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

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AAPM 2014, Austin Texas

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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.


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 mechanism 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


C3H-10T1/2 Cell Transformation Assay

Type III Foci

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


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

Mild Hyperthermia Improved Survival of Myeloid Leukemia in Genetically Normal Mice


Role of Radiation and Risk - p53 “Knockout” Mouse Model

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

Lymphoma Latency

Do diagnostic CT and PET scans increase cancer risk?

**Breeding**

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?**

Initiator High Dose 4 Gy

Low Dose CT X-ray 10 mGy

Cancer Later

Cancer Later

Time (Latency Period)
A single CT scan did not increase risk?

**Experimental Setup**

- Female Trp53+/-
- 4 Gy

**Start Weekly**

- 10 mGy CT scans
- 4 weeks

**Daily Health Monitoring**

- Strict Objective Criteria for Endpoint
- Necropsy Analyses
- Histopathology Examinations

**Start Weekly**

- SHAM CT scans
- 4 weeks

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

Log rank statistics p = 0.040

**A single CT scan did not increase risk?**

Overall Lifespan

<table>
<thead>
<tr>
<th>Time (Days at Risk)</th>
<th>0</th>
<th>100</th>
<th>200</th>
<th>300</th>
<th>400</th>
<th>500</th>
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<tr>
<td>Survival</td>
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<td>0.8</td>
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<td>0.6</td>
<td>0.5</td>
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<td>0.3</td>
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</table>

**Lymphoma Latency (days at risk)**

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<tbody>
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<td>Survival Probability</td>
<td>1.0</td>
<td>0.8</td>
<td>0.6</td>
<td>0.4</td>
<td>0.2</td>
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</table>
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

US DOE
NSERC/McMaster University
Bruce Power
Colleagues: (M.-E. Cybulski, N. McFarlane
L. Laframboise

Students (N. Phan, K. Taylor)