Low-Level Radiation and Health

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http://www.radiation-scott.org

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- **Spontaneous and radiation-induced damage**
- **Radiation activated natural protection (radiation hormesis)**
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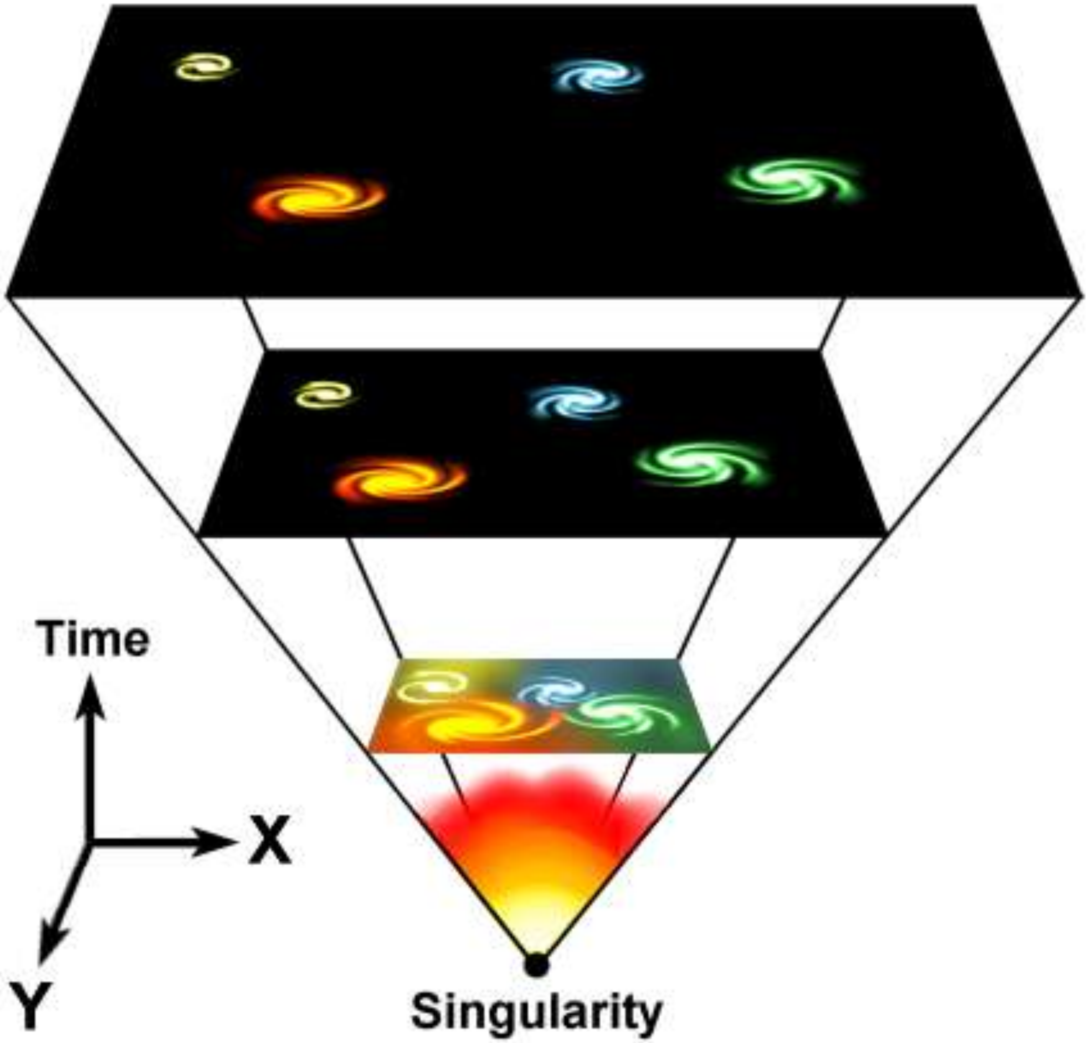
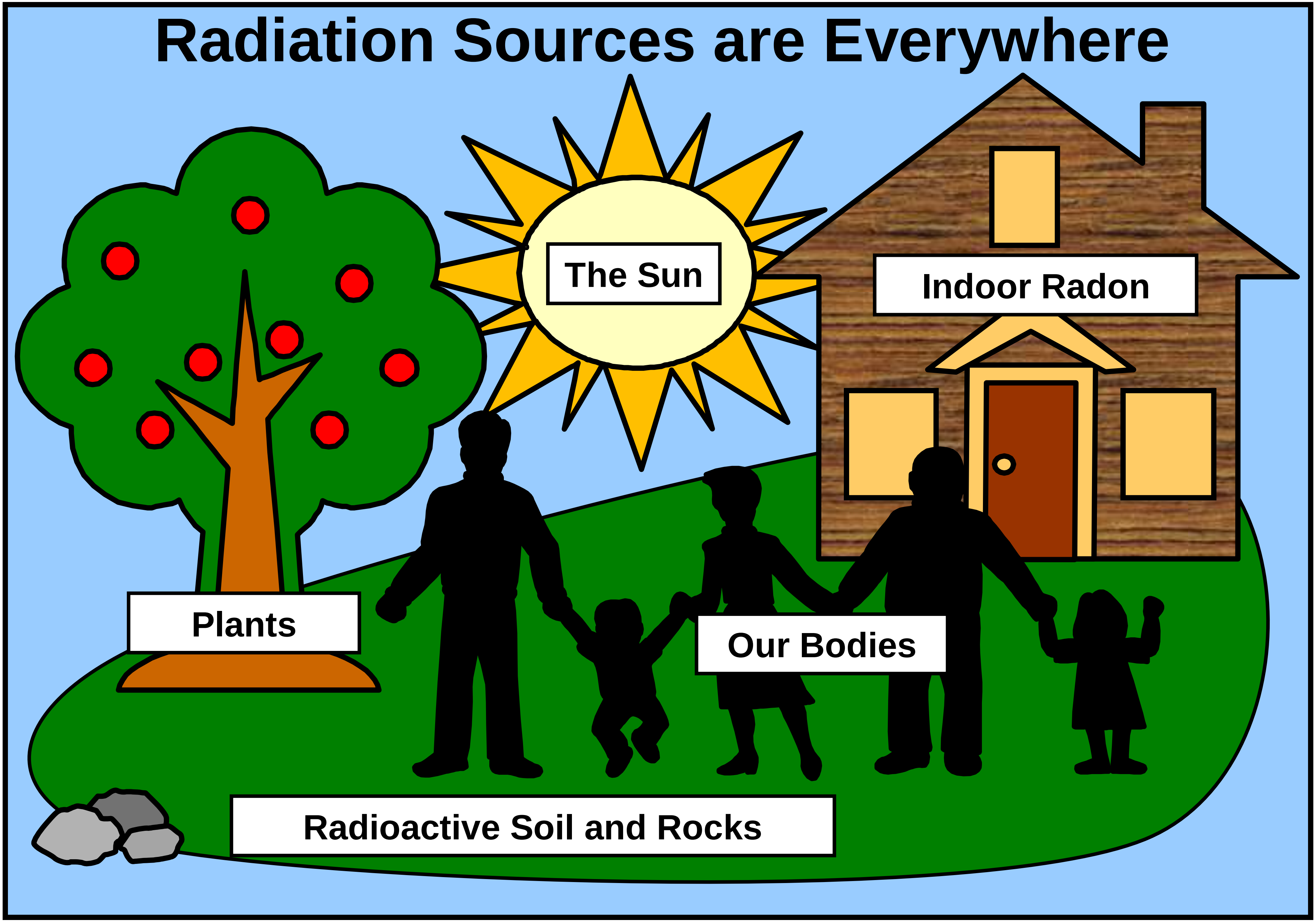
Contents (continued)

- **Abundant evidence for radiation hormesis**
- **Hormesis implications for low-dose cancer therapy**
- **Utopian-world LNT vs. real-world hormesis: Implications for radiation disaster preparedness**
- **Conclusions**

Radiation Has Existed Since the Beginning of the Universe

Universe created 10 - 20 billion years ago from a cosmic explosion




Radiation Sources are Everywhere
The Sun
Indoor Radon
Plants
Our Bodies
Radioactive Soil and Rocks

Man-made Radiation Sources

- X-ray machines
- Medical isotopes
- Televisions
- Smoke detectors
- Weapons fallout
- Radioactive waste

Low- and High-LET Forms of Radiation

- **LET (linear energy transfer) is the average energy lost by radiation when traversing a small thickness of material.**
- **Examples of low-LET radiation are X-rays gamma-rays, and beta particles.**
- **Examples of high-LET radiation are alpha particles, neutrons.**

Adverse Consequences of Exposure of Humans to Radiation

- **Low and high radiation doses can cause stochastic effects such as cancer and genetic effects.**
- **High doses and dose rates can cause life-threatening effects such as severe damage to organs as well as serious morbidity.**
- **Damage to DNA above the spontaneous level is largely responsible for most detrimental radiobiological effects.**

Radiation Bystander Effects

- **Deleterious signaling:** ***E. Azzam EI et al. Current Cancer Drug Targets 2:53, 2004.***
- **Protective signaling:** ***A. Hooker et al. Radiation Research 162:447, 2004.***

Deleterious Signals

- **Activated by low and high doses of high-LET radiation and by high doses of low-LET radiation.**
- **Can lead to stochastic bystander effects, including genomic instability.**
- **Elevated genomic instability elevates cancer risk.**

Protective Signals

- Form of natural defense.
- Induced by low-dose low-LET radiation and other stressors.
- Reactive oxygen (ROS) and nitrogen (RNS) species and specific cytokines (e.g., TGF-β1) participate.
- Enhances DNA repair capacity in bystander cells.
- Stimulates selective removal of aberrant bystander cells.

Portess et al. Cancer Res. 67:1246, 2007.

Radiation Hormesis

- **Survival of all organisms on Earth depends upon their ability to adapt to environmental and other stresses.**
- **Numerous genes evolved over time to mediate adaptive responses to both internal and external genotoxic stresses.**
- **Radiation Hormesis: low-dose radiation activated natural protection (ANP).**
- **Protective signaling regulates ANP (Scott 2007; in press and submitted papers).**

Radiation Activated Natural Protection Is Evolutionary Conserved

Occurs in:

- **Single cell organisms**
- **Insects**
- **Plants**
- **Lower vertebrates**
- **Mammalian, cells**
- **Mammals including humans**

Mitchel, REJ (2006 IHS Meeting presentation)

