DICHIARAZIONE

Relatore: Monica Mangoni

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazione ad Advisory Board **(NIENTE DA DICHIARARE)**
- Titolarietà di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Iscrizione convegno: IPSEN

UNIVERSITÀ DEGLI STUDI FIRENZE

SIMPOSIO AIRO-AIRB-SIRM
Le basse dosi nelle procedure radioterapiche con le nuove tecnologie: aspetti radioprotezionistici e radiobiologici

Update sugli effetti radiobiologici delle basse dosi di radiazioni

Monica Mangoni

What is meant by LOW DOSES of ionizing radiation?

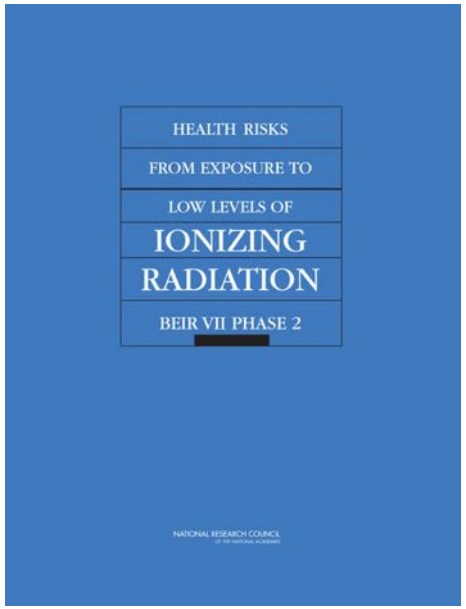
For this report, the committee has defined low dose as doses in the range of near zero up to about 100 mSv (0.1 Sv) of low-LET radiation.

TABLE 1 Units of Dose

Unit[a]	Symbol	Conversion Factors
Becquerel (SI)	Bq	1 disintegration/s = 2.7×10^{-11} Ci
Curie	Ci	3.7×10^{10} disintegrations/s = 3.7×10^{10} Bq
Gray (SI)	Gy	1 J/kg = 100 rads
Rad	rad	0.01 Gy = 100 erg/g
Sievert (SI)	Sv	1 J/kg = 100 rem
Rem	rem	0.01 Sv

NOTE: Equivalent dose equals absorbed dose times Q (quality factor). Gray is the special name of the unit (J/kg) to be used with absorbed dose; sievert is the special name of the unit (J/kg) to be used with equivalent dose.

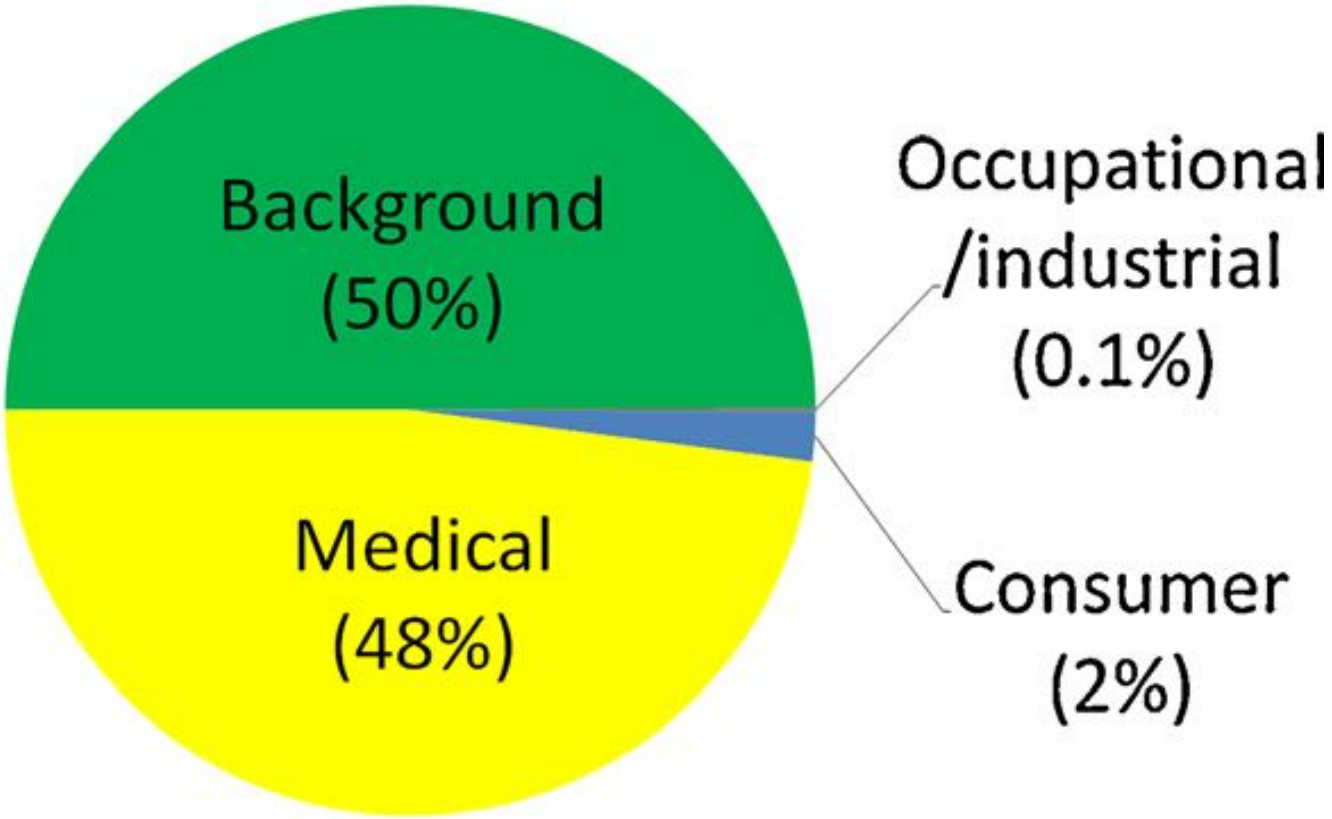
[a]International Units are designated SI.



Health Risks from Exposure to Low Levels of Ionizing Radiation:

Biological Effects of Ionizing Radiation- BEIR VII Phase 2 (2006)

