Non-Linear Biological Responses to Low Dose Radiation - Risk May Not be Proportional to Dose

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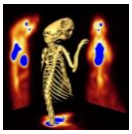
CANADA



Radiation Risk: LNT Hypothesis

- **Dose is additive.**
- **Dose is a surrogate for risk.**
- **Risk is proportional to dose without a threshold.**
- **Everyone is the same with respect to risk and dose.**
- **Biology does not influence risk.**

The New England Journal of Medicine
D. Brenner and E. Hall

November 29, 2007 Vol. 357:2277-2284

*"2% of all cancers in North America over the next decade will be **caused** by CT Scans"*

American Journal of Physicians and Surgeons

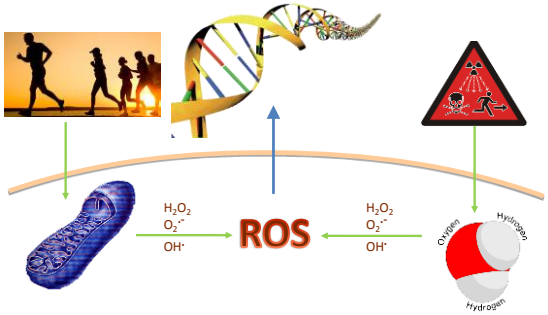
B. Scott, C. Sanders, R. Mitchel and D. Boreham

March 2008

*"Cancer risk in North America may be **reduced** by 2% over the coming decades because of low-dose medical CT exposures"*

Computerized Tomography
(10-40 mGy)

ROS Endogenous Damage and Radiation:
What's the Link?



Endogenous Free Radicals (ROS)

- A 10 mGy CT scan would be equate to an average of 10 photon tracks per cell in the body.
- Every hour, mammalian cells have 50-100 times as much spontaneous DNA damage as they would if they had 10 mGy dose of low-LET radiation (a CT scan).

Endogenous Free Radicals (ROS)

- There are 10,000 measurable DNA alterations per hour in each mammalian cell due to intrinsic causes (oxidative metabolism and ROS).
- Radiation literature states that 100 or fewer DNA alterations occur per 10 mGy (a CT Scan) of low LET radiation per mammalian cell.

Daniel Billen (1990) in Radiation Res. 1990 Nov;124(2):242-5 [7]

Adaption to radiation shown in:

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

This is an Evolutionarily Conserved Response

The Adaptive Response

Cellular response to an environmental stress that induces a mechanisms that confers resistance to subsequent stress.

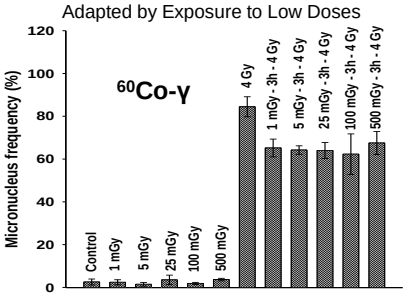
Signal ⟶ Time ⟶ Resistance

Stress
Hyperthermia
Chemical
Radiation

Spontaneous level changes
Endogenous Damage

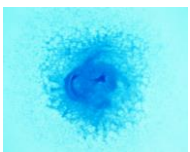
YEAST
INSECTS
PLANTS
CELLS
MAMMALS
HUMANS

Ability to Repair Broken Chromosomes in Cells Adapted by Exposure to Low Doses



Broome, Brown and Mitchel. Radiat. Res. 158, 181-186 (2002)

