# Biology versus Epidemiology

## The need for an integrated model of radiation risk

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# Acknowledgements

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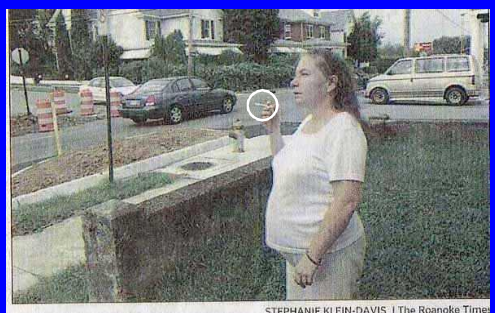
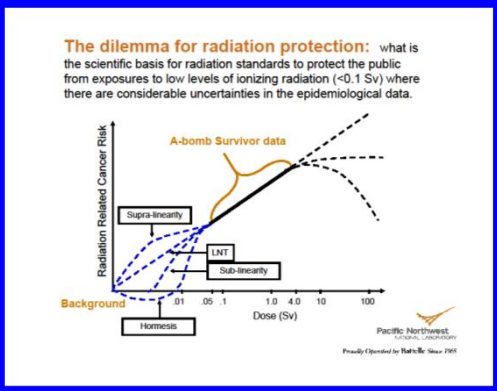
# Perceptions of Risk vs. Benefit

## Perceptions of Risk



STEPHANIE KLEIN-DAVIS | The Roanoke Times

Mellisa Williamson, 35, a Bullitt Avenue resident, worries about the effect on her unborn child from the sound of jackhammers.




## Cancer Mortality ERR in LSS 1950-1997[a]

| Dose (Sv) | ERR/Sv[b] | *P* Value[c] |
|---|---|---|
| 0-0.05 | 0.9 | 0.15 |
| 0-0.1 | 0.64 | 0.30 |
| 0-0.125 | 0.74 | 0.025 |
| 0-0.15 | 0.56 | 0.045 |
| 0-0.2 | 0.76 | 0.003 |
| 0-0.5 | 0.44 | <0.001 |
| 0-1 | 0.47 | <0.001 |
| 0-2 | 0.54 | <0.001 |
| 0-4 | 0.47 | <0.001 |

[a]Preston et al.*Rad Res* 160: 381-407;2003.

[b]BEIR VII ERR/Sv = 0.5 [c]One-side test that slope = 0

## AAPM & HPS Positions

- AAPM: Risks of medical imaging at effective 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.
- HPS: Recommends against quantitative estimation of health risks below an individual dose of 50 mSv in one year or a lifetime dose of 100 mSv above background.

## Average Doses

Radiation Doses from Various Imaging Procedures

| Procedure | Adult E (mSv) |
|---|---|
| Dental | 0.005-0.01 |
| Chest | 0.02 |
| CT | 2-16 |
| Fluoroscopy | 5-70 |

Mettler, et al. 2008

## Annual Dose Limits (mSv)

| | |
|---|---|
| Effective Dose | 50 |
| Lens | 150* |
| Skin | 500 |
| Single Organ | 500 |
| EPA PAG | 20 |

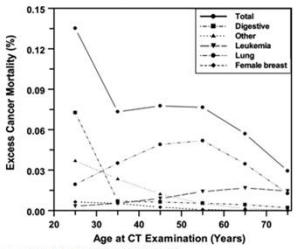
ICRP 103 recommends 20

## LNT

- Even the smallest quantity of radiation exposure carries some finite cancer risk.
- Thus, eliminate radiation exposure, reduce it ALARA, or optimize it.

## Risk from Medical CT

Figure 3. Graph shows excess cancer mortality risks estimated to be associated with radiation from a single full-body CT examination at a given age.




Brenner D J , Elliston C D Radiology 2004;232:735-738

Radiology

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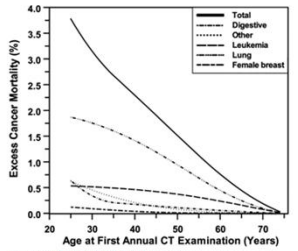
## Risk from Medical CT

Figure 4. Graph shows excess cancer mortality risks estimated to be associated with radiation from annual full-body CT examinations.

