Low-Dose Radiation Benefits, a New Paradigm

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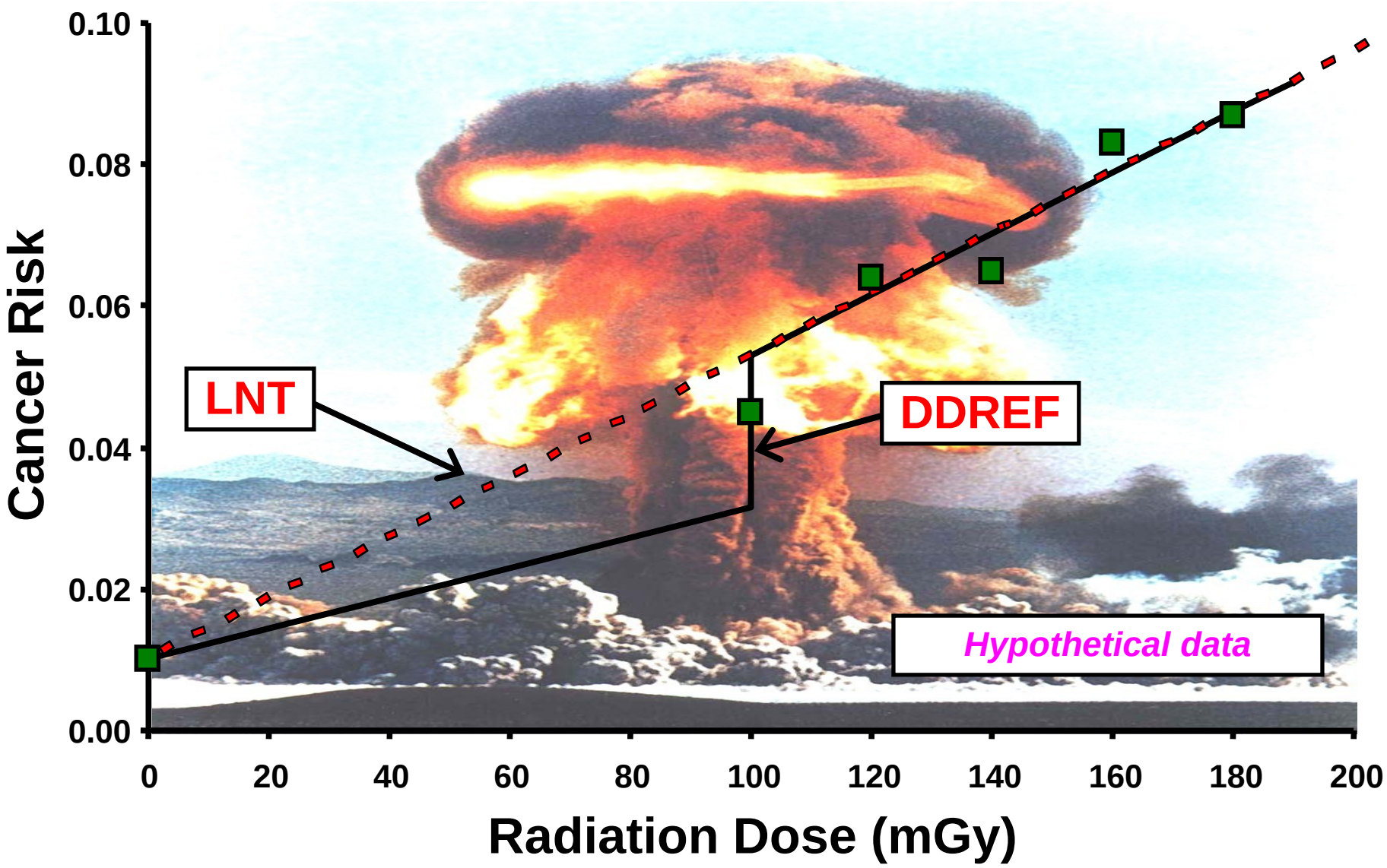
- LNT hypothesis
- Chuck Sanders' very large animal studies invalidating the LNT hypothesis
- Bernie Cohen's ecological study invalidating the LNT hypothesis
- Hormetic relative risk (HRR) model and novel benefit function $B(x)$

Contents (continued)

- Residential radon benefit $B(x)$ for preventing lung cancer caused by cigarette smoke carcinogens and other agents
- Eliminating hormetic responses via inappropriate data adjustments
- Conclusions

LNT Hypothesis



Margaret Maxey in 1997 on The LNT Hypothesis

"Slowly but inexorably, radiation scientist are recognizing that the LNT hypothesis … has in its maturity become scientifically illegitimate and ethically indefensible."