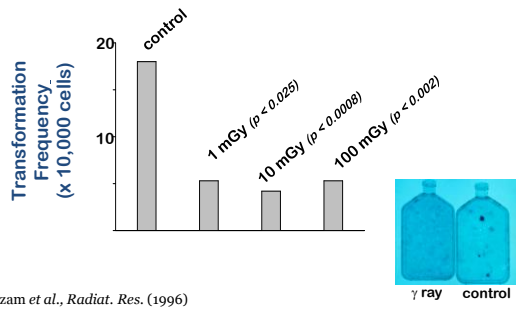
C3H-10T1/2 Cell Transformation Assay



Type III Foci

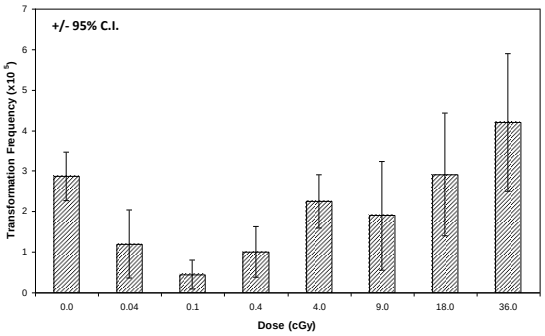
Azzam, de Tolido, Raaphorst and Mitchel, Radiat. Res. 146:369-373 (1996)

Low Dose γ-Rays Reduces the Spontaneous Transformation Frequency in Mouse Embryo Cells



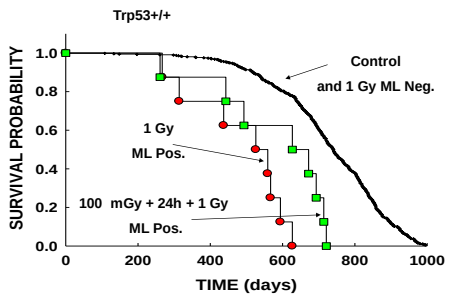
Azzam *et al., Radiat. Res.* (1996)

Effect of Low Doses of 60 kVp X-Rays on Neoplastic Transformation of Human Hybrid Cells *in vitro*



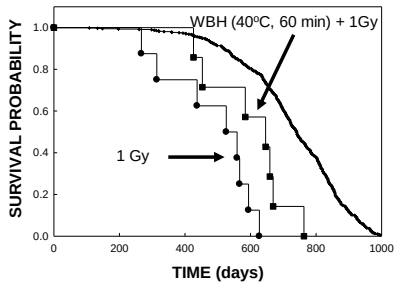
Redpath JL et al. 2000

Low Dose Radiation Improved Survival of Myeloid Leukemia in Genetically Normal Mice



Mitchel, Jackson, McCann and Boreham, Radiat. Res. 152:273-279 (1999)

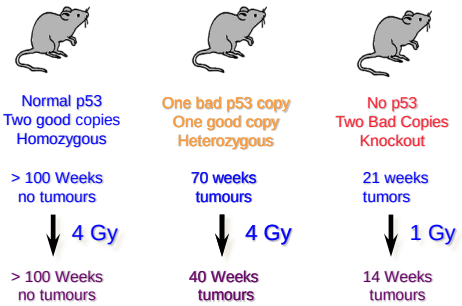
Mild Hyperthermia Improved Survival of Myeloid Leukemia in Genetically Normal Mice



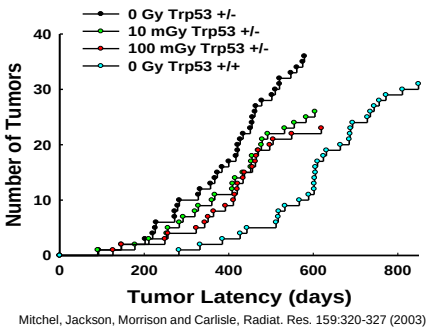
Mitchel, Jackson, McCann and Boreham, Radiat. Res. 152:273-279 (1999)

Role of Radiation and Risk - p53 "Knockout" Mouse Model

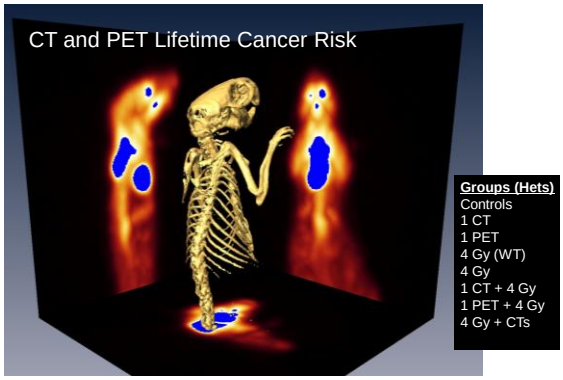
Kemp et al. Nature Genetics 8:66-69, 1994



Lymphoma Latency



Mitchel, Jackson, Morrison and Carlisle, Radiat. Res. 159:320-327 (2003)



Do diagnostic CT and PET scans increase cancer risk?