ionizing radiation exposure source

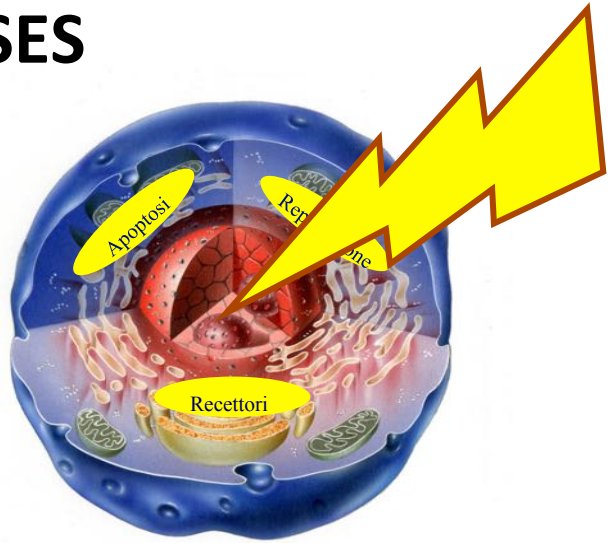


Cari M. Kitahara. Curr Envir Health Rpt (2015) 2:236–2491

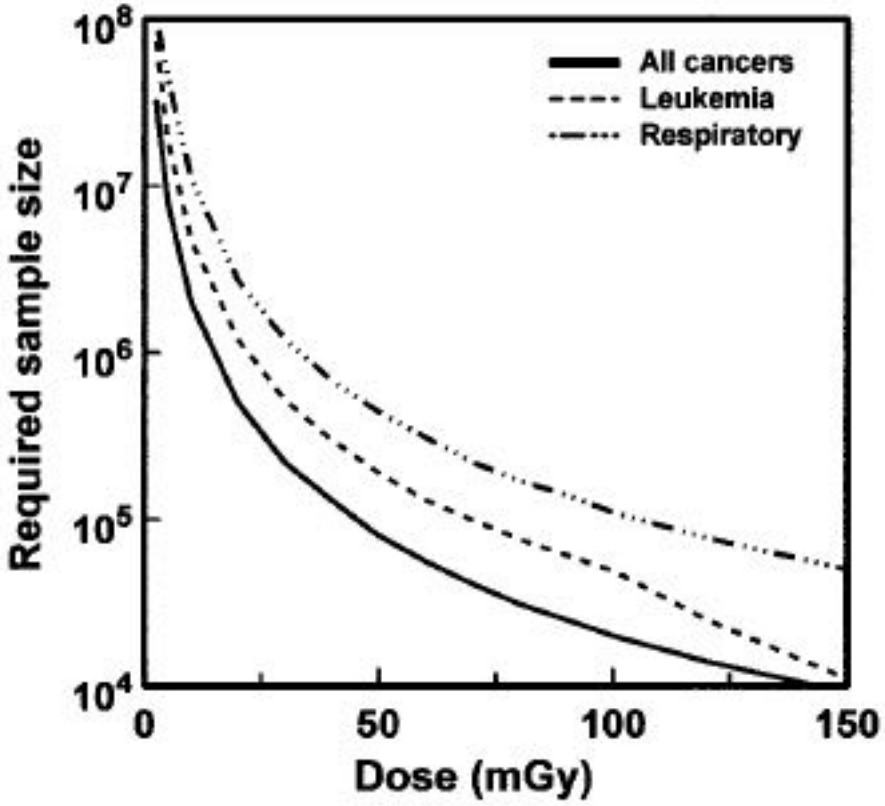
LOW DOSES

ADVERSE HEALTH EFFECTS?

→CANCER
→HEREDITARY DISEASES
→CARDIOVASCULAR DISEASES

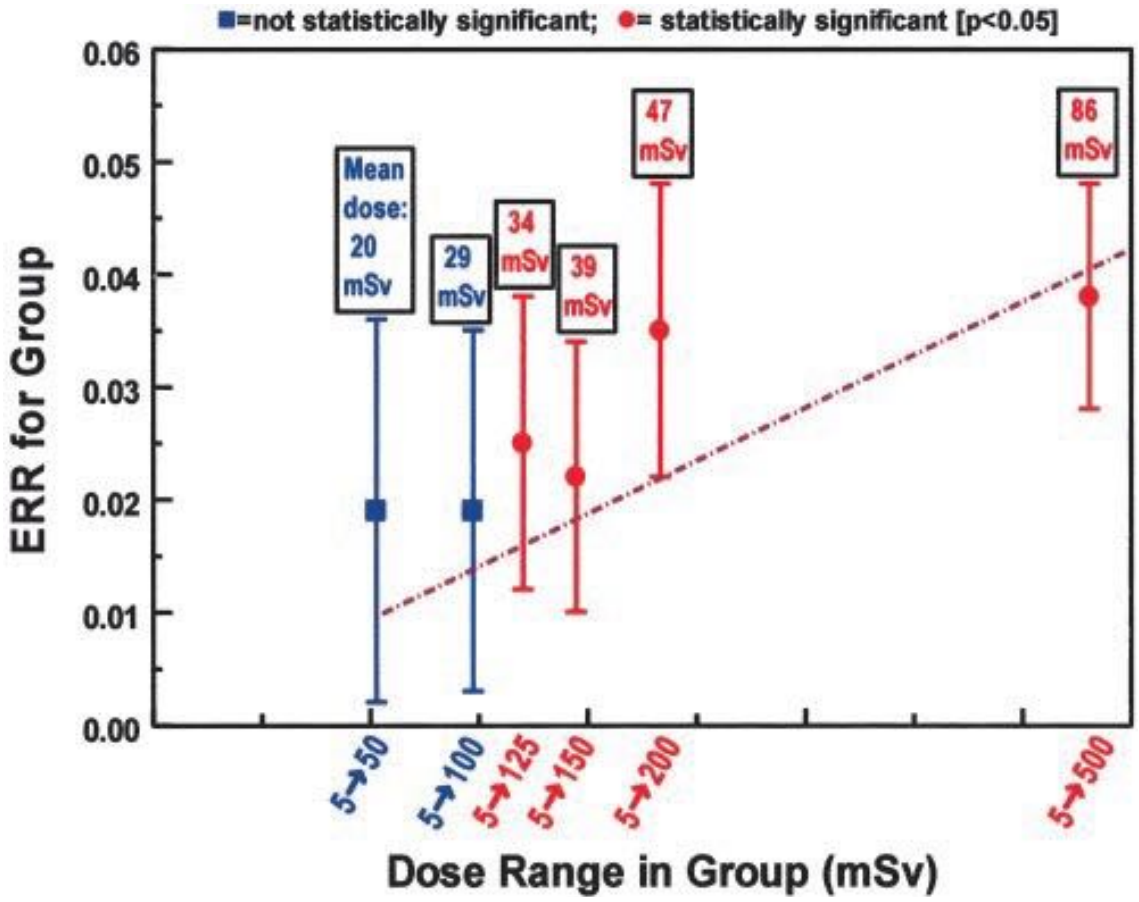


Required size of cohort exposed to detect significant increase of cancer



David J. Brenner, PNAS **2003** vol. 100 no. 24 **13761–13766**

Summary of Doses at Which Clear Evidence of Cancer Risks Is Shown.

