Medical and Therapeutic Radiation Hormesis: Preventing and Curing Cancer

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Contents

- Research approach
- LNT hypothesis vs. hormetic relative risk model
- Medical, therapeutic, environmental, and other forms of radiation hormesis
- Biological basis for radiation hormesis
- Radiation hormesis implications for cancer prevention and cancer therapy
- Conclusions

Research Approach

- Risk estimates are based on the biological-based hormetic relative risk (HRR) model recently introduced by our research group.
- Dose-response relationships were constructed based on absorbed radiation dose *D.*
- Data from medical, epidemiological, and ecological studies were used.

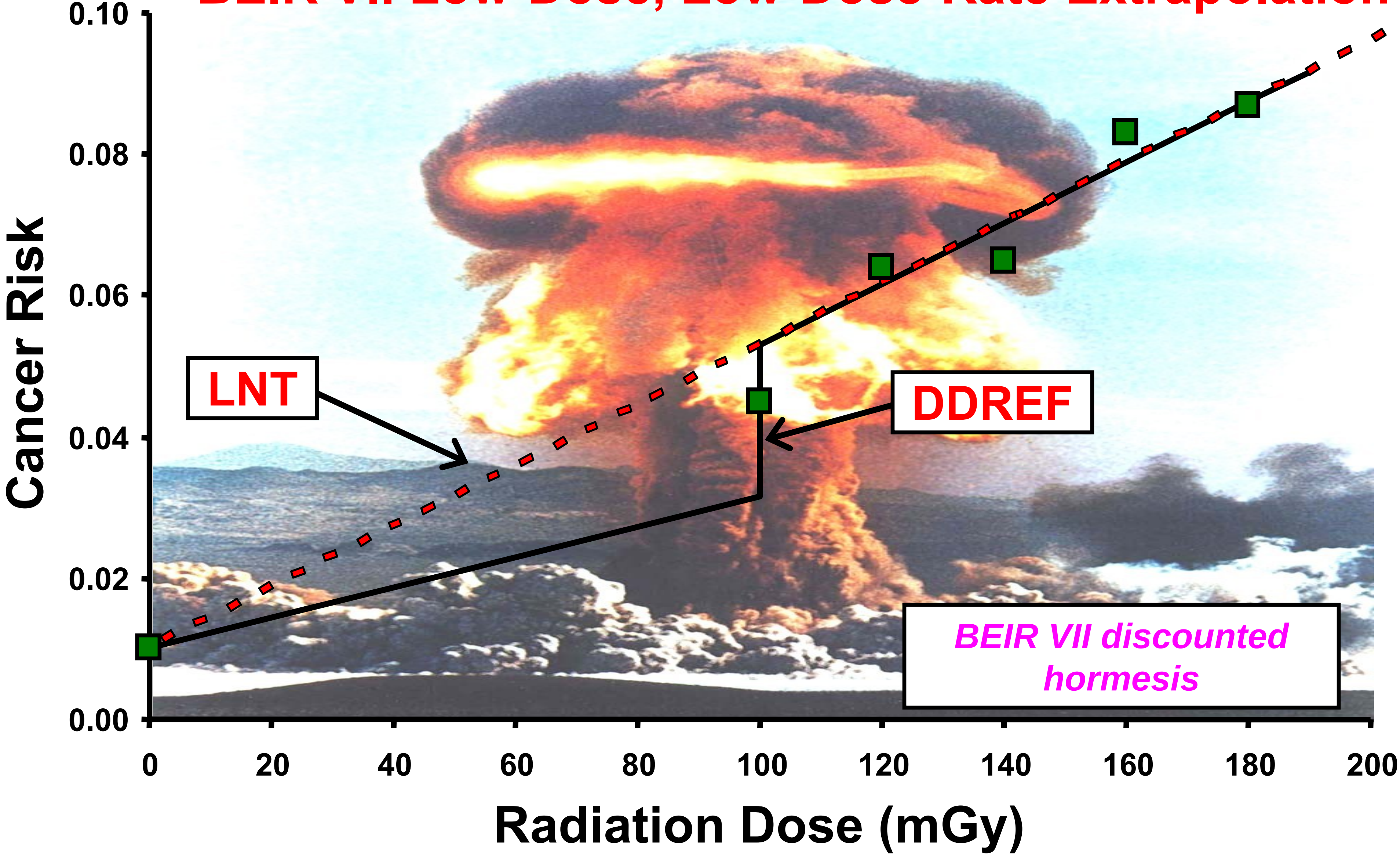
Scott BR. Dose-Response 3:547-567, 2005

Scott BR. Dose-Response (in press, 2006a)

Scott BR. Chapter In *New Research on Genomic Instability (tentative title), Nova Science Publishers, Inc., (accepted, 2006b)*

Current Regulatory Risk Assessment Paradigm

BEIR VII Low-Dose, Low-Dose-Rate Extrapolation



BEIR VII vs. French Academies on LNT and Radiation Hormesis

BEIR VII	French Academies
Selectively-chosen A-bomb survivor cancer data was consistent with LNT	LNT may not apply 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

Types of Radiation Hormesis

- Medical Radiation Hormesis
- Therapeutic Radiation Hormesis
- Environmental Radiation Hormesis
- Occupational-Exposure-Associated Radiation Hormesis

Medical Radiation Hormesis

Medical procedure (e.g., chest X-rays, mammograms, CT scans, nuclear medicine diagnosing) induced radiation hormesis is thought to be responsible for the elimination of precancerous and other genomically unstable cells from the body. Medical radiation hormesis likely also suppresses cancer metastasis.

Photo: WHO/TBP/Pierre Virot

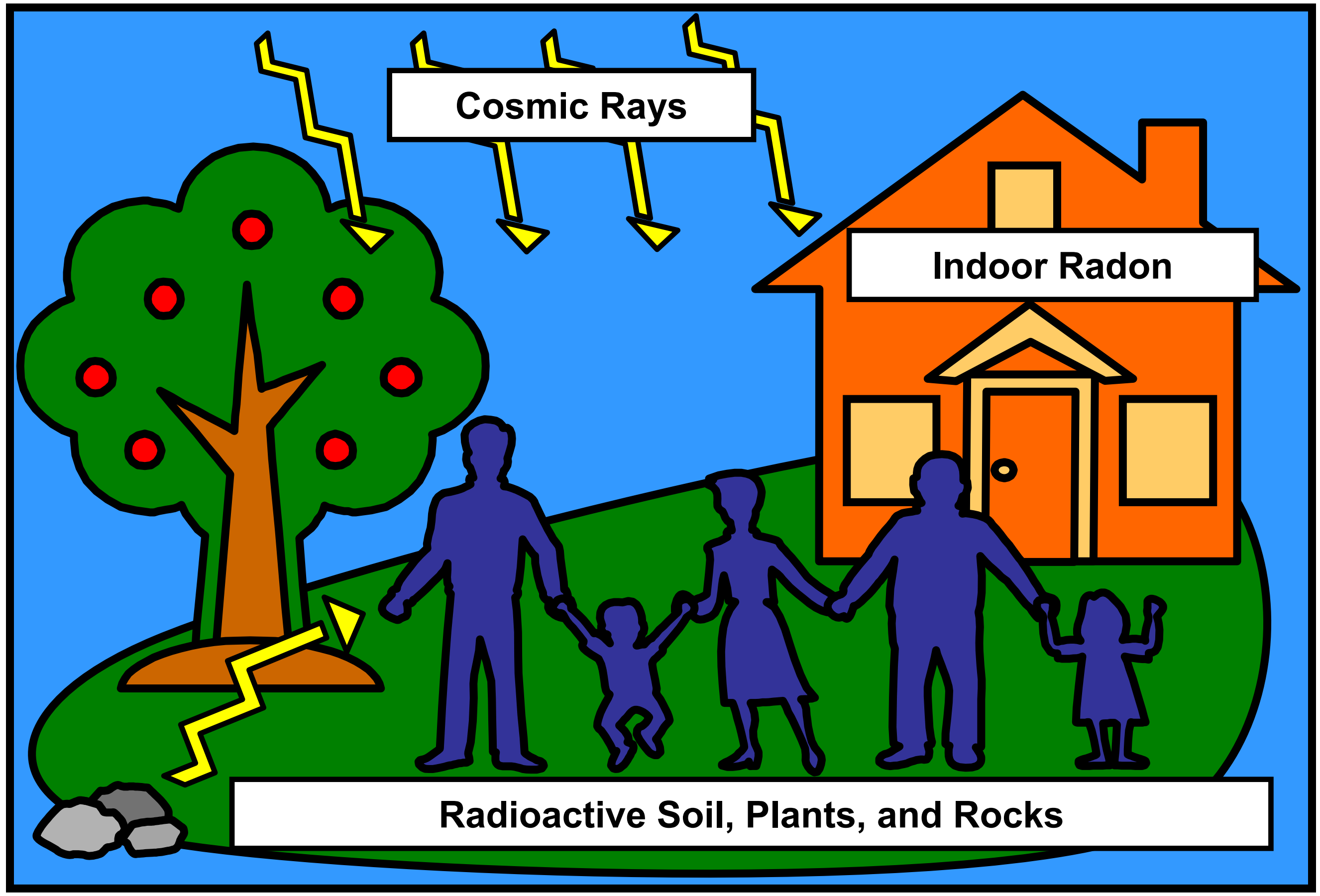
Therapeutic Radiation Hormesis

Low-dose radiation induced hormetic effects have been demonstrated to be beneficial in curing existing cancer. Low therapeutic doses can arise from fractionated X-ray or gamma-ray exposure, via low-LET radioimmunotherapy, or via use of radio-labeled pharmaceuticals.

Photo: Lexington Diagnostic Center

Environmental Radiation Hormesis

Natural and human-activity-related background radiation induced hormetic effects have been found to be associated with the suppression of spontaneous cancers and other diseases.



Occupational-Exposure-Associated Radiation Hormesis

Occupational low-LET (or low- plus high-LET) radiation exposure of nuclear workers has been found to induce hormetic effects associated with the suppression of spontaneous cancers and other diseases.