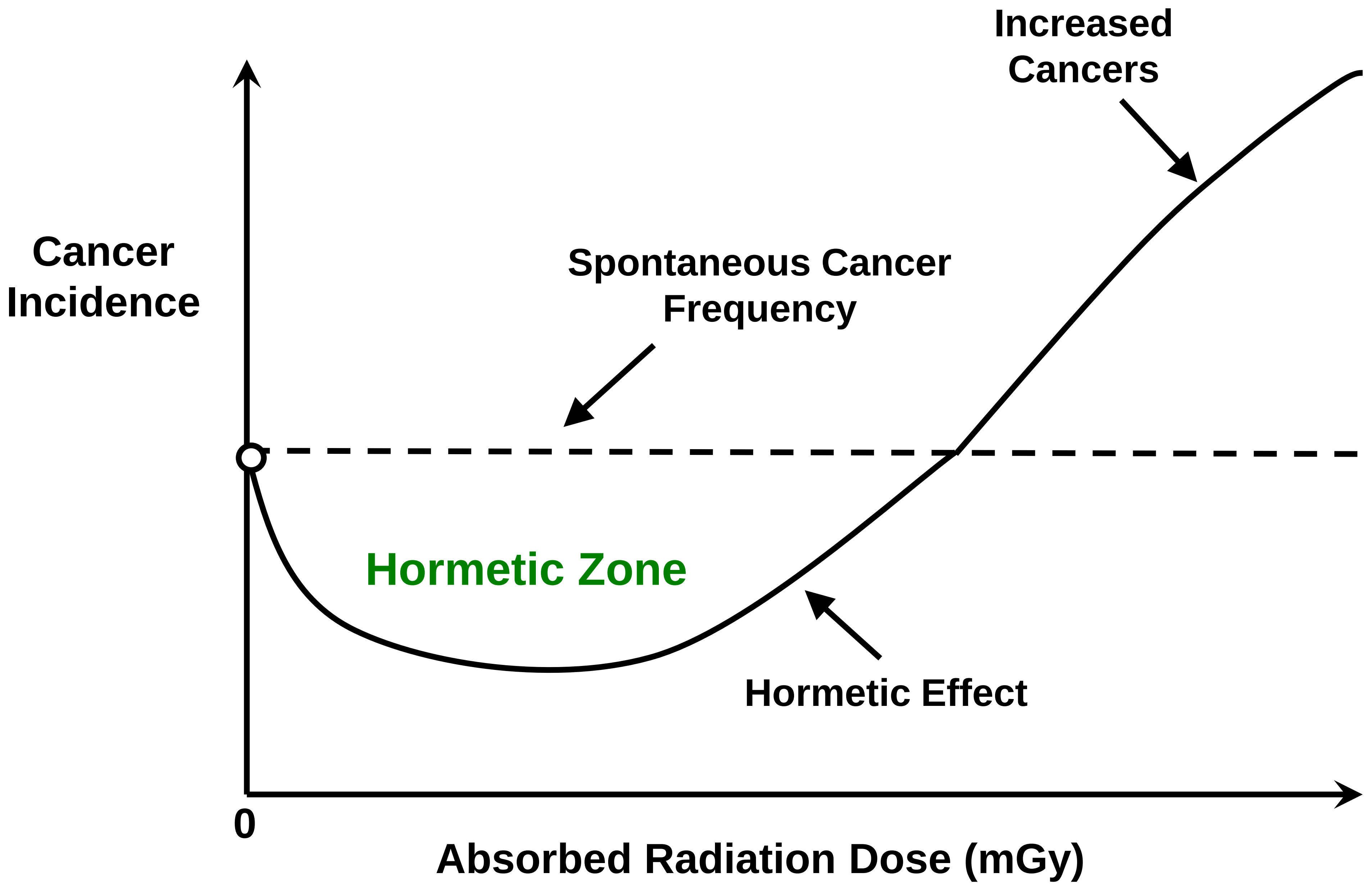
Low-Level, Low-LET Radiation Protects Us

- **Protects against chromosomal damage (Ed Azzam's group)!**
- **Protects against mutation induction (Pam Sykes' group), even when the low dose follows a large dose (Tanya Day's work)!**
- **Protects against neoplastic transformation (Les Redpath's group)!**
- **Protects against high dose chemical- and radiation-induced cancer (Kazou Sakai's group)!**
- **Enhances immune system defense (Shu-Zheng Liu's group)!**

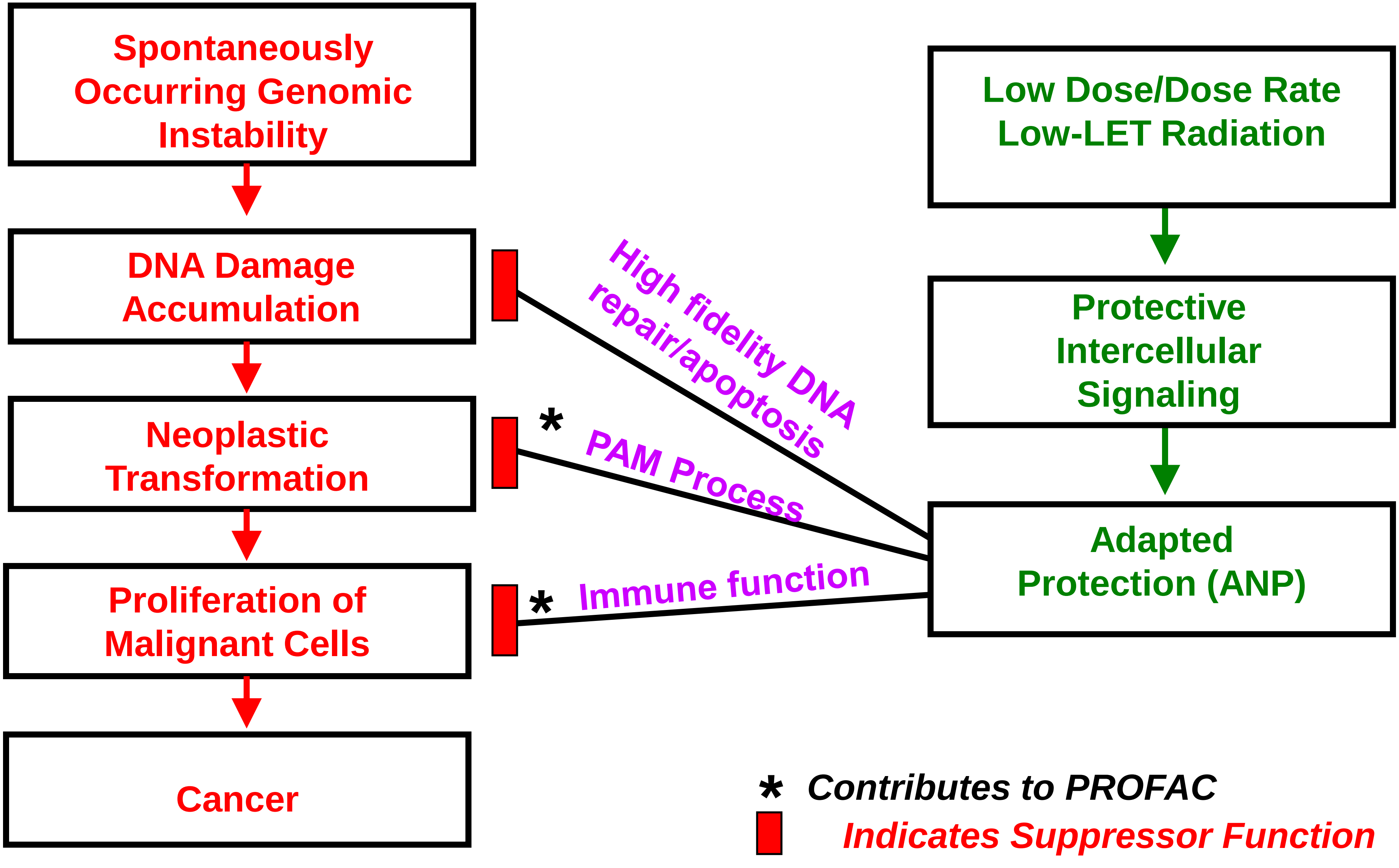
Low-LET Radiation Protects Us (continued)

- **Suppresses cancer induction by alpha radiation (Chuck Sanders group)!**
- **Suppresses metastasis of existing cancer (Kiyohiko Sakamoto's group)!**
- **Extends tumor latent period (Ron Mitchel's group)!**
- **Protects against diseases other than cancer (Kazuo Sakai's group)!**

Hormetic Risk (J-Shaped) Curve



Biological Basis for Hormetic Zone for Low-LET Radiation



Scott 2007

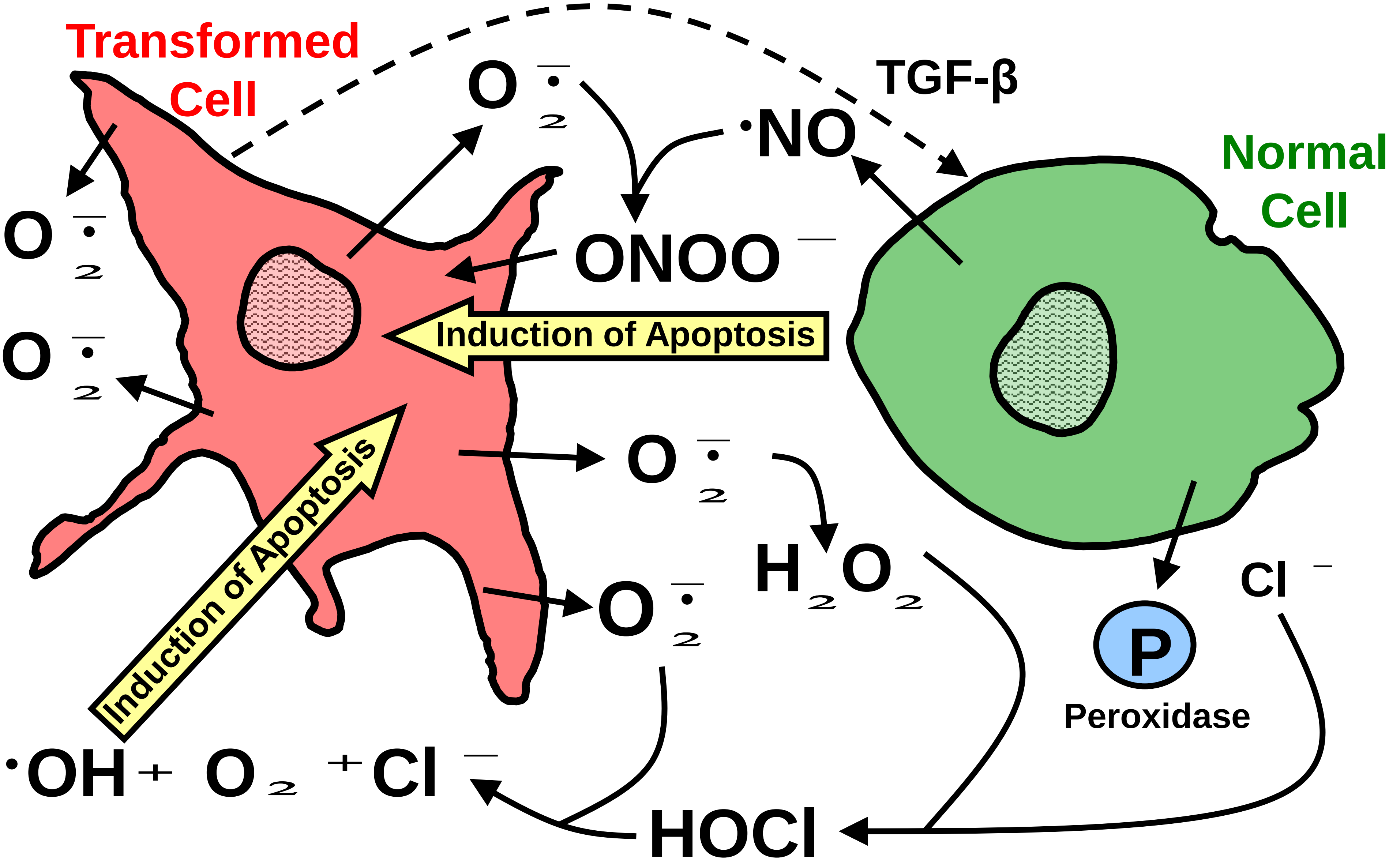
ROS scavenging contributes to protection

PROFAC, A Measure of ANP Efficiency

- ***PROFAC*** **stands for protection factor.**
- **Cancer suppression *PROFAC*: Expected fraction of cancer cases that do not occur that would have occurred in the absence of radiation ANP.**
- **ANP is regulated via protective intercellular signaling and the PAM process* component is a protective bystander effect.**

Explained on next slide.