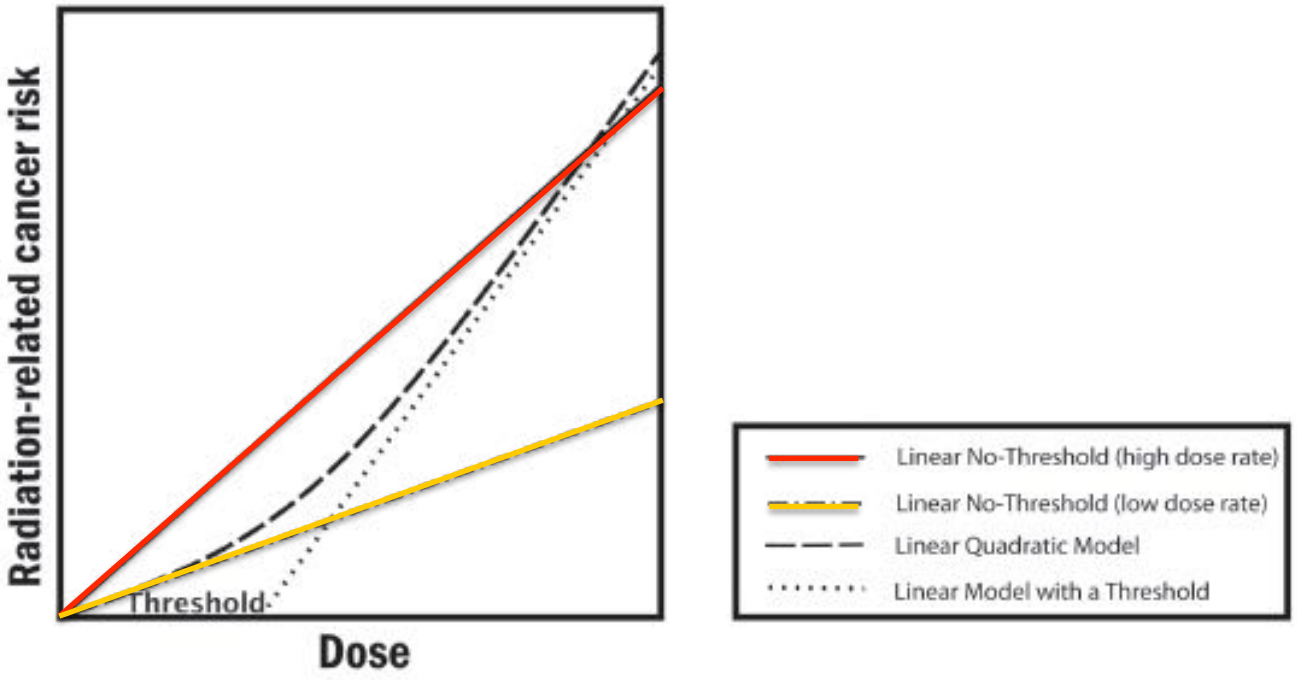


David J. Brenner, PNAS **2003** vol. 100 no. 24 **13761–13766**

Linear no-threshold model

Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII – Phase 2

PUBLIC SUMMARY

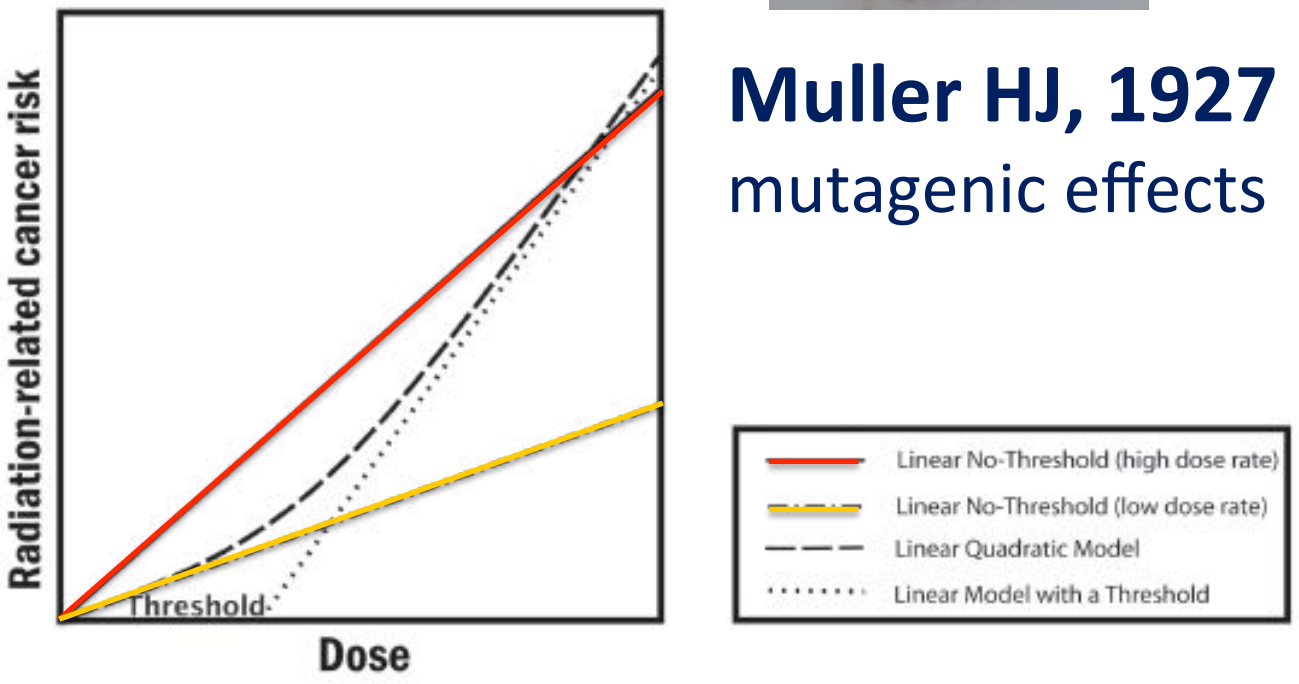


The linear no-threshold model assumption is that
there is no dose below which there is no cancer risk.

Linear no-threshold model

Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII – Phase 2

PUBLIC SUMMARY



Muller HJ, 1927
mutagenic effects

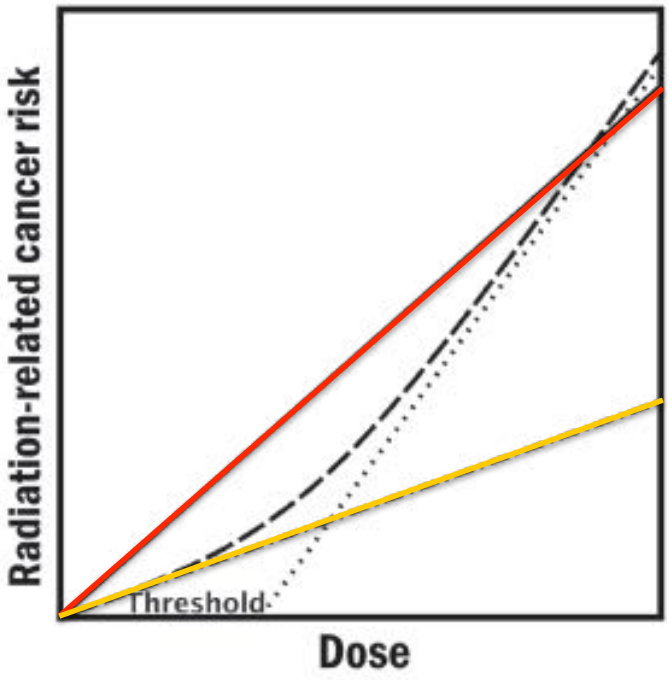
The linear no-threshold model assumption is that
there is no dose below which there is no cancer risk.

Rev in P. C. Kesavan Current Science 2014, Vol. 107, No. 1, 10

Linear no-threshold model

Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII – Phase 2

PUBLIC SUMMARY



Muller HJ, 1927

mutagenic effects

↓

Atomic bomb 1945

↓

Nobel prize 1946

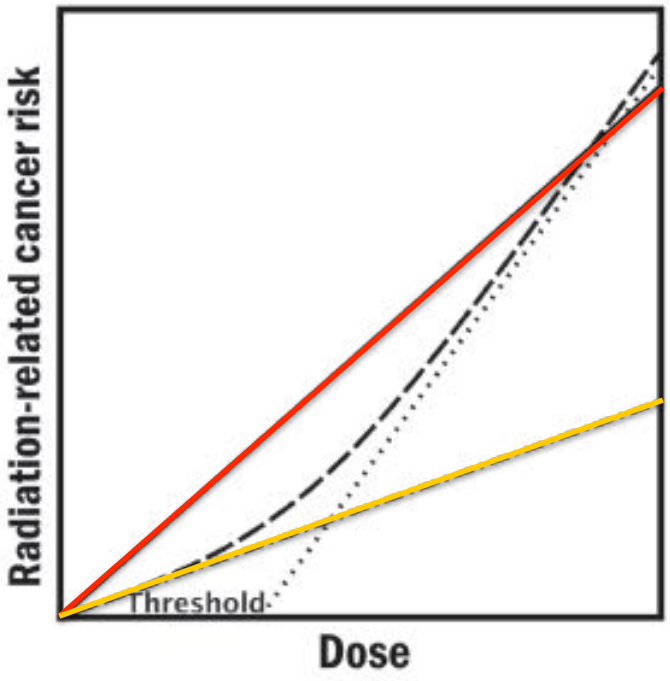
The linear no-threshold model assumption is that **there is no dose below which there is no cancer risk**.