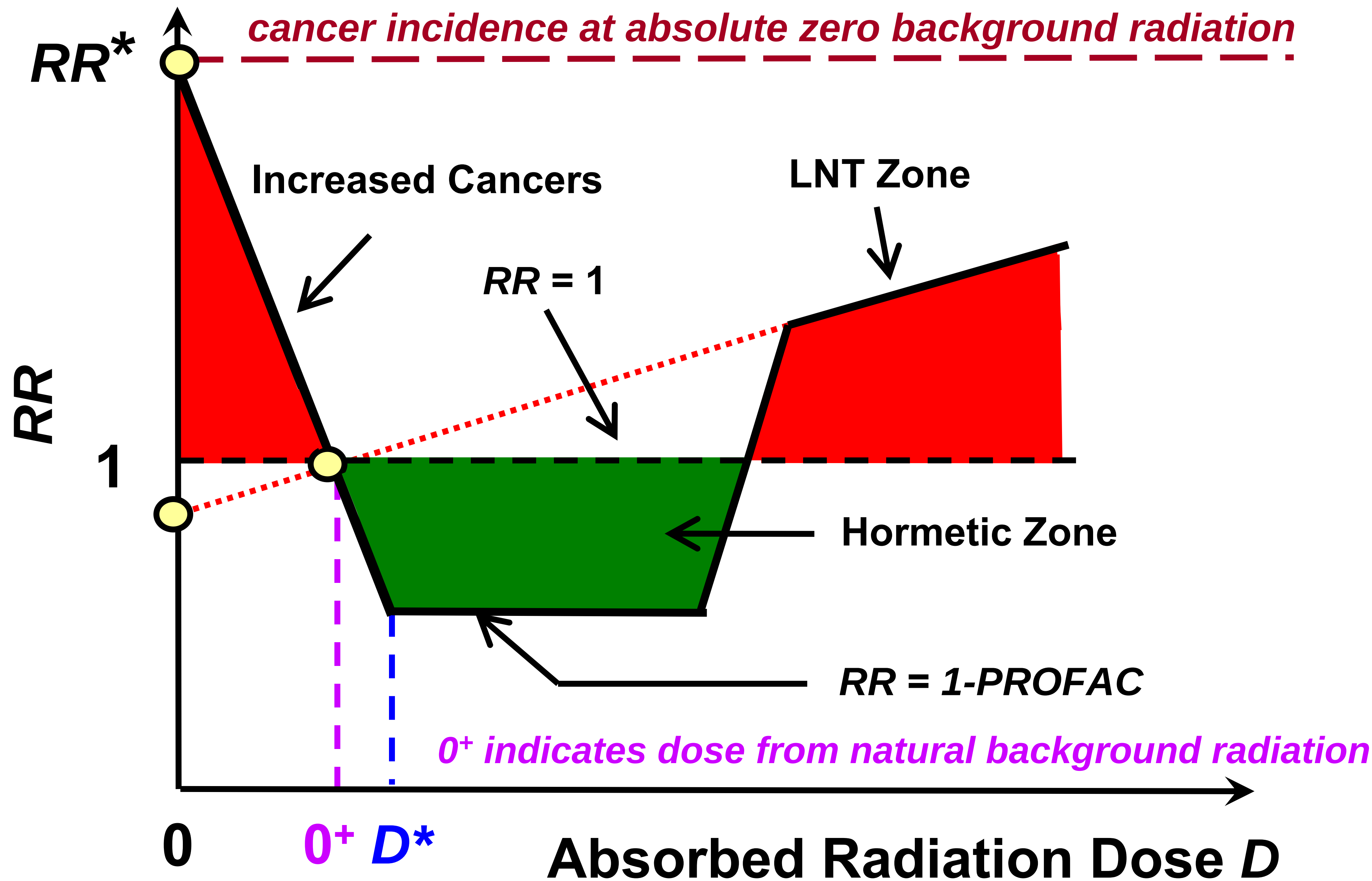
6966D-39

Photo: DOE Nuclear Material Disposition Project web site

Hormetic Relative Risk (HRR) Model for Cancer Induction

- The HRR model is an adaptation of our published $NEOTRANS_3$ model (Scott 2004, 2005a) for low-dose radiation-induced stochastic effects (mutations, neoplastic transformation).
- Key Assumption: cancer arises from cells with persistent genomic instability through a series of stochastic changes, independent of how the instability originate, but dependent on the number of cells with this instability in an organ.
- Relative risk for cancer is modeled as being proportion to the relative risk for neoplastic transformation [consistent with observations of Dr. Redpath's group (BELLE 2006 Conference)].

Cancer Hormetic Relative Risk (HRR) Model: Based on Absorbed Radiation Dose



Cancer Relative Risk in Hormetic Zone: HRR Model

$$RR \cong 1 - PROFAC$$

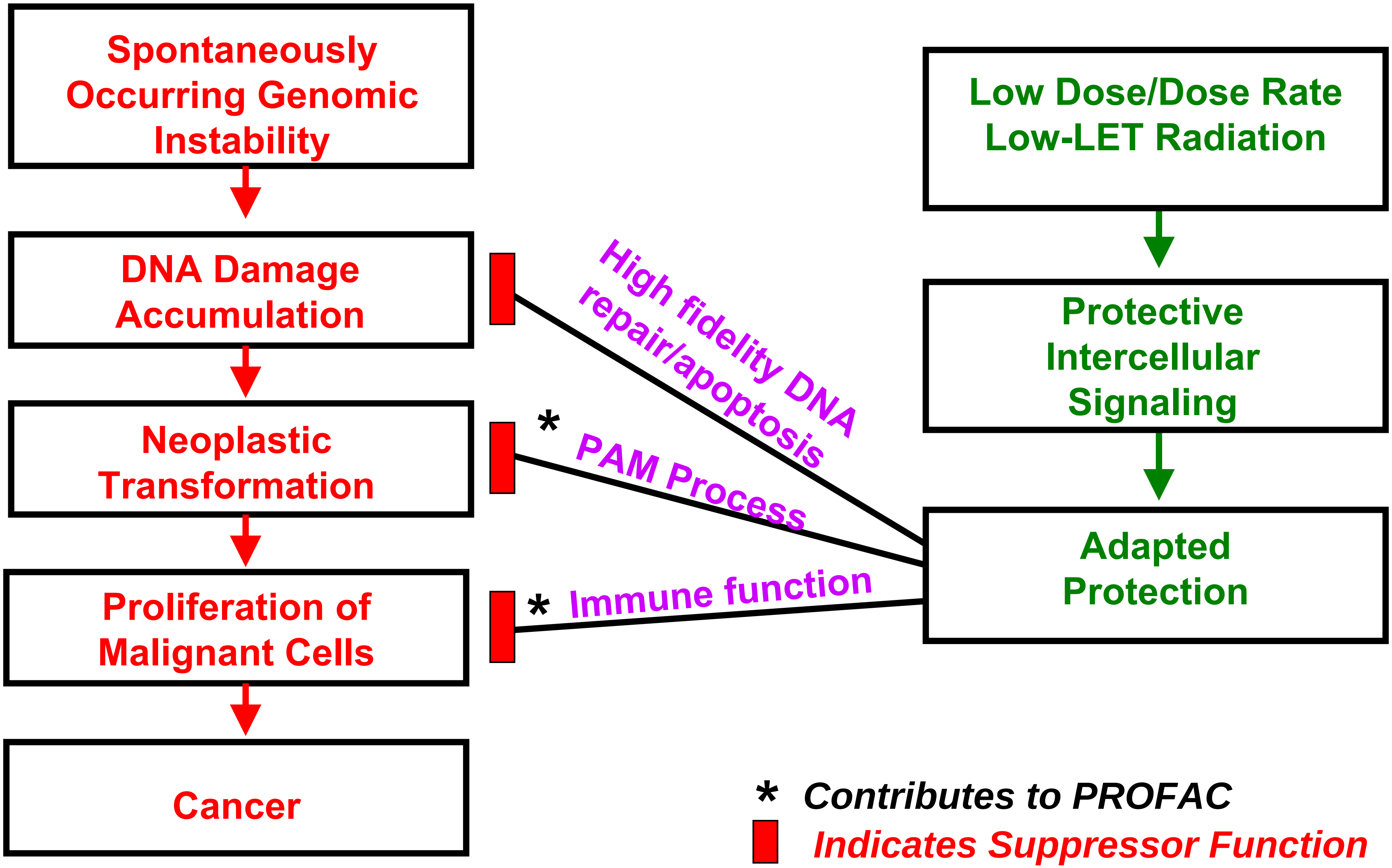
- Protection factor (*PROFAC*) gives the proportion of cancer cases avoided due to radiation hormesis; accounts for the PAM process and immunity.
- *PROFAC* depends on the type of radiation, number of dose fractions, dose rate and exposure duration. Appears quite large for protracted exposure of adults over years at very low rates.
- *PROFAC* increases with age.
- *PROFAC* appears to be very small or zero for pure alpha irradiation but not for radon (gamma-ray component).

