What Do Experiments Tell Us about the Health Effects of Low Dose & Low Dose Rate Ionizing Radiation

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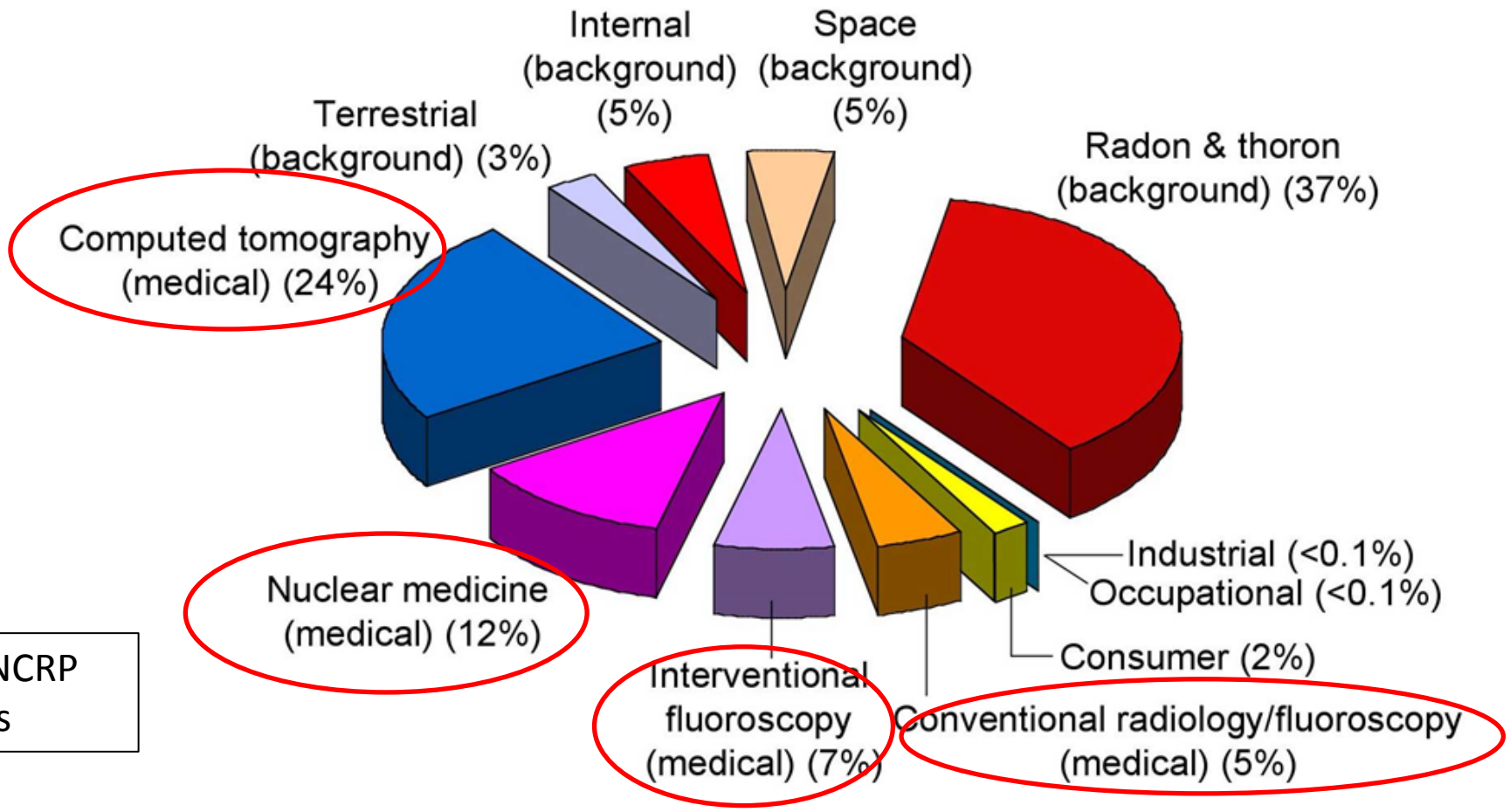
The Frequency of Human Exposure to Low Level Ionizing Radiation Has Been on the Increase



Adapted from NCRP publications

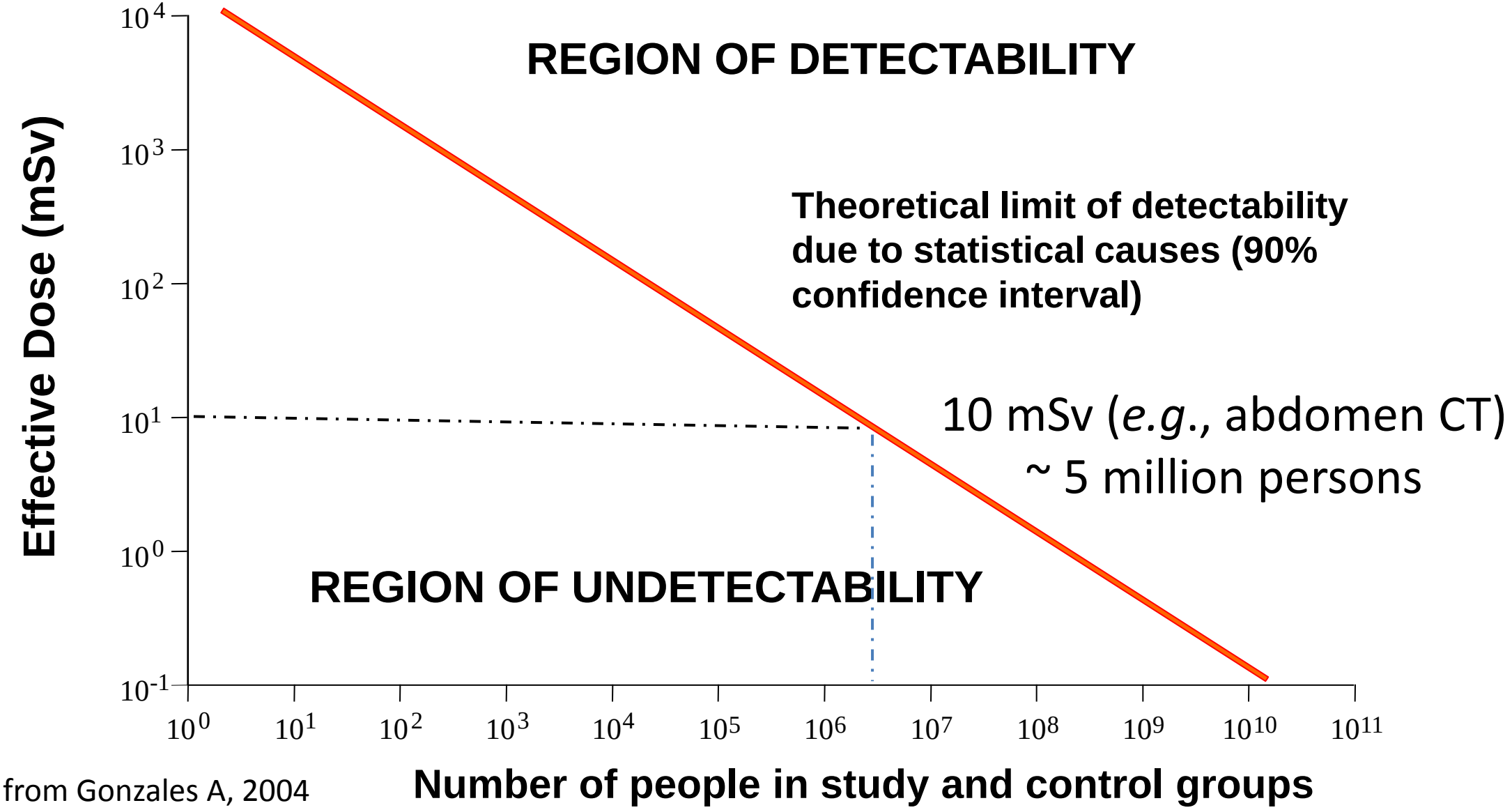
Currently, medical imaging procedures constitute ~48% of the radiation exposure to the US population; in 1980, they accounted for 15% of the exposure