Rev in P. C. Kesavan Current Science 2014, Vol. 107, No. 1, 10

Linear no-threshold model

Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII – Phase 2

PUBLIC SUMMARY



Muller HJ, 1927

mutagenic effects

↓

Atomic bomb 1945

↓

Nobel prize 1946

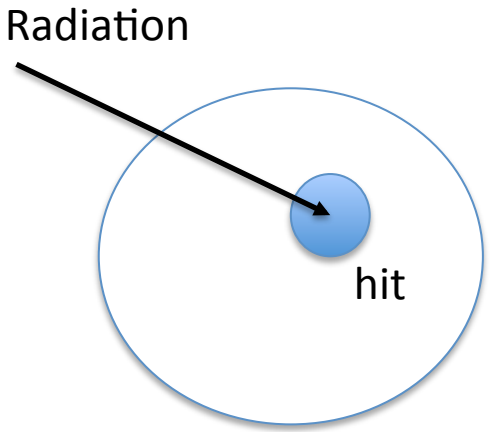
↓

BEAR committee 1955

LNT model was based on a flawed scientific foundation

Rev in P. C. Kesavan Current Science 2014, Vol. 107, No. 1, 10

Single hit model



The LNT model predicted that
a single alteration of DNA
could initiate the process of carcinogenesis,
and that once initiated,
this process was irreversible

this assumption has been consistently shown to be false

Rev in Edward J. Calabrese And Michael K. O'Connor Radiation Research 182, 463–474 (2014)

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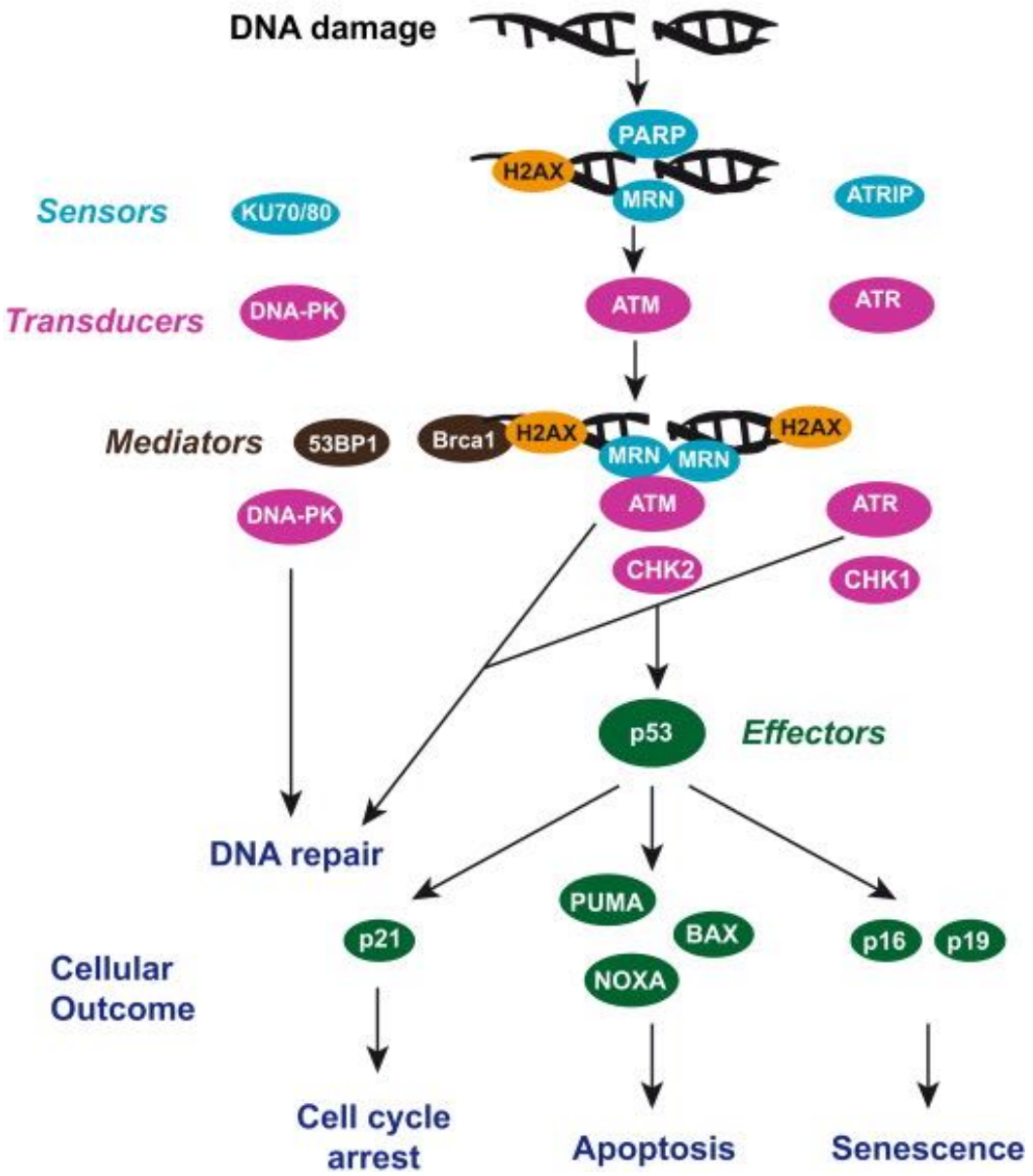
DDR DNA damage response

SENSE

RESPOND

REPAIR



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Response to ionizing radiation

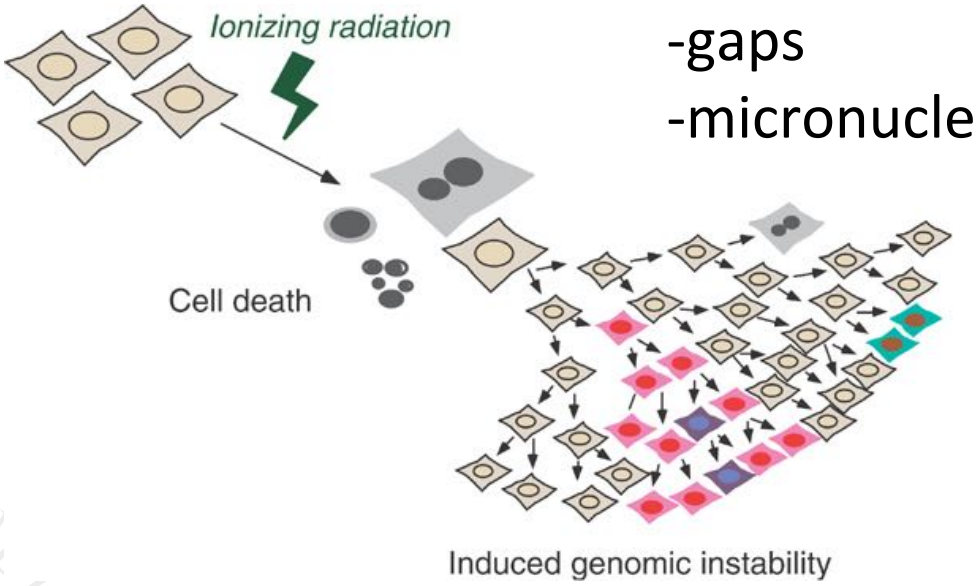
- Oxidative stress stimulates enzyme systems that detoxify ROS
- DNA repair/Cell cycle arrest/Apoptosis
- Induction of chromosome aberrations/gene mutations
- Genomic instability
- Hormesis
- Adaptive response
- Bystander effect
- Hyper radiation sensitivity
- Genes activation/inhibition