Protective Apoptosis Medicated (PAM) Process in Fibroblast: Protective Intercellular Signaling



G. Bauer. Histol. Histopathol. 11:237-255, 1996

PAM Process Signaling

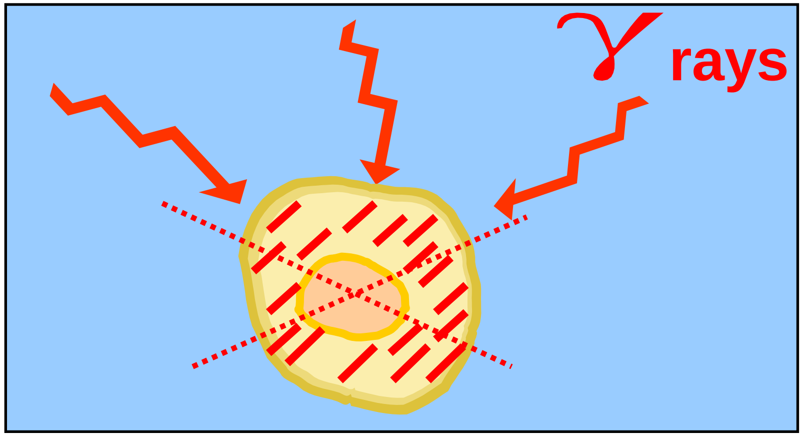
- Can eliminate precancerous and other genomically-unstable cells caused by different agents.
- May vary for different stressing agents (e.g., ionizing radiation, UV radiation, chemical, etc.).
- May differ for different organs/tissue.
- Appears independent of p53.
- TGF-β appears to play and important role in fibroblast.

NEOTRANS$_3$ Model for Radiation-Induced Stochastic Effects in Cells

- **Models the induction of genomically unstable cells by low dose radiation.**
- **DNA repair errors leads to mutations and neoplastic transformations.**
- **Normal apoptosis (presumably p53-dependent) when activated, removes moderately- and seriously-damaged cells.**
- **Auxiliary apoptosis (presumably p53-independent) when activated, removes some of the remaining aberrant cells including already existing precancerous cells (PAM Process).**

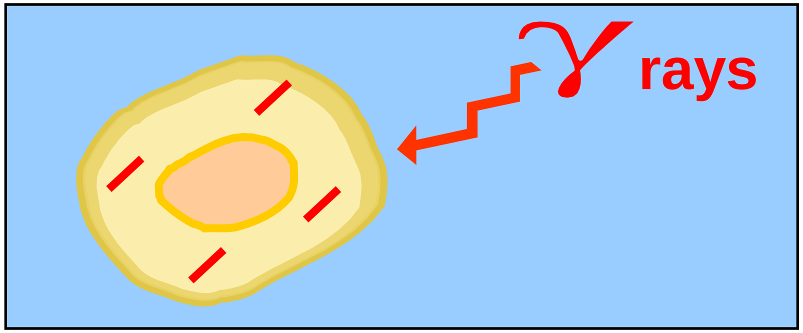
NEOTRANS$_3$ Model Modes of Death after Low Doses of Low-LET Radiation

Moderately damaged cell



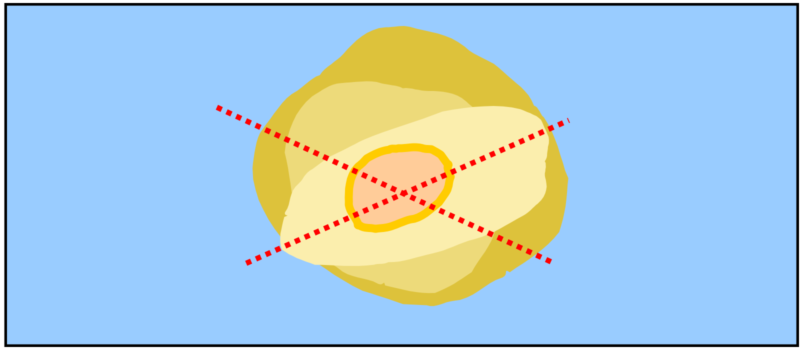
p53-related death sentence

Mildly damaged cell



p53-related DNA repair

Bystander precancerous cell

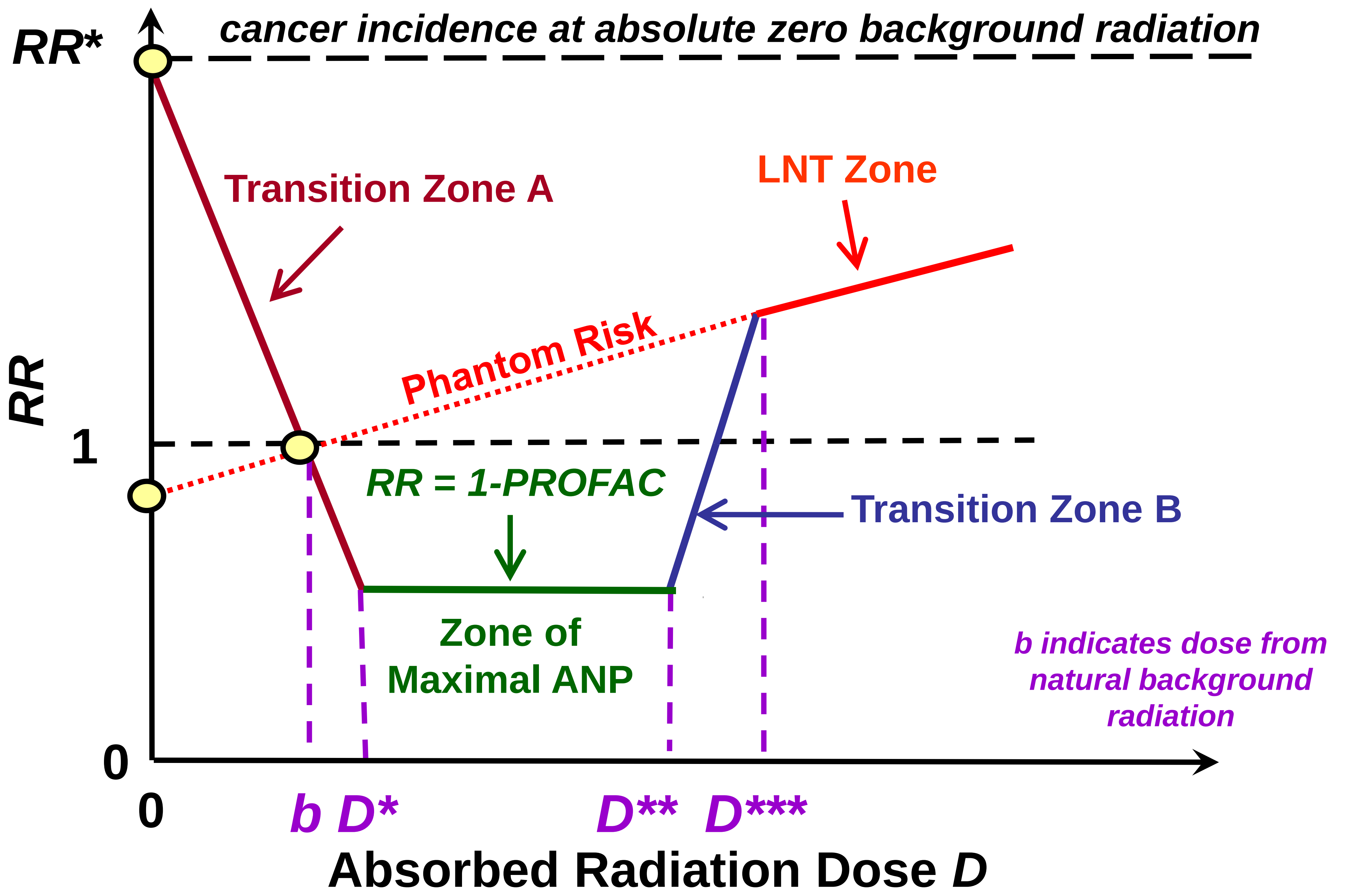


p53-independent death sentence: PAM process

Cancer Hormetic Relative Risk (HRR) Model

- **Key Assumption: Cancer arises from cells with persistent genomic instability through a series of stochastic changes, independent of how the instability originates, but dependent on the number of cells with this instability in an organ.**
- **Cancer relative risk (*RR*) proportional to neoplastic transformation *RR*.**
- **Neoplastic transformation *RR* based on $NEOTRANS_3$ model developed at LRRI.**
- **Protective and deleterious stochastic dose thresholds cause hormetic dose-response curve shape.**

Hormetic Relative Risk (HRR) Model



Radiation ANP from Some Diagnostic Procedures is Likely

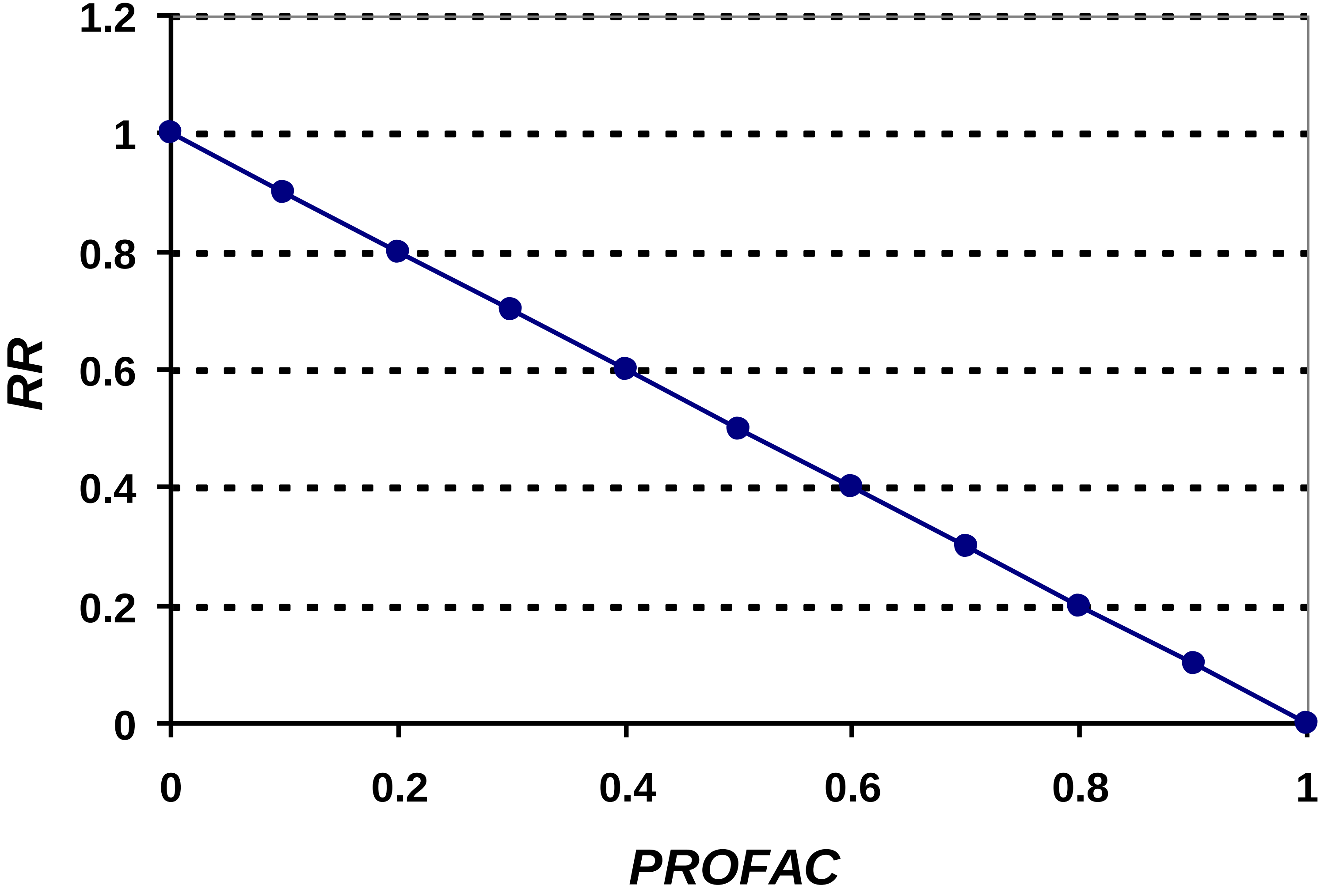
Doses from Diagnostic X Rays Fall in the Hormetic Zone		
Number of X Rays	Dose Range[a]	Hormesis Induced?
< 5	0.01 mGy - 30 mGy	> 0.01 mGy Yes
5 – 14	0.1 mGy – 50 mGy	Yes
≥ 14	1 mGy – 230 mGy	Yes