Maxey M. The LNT Hypothesis: Ethical Travesties. 1997 Speech printed by Rod Adams 14 April 2011 in Atomic Insights

Ed Hiserodt on LNT and Fukushima and a Political Agenda

"… anti-nuclear activist will predict thousands of cancer deaths based on the LNT, which will not happen, but no matter. Fear is the objective."

Hiserodt H. Fukushima: Just how dangerous is radiation? The New American. 27 April 2011.

Large Animal Studies of C.L. Sanders Invalidating the LNT Hypothesis

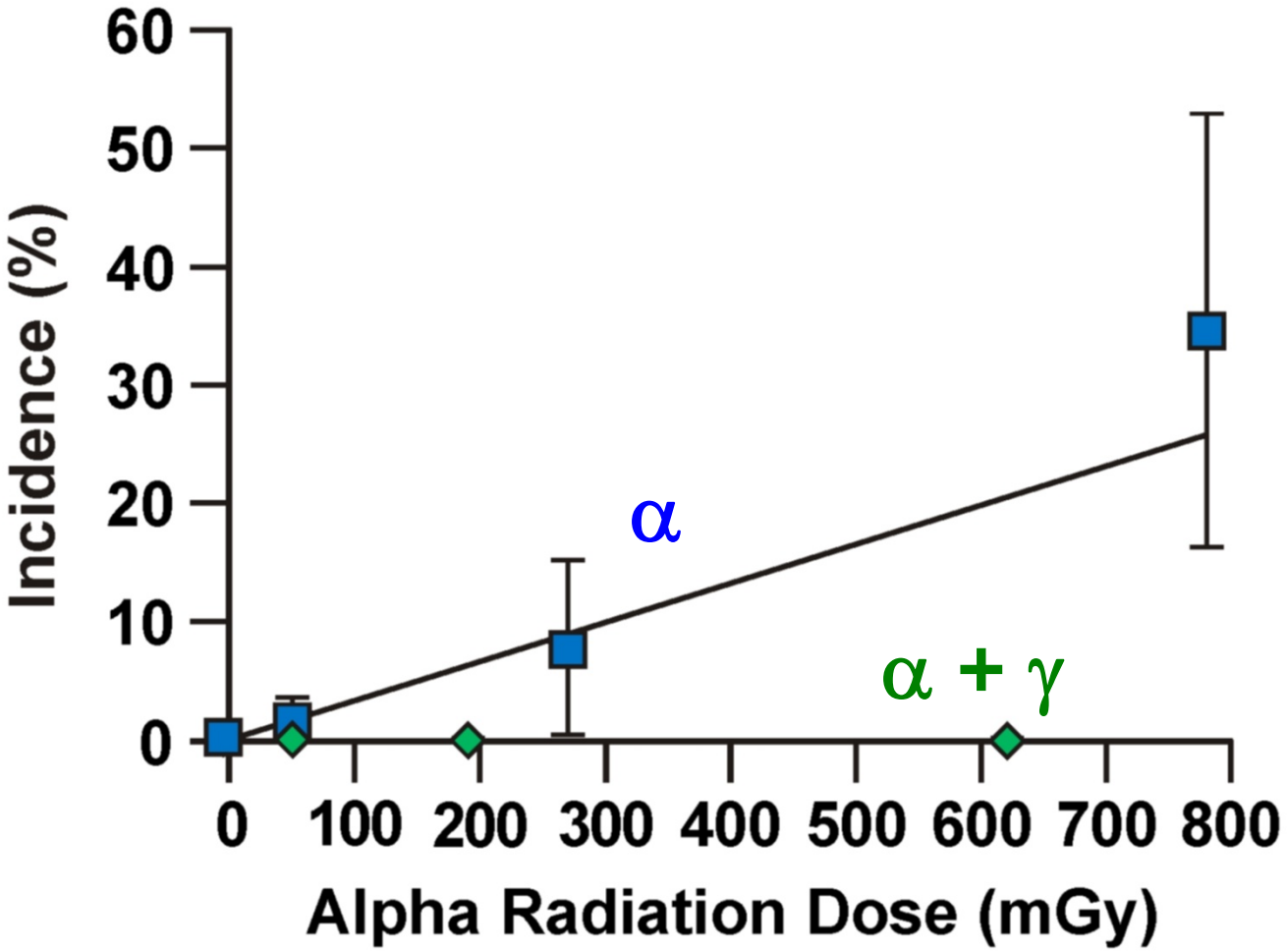
Lung cancer in α (Pu-239) and α + γ (Yb-169) exposed Wistar rats