Doses from Diagnostic Radiation Sources Fall in The Hormetic Zone

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

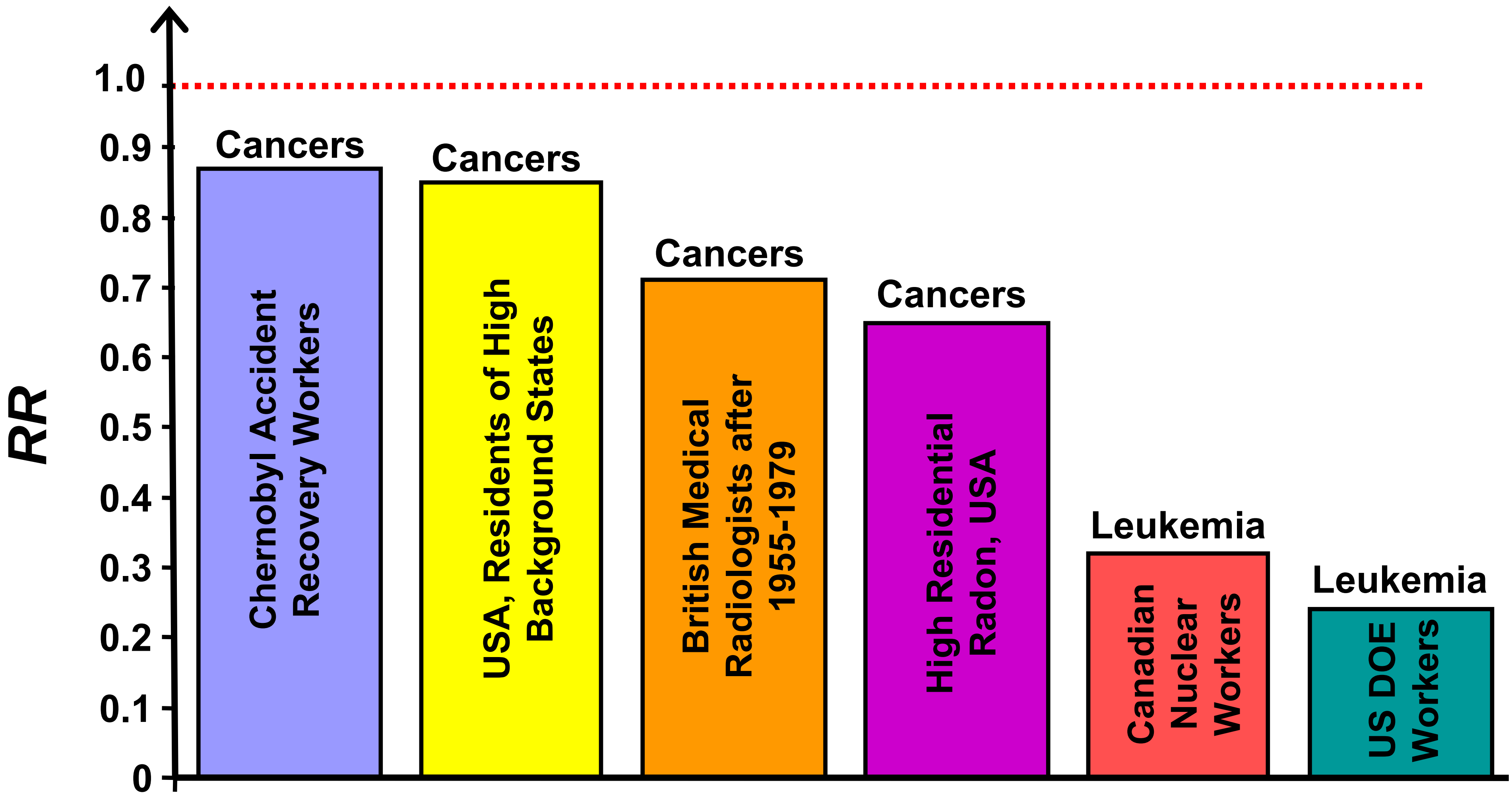
Kauffman. Journal of American Physicians and Surgeons 8(2):54-55, 2003

Biological Basis for Hormetic Zone for Low-LET Radiation



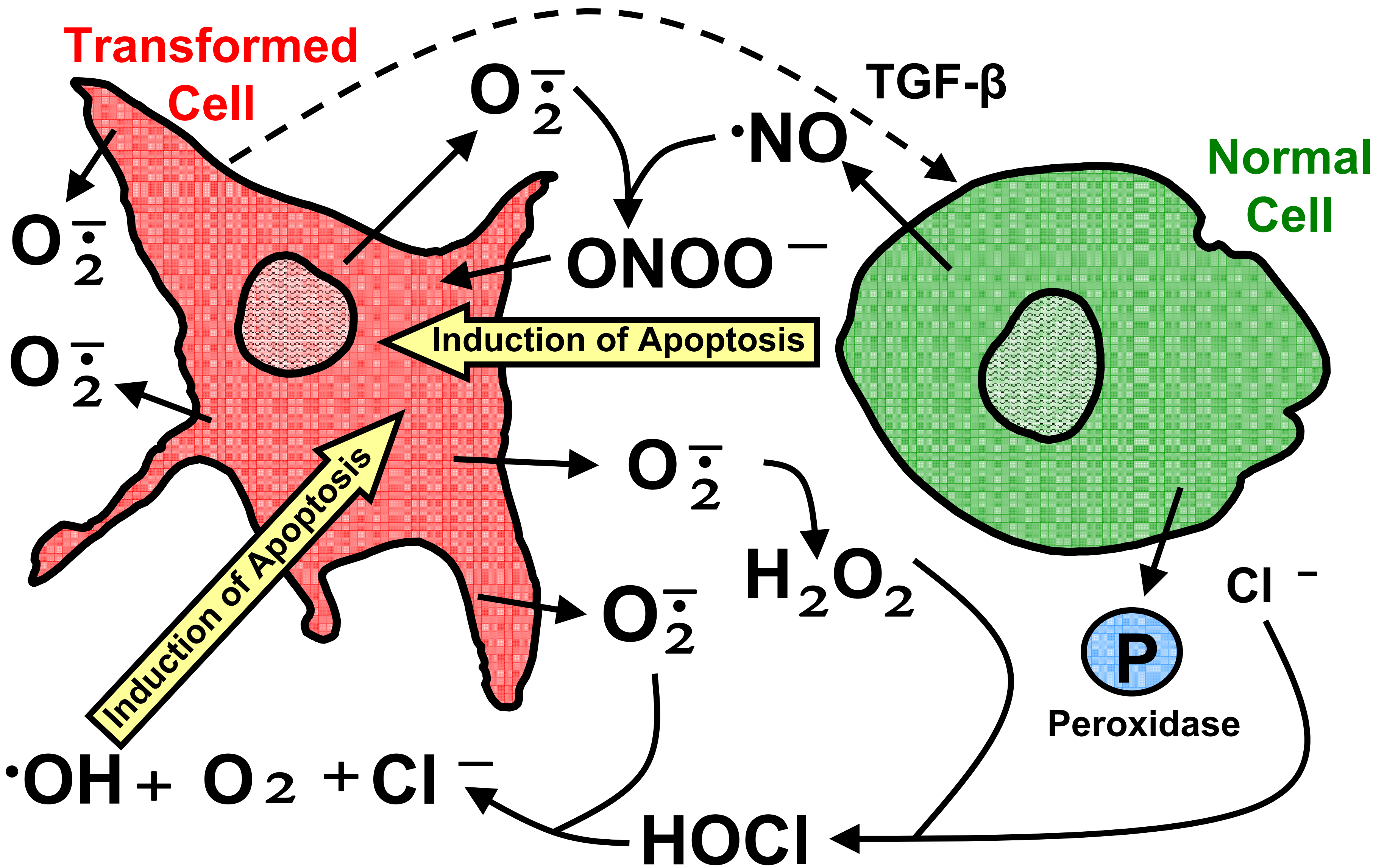
Scott 2006a,b

Cancer Relative Risk In Hormetic Zone: Irradiated Human Populations



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

PAM Process In Fibroblast: Protective Intercellular Signaling



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

PAM Process Explains Classical Two-Dose Adaptive Response (Radiation Preconditioning Hormesis)

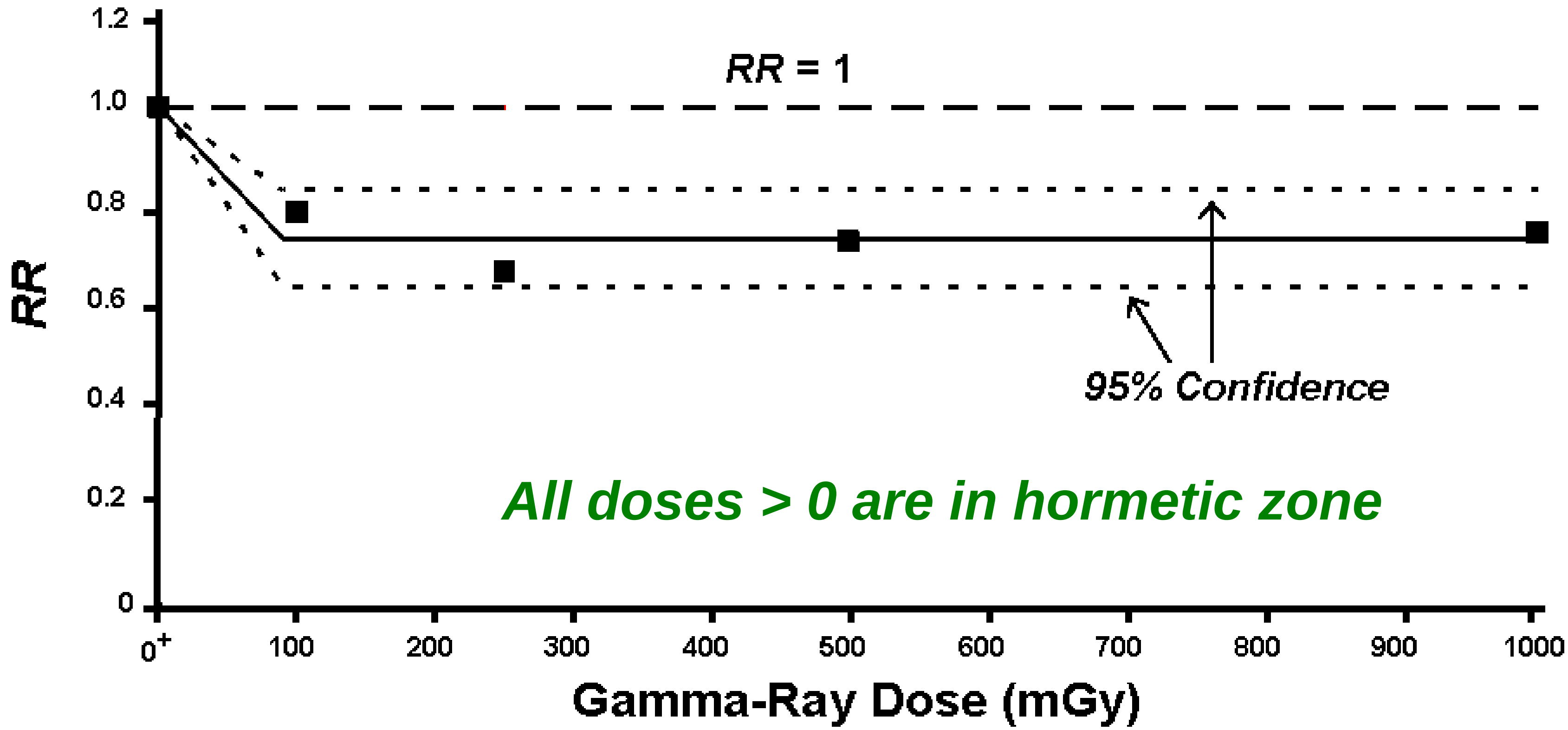
- **Second dose (> 1 mGy) activates high fidelity DNA repair, so DNA repair activation appears not to explain the two-dose adaptive response!**
- **First dose (> 0.01 mGy low-LET radiation) activates/potentiates the PAM process in addition to DNA repair, based on modeling data from sensitive pKZ1 mouse inversion assay (Pamela Sykes group) [Scott *et al.*, 2006].**
- **The PAM process explains inverse adaptive response study, since the first dose, when moderate or large, activates high fidelity DNA repair; the second small dose adds the PAM process (radiation postconditioning hormesis).**

