

MINIREVIEW

Health Risks of Low Dose Ionizing Radiation in Humans: A Review

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Radiobiologists have been struggling to estimate the health risks from low doses of radiation in humans for decades. Health risks involve not only neoplastic diseases but also somatic mutations that may contribute to other illnesses (including birth defects and ocular maladies) and heritable mutations that may increase the risk of diseases in future generations. Low dose radiation-induced cancer in humans depends on several variables, and most of these variables are not possible to correct for in any epidemiologic study. Some of the confounding factors include (i) interaction of radiation with other physical (UV light), chemical, and biological mutagens and carcinogens in a synergistic manner; (ii) variation in repair mechanisms that depend on dose; (iii) variation in sensitivity of bystander cells to subsequent radiation exposure that depends on whether they have been pre- or postirradiated; and (iv) variation in adaptive response that depends on radiation doses and protective substances (antioxidants). In our opinion, both the linear no-threshold-response and the threshold-response models might not be suitable in predicting cancer risk at low radiation doses in a quantitative sense. Low doses of ionizing radiation should not be considered insignificant for risks of somatic and heritable mutations and neoplastic and nonneoplastic diseases in humans. *Exp Biol Med* 229:378–382, 2004

Key words: ionizing radiation; low dose; health risk; mutations; cancer

Radiobiologists have been struggling to estimate the health risks from low doses of radiation in humans for decades. This is evidenced by the fact that six BEIR (Biological Effects of Ionizing Radiation) reports

have extensively discussed this issue referencing *in vitro*, animal and human studies on somatic and heritable mutations, and the incidence of neoplastic diseases and birth defects following radiation exposures. Heritable mutations are of particular concern, especially among women, because the number of oocytes are fixed at birth, and mutations, if not repaired, are cumulative. At present, two opposing hypotheses on the potential risks of low-dose radiation in humans are being debated among radiobiologists, geneticists, and health physicists because of their enormous impact on the health of current and future generations. The first hypothesis, supported by most radiobiologists and geneticists, proposes that there is no dose of radiation that can be considered completely safe and that the use of radiation must always be determined on the basis of risk versus benefit. The second hypothesis suggests that the health risks of diagnostic doses less than 10 cGy are not measurable and may even be nonexistent (1). Health risks involve not only neoplastic diseases but also somatic mutations that may contribute to other illnesses (including birth defects and ocular maladies) and heritable mutations that may increase the risk of diseases in future generations. Unfortunately, general statements on the health risks of low-dose radiation are usually made by the analysis of data on the risk of cancer alone.

Risk of Cancer

Human cancers arise from the accumulation of multiple genetic abnormalities (overexpression of genes, deletion of genes, or gene mutations), some of which must occur in critical genes that regulate proliferation and differentiation. Radiation-induced cancer in humans has long latent periods; 10 years for leukemia and over 30 years for solid tumors (2). Thus, there is a long period between radiation exposure and the appearance of tumors. This implies that radiation-induced mutations (due to gene mutations and/or chromosomal damage) that can be detected within 24 hrs of radiation exposure are not directly responsible for initiating

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carcinogenesis in normal human cells. However, such mutations induce genetic instability that make cells more sensitive to accumulation of additional genetic abnormalities caused by exposure to additional radiation doses, chemical mutagens and carcinogens, tumor promoters, oncogenic viruses, or their combinations. Cells may continue to carry genetic abnormalities for a long time until the expression of genes regulating differentiation is altered. This could lead to a cell immortalization phase, the first step in carcinogenesis. Immortalized cells can continue to proliferate until some key cellular genes, oncogenes, or antioncogenes are altered by additional exposure to carcinogens and/or tumor promoters. These cells then become fully transformed and can induce cancer when tested in appropriate hosts (3).

Dose-Response Models to Estimate Cancer Risk

Two opposing dose-response models have been used to estimate cancer risk in humans. The first model proposes that cancer risk following exposure to low doses of radiation (10 cGy or less) may be best estimated by a linear no-threshold relationship since any dose has the potential to induce cancer (4–6). The second model suggests that there is a threshold dose below which radiation may not induce cancer in humans (1, 7, 8). Both models have relied on mathematical modeling and human radioepidemiologic studies. The second model also utilizes data that support hormesis (8). “Radiation hormesis” is the name given to the putative stimulatory/adaptive effects of low-level ionizing radiation (generally in the range of 1–50 cGy of low-LET radiation). Based on historical and pharmacologic principles reminiscent of some of the major tenets of homeopathy, most of these effects are now generally ascribed to protective feedback systems that, on exposure to low concentrations of toxins, proceed to stimulate metabolic detoxification and repair networks. The activation of these networks may then result in net beneficial effects on the cell, organism, or species (9–21).