Thus, evaluation of adverse human health effects following exposure to low dose ionizing radiation is an important issue in **radiation protection**

- Human *epidemiological studies* would be ideal to characterize the health risks of exposure to low doses/low fluences of radiation

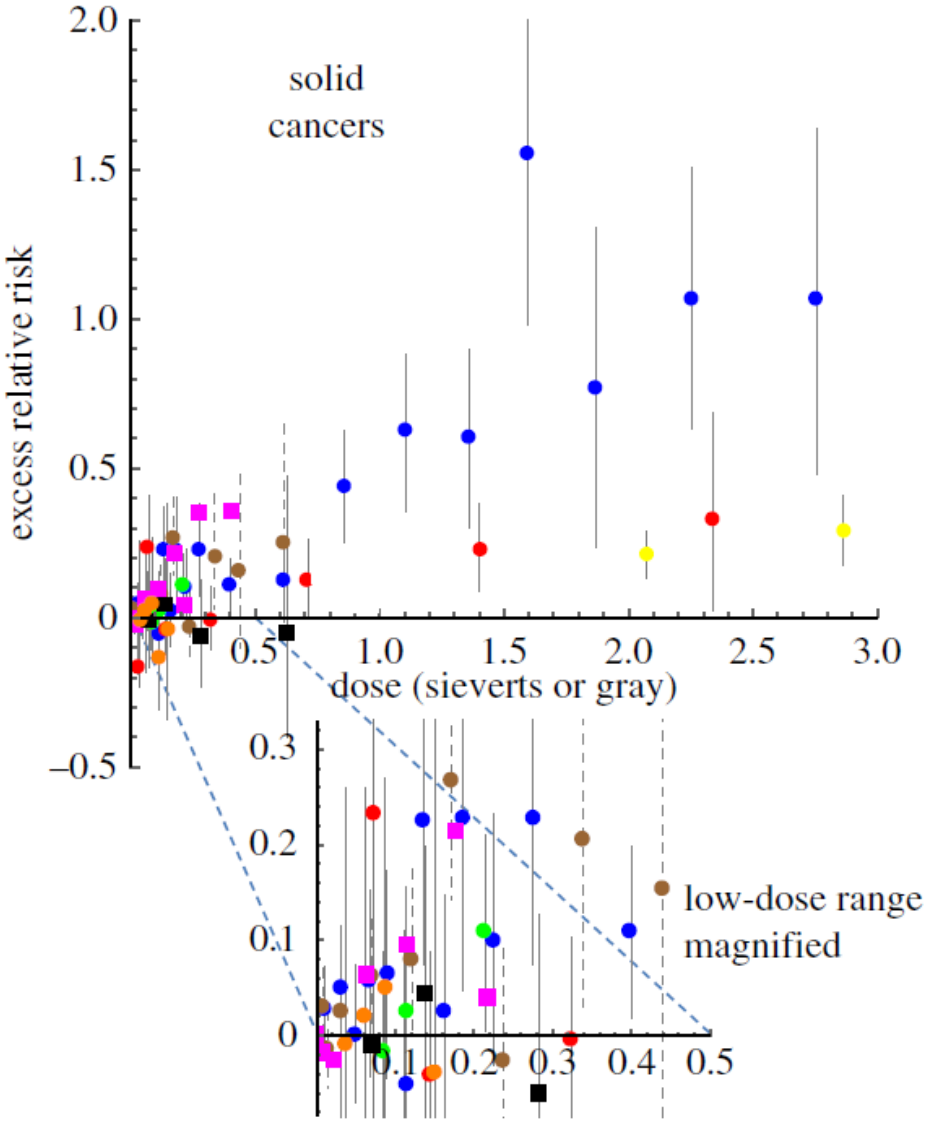
Limits of Epidemiology

(detectability of solid cancers in irradiated humans)



Adapted from Gonzales A, 2004

Estimates of Excess Relative Risk of Cancers from Large Epidemiological Surveys



- Japanese Life Span Study (LSS)
- International workers (INWORKS)
- Chernobyl workers
- Mayak workers
- Techa River residents
- Kerala background radiation
- Yangjiang background radiation
- ankylosing spondylitis patients

McLean et al., *Proc. R. Soc. B*, 2017

Complexities in Epidemiological Low Dose Surveys

- Limited statistical power & uncertain dosimetry in some studies
- In Life Span Study (LSS), survivors of A-B were exposed to single dose at a relatively high dose rate, rather than at low dose rate or in a fractionated manner
- Confounding factors (*e.g.,* smoking, exposure to other carcinogens, immuno-suppressive effect of stress, wounds..)
- Effect of exposure to mixed radiation (γ, neutron, beta)
- Impact of additional experiences during the intervening years between exposure and manifestation of health effect

Due to limitations in many human **epidemiological studies** in determining risks from exposures to low dose radiation, **mechanistic studies** are being considered essential to understand biological effects and help evaluate risks at low doses

Several factors determine the biological/health effects of exposure to ionizing radiation. They include:

- Total dose received
- Exposure rate
- Physical characteristics of the radiation
- Area of the body that was exposed
- Biological variability

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- **Physical characteristics of the radiation**
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NCRP defined - low dose: 0 to 100 mGy
- low dose rate as < 5 mGy/h

In this talk …

- **Radiobiology** at low dose and its potential at **alleviating the uncertainty** in predicting risks of adverse health effects

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- Radiobiology at low dose and its potential at **alleviating the uncertainty** in predicting risks of adverse health effects

  - From primary damages to biological responses

  - ➢ Responses induced following exposures to low doses of **sparsely ionizing radiations**

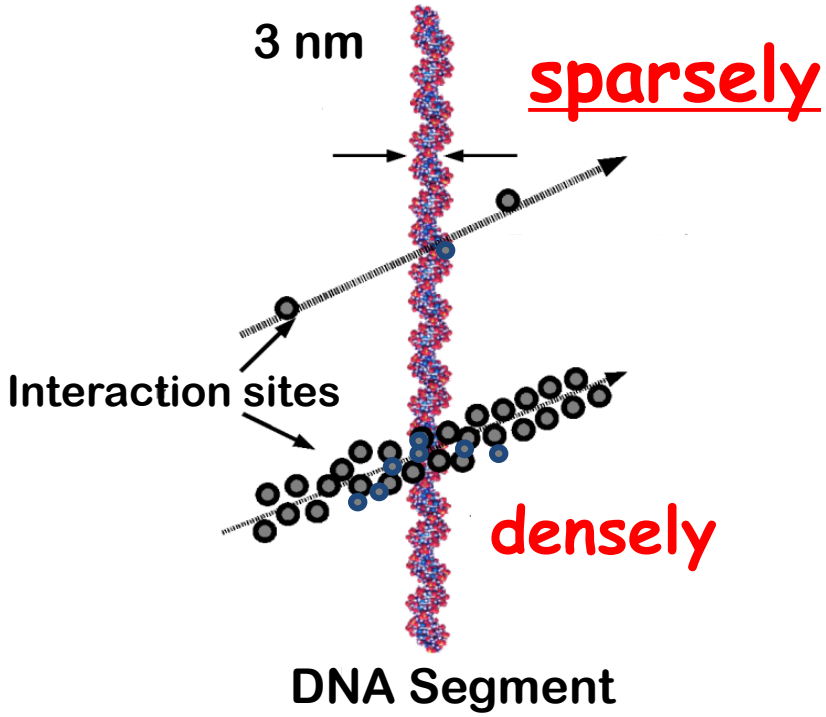
  - ➢ Responses induced following exposures to low fluences of **densely ionizing radiations**

