce the severity of inflammatory diseases and may aid in preventing cancer. Indeed, residential radon may be helping to prevent lung cancer in heavy smokers. If so, reducing the radon level in the home could in some cases actually increase the risk of smoking-related lung cancer.[87]

The existence of protective effects of low-dose radiation reflected by hallmarks of cancer suppression essentially invalidates the LNT risk model for radiogenic cancer. Thus, one may ask: Why, with such overwhelming evidence for health benefits rather than harm from low radiation doses, is the LNT cancer risk model still used by regulatory and other governmental agencies worldwide? This question is especially

Table 1. Hallmarks of Cancer Suppression

Hallmark	Health benefit
Epigenetically regulated DNA damage repair and antioxidant production	Prevents persistent genomic damage
p-53-independent selective apoptosis of aberrant cells	Removes neoplastically-transformed cells
Inflammation suppression	Reduces cancer risk
Anti-cancer immunity and diminution of growth signaling	Destroys cancer cells and inhibits tumor growth

important given that thousands of needless radiation-phobia-related abortions followed the 1986 Chernobyl nuclear power accident, and there were more than 1,000 deaths after the 2011 Fukushima nuclear power plant accident related to LNT-linked evacuation stresses (deaths largely among the fragile elderly).[88-90] The answer is that continued use of LNT is now justified on the basis of unreliable and seriously flawed epidemiological studies that employ data adjustments that seem to be untested for their reliability and validity, and other procedures that favor an LNT outcome including inappropriately using the LNT assumption as the null hypothesis.[88]

Relying on results of unreliable epidemiological studies while ignoring results of basic and applied scientific research has indeed been quite costly to the world community. This approach has limited the use of low-dose radiation in cancer and other disease prevention and in disease therapy. Indeed, it is time to end reliance on the LNT model for low-dose cancer risk assessment, and instead rely on a scientifically valid approach. This view is supported in numerous other publications.[9,10,14,15,19,43,44,51,54,57,84-88,91]

Conclusions

Low doses of ionizing radiation are more likely to be beneficial rather than harmful. These doses enhance our natural cancer barriers rather than reducing them, in contrast to the effect of high doses. The examination of biological mechanisms and empiric results show that the LNT model is implausible and harmful, and should be replaced.

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Disclosures: Author declares that he did not receive financial support for preparation of this review publication, and has no conflicts of interest.

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