Mathematical modeling may assume certain constant physical factors such as body weight (7) that may not reflect the inherent biological variability associated with radiation-induced carcinogenesis. This variability includes differences in radiosensitivity with respect to age, organs, body mass, and differences in the efficacy of repair mechanisms. Numerous epidemiologic studies are available in the literature (2, 4, 22–27) and, if selectively used, can support both hypotheses. Radioepidemiologic studies have so many confounding factors that it is not possible to quantify purely radiation-induced cancer risk in humans. These confounding factors include environment, diet, and lifestyle-related factors that contribute mutagens, carcinogens, and tumor promoters as well as cancer-protective substances. The efficacy of cellular repair systems may vary from one individual to another because of variation in age, environment, and diet and lifestyle-related factors. Other confound-

ing factors include (i) interaction of radiation with other physical (UV light), chemical, and biological mutagens and carcinogens in a synergistic manner; (ii) variation in repair mechanisms that depend on dose; (iii) variation in sensitivity of bystander cells to subsequent radiation exposure that depends on whether they have been pre- or postirradiated; and (iv) variation in adaptive response that depends on radiation doses and protective substances (antioxidants). Thus, humans are simultaneously exposed to varieties of mutagens, carcinogens, and tumor promoters as well as to cancer-protective agents in addition to radiation. Therefore, low dose radiation-induced cancer in humans depends on several variables, and most of these variables are not possible to correct for in any epidemiologic study. This may explain why radioepidemiologic studies have produced inconsistent results. Thus, constructing a dose-response relationship for cancer based on epidemiologic data and on any mathematical modeling that cannot take into account the biological variability described previously may not provide meaningful data on the estimation of low dose radiation-related cancer risk in humans.

Adaptive Response and Hormesis

The use of data on radiation hormesis in support of the second hypothesis as was used in a recent publication (8) may not be very helpful. Some, but not all, analyses of data from various sources, including the Japanese survivors of the atomic bombs and residential radon studies, suggest that low levels of ionizing radiation may be beneficial to human health. The evidence, however, has not been viewed as compelling for the following reasons: (i) data in support of radiation hormesis in human populations are limited, and much of it is based on reevaluation of selected epidemiological data that has been used to test a different hypothesis; (ii) hormetic effects are weak and inconsistent and are subject to large statistical uncertainties as is the case for carcinogenic effects at small doses; (iii) a consensus is lacking on how hormesis should be defined and quantified; and (iv) it is unclear how hormesis can be incorporated into the regulatory framework when beneficial health effects exceed the requirement for protection of health (28, 29). It should be noted that adaptive responses are commonly observed with tissue insults regardless of the source of the insult. For example, hyperthermia and acute trauma also induce adaptive responses. Unlike other injurious agents, such as heat and trauma, ionizing radiation is a potent mutagen and carcinogen, and measuring radiation-induced adaptive responses does not reflect the mutagenic changes that might occur. Therefore, adaptive responses based on certain biological criteria following exposure to low doses of radiation may not be compelling evidence for the statement that such doses are beneficial to humans. On the contrary, they simply reflect that cells have been exposed to injurious agents and that attempts are being made to repair some of the damage.

Delayed Cell Death, Genomic Instability, and the Bystander Effect

Currently, human health risks associated with radiation exposures are based primarily on the assumption that the detrimental effects of radiation occur in irradiated cells. Over the years, a number of nontargeted effects of radiation exposure *in vivo* have been described that challenge this concept. These include radiation-induced genomic instability, bystander effects, clastogenic factors produced in plasma from irradiated individuals that can cause chromosomal damage when cultured with nonirradiated cells, and transgenerational effects of parental irradiation that can manifest in the progeny (30). Radiation-induced genomic instability is characterized by an increased rate of genetic alterations, including cytogenetic rearrangements, mutations, gene amplifications, transformation, and cell death in the progeny of irradiated cells multiple generations after the initial insult. Chromosome breakage syndromes are defined by chromosome instability, and individuals with these diseases are cancer prone. Consequently, chromosomal instability as a phenotype may underlie some fraction of those changes leading to cancer (31). Delayed expression of lethal mutations in the progeny of cells that survived a toxic insult was first shown for ionizing radiation and is one of the signs of induced genomic instability. The effect appears to be related to DNA strand breakage or repair but not to the physical break itself. The results clearly linked expression of delayed lethal mutations with radiation-induced DNA strand breaks, known also to induce oxidative stress. Alkylating agents or microtubule poisons that do not permit repair of DNA damage did not cause any delayed death. It is concluded that delayed cell death may be caused by widespread radical damage to DNA that is either signaled, thereby inducing an apoptotic response, or (mis-)repaired, yielding a weak or unstable genome. It is likely that the process may be an important factor in determining the long-term response of populations to "sublethal" levels of ionizing radiation (32–36).