In this talk …

- Relevance of radiobiology at low dose in **alleviating the uncertainty** in predicting risks of adverse health effects
    - From primary damages to biological system responses
        - Responses induced following exposures to low fluences of **densely** ionizing radiations
        - Responses induced following exposures to low doses of **sparsely** ionizing radiations

- Focus on two phenomena, namely **adaptive** responses and **bystander** effects that are thought to impact the health risk of exposure to low dose/low fluence ionizing radiation

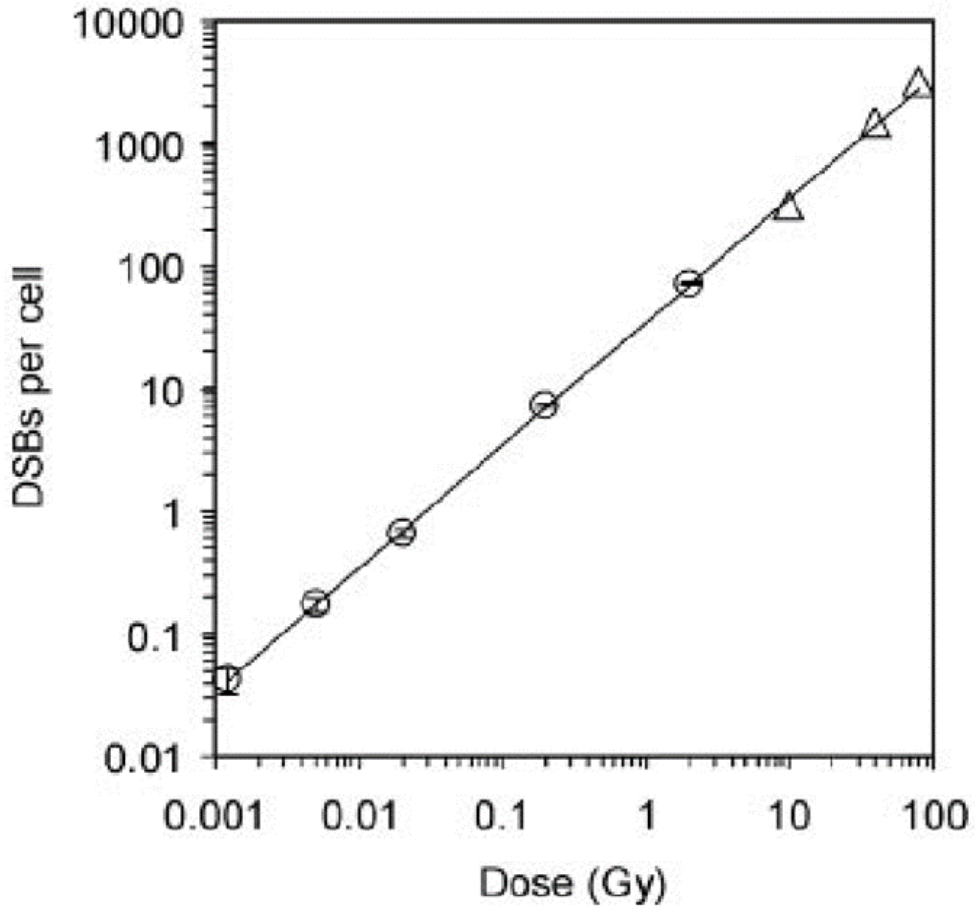
In diagnostic procedures & many terrestrial occupational activities, exposure is likely to be from low doses of sparsely ionizing radiations



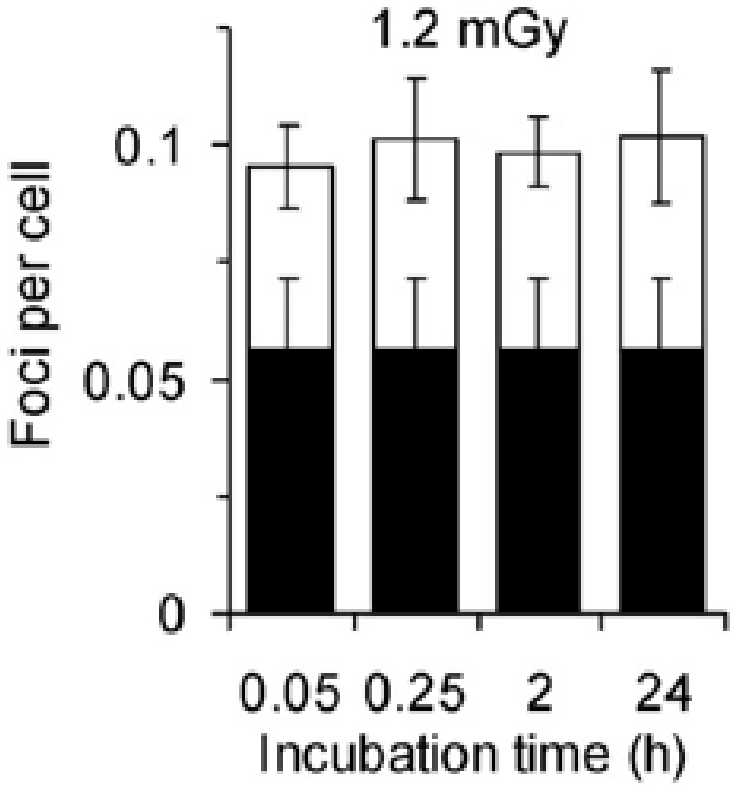
What Does Radiation Biology Inform?

A few examples

Induction of DSBs in DNA increases linearly with dose of X rays



Absence of DNA repair at very low doses of X rays



(Rothkamm and Löbrich , *PNAS* 2003;100:5057-5062)

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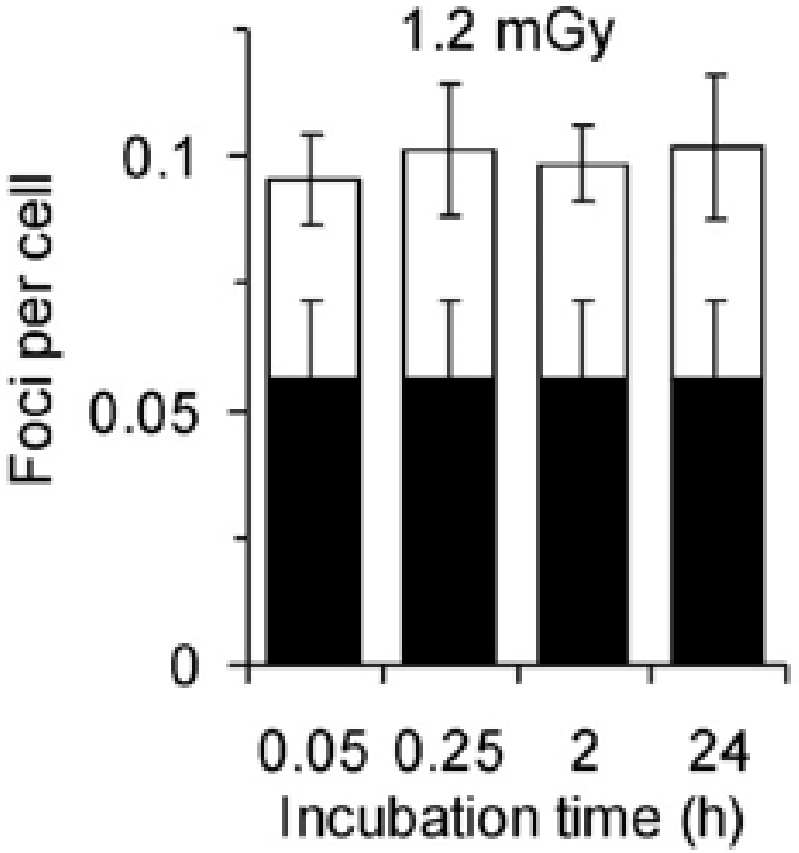