Number of rats used =**3793**

Scott BR et al. J. Am. Physicians Surg. 13(1): 8-11, 2008.

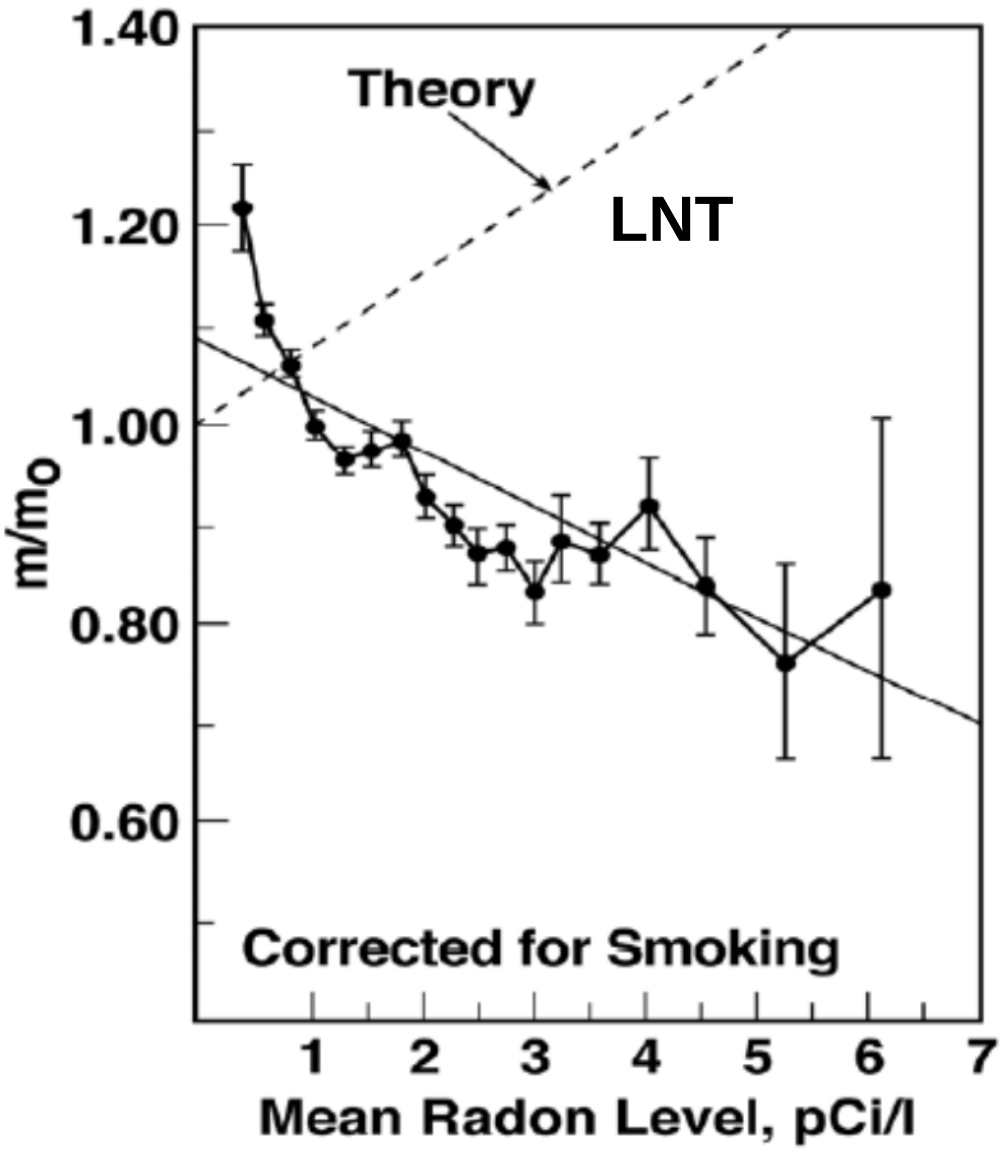
Sanders CL. Radiation Hormesis and the Linear-No-Threshold Assumption, Springer-Verlag, New York, 2009