Medical Radiation Hormesis

- Diagnostic exposures to X-rays (e.g. chest X-rays, CT scans) and gamma and beta rays (used in nuclear medicine) induce adapted protection against cancer and other genomic-instability-associated diseases.
- Maximal hormetic protection is expected to occur after protracted or fractionated exposures that over and over induce transient adapted protection.
- For maximal hormetic protection, total doses should be restricted to the hormetic zone, which appears to be greatly extended with fractionated and protracted exposure.

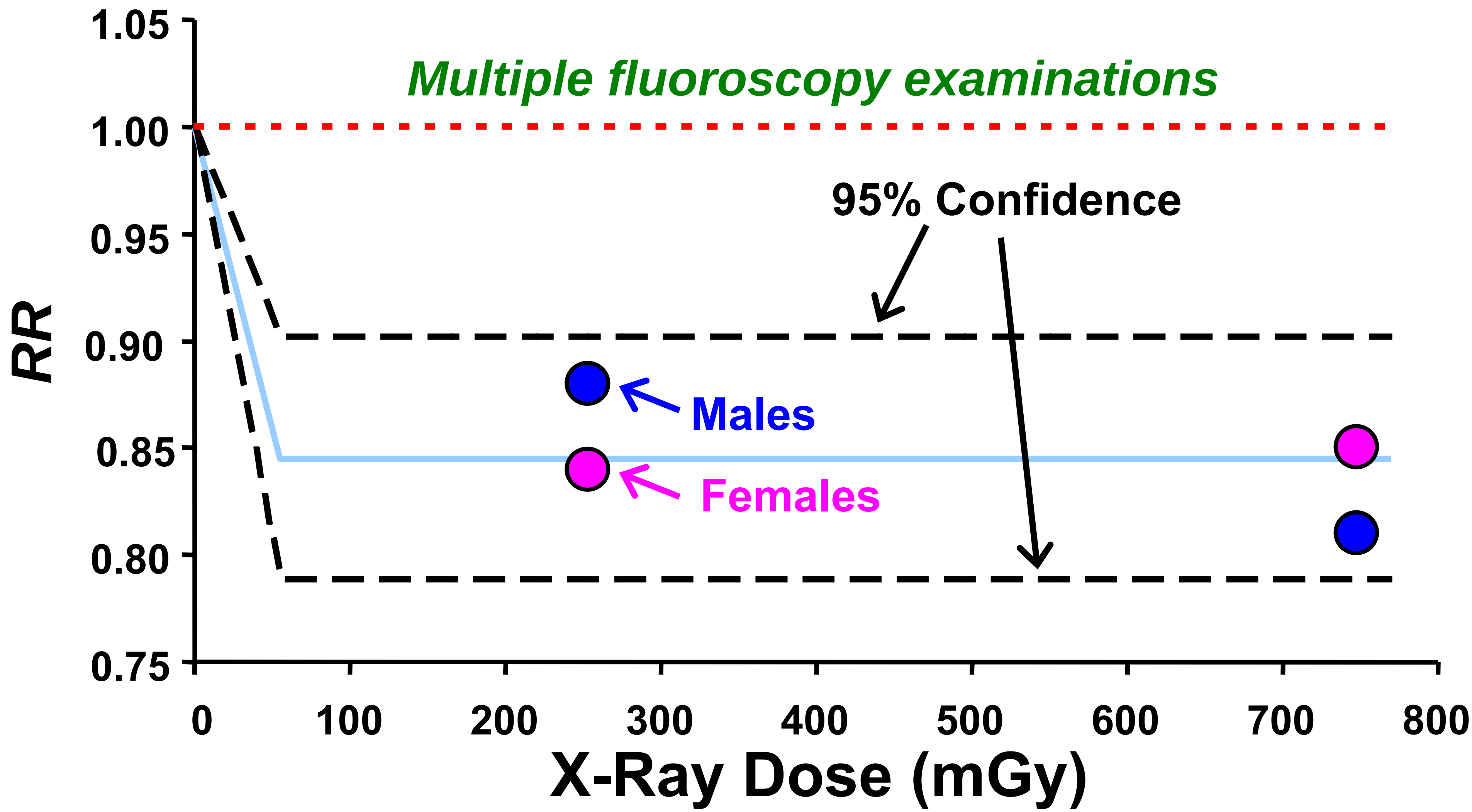
Suppression of Spontaneous Lung Cancer in Mice:
Indirect Evidence for Medical Radiation Hormesis

(HRR Model)



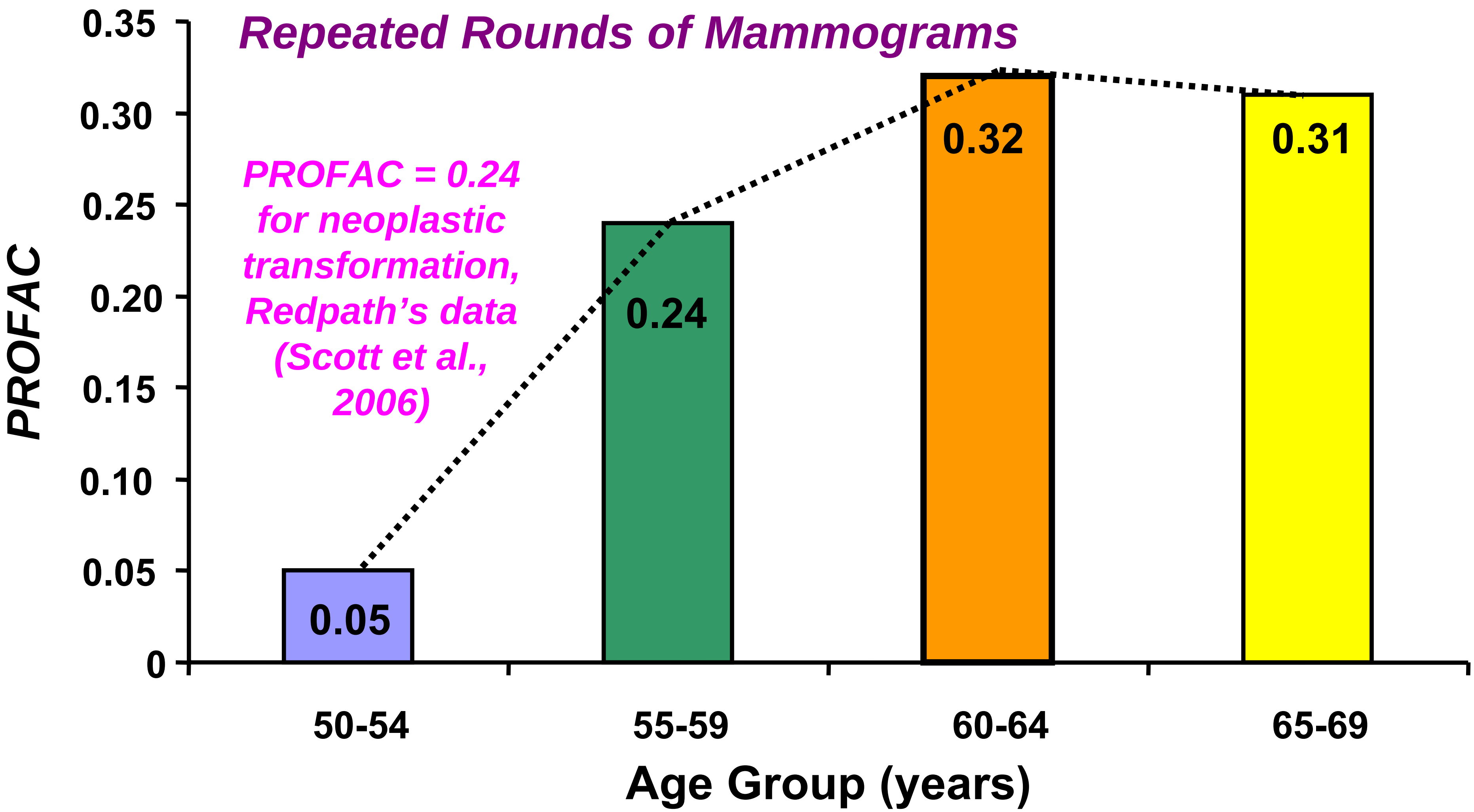
Study involved more than 15,000 mice (Ulrich et al., 1976).