However, the authors present evidence suggesting that the damaged cells are eliminated when irradiated quiescent cell cultures are allowed to proliferate

(Rothkamm and Löbrich , *PNAS* 2003;100:5057-5062)

Whereas several biological experiments indicate that the damaging effects of radiation increase linearly with dose, others show that cellular exposure to low doses of radiation can induce adaptive protection, especially when the dose is delivered at low dose rates

Experimental evidence indicates that adaptive responses are induced by low doses of sparsely ionizing radiations

Observed in :

- Single cell organisms
- Insects
- Plants
- Lower vertebrates
- Mammalian cells, including human cells

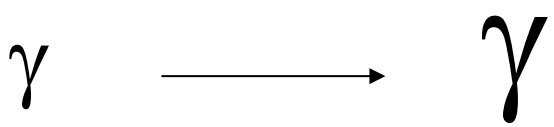
Biological endpoints include: gene expression, mutations, Chromatid/chromosomal aberrations, oxidative stress, survival, neoplastic transformation, …

Stressors: Ionizing radiation but also others (*e.g.*, heat, chemicals …)

Part I

***The Adaptive Response* is a phenomenon induced by low doses of sparsely ionizing radiations that protect cells and whole organisms against endogenous damage or damage due to a subsequent dose of radiation**

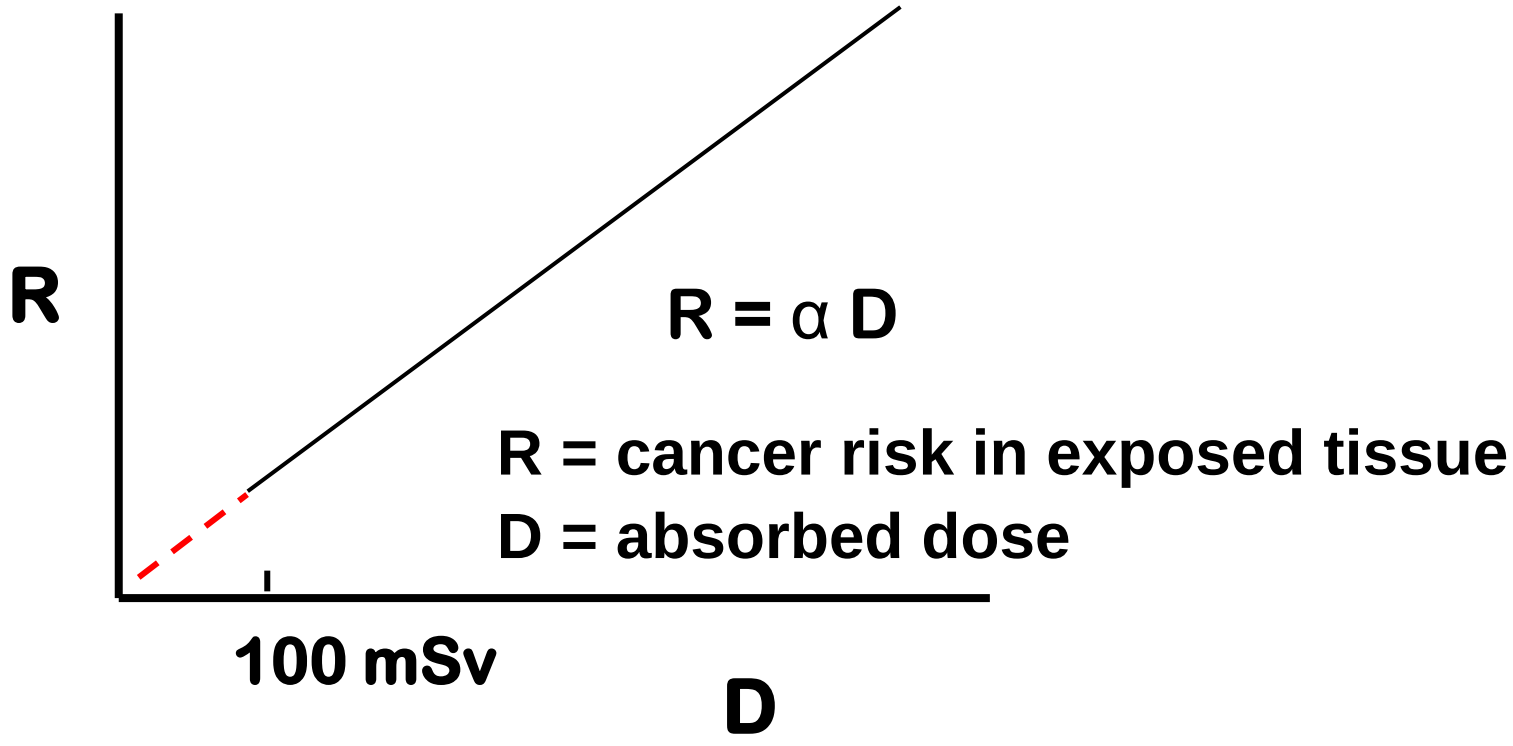
Common Study Protocol



(Importance of dose rate)

BEIR VII Charge: "How to extrapolate radiation risks known at epidemiologically tractable doses, down to still lower doses"

<u>Prudent guidance</u>: Any dose, no matter how small, increases health risk



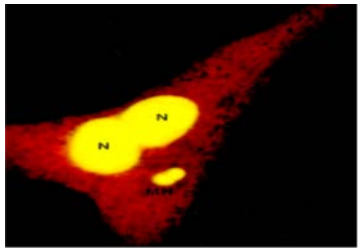
Low Doses Can Decrease DNA Damage from a High Dose

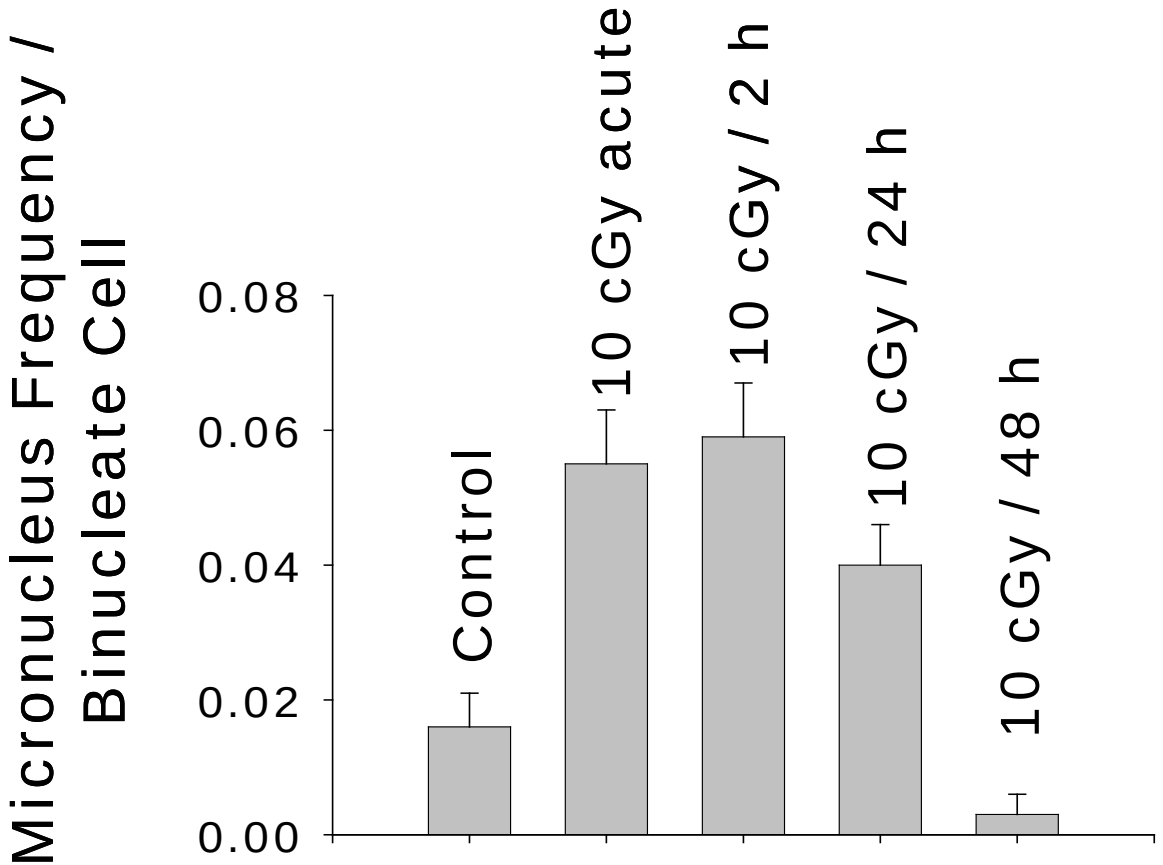
"Adaptive response of human lymphocytes to low concentrations of radioactive thymidine"
Olivieri G, Bodycote J, Wolff S.
***Science*, 223:594-7, 1984**