Suppression of Alpha-Radiation-Induced Lung Cancer by Low-Dose Gamma Rays



Cohen's Invalidation of LNT

Corrected lung cancer mortality rate for males



1729 U.S. counties (Cohen, 1995)

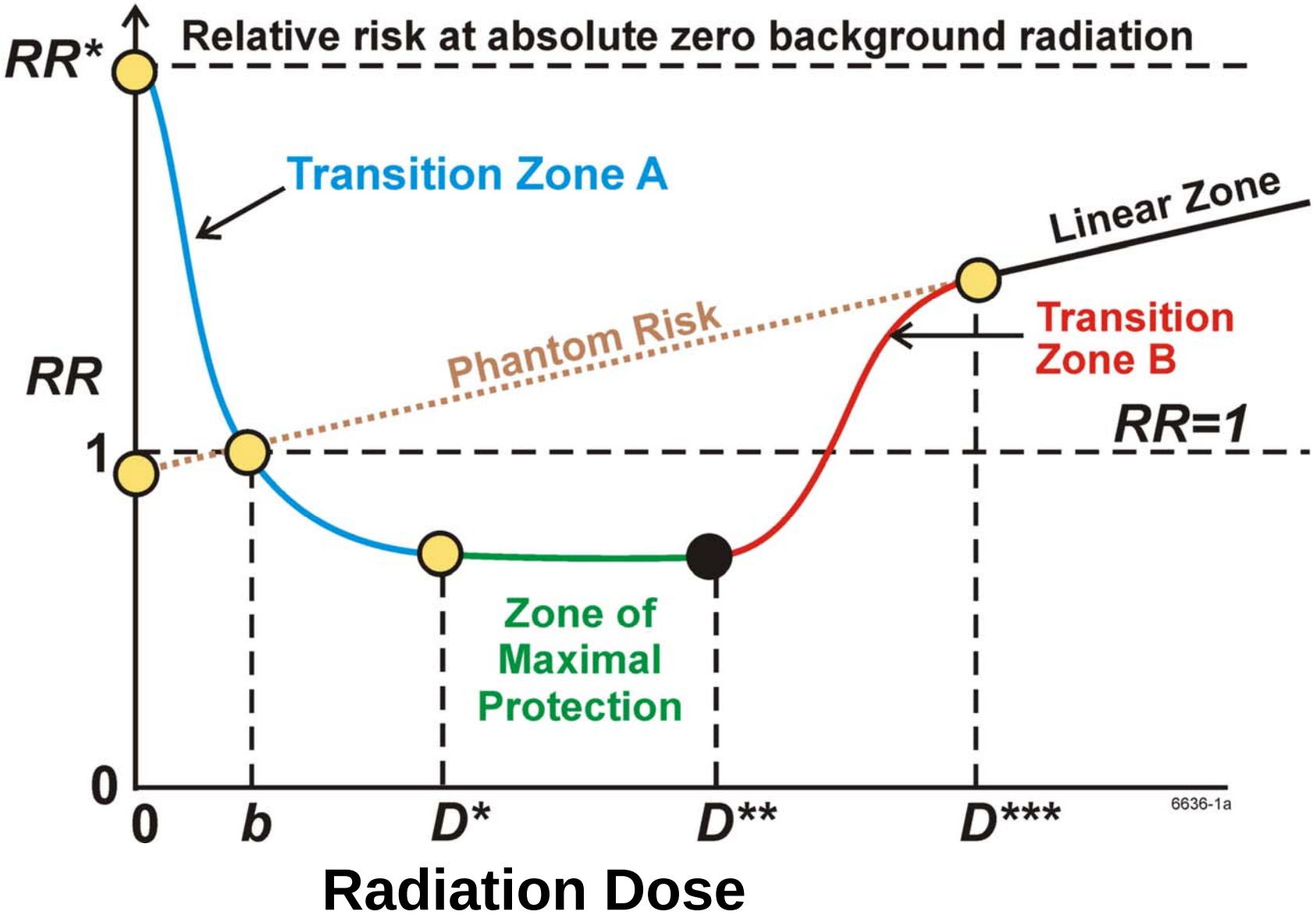
Adaptive-Response-Based Hormetic Relative Risk (HRR) Model