Suppression or Spontaneous Lung Cancer in Canadian TB Patients: Medical Radiation Hormesis



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

Proportion of Breast Cancer Cases Avoided Due to Medical Radiation Hormesis



Based on data from Nyström et al. 2002

Therapeutic Radiation Hormesis

- **Cancer cells are resistant to undergoing apoptosis.**
- **New research is demonstrating ways of sensitizing cancer cells to undergo apoptosis (e.g., resveratrol).**
- **Applying low-dose, low-LET radiation (in the hormetic zone) alone or in combination with apoptosis sensitizing agents that target tumor cells can lead to curing cancer.**

Therapeutic Radiation Hormesis (continued)

- **Fractionated or protracted low doses of low-LET radiation in the hormetic zone are expected to be the most effective forms of therapeutic radiation hormesis.**
- **Therapeutic radiation hormesis 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

Low-Dose Total- and Half-Body Irradiation Increases Survival in Non-Hodgkin's Lymphoma Patients: Therapeutic Radiation Hormesis

- 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%.
- Doses given were 100-150 mGy, totaling 300 mGy per week: a total fractionated dose of 1,500 mGy.

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

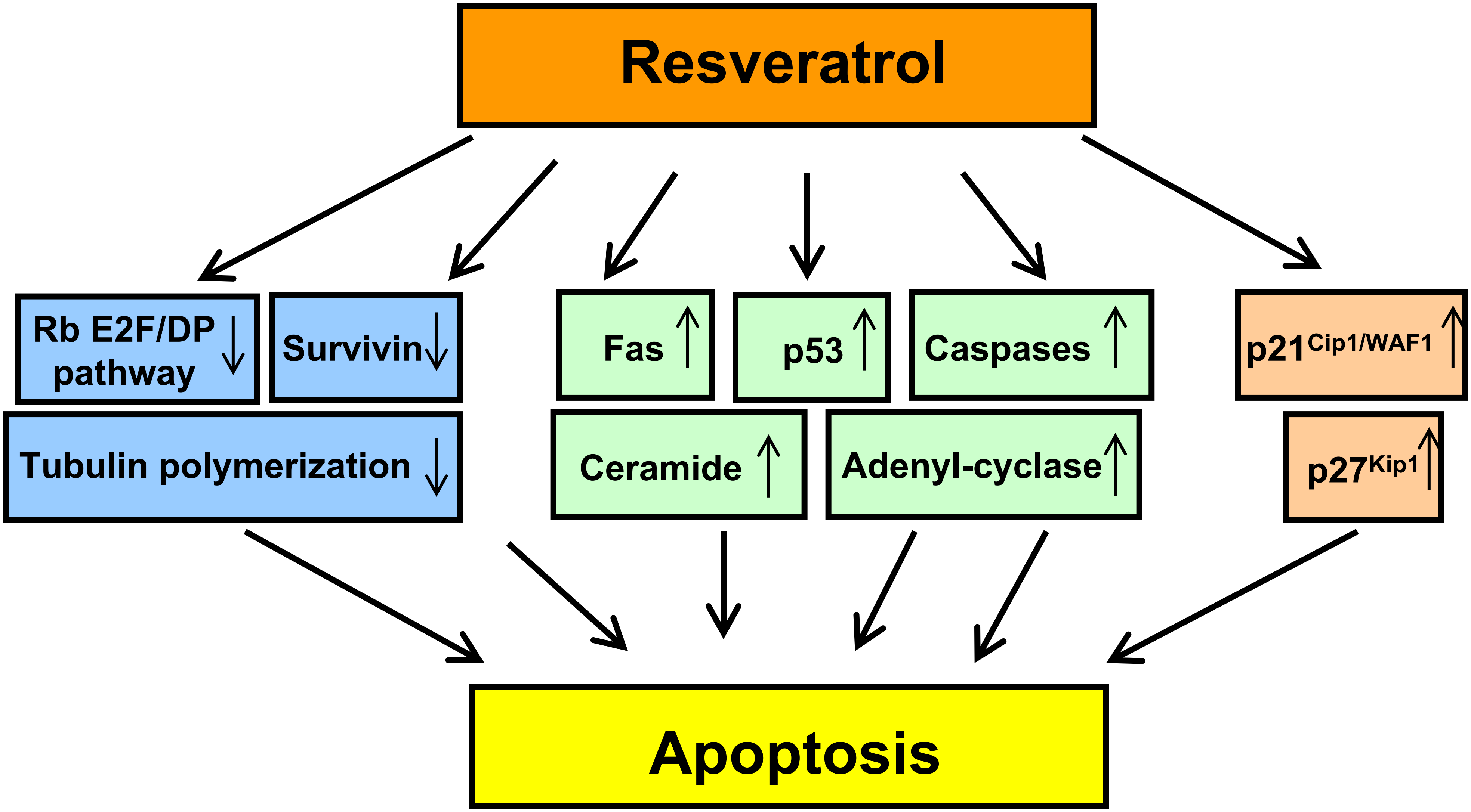
Ways To Improve The Therapy Based on Our Research Results

- **Use smaller dose fraction sizes, possibly as low as 1 mGy. Extend the period of treatment. *[Same strategy as discussed by Judah Folkman for antiangiogenic therapy for Lewis lung cancer (BELLE 2006 conference)]*.**
- **Use apoptosis-sensitizing agents (e.g., resveratrol) in combination with an antiangiogenic drug and multiple low doses (or chronic low rates) of low-LET radiation.**
- **Conduct new research to determine the average duration of the activated PAM process and induced immunity. Durations are expected to differ for these processes as was implicated by Ludwig Feinendegen (BELLE 2006 Conference).**
- **Use the knew knowledge to develop optimal therapeutic schemes.**

Resveratrol

- Trans-3,5,4'-trihydroxystilbene (resveratrol) is found in grapes, berries, peanuts, and other plants.
- Resvertrol sensitizes cancer cells to undergoing apoptosis and suppresses proliferation of a wide variety of tumor cells (e.g., lymphoid and myeloid cancers; multiple myeloma; cancers of the breast, prostate, stomach, colon, pancreas, and thyroid)

Aggarwal BB et al. (Anticancer Res. 24, 2004)



Effect of resveratrol on signaling proteins involved in apoptosis
(Aggarwal *et al. Anticancer Research* 24:3-60, 2004)

Therapeutic Radiation Hormesis Via Radon Exposure

Some Health Conditions Currently Being Treated at a Radon Health Mine in Boulder, Montana, USA Include:

- **Ankylosing Spondylitis**
- **Arthritis (RA)**
- **Asthma**
- **Carpal Tunnel**
- **Fibromyalgia**
- **Multiple Sclerosis**
- **Osteoarthritis**
- **Psoriasis**
- **Scleroderma**
- **Ulcerative Colitis**

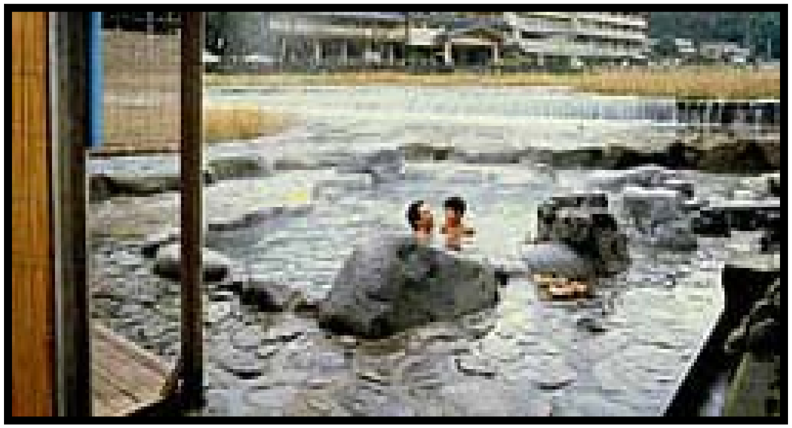
Photo: Lewis & Anderson's Free Enterprise Radon Health Mine, Boulder, Montana, USA

http://www.radonmine.com/area.html

Environmental Radiation Hormesis: Radon-Spa Areas in Japan (Misasa)

Cancer Site or Type	100*PROFAC (%)	
	Females	Males
Leukemia	47 ± 1.6	56 ± 1.6
Stomach	55 ± 1.6	60 ± 1.6
Breast	74 ± 1.4	(results not reported)
Lung	81 ± 1.2	53 ± 1.6
Colon/rectum	86 ± 1.1	70 ± 1.5

Radon exposure involves a gamma radiation component, which is considered responsible for activating the PAM process and inducing immunity. ***Data from Mifune et al. 1992***



Conclusions

- Many cancer cases (and other diseases) are likely being prevented worldwide via medical and environmental radiation hormesis.
- Less costly, more tolerable, and possible more successful cancer therapy could be achieved via use of multiple low doses of low-LET radiation (or chronic low rates) in combination with agents (e.g. resveratrol) that selectively sensitize cancer cells to undergoing apoptosis and with antiangeogenic therapy.
- Current high-dose radiation and chemotherapy may be promoting cancer metastasis. Medical radiation hormesis likely suppresses cancer metastasis.
- Radon in the home is likely suppressing cancer occurrence and other diseases. Removing radon therefore may be more harmful than beneficial.

Acknowledgments

This research was supported by the Office of Science (BER), U.S. Department of Energy (DOE) Grants DE-FG02-03ER63671 and DE-FG02-03ER63657.

Backup Slides

Doses from Diagnostic X-Rays Fall in the Hormetic Zone

Number of X-Rays	Dose Range[a]	Hormesis Likely?
< 5	0.01 mGy - 30 mGy	> 0.01 mGy Yes
5 – 14	0.1 mGy – 50 mGy	Yes
≥ 14	1 mGy – 230 mGy	Yes

Routine nuclear medicine diagnostic procedures involve low-LET doses < 30 mGy.

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

Hormetic Effect in Chernobyl Workers

Hormetic effect observed for the solid cancer incidence among nuclear workers who participated in recovery operations following the accident at the Chernobyl plant and for cancer mortality among the Chernobyl emergency workers.