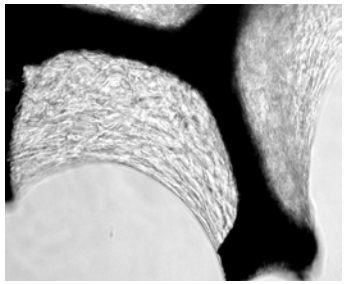
1929-2008

Treatment	*# chromatid aberrations*
None	0
[^{3}H]dThd (0.1 μCi/ml)	5
150 cGy (X-rays)	36
[^{3}H]dThd (0.1 μCi/ml) + 150 cGy	13

Effect of a single dose of ^{137}Cs γ-rays delivered at <u>various dose rates</u> on DNA Damage in normal human cells growing in 3-D



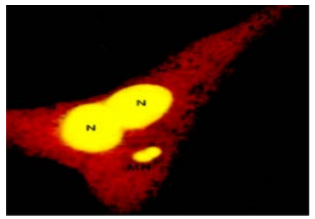


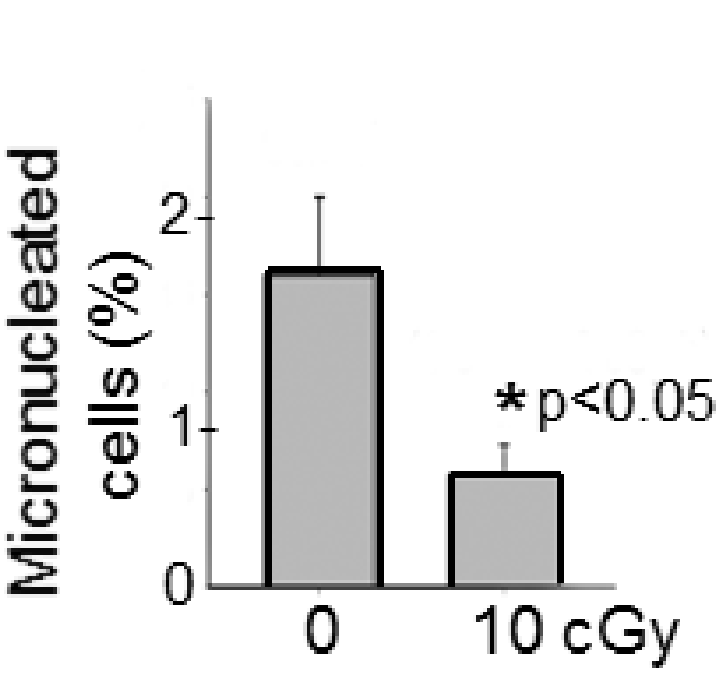


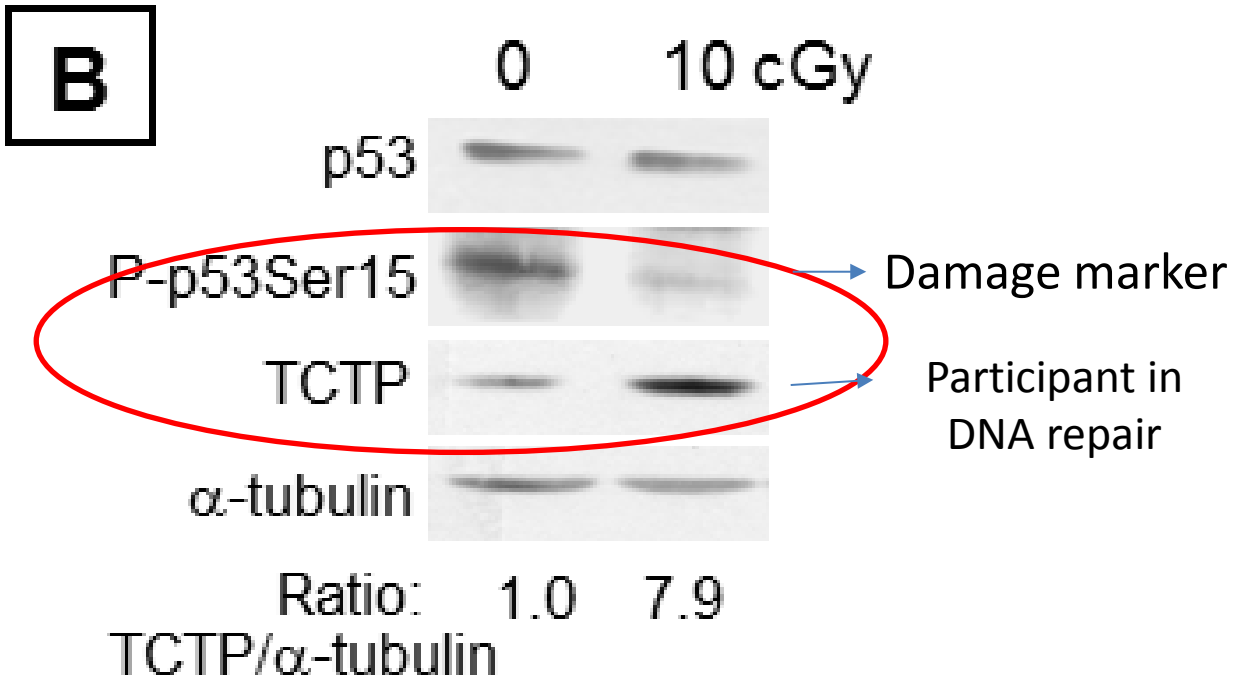
^{137}Cs rays
LET ~ 0.9 keV/μm

de Toledo *et al.*, *Radiat. Res.*, 2006

Exposure to Low Dose/Low Dose Rate γ rays Upregulates DNA Repair:





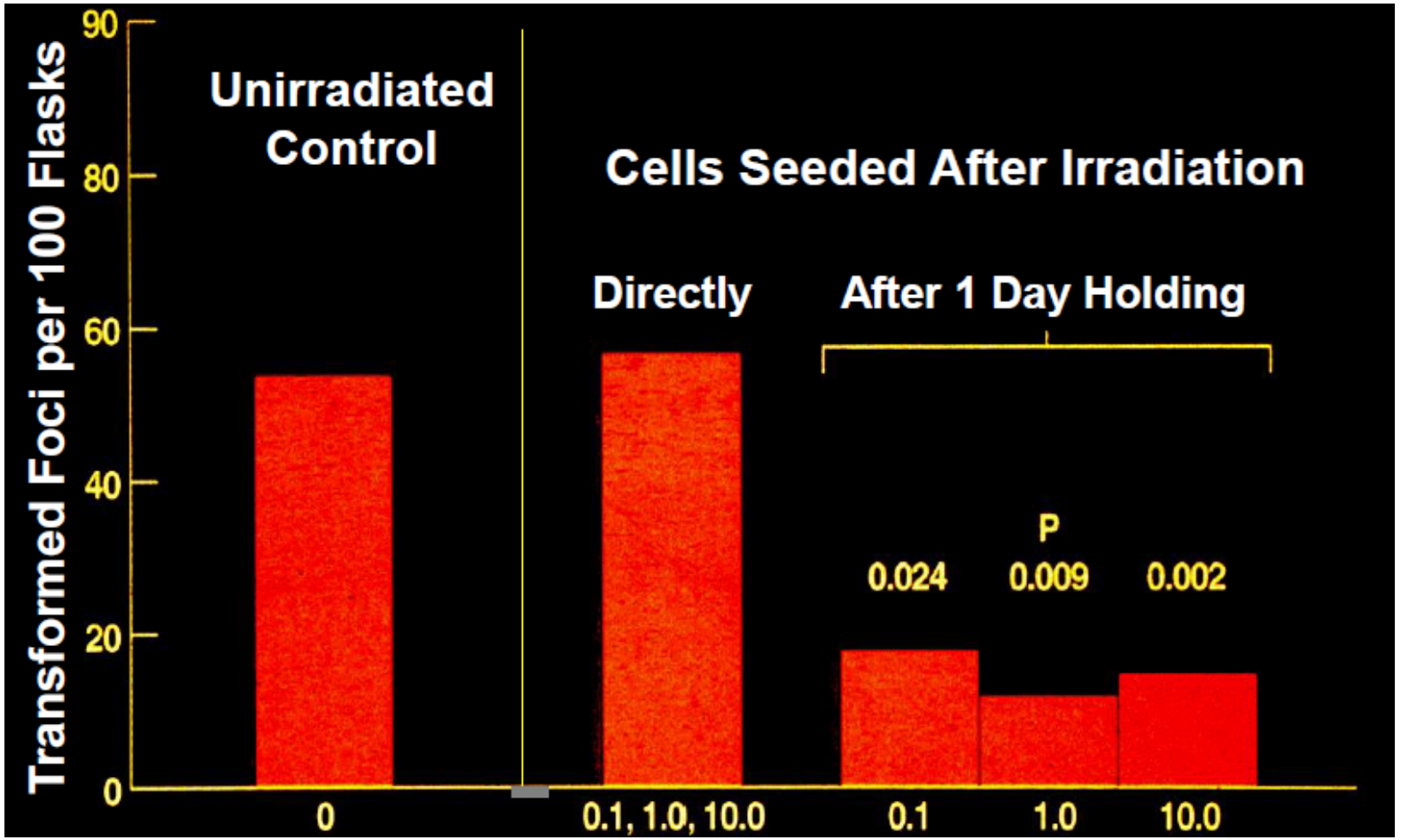


The TCTP protein participates in sensing and repair of DNA damage

Zhang *et al.*, *PNAS* 2012

<u>Implication</u>: At low dose, biology may be more important than physics in determining risk

Exposure to low dose ^{137}CS γ-rays can reduce the neoplastic transformation frequency in mouse embryo cells to below the spontaneous level



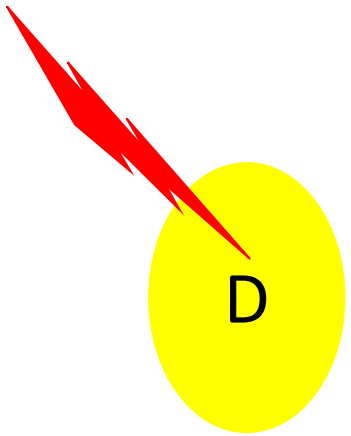
Azzam *et al.*, 1996
Redpath *et al.*, 1998 ..

Mechanisms: Understanding of the molecular/biochemical events underlying the expression of adaptive responses to ionizing radiation has greatly advanced during the past decade

- **Distinct molecular events underlie cellular responses at low *vs*. high dose**
- Modulation of mitochondrial functions; up-regulation of antioxidant potential
- Enhanced DNA repair activity
- ↑ proteases to remove oxidized proteins (e.g. Lon protease)
- Modulation of cell cycle checkpoints --- Chromatin conformation --- Cell death
- Modulation of intercellular communication, including propagation of protective effects

There is evidence that several protective processes act in concert

Conclusion (Part 1)



Primary damage

$DNA_d = \alpha_1 \bullet D$

Linear response

Biological System Responses

Damage modulation:
Propagation, elimination

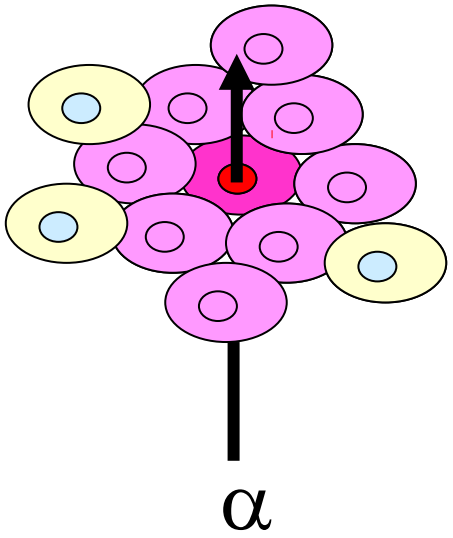
$R_{Ca} \neq \alpha_2 \bullet DNA_d$

Non-linear responses

Part II

Non-Targeted Responses

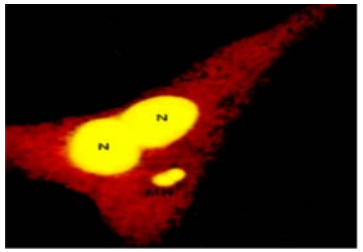
- Responses induced following exposures to low fluences of **densely** ionizing radiations [*e.g.*, α particles, high atomic number (Z) high Energy (E) HZE particles]

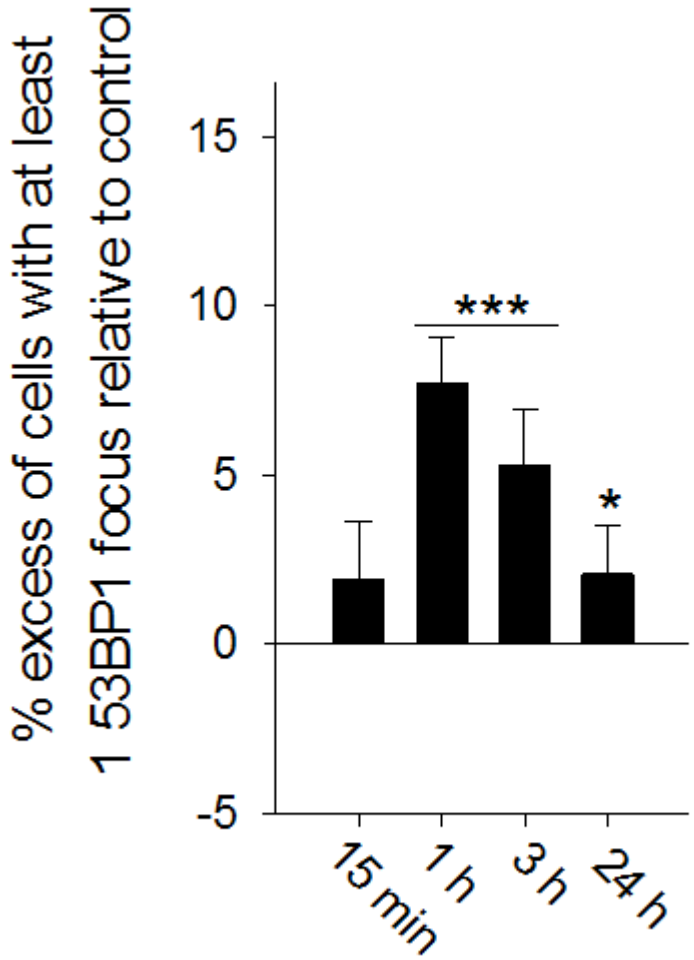


Classic Bystander Effects

Abscopal Effect

Harmful Effects Induced in α Particle-Irradiated Human Cells Spread to Neighboring Bystander Cells