Interaction Between Radiation-Induced Adaptive Response and Bystander Effects

It has been reported that cells lethally irradiated with α -particles could induce mutations in cells that were not exposed to α -particles and that reactive oxygen species (ROS) were not directly involved (37). A recent study showed that pretreatment of cells with low-dose x-rays before α -particle irradiation reduced α -particle-induced bystander mutagenesis (38). However, bystander cells exhibited increased radiosensitivity after a subsequent irradiation with x-rays (38). These data further complicate the interpretation of any dose-response model. It is unknown how long beneficial effects in reducing subsequent radiation damage or worsening subsequent damage to bystander cells is mediated by the adaptive response. How both adaptive response and bystander effects are influenced

by repair mechanisms at low radiation doses remains unknown.

Interaction of Radiation with Other Carcinogens and Tumor Promoters

Human cancer is caused by the interaction between several carcinogens and tumor promoters, by the interaction between carcinogenic agents and anticarcinogenic substances, and by the efficacy of repair systems. While assessing the effect of low doses of radiation on cancer risk, fundamental radiobiological studies that show that radiation can interact with other carcinogens and tumor promoters in a synergistic manner are often ignored. For example, x-radiation enhances chemical carcinogen-induced transformation in normal mammalian cells by about 9-fold (39) and UV-induced transformation by about 12-fold (40). X-irradiation also enhances the level of ozone- (41) and viral-induced (42) transformation in cell culture. Radiation doses that alone do not transform normal fibroblasts do so when combined with a tumor promoter (43). Ionizing radiation in combination with tobacco smoking increases the risk of lung cancer by about 50% (2). A low dose of radiation (2 cGy) does not produce detectable levels of mutations as measured by chromosomal damage; however, in the presence of caffeine (which inhibits repair of DNA damage), mutations become detectable (44). Low doses of radiation (2 and 5 cGy) can act as a mitogen (45), and even lower doses (about 1 mcGy) do not activate double-strand DNA break repair mechanisms (46). This lack of repair can lead to accumulation of mutations. Thus, it is nearly impossible to estimate the health risks of low doses of radiation alone in a real human population.

Using a microbeam technology, it was found that below 200 mGy, the survival potential was dominated by the bystander effect and that at higher doses, the direct effect of radiation on cell killing becomes dominant (47, 48). The cell survival data exhibited a linear-quadratic response when all cells were x-irradiated (with evidence for hypersensitivity at lower doses). When only a single cell was irradiated, 10% cell kill was observed (48). Below 200 mGy, the response after irradiation of a single cell was not significantly different from the response when all cells were irradiated (46). This observation is particularly significant because, at low doses, certain repair mechanisms are not activated. These results further support the suggestion that no dose of radiation can be insignificant or totally safe.

Risk of Cancer in Children of Women Exposed to Low-Dose Radiation Before and After Conception

In recent debates, issues of radiation damage to children of women who have been exposed to diagnostic doses of radiation before and after conception have been ignored. Since the number of oocytes is fixed at birth, radiation damage to oocytes, one of the most radiosensitive cells, may be cumulative and therefore may be very crucial for

inducing heritable genetic damage. Although radioepidemiologic studies are not considered very reliable, they have addressed these issues in women. Stewart and Kneale (26) have reported that an increase in cancer risk is directly proportional to the number of x-ray films or fetus doses received. It was estimated that 1 cGy delivered to the fetus shortly before birth would cause an increase of 300–800 deaths per million before the age of 10 years due to cancer. A significant increase (25) in malignancy has been found even after 2.0–2.5 mGy to human fetuses (relative incidence of cancer = 1.25). One of the most surprising results was published showing an increased cancer risk by a factor of 1.6–2.0 among women who received diagnostic doses of radiation before conception (49). Another study (27) reported that diagnostic doses (0.5–7 cGy) to the gonads before conception induced aneuploidy in 10 children (eight mongoloid and two trisomy) among 975 exposed women in comparison to one aneuploidy case among unexposed women. Gonadal exposure of 5 cGy increased eye defects (23) and of 3 cGy increased the mutation rate by 1% (24).