Photo: Ukrainian citizen's private web site

Ivanov et al. NPP. J Radiat Res. 45:41–4, 2004
Ivanov et al. Health Phys. 81:514–21, 2001

Expected Lives Saved From Diseases Other Than Cancer Due to Radiation Hormesis in Nuclear Shipyard Workers

Cause of Death	*100∗PROFAC (%)*★	p value
Nervous and sensory organs	52	$< 10^{-7}$
Cirrhosis of liver	37	1.3×10^{-3}
Digestive system diseases	29	$< 10^{-7}$
Vascular lesions of CNS	27	5.9×10^{-5}
Diabetes mellitus	24	1.1×10^{-5}
Total mortality	22	1.1×10^{-7}
All circulatory diseases	20	$< 10^{-7}$
Arteriosclerotic heart disease	17	5.8×10^{-6}

★ *Based on standardized mortality ratios adjusted for the healthy worker effect. Sponsler R and Cameron JR. Int. J. Low Radiat. 1(4):463-478, 2005*

Expected Lives Saved From Cancer Due to Radiation Hormesis in Oak Ridge Nuclear Workers

Cause of Death	*100*PROFAC (%)*	*p* value
Cancer of buccal cavity & pharynx	79	$p < 10^{-4}$
Rectal cancer	46	$p < 0.05$
Leukemia and aleukemia	40	$p < 0.05$
Stomach cancer	36	$p < 0.05$
Bladder cancer	28	$p < 0.05$
All lymphopoietic cancer	17	$p < 0.05$
Cancer of digestive organs and peritoneum	15	$p < 0.05$

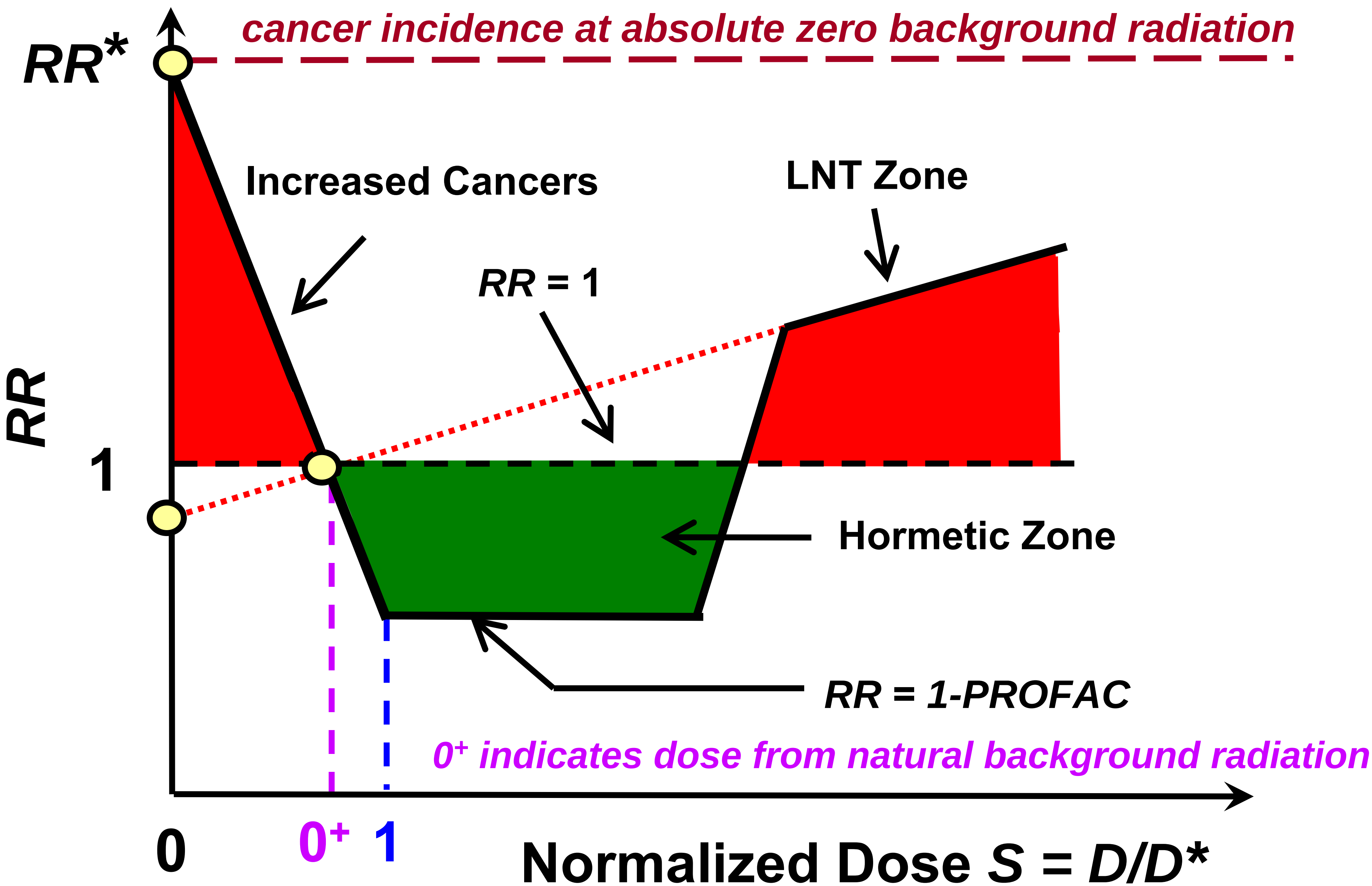
Based on data from Loomis and Wolf. Int. J. Low Radiat. 1(4):463-478, 2005

Expected Lives Saved From Diseases Other Than Cancer Due to Radiation Hormesis in Oak Ridge Nuclear Workers

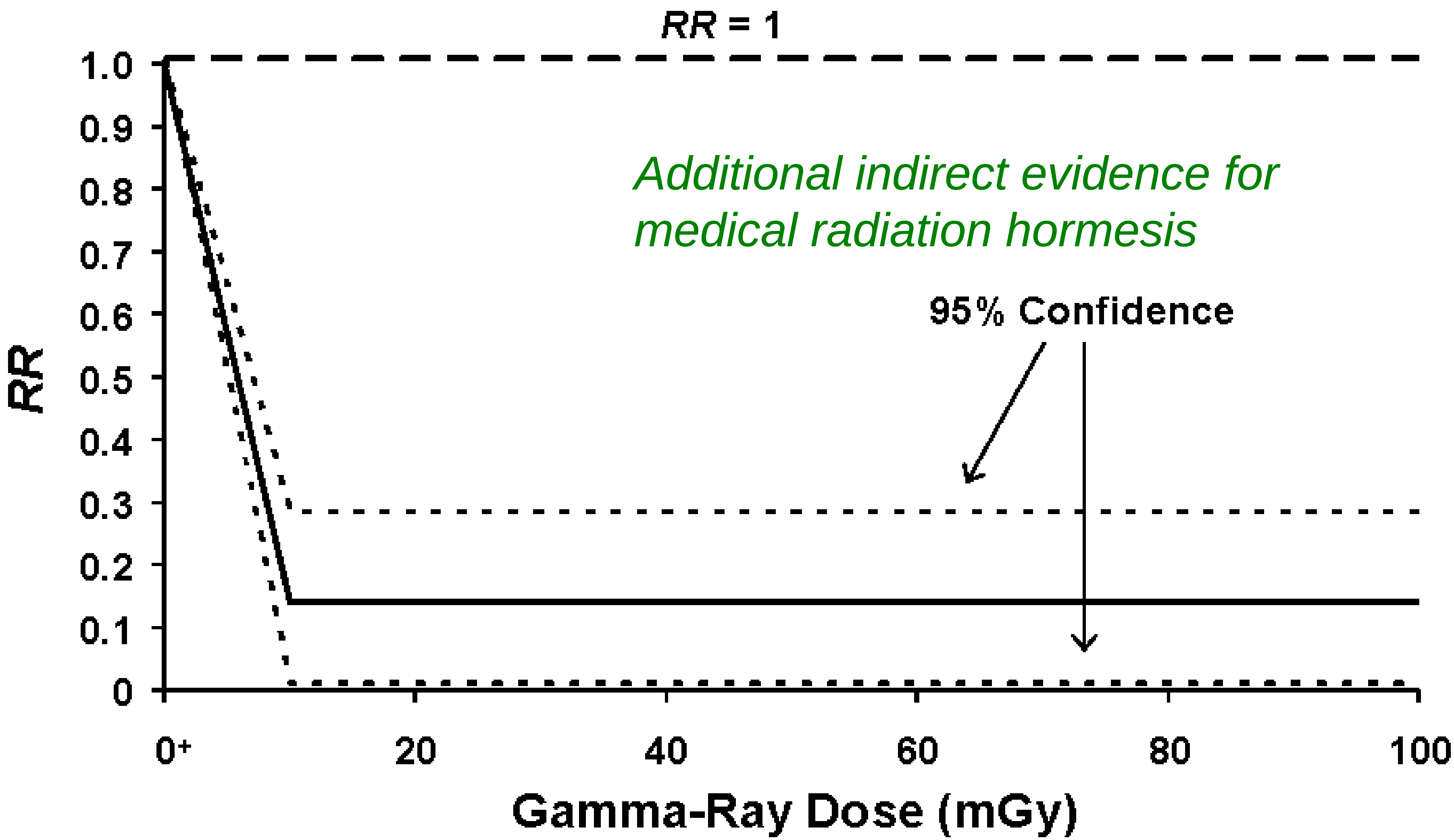
Cause of Death	*100*PROFAC (%)*	*p* value
All infective & parasitic diseases	62	$p < 10^{-3}$
Diseases of nervous system & sense organs	45	$p < 10^{-2}$
Allergic, endocrine, metabolic, nutritional diseases	44	$p < 10^{-2}$
All diseases of genitourinary system	41	$p < 0.05$
All diseases of digestive system	40	$p < 10^{-5}$
All diseases of circulatory system	17	$p < 10^{-8}$
All respiratory diseases	15	$p < 0.05$