[a]*Boice JD, Jr. et al. JAMA 265(10):1290-1294, 1991.*

Doses from Other Diagnostic Sources	
Source	mGy
Dental, full-mouth (X ray)	0.17
Chest X ray	0.25
Mammograms (X ray)	4
CT scan, head (X ray)	20
CT scan, body (X ray)	60
Thyroid scans:	
Iodine-131 (β + γ radiation)	50-100
Iodine-123 (γ radiation)	30-50
Technetium-99 (β radiation)	10

Kauffman, Journal of American Physicians and Surgeons 8(2):54-55, 2003

Cancer Relative Risk as a Fuction of the ANP-Related *PROFAC* for the Hormetic Zone



Protection Factors Against Cancer in Humans[1]

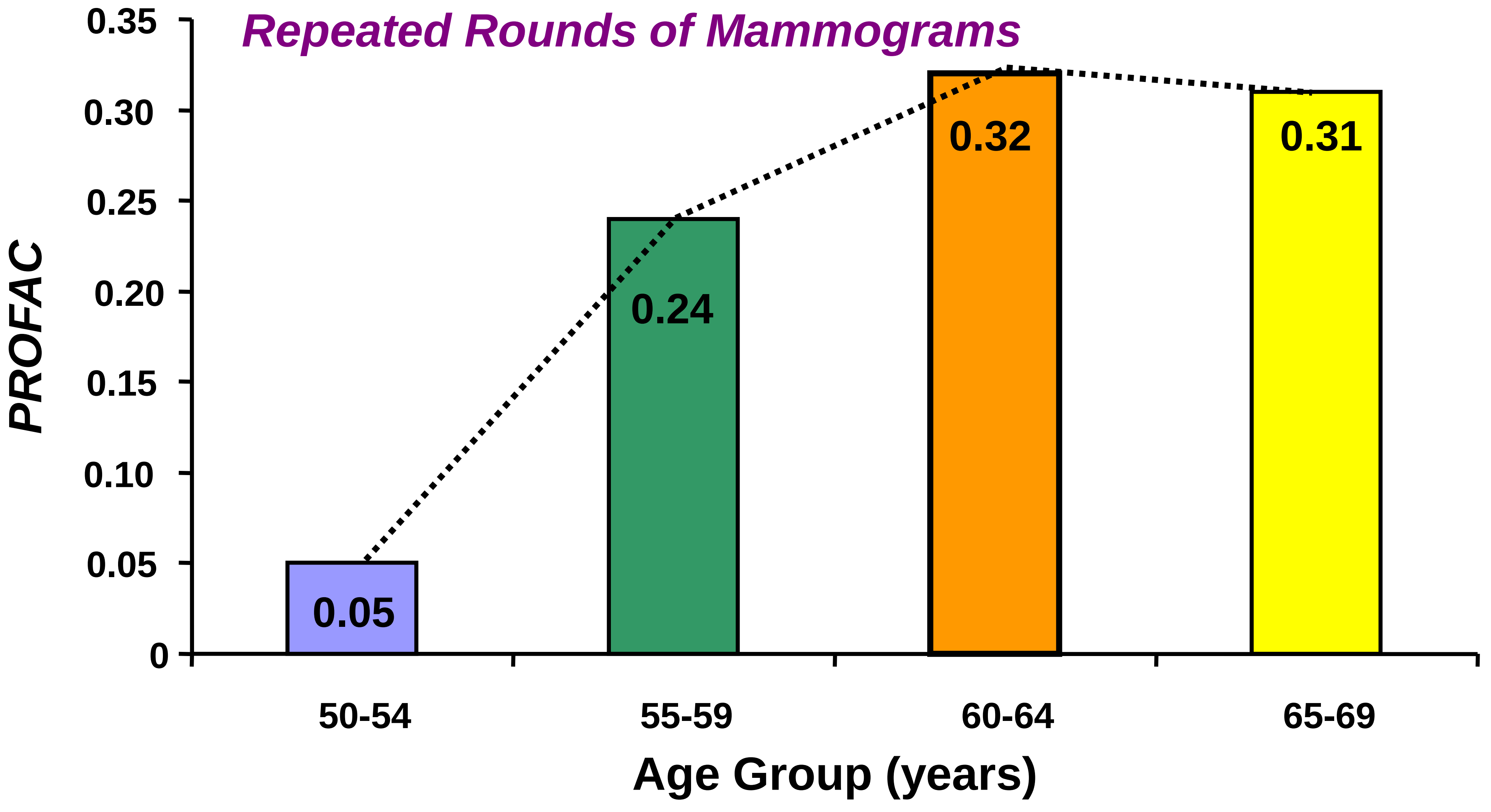
Region or Group	Effect	*PROFAC*
High radon levels, USA	all cancers	0.35
Canada, nuclear industry workers	Leukemia	0.68
US DOE labs workers	Leukemia	0.78
Mayak Plutonium facility workers	lung cancer	0.86[2]

Proportion of spontaneous and other cancers prevented!

[1]Jaworowski Z. Symposium "Entwicklungen im Strahleschutz", Munich, 29 November 2001.

[2]Scott BR. Dose-Response, 2007 .

Age-Dependent Protection Factors Against Breast Cancer for Diagnostic X-Rays



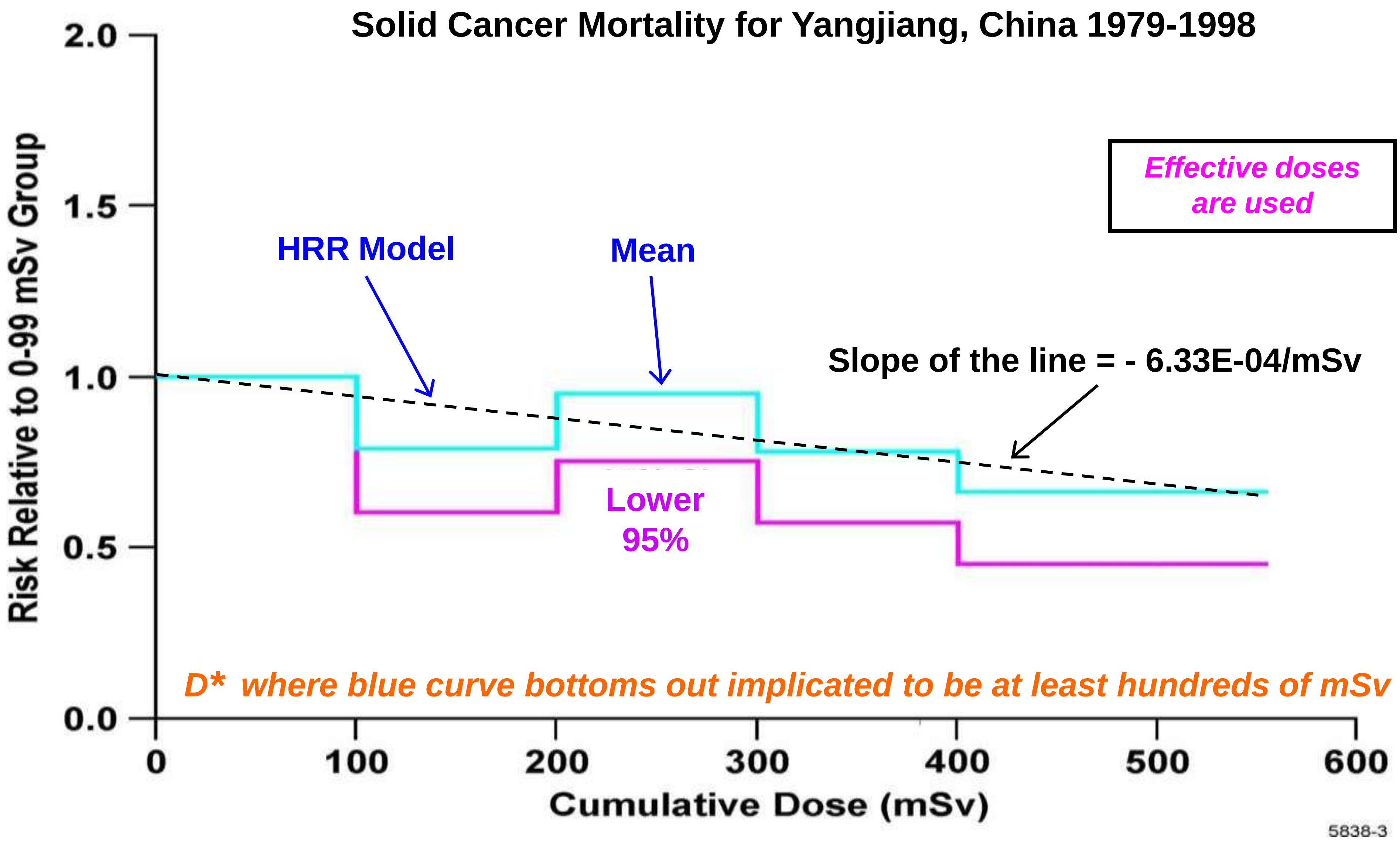
Based on data from Nyström et al. 2002

*PROFAC*s for Nuclear Shipyard Workers Chronically Exposed to γ Rays

Cause of Death	SMR	*p* value	*PROFAC*
Allergic, endocrine, metabolic	0.69 0.12	4.3×10^{-3}	0.31
All respiratory disease	0.62 ± 0.08	1.4×10^{-6}	0.38
Pneumonia	0.68 ± 0.04	2.4×10^{-14}	0.32
Emphysema	0.63 ± 0.26	7.2×10^{-2}	0.37
Asthma	0.30 ± 0.43	5.1×10^{-2}	0.70
All infectious & parasitic	0.86 ± 0.72	4.2×10^{-1}	0.14
Total mortality	0.78 ± 0.04		0.22

Based on combining SMR data from Sponsler and Cameron (2005).