- Stochastic threshold model.
- Provides an alternative to the invalid LNT model.

Scott BR et al. Dose-Response 7(2): 104-131, 2009.

Scott BR. Residential radon appears to prevent lung cancer. Dose-Response 9:444-464, 2011.

HRR Model: Population Average *RR*



Transition Zone A: Part 1

- Ultra low dose region: includes doses less than current natural background at a given location.
- Stochastic threshold doses for activated natural protection (ANP).
- Relative Risk, $RR = 1 - PROFAC \bullet B(x)$, where $B(x)$ is the benefit function (adaptive protection probability).

Transition Zone A, Part 2: ANP

ANP includes the following:

- DNA double-strand break repair
- Epigenetically-regulated apoptosis (epiapoptosis)
- Epigenetically regulated anticancer immunity

Scott et al. 2009

Transition Zone A, Part 3: *PROFAC*

- *PROFAC* is the average over the individual-specific protection factor, *profac*, for everyone in the at-risk population.
- *PROFAC* is assumed to relate only to the low-LET component of the dose.
- A lung cancer *PROFAC* of 0.75 means that on average 75% of sporadic (mainly smoking-related) lung cancer cases would be expected to be prevented by radiation ANP when fully activated.

Scott BR et al., Dose-Response 7(2):104-131, 2009.

Transition Zone A, Part 3 (continued)

- Because each person has different genetic characteristics, *PROFAC* depends on the genetic make-up of the at-risk population.
- The lung cancer *PROFAC* was found to differ for different populations (*Sanders 2009*).

Zone of Maximal Protection

- Stochastic thresholds for all adaptive responses exceeded for everyone [$B(x) = 1$].
- Cancer relative risk = 1 – *PROFAC.*
- Zone width expands as the low-LET radiation dose rate decreases (*Tanooka H, Int J. Radiat. Biol., in press*).

Transition Zone B

- Stochastic thresholds for epigenetic silencing (episilencing) of adaptive-response genes.
- Immunosuppression in some but not all.
- Induction of some cancer-facilitating mutations.

High-Dose Linear Zone

- Zone where most previous epidemiological studies conducted.
- Stochastic threshold for episilencing of adaptive response genes exceeded for everyone.
- Immune system suppressed in everyone.
- Induction of cancer facilitating mutations increases as the radiation dose increases.
- Excess relative risk (*RR*) increases linearly as dose increases.

Radiation Benefit vs. Risk Paradigms for Cancer

Low-Dose Benefits	High-Dose Risks
Adaptive protection (AP) function $A(x)$	Hazard function $H(x)$
Benefit function: $B(x) = 1 - exp[-A(x)]$	Risk function: $R(x) = 1 - exp[-H(x)]$
Density function: $b(x) = dB(x)/dx$	Density function: $r(x) = dR(x)/dx$

"x" is the dose.