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## Radiation Risks in Medicine

- Radiation risk from nth scan = 5 X $10^{-2}$ $Sv^{-1}$
  - For patient with history of 1 scan, additional risk = 5 X $10^{-2}$ $Sv^{-1}$
  - For patient with history of 10 scans, additional risk = 5 X $10^{-2}$ $Sv^{-1}$
  - For patient with history of 100 scans, additional risk = 5 X $10^{-2}$ $Sv^{-1}$

## Radiation Risks in Medicine

- LNT: medical imaging may cause up to 2% of future cancers in the United States[1]
- Cumulative dose estimates for patients are of little clinical relevance and never constitute a logical reason to avoid an imaging evaluation that is otherwise medically indicated[2].

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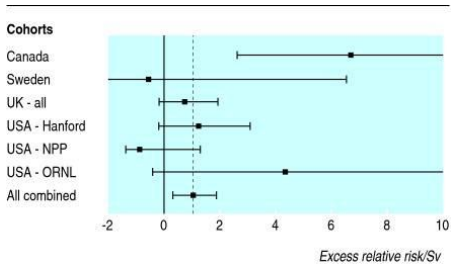
[1]Brenner & Hall; *N Engl J Med* 2007;357:2277–2284

[2]Durand; AJR 2011;197:160–162

To help protect your privacy, PowerPoint has blocked automatic download of this picture.

## Excess Relative Risk per Sv in Workers



## Comments on Cardis

- Shigematsu. (2005 BMJ 331 August 9): ERR due to radiation loses statistical significance when the Canadian data are excluded.
- Lagarde. (2005 BMJ 331 August 9): ERR estimates reported may actually be underestimating the real risks.
- Debrouwer. (2005 BMJ 331 Sept 9): non-systematic bias, but maybe not, can make the results of the studies dubious.
- McGeoghegan. (2005 BMJ 331 Oct 3): elimination of Canada and smokers eliminates significance.

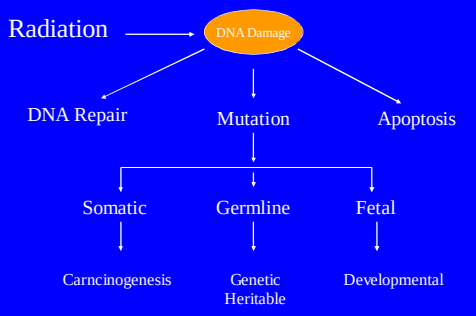
## On the Other Hand - Biology

- Complex biological systems have physiological barriers and repair mechanisms against damage and disease.
- Primary damage linear with dose, secondary damage often non-linear.
- Cellular processes block damage.
- Propagation to clinical disease is complex.

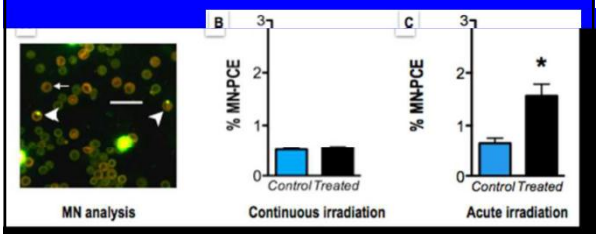
## In the Context Of Radiation Protection

- How to extrapolate biological effects at low doses to risk?
- Are extrapolations from ñhigh doseò acute exposures appropriate when human exposure is primarily chronic low dose exposure?

## The Current Paradigm of Radiation Risk




Acute irradiation of 10.5 Gy (71 mGy/min) induces micronuclei in polychromatic erythrocytes, while low dose-rate (2 uGy/min) does not. (Olipitz et al. 2012).