Benefits of Natural Background Radiation

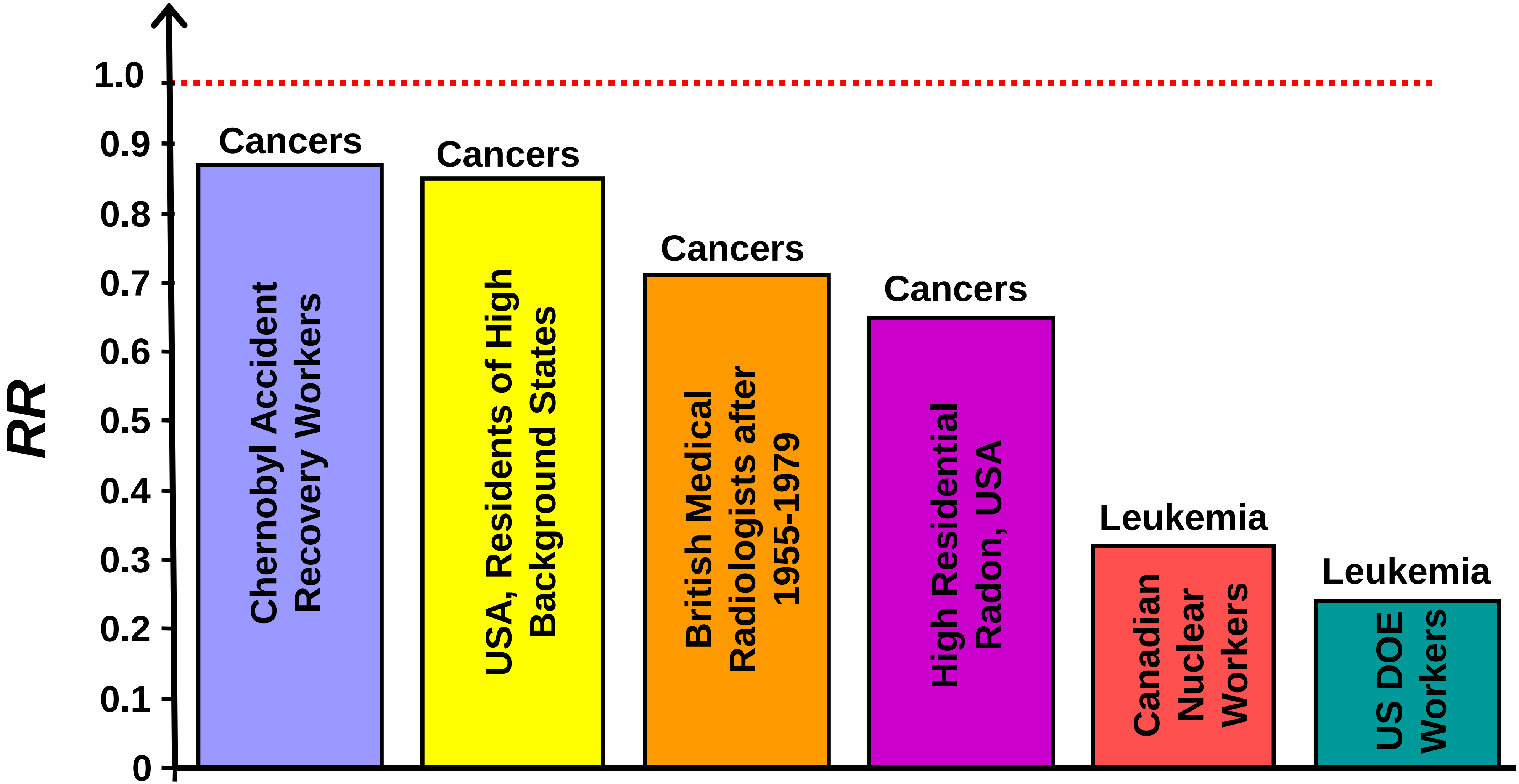


Wei and Sugahara. Int. Congress Series 1236:91-99 (2002)

Epidemiological Studies with Appropriate Internal Controls that Negate the Healthy Worker Effect (C. L. Sanders, 2007)

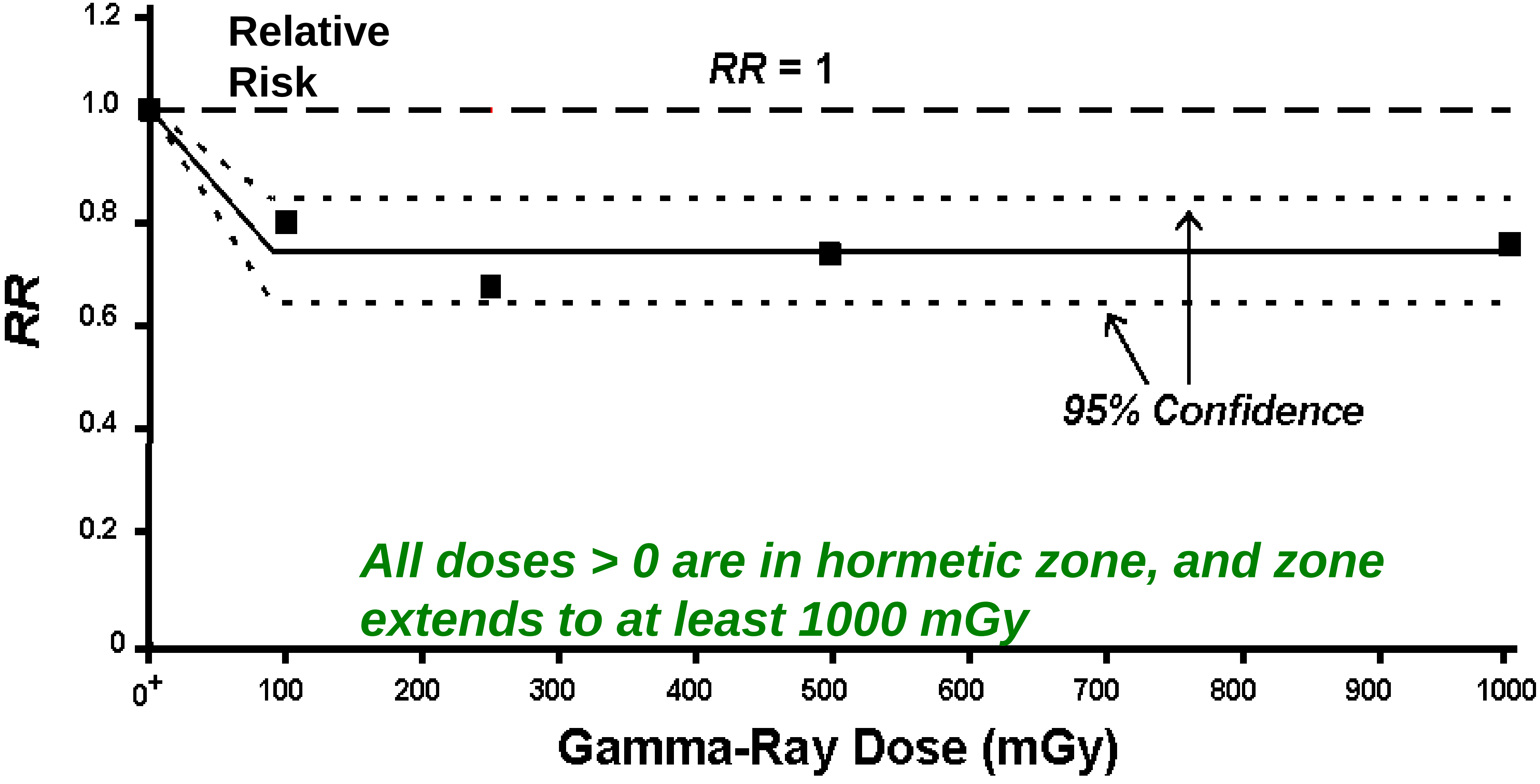
Worker Comparison	SMR	
	All Cancer	Lung Cancer
Badged/Unbadged DOE Female Workers	0.83	0.51
UK Radiologists/Physicians	0.71	As low as 0.00
High-Dose/Control Shipyard Workers	0.84	0.93
Monitored/Unmonitored UK Nuclear Utility Workers	0.73	0.61
Radiation/Non-Radiation UKAEA Workers	As low as 0.30	0.89

Cancer Relative Risk In Hormetic Zone: Irradiated Human Populations



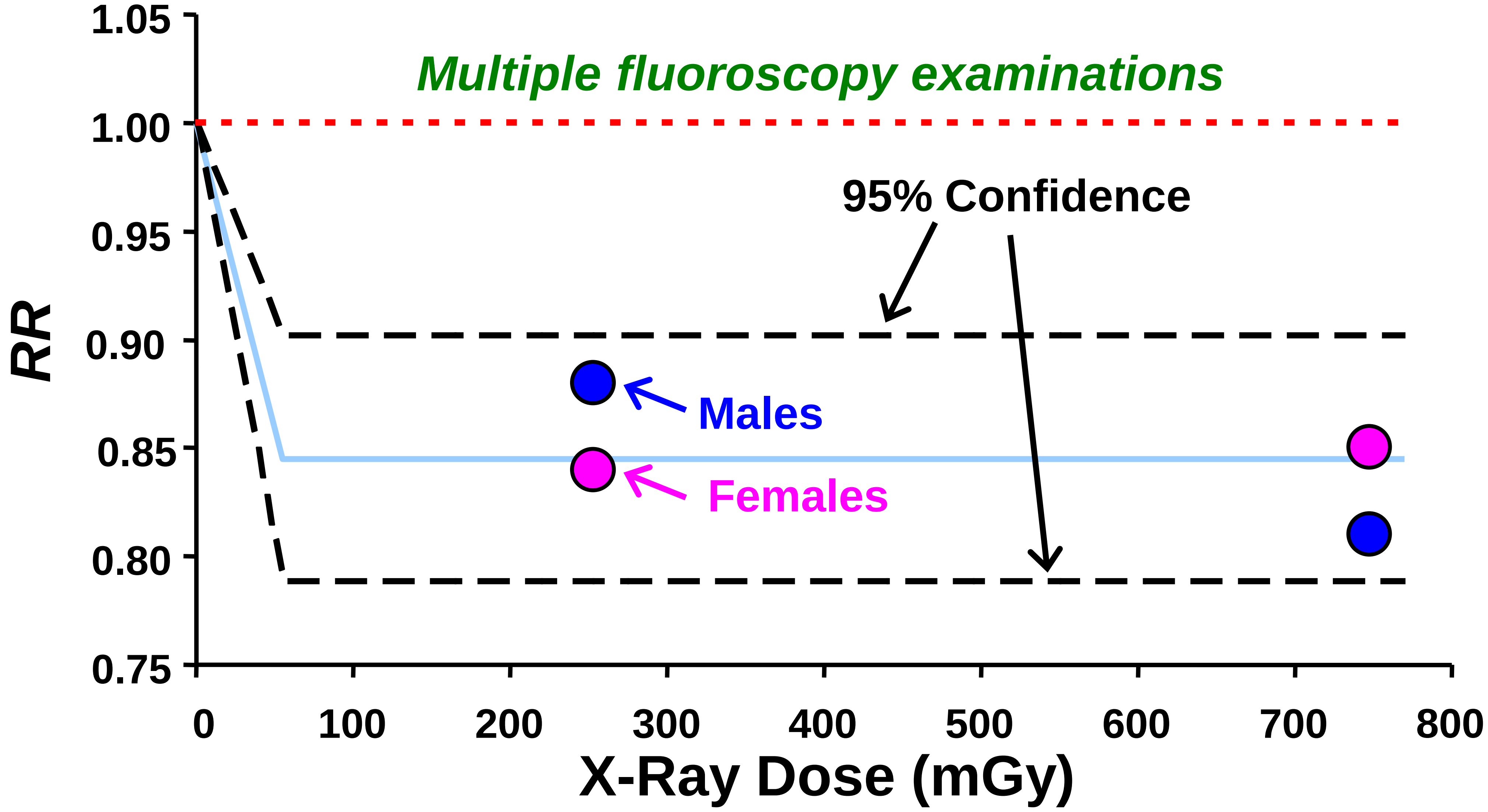
RR< 0.85 cannot be due to healthy worker effect (Sponsler and Cameron, 2005)