Based on data from Loomis and Wolf. Int. J. Low Radiat. 1(4):463-478, 2005

HRR Model: Based on Normalized Dose *S*



Suppression of Spontaneous Lung Cancer in Mayak Plutonium Facility Workers



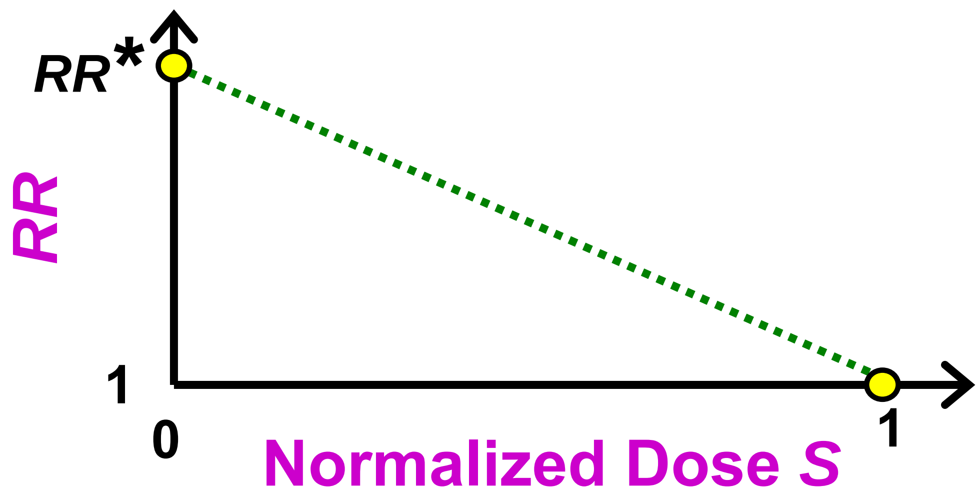
Data corrected for influence of alpha radiation (Scott, 2006a).

How Hormesis is Inappropriately Discounted by Regulatory Agencies

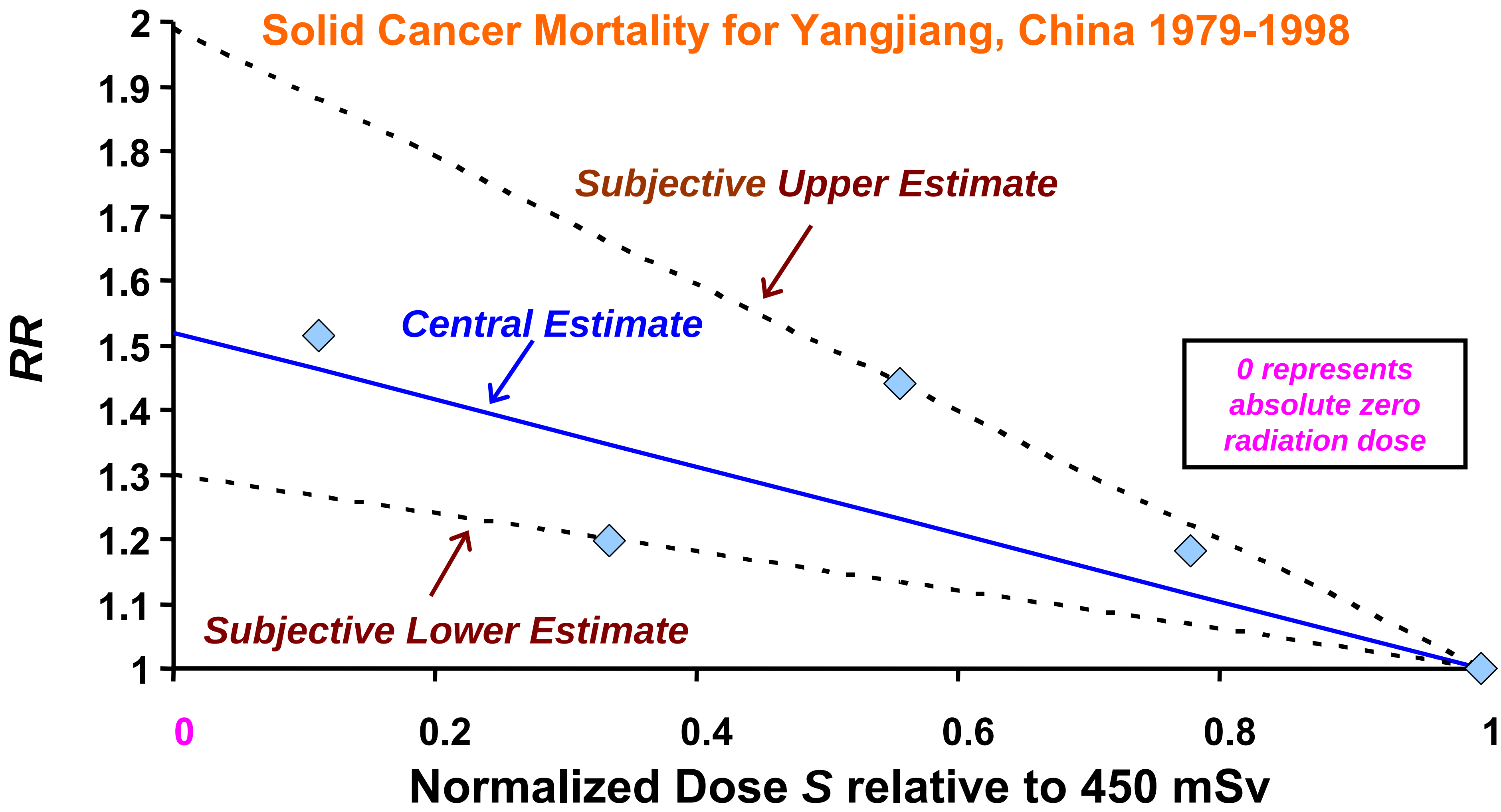
- All radiation assumed harmful including doses from diagnostic low-LET radiation (e.g., routine chest X-rays, CT scans, nuclear medicine diagnostic procedures).
- Persons receiving low doses included with controls when evaluating the shape of the dose-response curve.
- Low-dose data are excluded, ignored, or assigned low statistical weight.
- Evidence for nonlinearity is ignored.
- Ecological data showing hormesis are discounted based on poor dosimetry.
- DNA repair, protective apoptosis, and induced immunity are ignored.
- Lifespan prolongation is not considered.
- Hormetic effects missed due to assuming a healthy worker effect.
- Years of radiation dose accumulation are simply thrown away (called dose lagging) changing threshold-like dose responses into what appears to not have a threshold.

Relative Risk at Reduced Natural Background Radiation

- ***RR*** **at reduced natural background radiation level can be evaluated based on the normalized dose** $S = D/b$ **relative to** b**, where** b **is a reference natural background low-LET dose evaluated over the period of interest and** D **is the corresponding reduced background low-LET dose.**
- ***RR*** **increases linearly from 1 at current natural background to a value > 1 at zero natural background radiation. Only the low-LET component to the dose is considered important for this dose region since it is responsible for inducing the adapted protection that is lost when dose is reduced (Scott, 2006b).**