Intermediate Health Risk Factors in Children Exposed to Low Doses of Radiation

The incidence of nonneoplastic diseases and intermediate health risk biochemical markers were studied in children living in radiation-contaminated areas near the Chernobyl nuclear accident site. The incidence of thyroid gland enlargement and vision disorders, mostly dry eye syndrome, was closely related to the levels of contamination (50). Increased levels of oxidized conjugated dienes, products of lipid peroxidation, were found among these children. In another report, increased levels of spontaneous chemiluminescence, an indicator of enhanced oxygen radical activity, in leukocytes of children living in contaminated areas were observed (51). These epidemiologic data have limitations such as those described previously. However, in subsets of the population with relatively increased exposure to other carcinogens and tumor promoters compared to cancer-protective agents and relative suboptimal repair systems, radiation doses even lower than the previously given examples may cause similar damage.

Conclusion

In our opinion, the health risks of 10 cGy or less in humans may not be accurately estimated by any current mathematical model because of numerous inherent environmental, dietary and biological variables that cannot be accounted for in epidemiologic studies. In addition, the expression of radiation-induced damage depends not only on dose, dose rate, LET, fractionation, and protraction but also on repair mechanisms, bystander effects, and exposure to chemical and biological mutagens, carcinogens, tumor promoters, and other toxins as well as radioprotective substances, such as antioxidants. Therefore, low doses of ionizing radiation may not be considered insignificant risks

for somatic and heritable mutations and disease (neoplastic and nonneoplastic) in humans. We continue to support the well-established radiobiological concept that no radiation doses can be considered completely safe and that all efforts must be made to reduce both the radiation dose and damage, no matter how small.

1. Health Physics Society. Radiation risk in perspective: position statement of the Health Physics Society. In: Health Physics Society Directory and Handbook, 1998–1999. McLean, VA: Health Physics Society, pp238–244, 1998.
2. Anonymous. Biological Effects of Ionizing Radiation BEIR V. Washington, DC: National Academy Press, Committee on the Biological Effects of Ionizing Radiation, 1990.
3. Prasad KN, Hovland AR, Nahreini P, Cole WC, Hovland P, Kumar B, Prasad KC. Differentiation genes: are they primary targets for human carcinogenesis? *Exp Biol Med* 226:805–813, 2001.
4. Court-Brown W, Doll R, Eds. Leukemia and Aplastic Anemia in Patients Irradiated for Ankylosing Spondylitis. London: Her Majesty's Stationery Office, 1957.
5. National Council Radiation Protection Measurements. Recommendations on Limits for Exposure to Ionizing Radiation. Publication 91. Bethesda, MD: National Council on Radiation Protection & Measurements, 1987.
6. Snowby F. Annals of the ICRP. Publication 26. New York: Elsevier, pp1–53, 1977.
7. Bond VP, Benary V, Sondhaus CA. A different perception of the linear, nonthreshold hypothesis for low-dose irradiation. *Proc Natl Acad Sci U S A* 88:8666–8670, 1991.
8. Cohen BL. Cancer risk from low-level radiation. *Am J Roentgenol* 179:1137–1143, 2002.
9. Macklis RM, Beresford B. Radiation hormesis. *J Nucl Med* 32:350–359, 1991.
10. Makinodan T, James SJ. T cell potentiation by low dose ionizing radiation: possible mechanisms. *Health Phys* 59:29–34, 1990.
11. Makinodan T. Cellular and sub-cellular alteration in immune cells induced by chronic intermittent exposure in vivo to very low dose of ionizing radiation and its ameliorating effects on progression of autoimmune disease and mammary tumor growth. In: Sugahara T, Sagan L, Aoyama T, Eds. *Low Dose Irradiation and Biological Defense Mechanisms*. Amsterdam: Elsevier Science, pp233–237, 1992.
12. Fritz-Niggli H, Schaepfi-Buechi C. Adaptive response to dominant lethality of mature (class A) and immature (class B) oocytes of *D. melanogaster* to low doses of ionizing radiation: effects in repair-proficient (yw) and repair-deficient strains (mei 41D5 and mus 302D1). *Int J Radiat Biol* 59:175–184, 1991.
13. Kelsey KT, Memisoglu A, Frenkel D, Liber HL. Human lymphocytes exposed to low doses of X-rays are less susceptible to radiation-induced mutagenesis. *Mutat Res* 263:197–201, 1991.
14. Yamaoka K, Edamatsu R, Mori A. Increased SOD activities and decreased lipid peroxide levels induced by low dose X irradiation in rat organs. *Free Radic Biol Med* 11:299–306, 1991.
15. Anderson R: Effects of low dose radiation on the immune response. In: Calabrese E, Ed. *Biological Effects of Low Level Exposures to Chemicals and Radiation*. Chelsea, MI: Lewis, pp95–112, 1992.
16. Liu S. Multilevel mechanisms of stimulatory effect of low dose radiation on immunity. In: Sugahara T, Sagan L, Aoyama T, Eds. *Low Dose Irradiation and Biological Defense Mechanisms*. Amsterdam: Elsevier Science, pp225–232, 1992.
17. Azzam EI, de Toledo SM, Raaphorst GP, Mitchel RE. Low-dose ionizing radiation decreases the frequency of neoplastic transformation