3.7 MeV α particles
LET: ~107 keV/μm

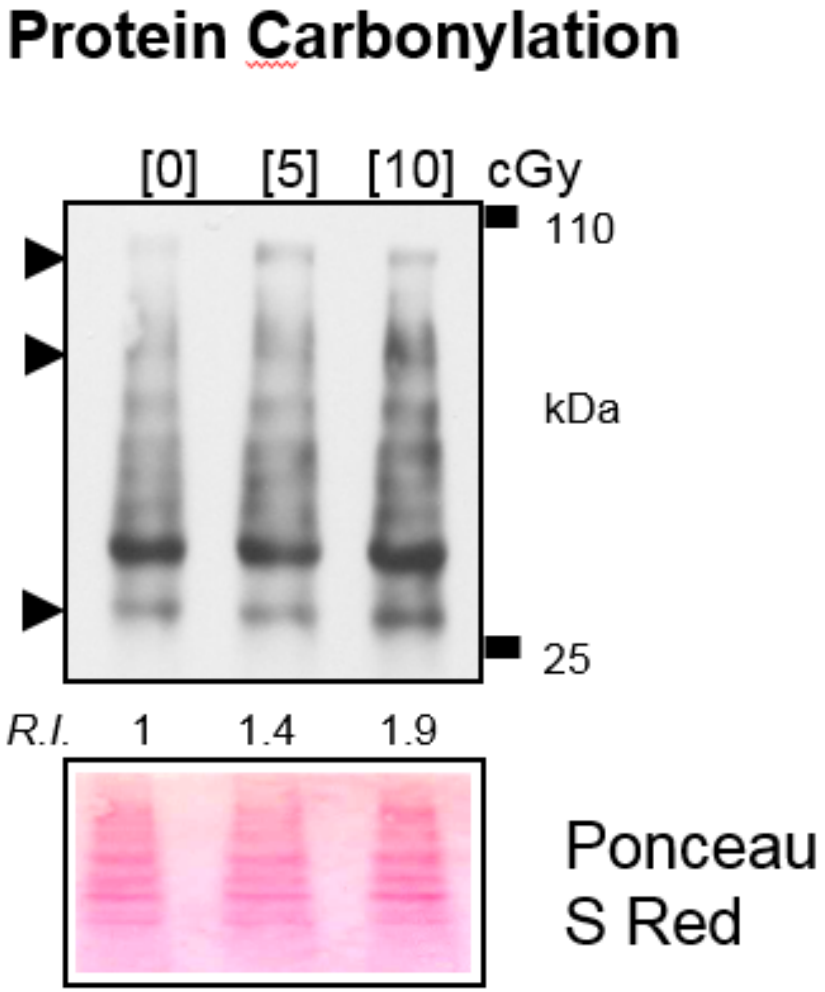
Gonon *et al.*, *Radiat Res*, 2013

Time after exposure of cell culture to 0.2 cGy

(at mean dose of 0.2 cGy, 1 cell in 100 cells are traversed through the nucleus)

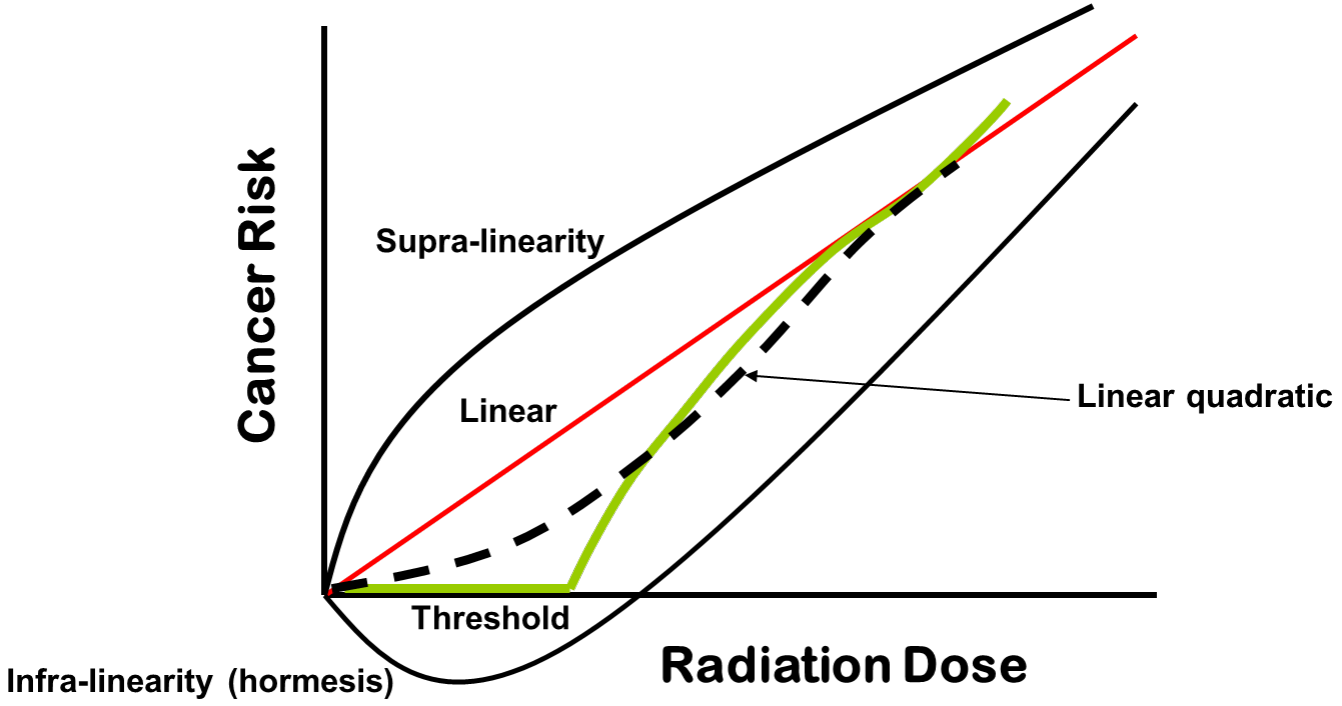
Oxidative Stress in Bystander Cells Co-cultured with α-Particle Irradiated Cells

Experiments with normal human fibroblasts



de Toledo *et al.*, *IJRB* 2017

VALIDATED radiobiology experiments can be a significant guide to empirical epidemiological analyses in areas where there is uncertainty



→ **As knowledge increases, re-evaluation of the shape of the dose-response relation may be necessary**

A few thoughts

- **Interaction of biological matter with ionizing radiation results in primary damages. This damage triggers system responses.**
- Therefore, the **importance of considering all levels of biological organization when extrapolation of results is performed**