Gamma-Ray ANP Against Spontaneous Lung Cancer in Mice



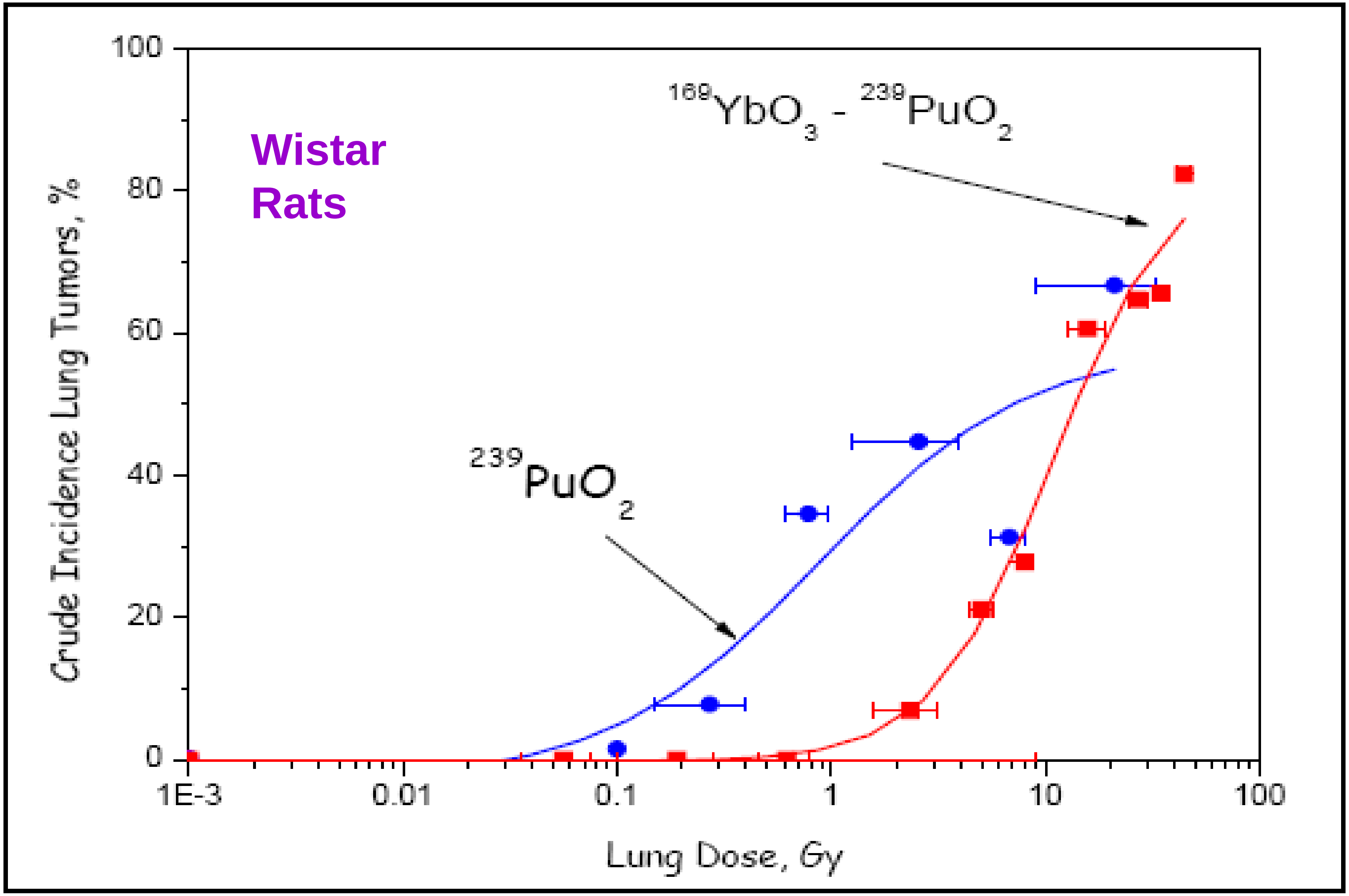
Study involved more than 15,000 mice (R. Ulrich et al., 1976)

Gamma-Ray ANP Against Spontaneous Lung Cancer in Humans



Data from GR Howe. Radiat. Res. 142:295-304,1995. Similar findings have been reported for breast cancer (Miller. N. Engl. J. Med. 321:1285-1289, 1989)

Low-Dose-Rate, Gamma-Ray ANP Against Alpha-Radiation-Induced Lung Cancer



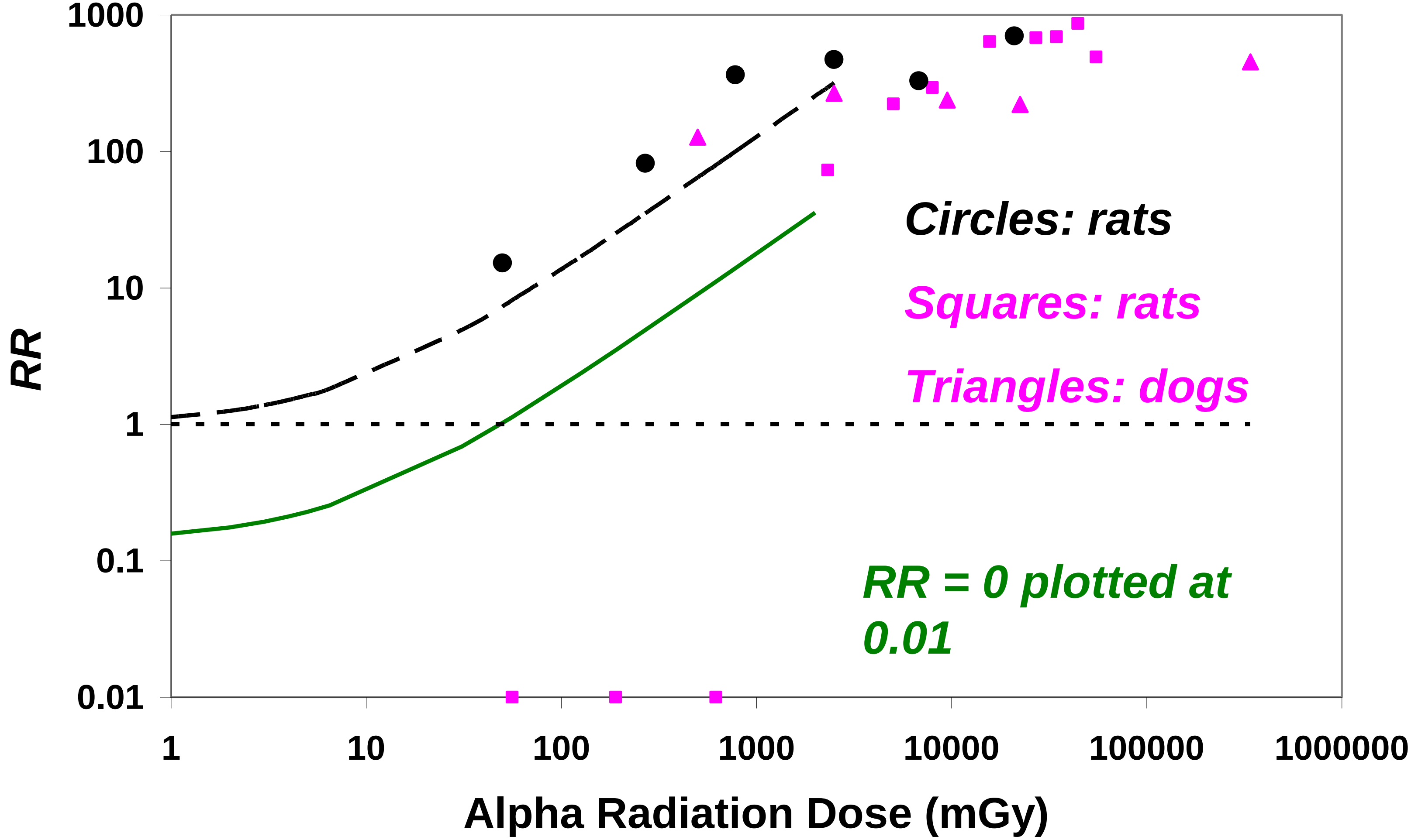
C. L. Sanders, International Hormesis Conference, 2006

Expected and Observed *RR* for Lung Cancer in Wistar Rats Exposed to Pu-239 + Yb-169

Average Alpha Dose (mGy)	Average Gamma Dose (mGy)	Expected *RR*	Observed *RR*	*PROFAC*
0	0	1	1	
56	0.9	21	0	1.0
190	1.8	67	0	1.0
620	1.3	218	0	1.0

Gamma-ray dose from Yb-169 protracted over several months.

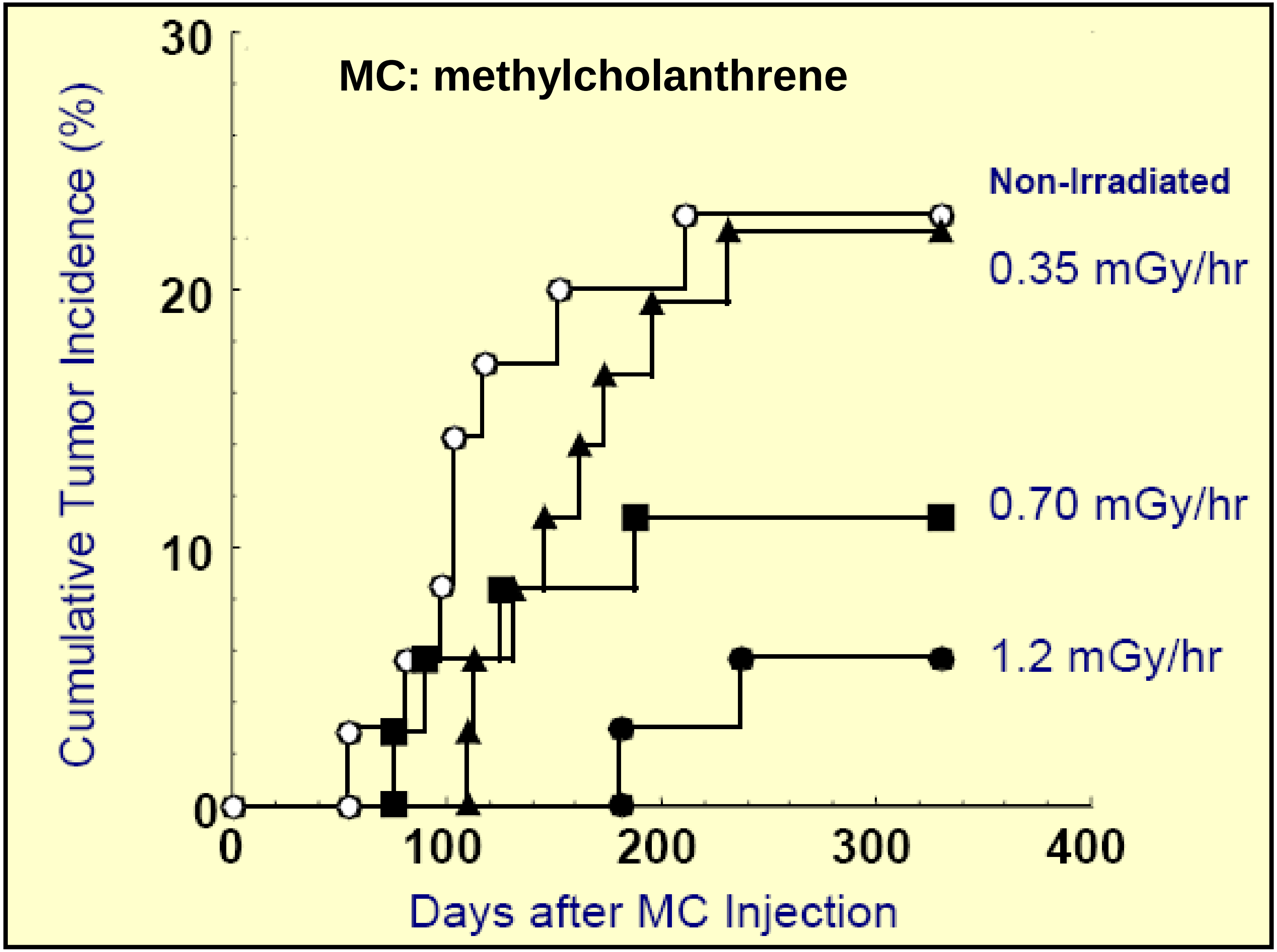
Gamma-Ray ANP Against Alpha-Radiation-Induced Lung Cancer