- to a level below the spontaneous rate in C3H 10T1/2 cells. *Radiat Res* 146:369–373, 1996.
18. Sakamoto K, Myogin M, Hosoi Y, Ogawa Y, Nemoto K, Takai Y, Kakuto Y, Yamada S, Wataben N. Fundamental and clinical studies on cancer control with total and upper half body irradiation. *Jpn Soc Ther Radiol Oncol* 9:161–175, 1997.
 19. Le XC, Xing JZ, Lee J, Leadon SA, Weinfeld M. Inducible repair of thymine glycol detected by an ultrasensitive assay for DNA damage (comment). *Science* 280:1066–1069, 1998.
 20. Redpath JL, Antoniono RJ. Induction of an adaptive response against spontaneous neoplastic transformation in vitro by low-dose gamma radiation. *Radiat Res* 149:517–520, 1998.
 21. Hashimoto S, Shirato H, Hosokawa M, Nishioka T, Kuramitsu Y, Matushita K, Kobayashi M, Miyasaka K. The suppression of metastases and the change in host immune response after low-dose total-body irradiation in tumor-bearing rats. *Radiat Res* 151:717–724, 1999.
 22. Howe GR. Lung cancer mortality between 1950 and 1987 after exposure to fractionated moderate-dose-rate ionizing radiation in the Canadian fluoroscopy cohort study and a comparison with lung cancer mortality in the Atomic Bomb survivors study. *Radiat Res* 142:295–304, 1995.
 23. Prasad KN, Ed. *Handbook of Radiobiology*. Boca Raton, FL: CRC Press, 1995.
 24. Herskowitz I. Damage to offspring of irradiated women. *Prog Immunol Gynecol* 3:374–379, 1957.
 25. Newcombe HB, McGregor JF. Childhood cancer following obstetric radiography. *Lancet* 2:1151–1152, 1971.
 26. Stewart A, Kneale GW. Radiation dose effects in relation to obstetric x-rays and childhood cancers. *Lancet* 1:1185–1188, 1970.
 27. Uchida IA, Holunga R, Lawler C. Maternal radiation and chromosomal aberrations. *Lancet* 2:1045–1049, 1968.
 28. Mossman KL. Deconstructing radiation hormesis (comment). *Health Phys* 80:263–269, 2001.
 29. Smith H. Radiation hormesis in relation to radiation protection. *Chin Med J* 107:615–623, 1994.
 30. Morgan WF. Non-targeted and delayed effects of exposure to ionizing radiation: II. Radiation-induced genomic instability and bystander effects in vivo, clastogenic factors and transgenerational effects. *Radiation Research* 159:581–596, 2003.
 31. Huang L, Snyder AR, Morgan WF. Radiation-induced genomic instability and its implications for radiation carcinogenesis. *Oncogene* 22:5848–5854, 2003.
 32. McIlrath J, Lorimore SA, Coates PJ, Wright EG. Radiation-induced genomic instability in immortalized haemopoietic stem cells. *Int J Radiat Biol* 79:27–34, 2003.
 33. Mothersill C, Seymour C. Low-dose radiation effects: experimental hematology and the changing paradigm. *Exp Hematol* 31:437–445, 2003.
 34. Mothersill C, Crean M, Lyons M, McSweeney J, Mooney R, O'Reilly J, Seymour CB. Expression of delayed toxicity and lethal mutations in the progeny of human cells surviving exposure to radiation and other environmental mutagens. *Int J Radiation Biol* 74:673–680, 1998.
 35. Evans HH, Hornig MF, Ricanati M, Diaz-Insua M, Jordan R, Schwartz JL. Induction of genomic instability in TK6 human lymphoblasts exposed to 137Cs gamma radiation: comparison to the induction by exposure to accelerated 56Fe particles. *Radiat Res* 159:737–747, 2003.