To further understand risk at low dose

- Need of *in vivo* studies examining whether exposure to low dose radiation at younger age modulates the latency of expression of age-related diseases such as cancer, cardiovascular diseases
- Need for *in vivo* studies to examine effects of irradiation when the homeodynamic space is perturbed with other forms of stress & ageing
- Need for studies in stem cells & cells/animals with differing genetic susceptibility, and gender

To facilitate the task of the Radiation Protection Professionals (RPP)

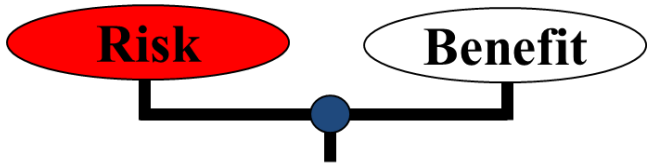
- There is a need for **training** a new generation not only in the physics of radiation but also in:
- The biological effects of single and repetitive exposures such as from CT
- Radiologists should be encouraged to collect **biosamples**: This will help identify **bioindicators** of single and repetitive exposures
- These bioindicators will be of use in directing research efforts to gather appropriate quantitative data to integrate into **mechanistic models**

When asked **“Is a low dose of radiation safe?”**

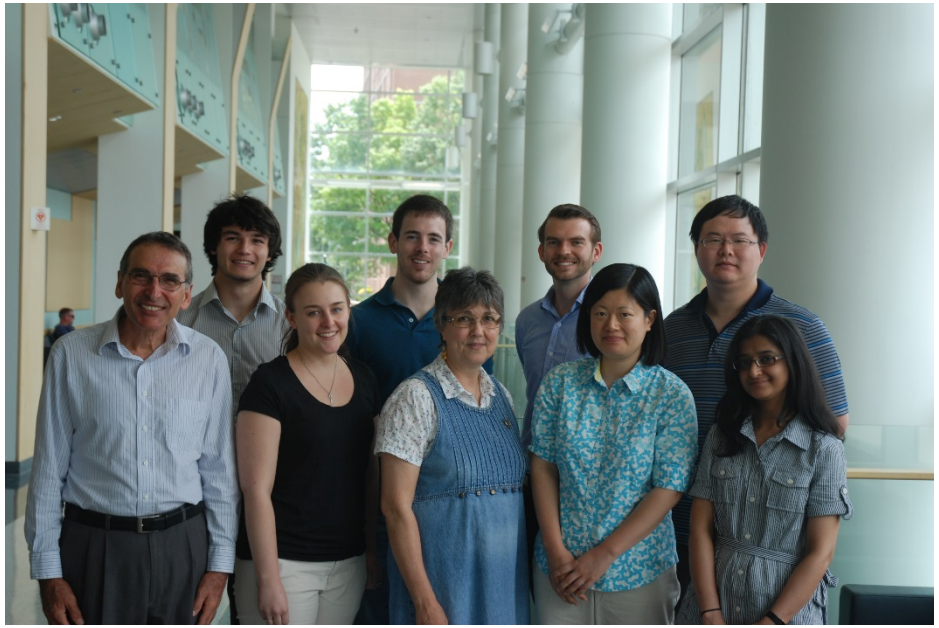
Will you say ‘YES’?

Or will you say “There is always the possibility of a detrimental effect, but at low doses it’s very, very small”

Radiobiology experiments will likely further inform our answer



Thank you



Mentors and Colleagues

NATIONAL CANCER INSTITUTE

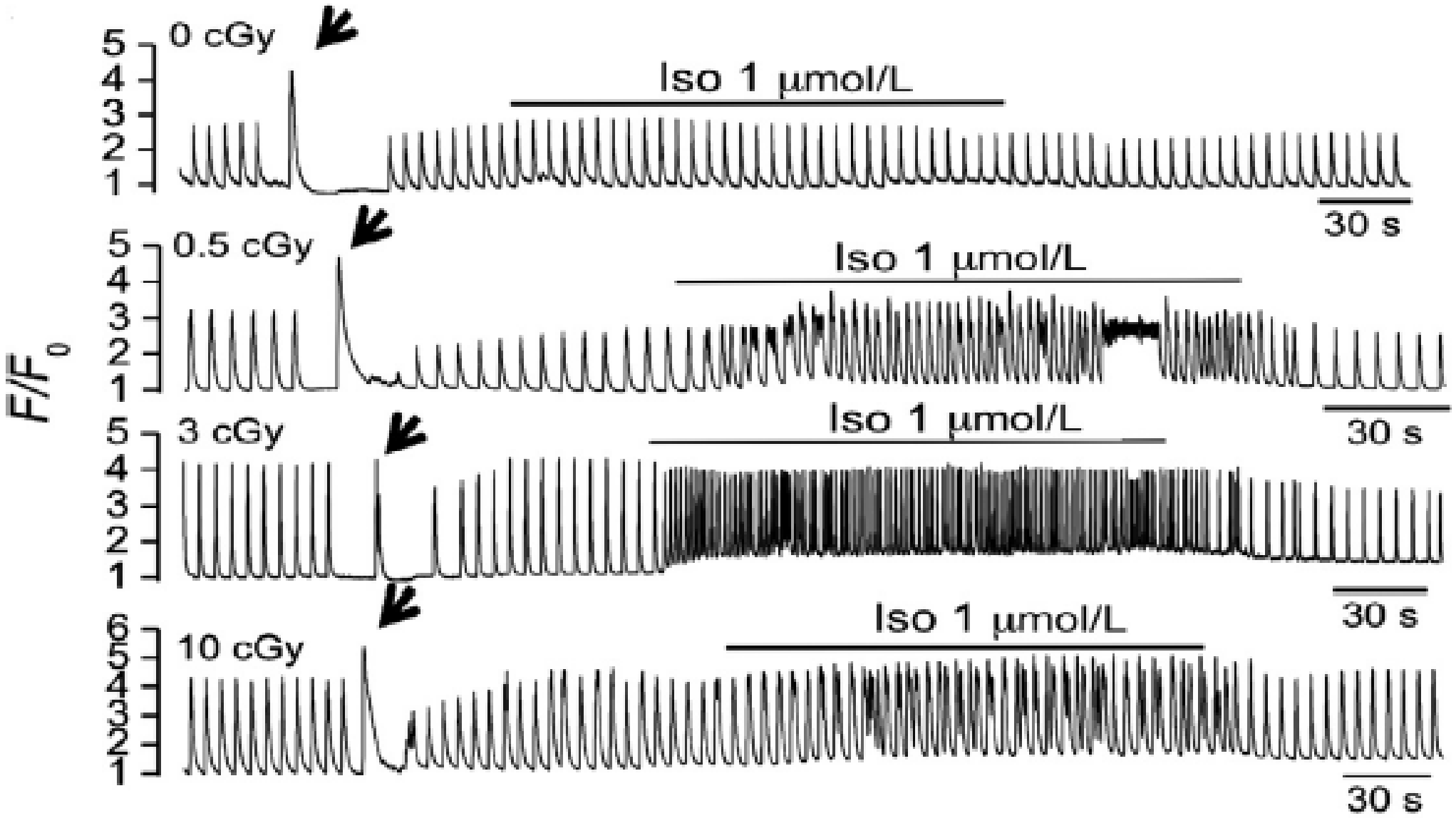
DEPARTMENT OF ENERGY · UNITED STATES OF AMERICA

Space Radiation · NASA

NJCCR NEW JERSEY COMMISSION ON CANCER RESEARCH

New Jersey Health Foundation, Inc.

α-Particle irradiation of HiPSCs exacerbates rhythm disturbance in differentiated cardiomyocytes



Baljinnyam *et al*. *Physiol Reports*, 2017