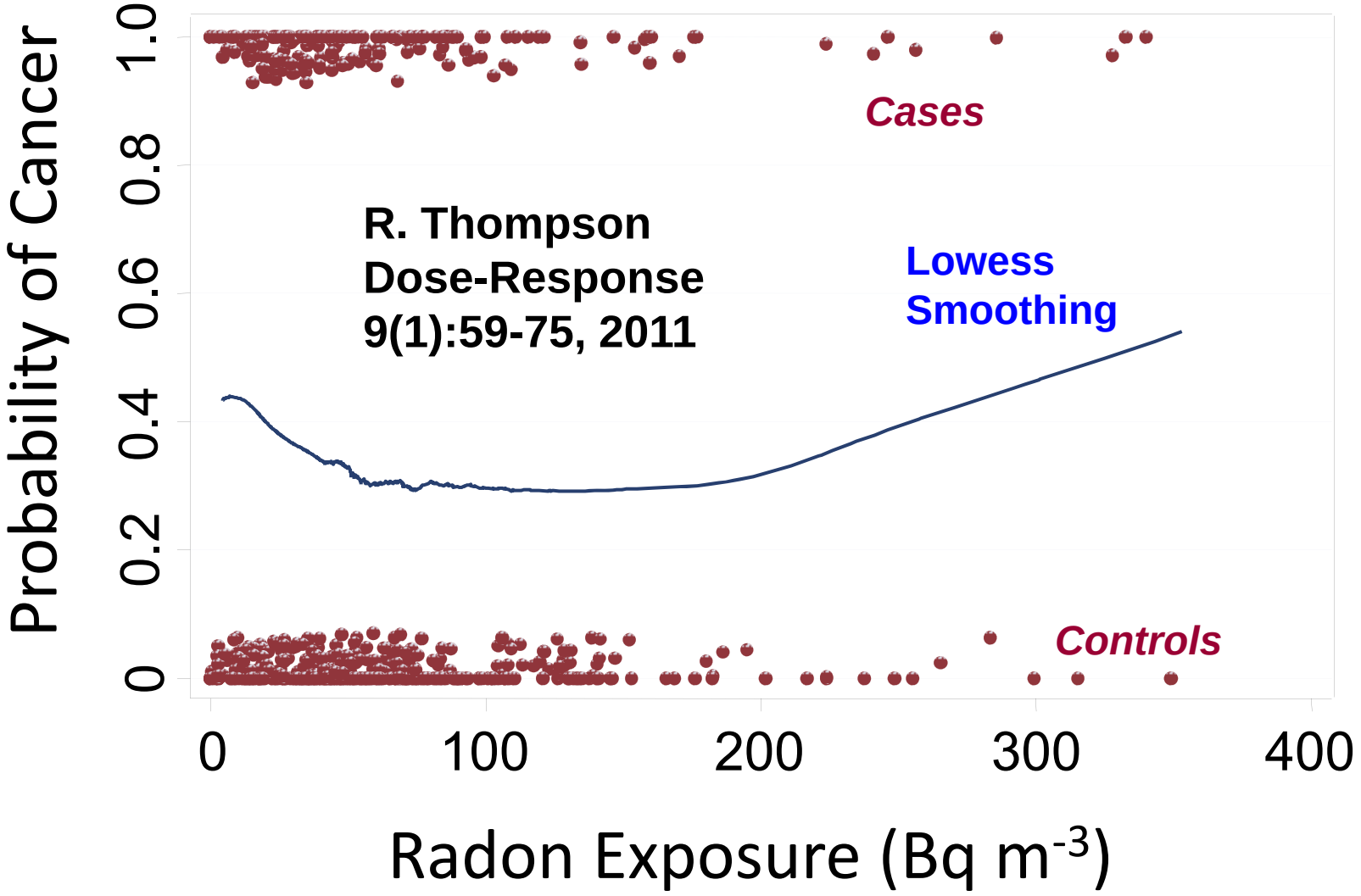
Study Demonstrating Residential Radon Benefit: Lung Cancer Suppression

Richard Thompson et al. Case-control study of lung cancer risk from residential radon exposure in Worcester County, Massachusetts. *Health Phys. 94(3):228-241, 2008*.