 36. Lorimore SA, Wright EG. Radiation-induced genomic instability and bystander effects: related inflammatory-type responses to radiation-induced stress and injury? A review. *Int J Radiat Biol* 79:15–25, 2003.
 37. Zhou H, Randers-Pehrson G, Waldren CA, Vannais D, Hall EJ, Hei TK, Chatterjee A. Induction of a bystander mutagenic effect of alpha particles in mammalian cells. *Proc Natl Acad Sci U S A* 97:2099–2104, 2000.
 38. Zhou H, Randers-Pehrson G, Geard CR, Brenner DJ, Hall EJ, Hei TK. Interaction between radiation-induced adaptive response and bystander mutagenesis in mammalian cells. *Radiat Res* 160:512–516, 2003.
 39. DiPaolo JA, Donovan PJ, Popescu NC. Kinetics of Syrian hamster cells during x-irradiation enhancement of transformation in vitro by chemical carcinogen. *Radiat Res* 66:310–325, 1976.
 40. DiPaolo JA, Donovan PJ. In vitro morphologic transformation of Syrian hamster cells by U.V.-irradiation is enhanced by X-irradiation and unaffected by chemical carcinogens. *Int J Radiat Biol Relat Stud Phys, Chem Med* 30:41–53, 1976.
 41. Borek C, Zaider M, Ong A, Mason H, Witz G. Ozone acts alone and synergistically with ionizing radiation to induce in vitro neoplastic transformation. *Carcinogenesis* 7:1611–1613, 1986.
 42. Pollock EJ, Todaro GJ. Radiation enhancement of SV40 transformation in 3T3 and human cells. *Nature* 219:520–521, 1968.
 43. Little JB. Influence of noncarcinogenic secondary factors on radiation carcinogenesis. *Radiat Res* 87:240–250, 1981.
 44. Puck TT, Morse H, Johnson R, Waldren CA. Caffeine enhanced measurement of mutagenesis by low levels of gamma-irradiation in human lymphocytes. *Somat Cell Mol Genet* 19:423–429, 1993.
 45. Suzuki K, Kodama S, Watanabe M. Extremely low-dose ionizing radiation causes activation of mitogen-activated protein kinase pathway and enhances proliferation of normal human diploid cells. *Cancer Res* 61:5396–5401, 2001.
 46. Rothkamm K, Lobrich M. From the cover: evidence for a lack of DNA double-strand break repair in human cells exposed to very low x-ray doses. *Proc Natl Acad Sci U S A* 100:5057–5062, 2003.
 47. Brenner DJ, Little JB, Sachs RK. The bystander effect in radiation oncogenesis: II. A quantitative model. *Radiat Res* 155:402–408, 2001.
 48. Schettino G, Folkard M, Prise KM, Vojnovic B, Held KD, Michael BD. Low-dose studies of bystander cell killing with targeted soft X rays. *Radiat Res* 160:505–511, 2003.
 49. Graham S, Levin ML, Lilienfeld AM, Schuman LM, Gibson R, Dowd JE, Hempelmann L. Preconception, intrauterine, and postnatal irradiation as related to leukemia. *National Cancer Institute Monographs* 19:347–371, 1966.
 50. Ben-Amotz A, Yatziv S, Sela M, Greenberg S, Rachmilevich B, Shwarzman M, Weshler Z. Effect of natural beta-carotene supplementation in children exposed to radiation from the Chernobyl accident. *Radiat Environ Biophys* 37:187–193, 1998.
 51. Korkina LG, Afanas'ef IB, Diplock AT. Antioxidant therapy in children affected by irradiation from the Chernobyl nuclear accident. *Biochem Soc Trans* 21:314S, 1993.