Genomic instability

manifestation of genetic damage in a certain fraction of irradiated cells over many cell cycles after they were irradiated

Persistent instability is expressed as:

- -chromosomal rearrangements
- -chromosomal bridge formation
- -chromatid breaks
- -gaps
- -micronuclei



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Hormesis

induction of stimulating effect (ie cell division and growth)
by low doses
and inhibition of these by high doses

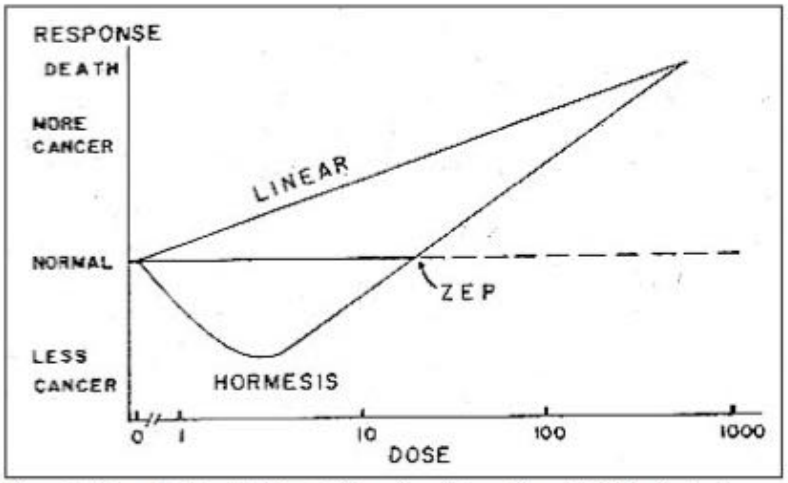
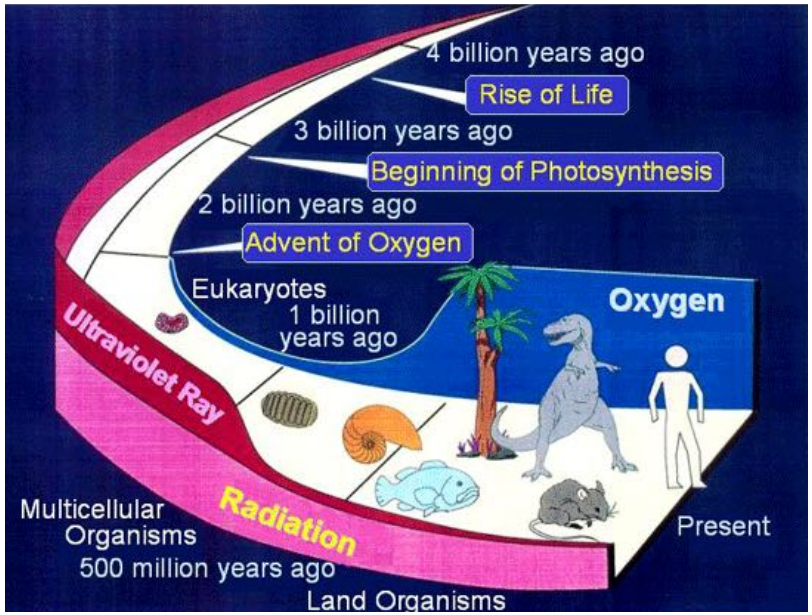


Figure 1: 'Linear-No Threshold' model (linear) vs. 'Hormesis' model. ZEP refers to 'zero-equivalent point' or the level of radiation that neither does harm nor good. (Adapted from Luckey, 1991.')

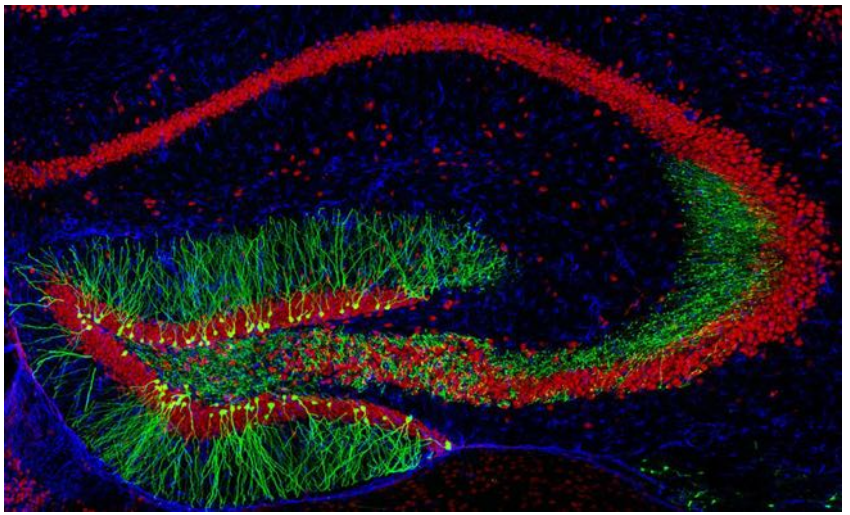


Rev in P. C. Kesavan Current Science 2014, Vol. 107, No. 1, 10

Curr Alzheimer Res. 2012 Mar;9(3):278-89.

Low-dose radiation stimulates Wnt/β-catenin signaling, neural stem cell proliferation and neurogenesis of the mouse hippocampus in vitro and in vivo.

Wei LC[1], Ding YX, Liu YH, Duan L, Bai Y, Shi M, Chen LW.