## Hot Topics in Radiobiology

- Low dose radiation hypersensitivity
- Adaptive responses
- Epigenetic modifications
- Non-targeted genomic instability
- Non-targeted bystander effects
- Non-cancer effects
- Formation of DNA repair centers

## Adaptive Response

- When large radiation exposure is preceded by a small ñtickleò dose, the effect of the large dose is sometimes diminished.
- Small doses of radiation appear to stimulate protective responses, triggering DNA repair mechanisms and the elimination of severely damaged cells (apoptosis).

## Radiation Induced Neoplastic Transformation *In Vitro*

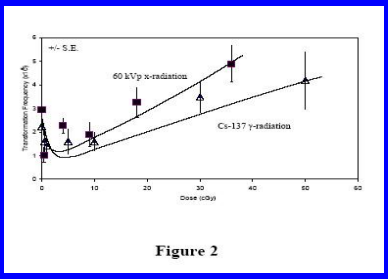



**Figure 2**

Redpath et al. 2001

## Bystander Effects
(Field Effect in Cancer)*

- Signals sent by bystander cells may help repair the damaged cell, or they may trigger apoptosis in damaged cell.

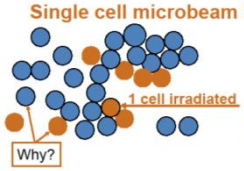
OR

- Signals in damaged cell may disrupt normal function of bystander cells.

*Slaughter et al., Cancer 1953;6:963ï 968.

**Radiation induced bystander effects:**
Effects observed in cells that were not irradiated but were "bystanders" at the time of irradiation

**Single cell microbeam irradiation**




gene expression
mutation
transformation
micronuclei
cell killing

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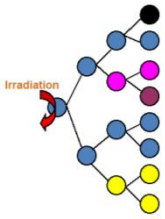
## Observed Bystander Effects

- Changes in gene expression.
- Mutations.
- Apoptosis.
- Chromosome aberrations.
- Cell transformation.
- Cancer.
- Changes in sister chromatid exchanges.

**Radiation-Induced Genomic Instability**
Increased rate of genomic alterations in the progeny of irradiated cells




**Manifests as:**
chromosomal rearrangements
micronuclei
aneuploidy
delayed mutation
(spectrum different)
gene amplification
cell killing

**Non clonal - not necessarily a fixed genetic change that is passed on.**

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## Genomic Instability
(Delayed Genetic Effects)

- Detrimental effects that occur several cell generations after radiation exposure.
- Often, cells repair DNA damage and reproduce normally.
- In some cases genetic damage is observed several generations after damage occurred.

## Genomic Instability

- Provides a mechanism to explain how radiation can produce the multiple steps needed to transform a normal cell into a malignant cell.
- Supports LNT if cellular genomic instability can be shown to increase cancer frequency.

## DNA Damage & Repair

- DNA damage caused by radiation exhibits multiply damaged sites.
- Single strand breaks are more common in normal endogenous DNA damage.
- Double strand breaks are more common in radiation induced damage.

## DNA Damage & Repair

- Single strand break repair is usually error free.
- Double strand breaks can be either error free or error prone, containing a high error rate.
- Data suggest non-linear process.

## Formation of DNA Repair Centers (Nonlinear)

Radiation Induced Foci (DSB clustering into repair centers):

- 15 RIF/Gy after 2 Gy
- 64 RIF/Gy after 0.1 Gy.

Discovery of DSB clustering casts considerable doubt on assumption that radiation risk is proportional to dose.

Neumaier. PNAS **109**: 443-48; 2012

## Radiation Response Model

- Public & Worker Protection based on LNT
- Realities: Tissue sensitivity varies with:
  - Age
  - Sex
  - Socio-economic status
  - Diet & lifestyle
  - Genetic makeup & race
  - Dose & dose rate
  - Radiation quality

## Conclusions

- Epidemiology isn't sensitive enough to provide definitive information at low doses.
- Radiobiology research will continue to elucidate mechanisms, but not population risk.
- Use of LNT works for prospective protection of public health but doesn't provide accurate results for risk.

## Conclusions

- LNT: biology suggests that not all systems respond to radiation linearly.
- Regulatory use of LNT is "safe bet."
- Use of LNT to calculate risk from medical radiation is "risky."