Dashed curve: unprotected α-irradiated humans

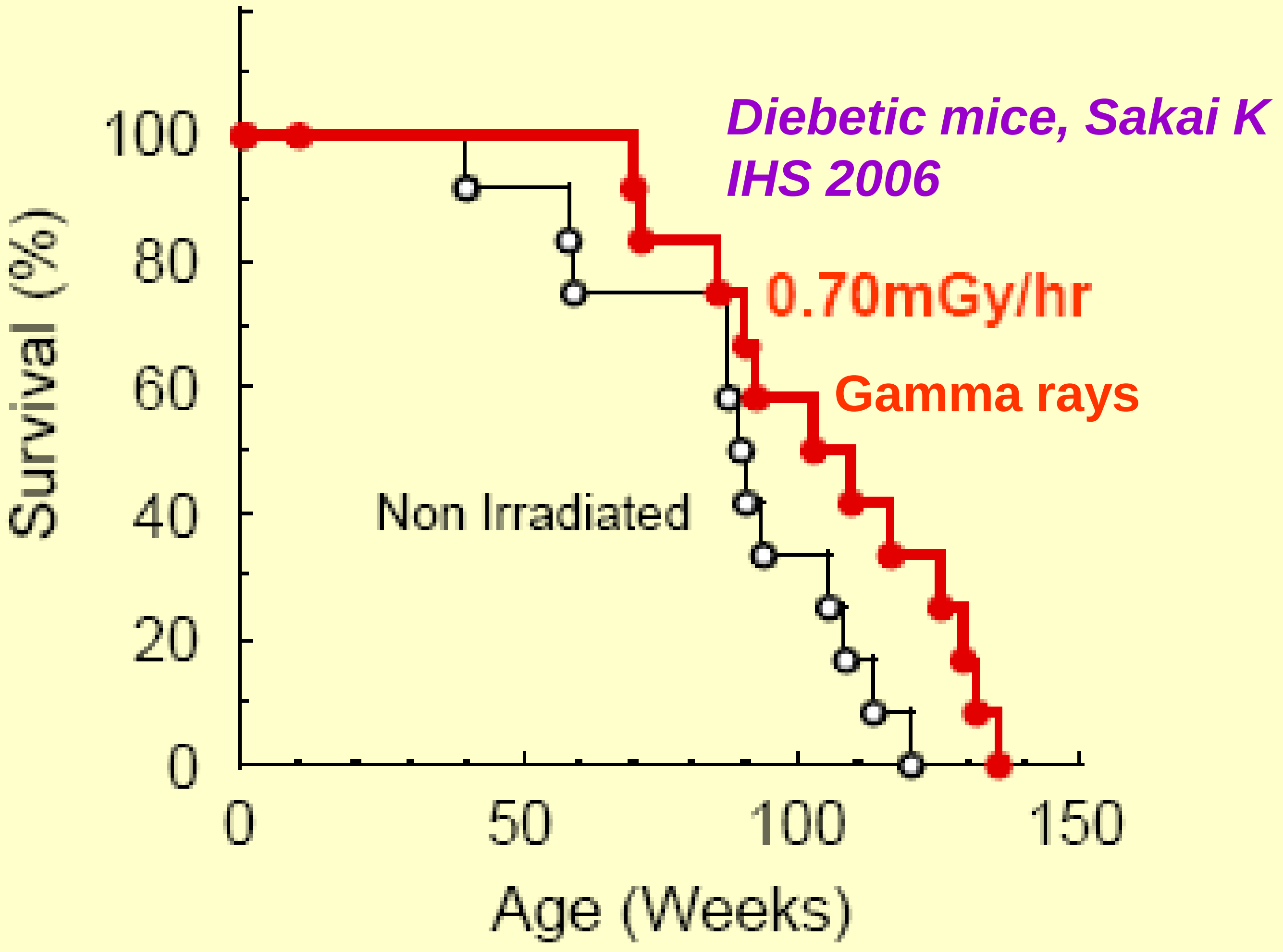
Smooth curve: gamma-ray protected α-irradiated humans

Low-Rate Gamma-Ray ANP Against MC-Induced Skin Tumors in Mice



K. Sakai, International Hormesis Conference 2005

Prolongation of Life Span of db/db Mice by Low Dose Rate Irradiation



Appearance of *db/db* Mice at 90 Weeks of Age

Irradiated

Non-Irradiated

Sakai K, IHS 2006

Low-Dose vs. High-Dose Cancer Therapy

Radiation Hormesis and Low-Dose Cancer Therapy

- **Cancer cells are resistant to undergoing apoptosis.**
- **New research is demonstrating ways of sensitizing cancer cells to undergo apoptosis (e.g., resveratrol, gene therapy).**
- **Applying low-dose, low-LET radiation (in the hormetic zone) alone or in combination with apoptosis sensitizing agents that target tumor cells could lead to curing cancer.**
- **Adding multiple small doses of antiangiogenic drugs may enhance efficacy some treatments.**

High-Radiation-Dose Therapy

- **Severely harms the patient via massive killing of normal cells!**
- **Suppresses the immune system, thereby promoting cancer metastasis!**
- **Inhibits signaling associated with the PAM process!**
- **Is unnecessary because multiple-low-dose radiation therapy or chronic low-rate radiation therapy could cure cancer without harming the patient!**

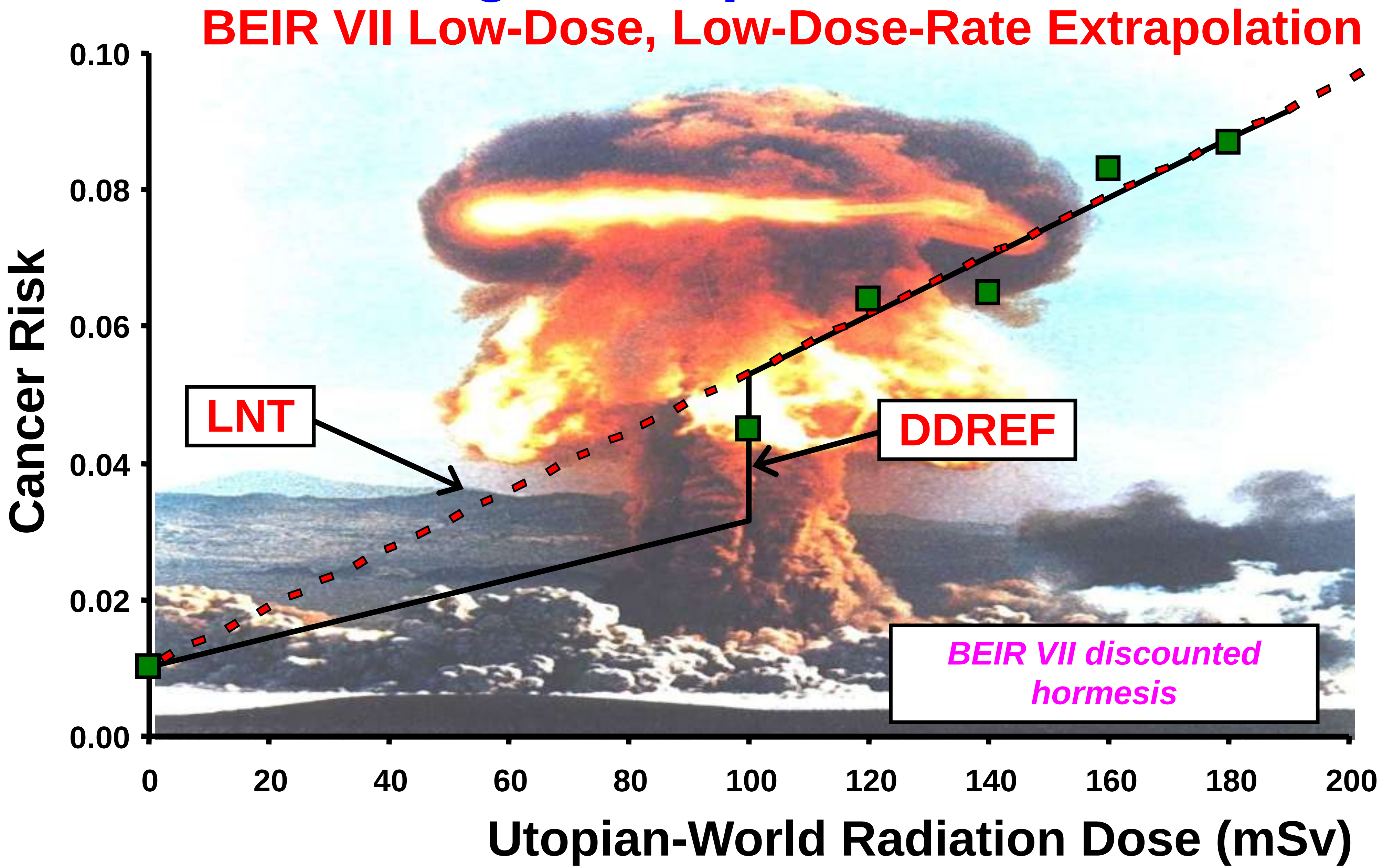
Low-Dose Radiation Therapy

- **Low-dose radiation therapy has been used to successfully treat ovarian, colon, and hematologic cancers without any symptomatic side effects.**
- **Low-dose, low-dose-rate immunotherapy (using beta radiation) has been used to successfully treat follicular lymphoma.**

Choi NC, et al. Cancer 43:1636-1642, 1979.
Cuttler JM. J. Amer. Phys. Surg. 8(4):108-111, 2003.
Kuminski MS et al. N. Engl. J. Med. 352(5):441-449, 2005.
Ruffolo SC and Shore GC. J. Biol. Chem. 278(27):25039-25045, 2003.

Utopian-World LNT vs. Real-World Hormesis: Implications for Radiation Disaster Preparedness

Current Radiation Risk Assessment Paradigm: Utopian-World LNT



LNT and Radiation Phobia

- The notion that any amount of radiation harms us is false and drives radiation phobia.
- LNT-related radiation phobia was responsible for the loss of more than 100,000 lives (via abortions) following the Chernobyl accident!

BEIR VII vs. French Academies on LNT and Radiation Hormesis

BEIR VII	French Academies
Selectively chosen A-bomb cancer data was consistent with LNT	LNT should not be applied to low-LET doses < 100 mGy
Even natural background low-LET radiation harms	No evidence of harm from natural background radiation; may be beneficial
Radiation hormesis dismissed	Radiation hormesis not dismissed
Looked at basic research results and ignored	Considered implications of basic research results

LNT-Associated Radiation Phobia Following a Dirty Bomb Incident

Radiation-Phobia-Associated Impacts:

- **Loss of lives associated with frantic evacuations.**
- **Severe injuries during evacuations.**
- **Increased suicides and abortions.**
- **Increased psychosomatic disorders.**
- **Increased drug/alcohol/cigarette abuse.**
- **Permanent abandonment of properties with low-level contamination.**

Things the U.S. Government Should Do Now to Reduce Casualties in the Event of a Future Dirty-Bomb Incident

Institute a well-funded program to educate the public, medical community, news media, and governmental agencies about:

- **The many radiation-phobia-related casualties LNT could cause: e.g., death by LNT slope factor!**
- **The abundant evidence for health benefits of low-level radiation exposure!**
- **How cancer and some other diseases could be prevented in high-risk groups by harmless low radiation doses!**
- **How cancers could be cured with low harmless doses of radiation in combination with other agents!**

Conclusions

- **The LNT risk model is invalid and promotes radiation phobia.**
- **Radiation-phobia-related casualties after a dirty bomb incident in a populated area are likely to be more prevalent than those related to actual radiation-induced damage.**
- **The public and others need to be better informed about low-dose radiation ANP against diseases.**
- **Persons receiving radiation doses in the hormetic zone would not likely be harmed and may be protected from developing some diseases that would otherwise occur.**

Conclusions (continued)

- **The public, news media, medical community, and others need to be informed about the powerful cancer preventative aspects of low-dose radiation ANP.**
- **They also need to be informed about the great potential for curing cancer using essentially harmless multiple low doses of radiation plus other agents that sensitize cancer cells to apoptosis.**

Conclusions (concluded)

- **Governmental agencies (e.g., NIH, DOE, NSF, DOD, NASA, DHS, FDA, others) need to support radiation adaptive response/hormesis research because of the enormous homeland-security, cancer-prevention, lifespan-prolongation, and cancer-therapy benefits that would be expected.**