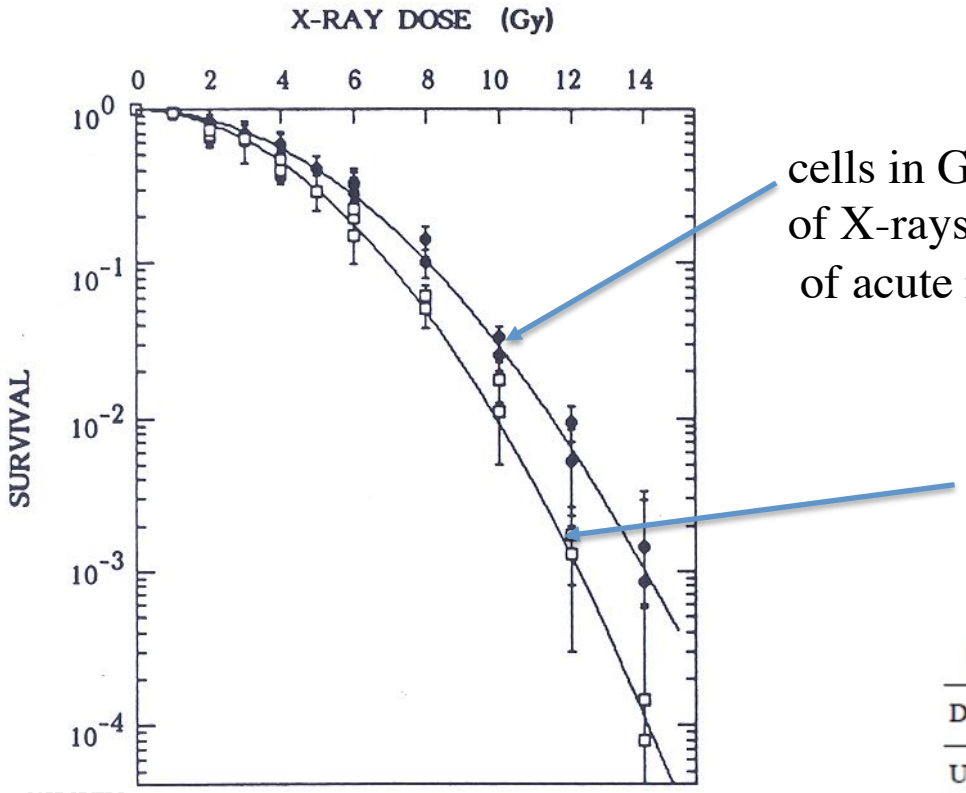
low-dose radiation (0.3Gy):

- ↑of Wnt1, Wnt3a, Wnt5a, and β-catenin expression
-enhanced the neurogenesis of hippocampus
-↑cell survival and ↓apoptotic death of neuronal stem cells
-behavioral improvement of animal learning in low-dose radiation group

Wei LC, Curr Alzheimer Res. 2012 Mar;9(3):278-89.

Adaptive Response

a low (i.e. priming) dose confers protection to cells subsequently exposed to much higher (i.e. challenging) doses of ionizing radiation



cells in G_1 preirradiated with 20 mGy of X-rays 5 h before graded doses of acute radiation

cells in G_1 given graded doses of acute radiation only

Table 1. X-ray induced mutations in *Drosophila melanogaster*

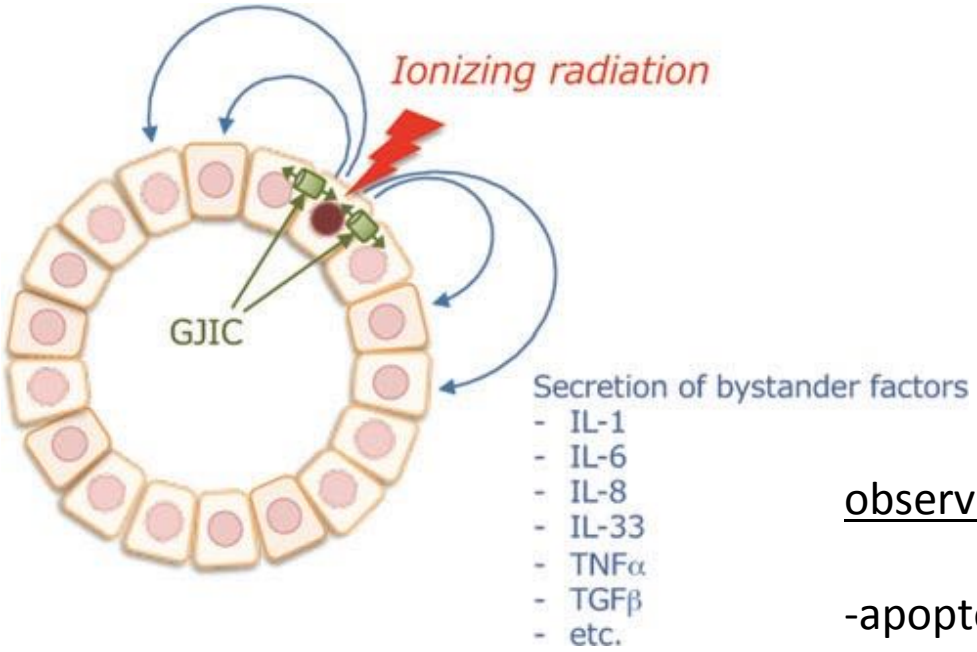
Dose	Mutation rate (%)
Unirradiated	0.33
0.2 Gy	0.07
10.0 Gy	0.79

Source: Koana *et al.*[14].

Rev in P. C. Kesavan Current Science 2014, Vol. 107, No. 1, 10
Sakai K. Radiat Res 2007, 167, 217-221

Bystander effects

response of unirradiated cells to the irradiation of their neighbours

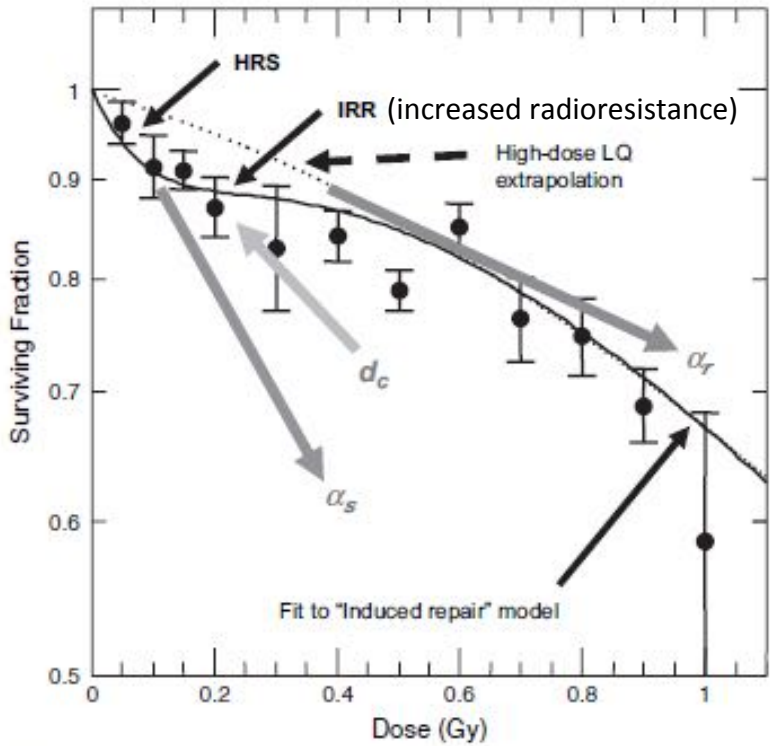


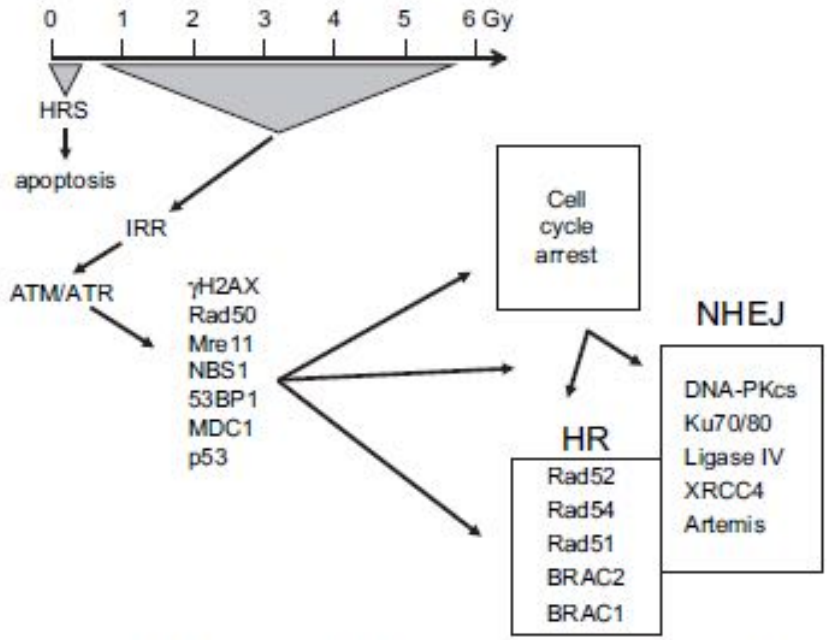
<u>observed for a range of biological endpoints</u>:

-apoptosis
-DNA damage
-up regulation of proteins DDR
-micronucleus induction
-cell proliferation
-cell survival
-genomic instability

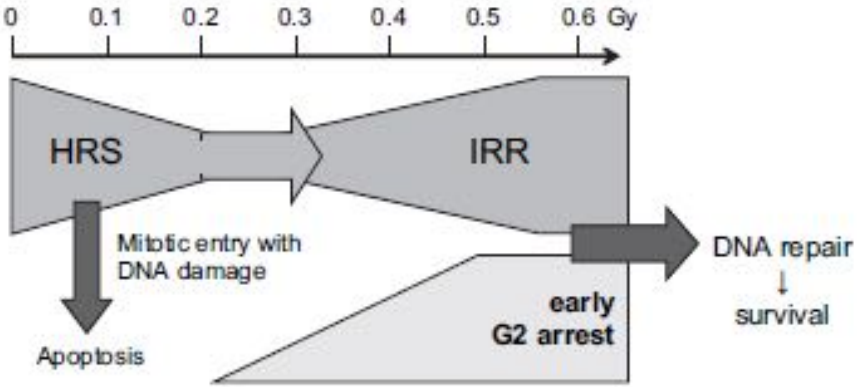
K. Manda et al. / Mutation Research 761 (2014) 6–14

Low dose hyper-radiosensitivity





0,3 Gy	HRS
0,3-0,6Gy	IRR
1 Gy	LQ



MARPLES B, Int. J. Radiation Oncology Biol. Phys. 2008, Vol. 70, No. 5, pp. 1310–1318

Differential gene expression induced by low and high doses

different doses, dose rates, levels of DNA damage lead
to activation of different families of genes

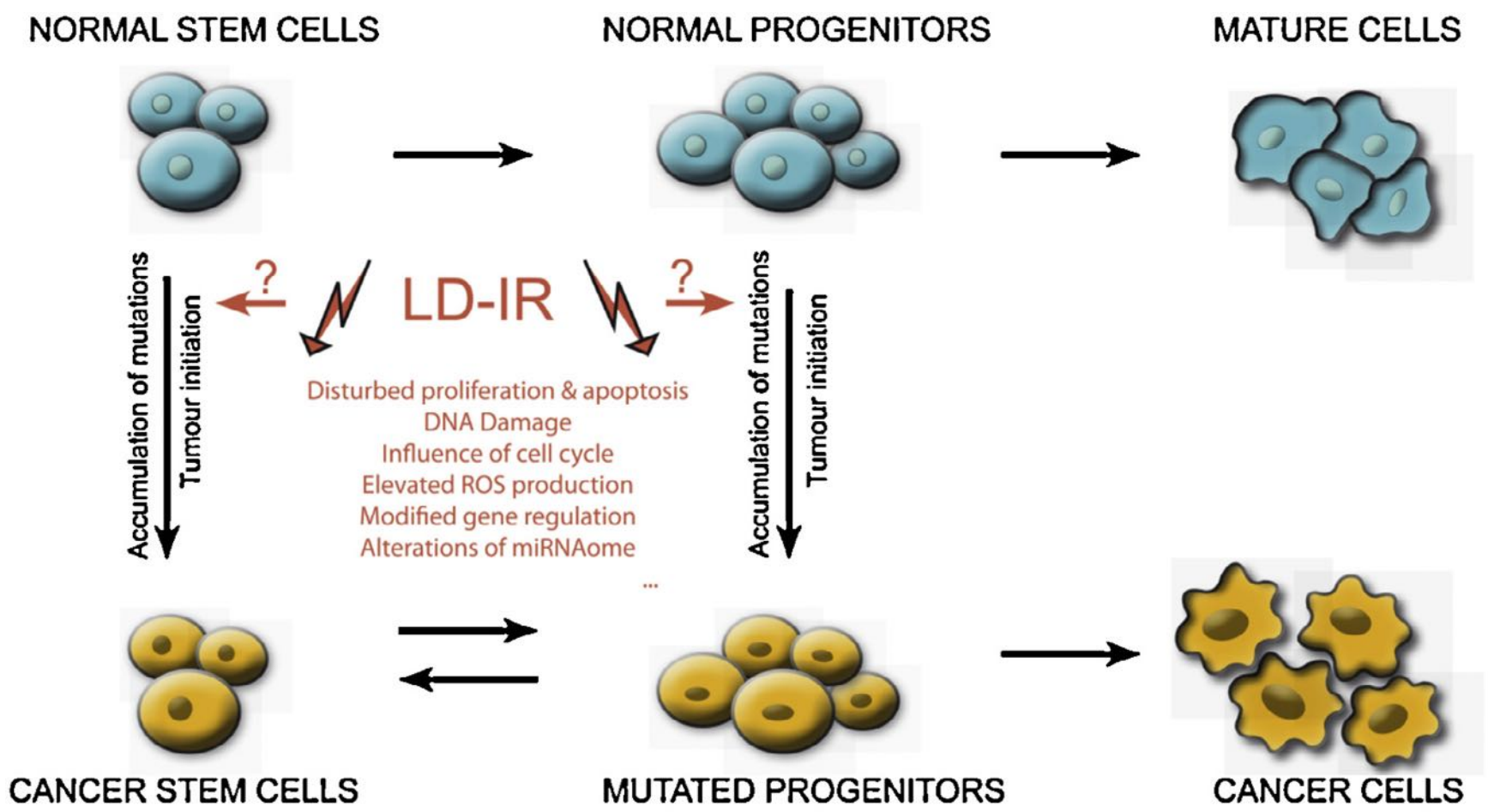
In a three-dimensional tissue model that imitates the structure and function of human epidermis, at 4, 16 and 24 h after exposure to high (2.5 Gy) and low (0.1 Gy) doses of low-LET protons:

low dose associated with recovery and tissue repair,
high dose resulted in loss of structural integrity and terminal differentiation

Mezentsev, A. Radiat. Res., 2011, 175, 677–688.