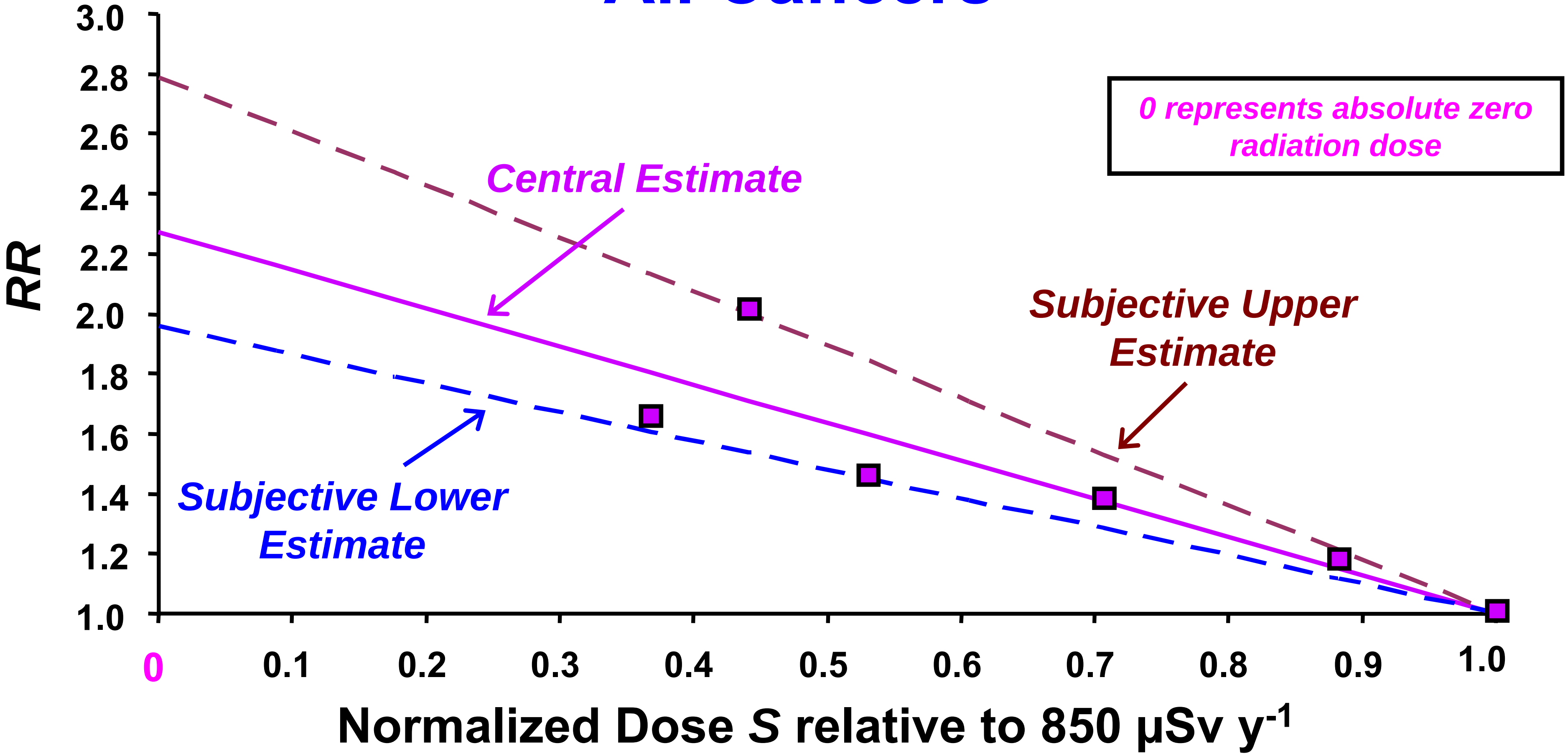


Expected Effects of Reducing Natural Background Radiation on Cancer Mortality



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

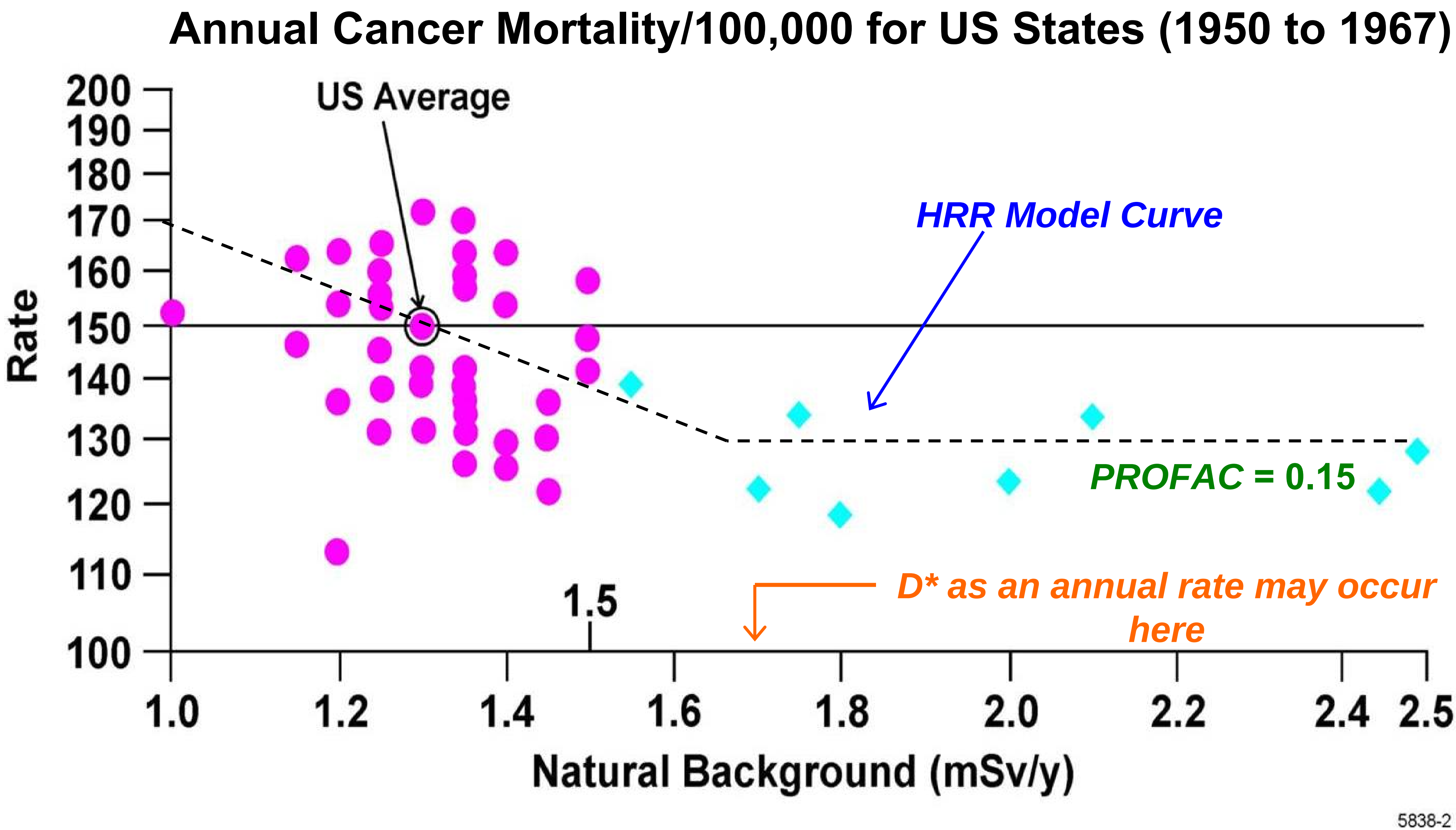
Expected Impact of Reducing Natural Background Radiation on Relative Risk for All Cancers



Data are based on various cities and states of India. Only gamma- ray exposures were evaluated. *RR = 1* at *0+* = 850 µSv y^{-1}.

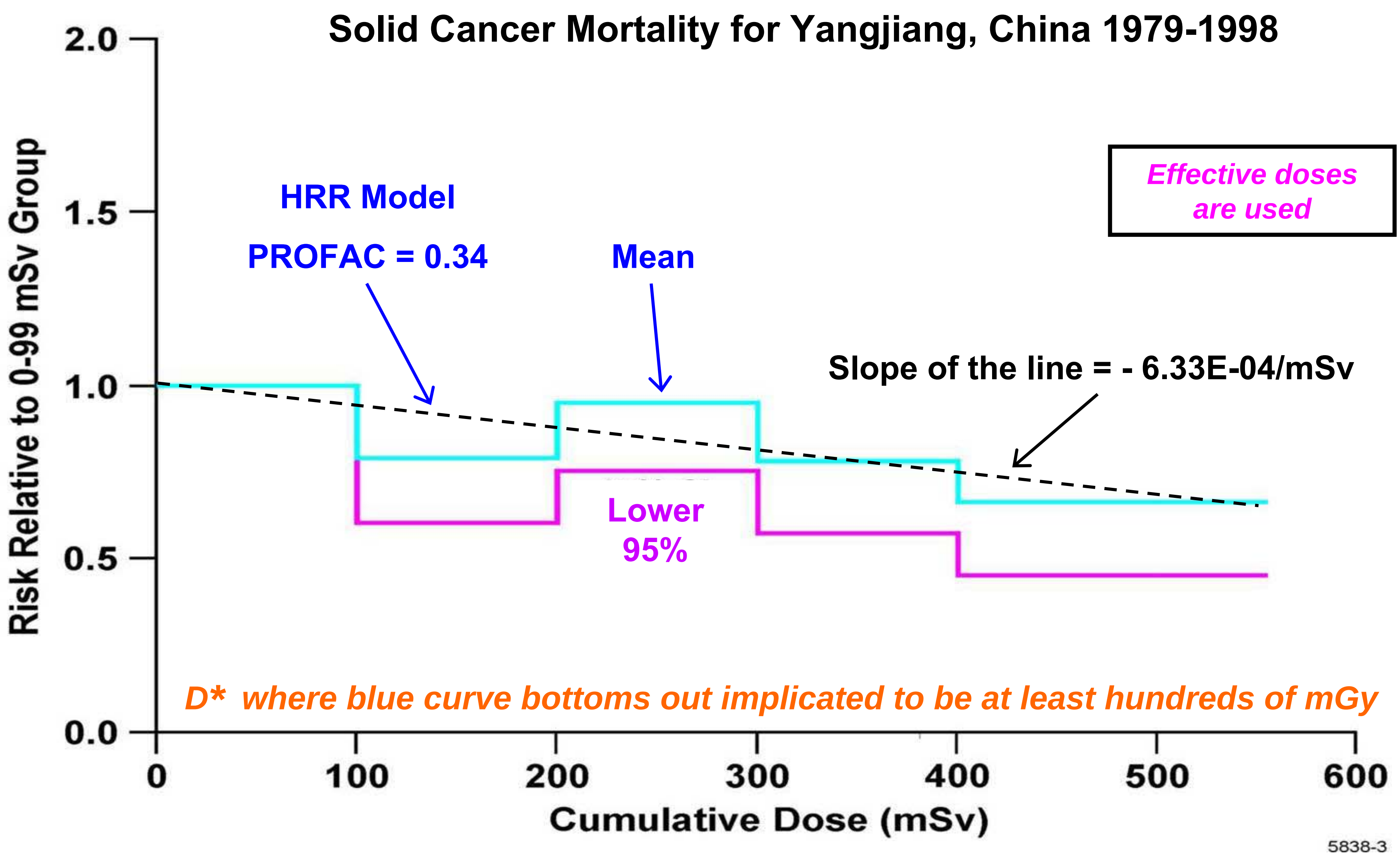
Data from Nambi KSV and Soman SD. Health Physics 53(5):653-657, 1987

Environmental Radiation Hormesis: Cosmic and Terrestrial Radiation



Frigerio and Stowe. IAEA Publication (1976)

Environmental Radiation Hormesis



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

Conclusions

- **Routine diagnostics (e.g., nuclear medicine procedures, chest X-rays, CT scans) protect us from cancer and other diseases (*medical radiation hormesis*). Likely suppresses metastasis.**
- **Low-LET radiation sources have been used to successfully treat cancers without any serious side effects. (*Therapeutic radiation hormesis*).**
- **Repeated exposures (or chronic low rate exposure) over a prolonged period to small doses of low-LET radiation in combination with antiagiogenic therapy and tumor sensization thearpy (e.g., application of resveratrol) might greatly increase the frequency of cancer cures.**
- **Benefits of radon therapy can be explained based on radiation hormesis.**
- **Reducing radon exposure in the home may cause more harm than benefit through loss of adapted protection.**