Breeding

x **64**

870 x

Male Breeders - B6.129S2
(Trp53 Heterozygous +/-)

Female Breeders – 129X1/SvJ
(Trp53 Wild-type +/+)

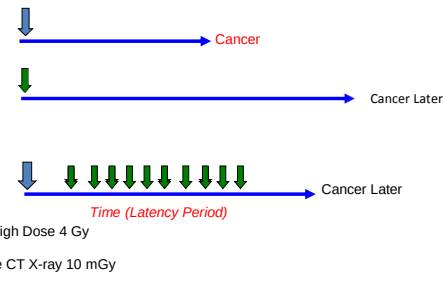
3500+ Male Mice Culled (21 days)

3689 Female Mice (F1)

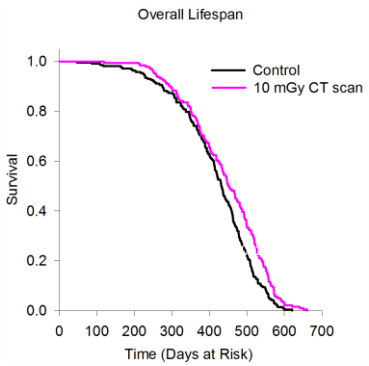
1867 Female Trp53
Heterozygous mice

1822 Female Trp53
Wild-type mice

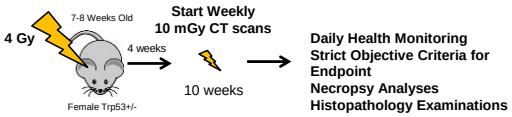
CT X-rays and Anti-Promotion
Low Dose Radiation?

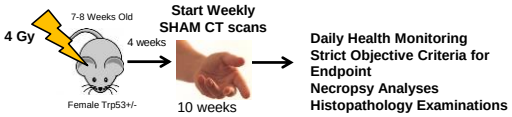


A single CT scan did not increase risk?

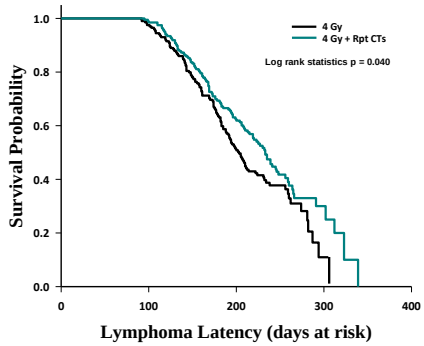


Experimental Setup

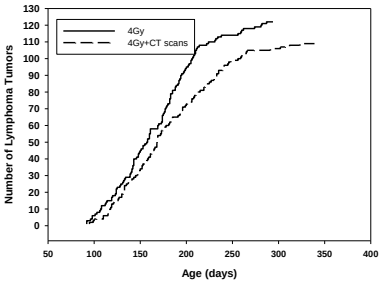




Multiple CT scans did not increase risk (significant increase in life span).



Lymphoma Latency



Conclusions

- Cellular Mechanism do not respond linearly to low dose radiation
- Risk from low doses is not linear
- A single CT scan increases lifespan in cancer prone mice
- Multiple CT scans after radiation-induced cancer initiation extends lifespan
- The effect is seen primarily in lymphoma and carcinoma not sarcoma
- The mechanism is independent or upstream of p53
- Multiple CT scans are not detrimental under these conditions.

Acknowledgements

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Apoptosis (Cell Death)