Rev in P. C. Kesavan Current Science 2014, Vol. 107, No. 1, 10

Stem cells as the target for the initiation of radiation carcinogenesis



Cancer stem cell hypothesis

Revised in K. Manda et al. / Mutation Research 761 (2014) 6–14

Effects of low dose (<0.5 Gy) irradiation on normal stem cells

- 200 and 500 mGy produced no detectable apoptosis (hESCs)
- Discontinuous dose-dependence (20 and 100 mGy had no effect on cell growth // 50 and 75 mGy significantly stimulated the cell growth of the rat mesenchymal stem cells)
- 400 mGy cause modifications in gene and protein expression patterns (hESCs) (genes involved in cell death, p53 signalling, organ and embryonic development as well as cell cycle control.)
- 30 mGy in mouse NSCs cause an altered protein expression profile (both, up- and down- regulation observed; affected proteins involved in neuronal development and function, neurodegeneration, cellular stress, apoptosis, cell cycle control and proliferation)
- 10 and 30 mGy diminished differentiation of the immature neural C17.2 stem cells to glial cells
- Radioadaptive effect (stimulation of wound healing and of proliferation of bone marrow hematopoietic progenitor cells)

Radiosensitivity :dependent on stem cell type and their tissue of origin.

Radioresistance of stem cells may provide increased possibilities for accumulation of mutations required for tumour initiation.

The influence of radiation on the microenvironment may also play a crucial role in carcinogenesis (niche)

Revised in K. Manda et al. / Mutation Research 761 (2014) 6–14

Individual Versus Population-Based Thresholds

OPEN ACCESS Freely available online

PLOS ONE

Genetic Differences in Transcript Responses to Low-Dose Ionizing Radiation Identify Tissue Functions Associated with Breast Cancer Susceptibility

Antoine M. Snijders, Francesco Marchetti[¤a], Sandhya Bhatnagar, Nadire Duru, Ju Han, Zhi Hu[¤b], Jian-Hua Mao, Joe W. Gray[¤b], Andrew J. Wyrobek*

Life Sciences Division, Lawrence Berkeley National Laboratory, Berkeley, California, United States of America

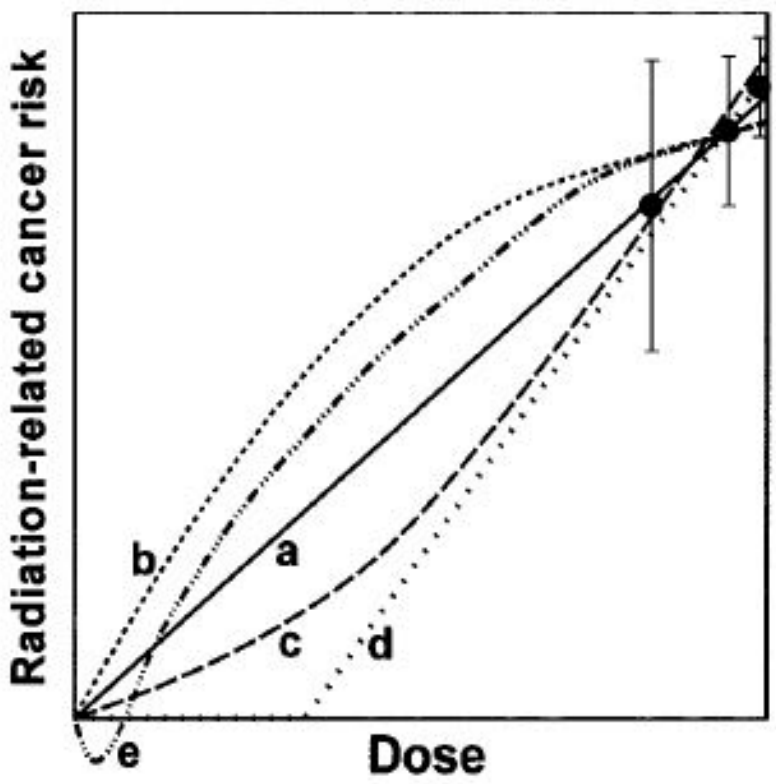
Abstract

High dose ionizing radiation (IR) is a well-known risk factor for breast cancer but the health effects after low-dose (LD, <10 cGy) exposures remain highly uncertain. We explored a systems approach that compared LD-induced chromosome damage and transcriptional responses in strains of mice with genetic differences in their sensitivity to radiation-induced mammary cancer (BALB/c and C57BL/6) for the purpose of identifying mechanisms of mammary cancer susceptibility. Unirradiated mammary and blood tissues of these strains differed significantly in baseline expressions of DNA repair, tumor suppressor, and stress response genes. LD exposures of 7.5 cGy (weekly for 4 weeks) did not induce detectable genomic instability in either strain. However, the mammary glands of the sensitive strain but not the resistant strain showed early transcriptional responses involving: (a) diminished immune response, (b) increased cellular stress, (c) altered TGFβ-signaling, and (d) inappropriate expression of developmental genes. One month after LD exposure, the two strains showed opposing responses in transcriptional signatures linked to proliferation, senescence, and microenvironment functions. We also discovered a pre-exposure expression signature in both blood and mammary tissues that is predictive for poor survival among human cancer patients ($p=0.0001$), and a post-LD-exposure signature also predictive for poor patient survival ($p<0.0001$). There is concordant direction of expression in the LD-exposed sensitive mouse strain, in biomarkers of human DCIS and in biomarkers of human breast tumors. Our findings support the hypothesis that genetic mechanisms that determine susceptibility to LD radiation induced mammary cancer in mice are similar to the tissue mechanisms that determine poor-survival in breast cancer patients. We observed non-linearity of the LD responses providing molecular evidence against the LNT risk model and obtained new evidence that LD responses are strongly influenced by genotype. Our findings suggest that the biological assumptions concerning the mechanisms by which LD radiation is translated into breast cancer risk should be reexamined and suggest a new strategy to identify genetic features that predispose or protect individuals from LD-induced breast cancer.

genetic heterogenicity
social, behavioral and cultural heterogenicity

➔ **Multistep cancer origin**

Extrapolation of Observed Risks to Lower Doses



NOT LINEAR

THRESHOLD?

ANNUAL ORATION ■ REVIEWS AND COMMENTARY

Radiation Risks of Medical Imaging: Separating Fact from Fantasy[1]

William R. Hendee, PhD
Michael K. O'Connor, PhD

Radiology

During the past few years, several articles have appeared in the scientific literature that predict thousands of cancers and cancer deaths per year in the U.S. population

(31): "The Health Physics Society recommends against quantitative estimation of health risks below an individual dose of 5 rem (50 mSv) in one year, or a lifetime dose of 10 rem (100 mSv), above that received from natural sources. For doses below 5–10 rem (50–100 mSv) risks of health effects are either too small to be observed or are nonexistent."

The American Association of Physicists in Medicine (AAPM) acknowledges that medical imaging procedures should be appropriate and conducted at the lowest radiation dose consistent with acquisition of the desired information. Discussion of risks related to radiation dose from medical imaging procedures should be accompanied by acknowledgment of the benefits of the procedures. Risks of medical imaging at patient doses below 50 mSv for single procedures or 100 mSv for multiple procedures over short time periods are too low to be detectable and may be nonexistent. Predictions of hypothetical cancer incidence and deaths in patient populations exposed to such low doses are highly speculative and should be discouraged. These predictions are harmful because they lead to sensationalistic articles in the public media that cause some patients and parents to refuse medical imaging procedures, placing them at substantial risk by not receiving the clinical benefits of the prescribed procedures.

Hendee WR, O'Connor MK. Radiology2012 Aug;264(2):312-21

Health Physics Society. Position statement of the Health Physics Society. Radiation risk in perspective. July, 2010. http://hps.org/documents/risk_ps010-2. pdf

American Association of Physicists in Medicine. Position statement of the American Association of Physicists in Medicine. Radiation risks from medical imaging procedures. December 2011. http://www.aapm.org/.