Radiation Hormesis Presentations on our Website (www.radiation-scott.org)

- *Hormesis Implications for Managing Radiological Terrorism Events*.
- *Low-Dose/Dose Rate Low-LET Radiation Protects Us from Cancer*.
- *Medical and Therapeutic Radiation Hormesis: Preventing and Curing Cancer.*
- *Biological Basis for Hormetic Relative Risk Model and Implications*

Collaborators and Student Participants

- **Scientists:** **Pam Sykes, Tanya Day, Les Redpath, Chuck Sanders, Zoya Tokarskaya, Galina Zhuntova, Ed Calabrese, Noy Rithidech and others**
- **Students:** **Jenni Di Palma, Munima Haque**

Acknowledgement

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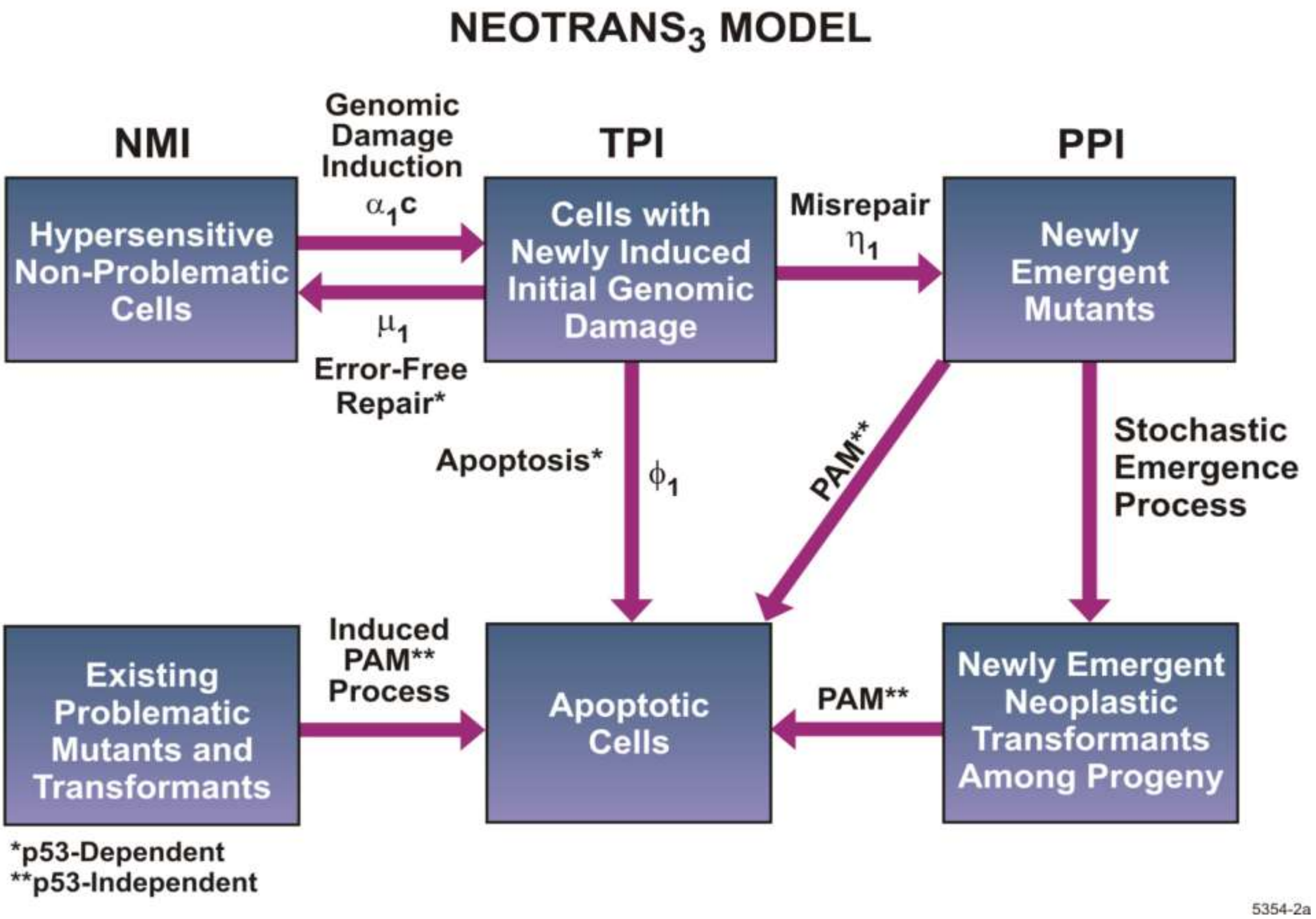
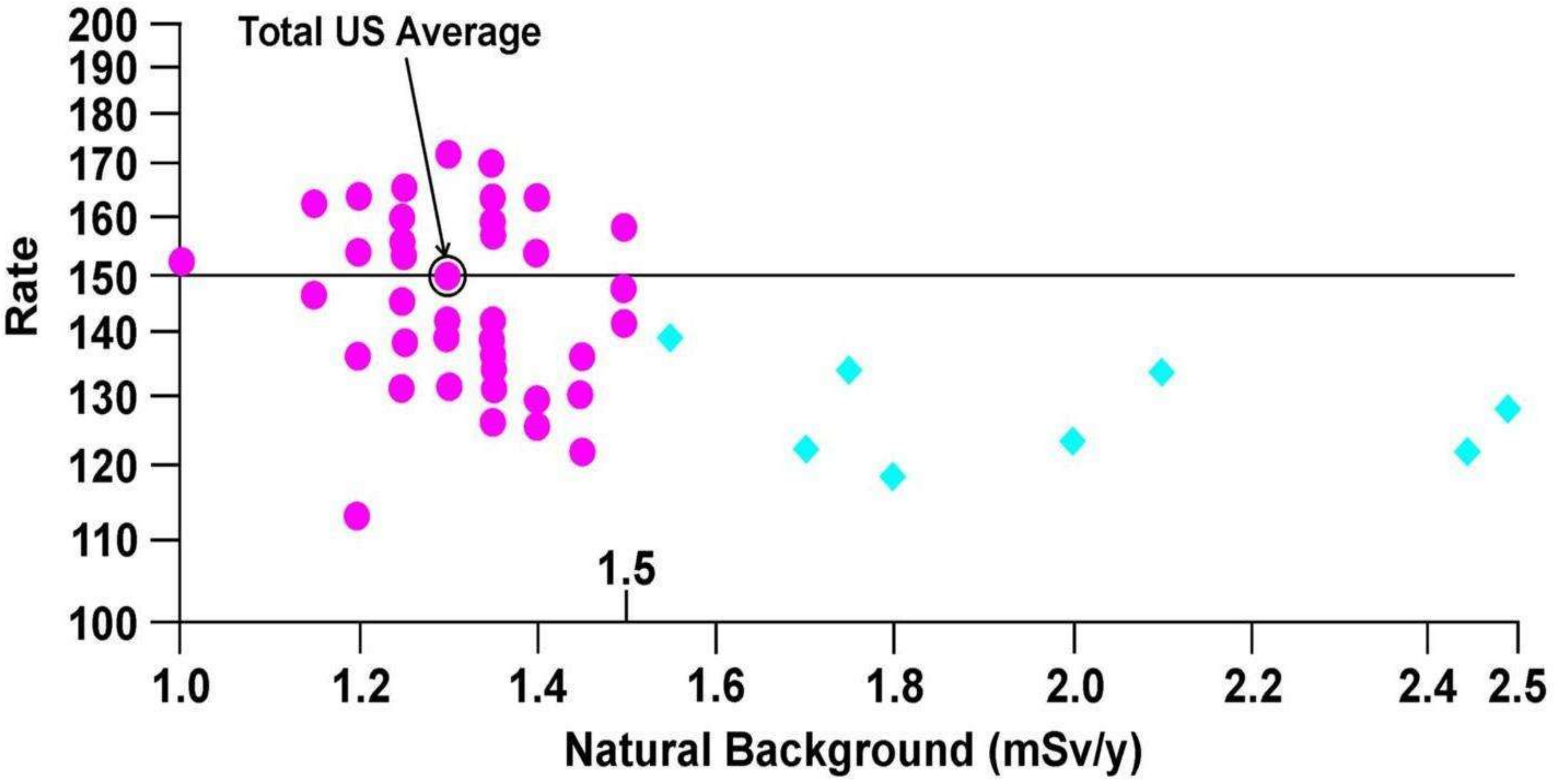
Backup Slides


NEOTRANS$_3$ MODEL
NMI
Hypersensitive Non-Problematic Cells
Genomic Damage Induction
$\alpha_1 c$
μ_1
Error-Free Repair*
TPI
Cells with Newly Induced Initial Genomic Damage
Misrepair
η_1
PPI
Newly Emergent Mutants
Apoptosis*
ϕ_1
PAM**
Stochastic Emergence Process
Existing Problematic Mutants and Transformants
Induced PAM** Process
Apoptotic Cells
PAM**
Newly Emergent Neoplastic Transformants Among Progeny
*p53-Dependent
**p53-Independent
5354-2a

Annual Cancer Mortality/100,000 for U.S. States (1950-1967)



Frigerio and Stowe, IAEA Publication, 1976.

Natural Background Radiation

- **Atlantic and Gulf Costal Plain: 1.05 mSv/y**
- **Middle America: 1.25 mSv/y**
- **Rocky Mountain Plateau: 1.45 mSv/y**
- **Denver, Colorado: 1.65 mSv/y**
- **Ramsar, Iran: 200 mSv/y**

Green indicates values that appear to be in the hormetic zone.

Stochastic Thresholds

- **Each of us has a different radiation threshold (organ specific) for activating protective natural processes (i.e., ANP).**
- **Each also has a different higher threshold for inhibiting some of the protection (e.g., p53-independent PAM process).**

Low-Dose Radiation Therapy for Non-Hodgkin's Lymphoma

- Total-body irradiation (TBI) (repeated doses of 100-150 mGy) increased the four-year survival to 70-74% compared to 40% of untreated controls and 52% of patients treated with localized high doses.
- Upper half-body irradiation (HBI) (repeated doses of 100-150 mGy) increased the four-year survival to 84% compared to 65% of patients treated with localized high doses.
- All patients treated with low-dose HBI or TBI survived to 10 years, compared to localized-high-dose-treatment controls, who survived to nine years at a rate of 50%.

J. Cuttler. Canadian Nuclear Society Bulletin 21(2):45, 2000

Hormetic Relative Risk (HRR) Model for Cancer Induction

Low-LET irradiation (dose-independent zone):

RR =1, Dose =0

RR = 1 – PROFAC, otherwise

PROFAC depends on dose rate pattern and exposure time; accounts for PAM and immune system stimulation. Dose-independent zone increases importance of highly-criticized ecological studies!

HRR Model Continued:
$\alpha + \gamma$ Irradiation, Low Doses

$RR = (1\text{-}PROFAC)[1 + F(B)KD]$, $D>0$

Low-LET radiation suppresses cancer via protection factor (*PROFAC*) (Scott 2005a,b).

F(B) = (1-B)/B, for baseline incidence B.

PROFAC=0, for alpha radiation.

D is the alpha radiation dose.

Markov Chain Monte Carlo Implementation HRR Model

- Why? To address stochastic threshold for ANP induction and inhibition.
- Number of chains = 1 or 2.
- WinBUGS software used.
- Uniform prior distributions assigned for model parameters.
- Predictions made for fixed baseline incidence.

WinBUGS Sampling Hierarchies

Sampling Type	Method of Sampling
1. Conjugate	Direct, using standard algorithms
2. Log-concave	Derivative-free adaptive rejection
3. Restrictive range	Slice
4. Unrestricted range	Current-point Metropolis
1. Finite upper bound	Inversion
2. Shifted Poisson	Direct, using standard algorithm
Green: continuous target dist.; red: discrete distribution	