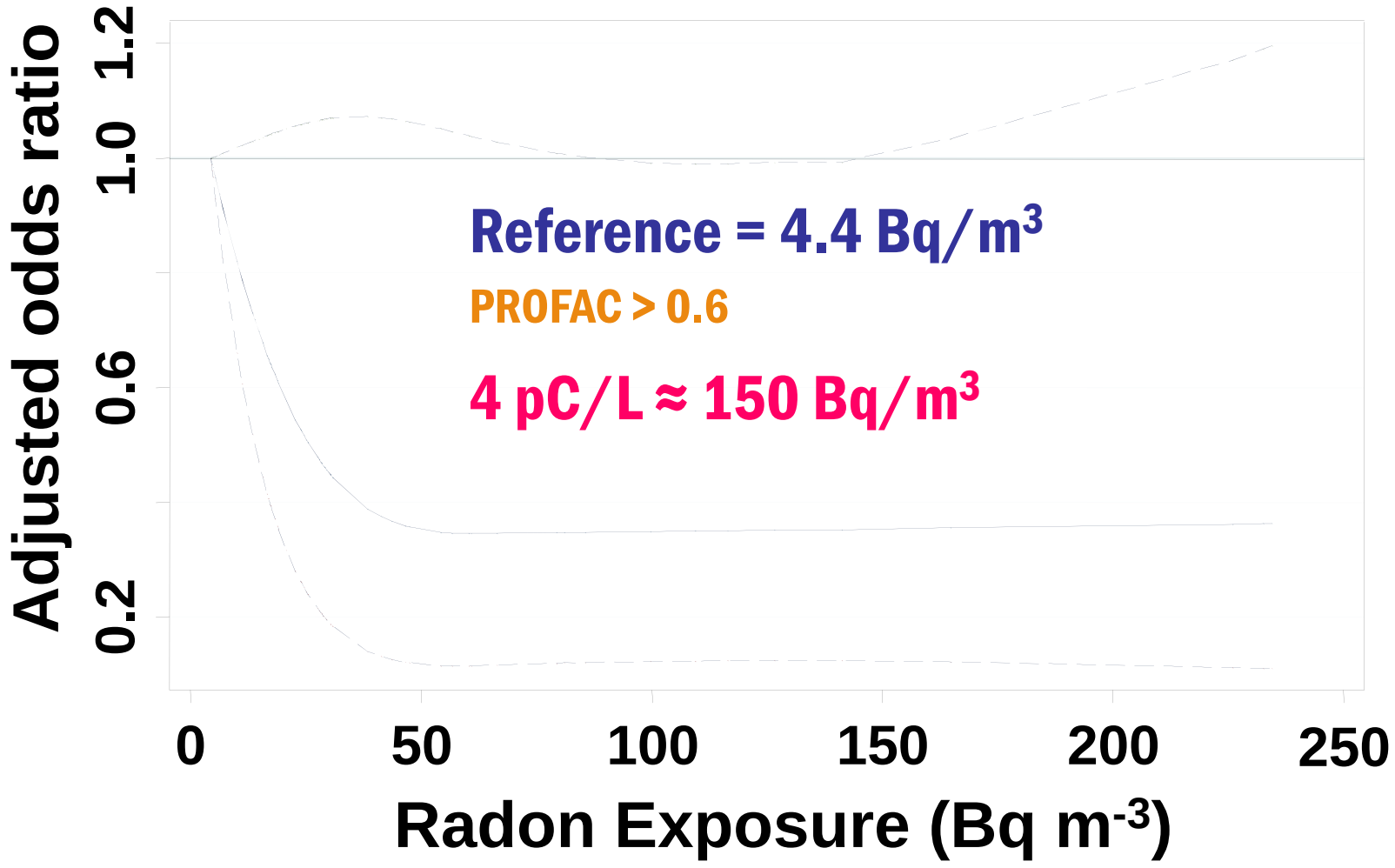
Study Design

- Radon measured in yearlong exposure (blanks and spikes in each batch).
- 1/10 homes had two detectors placed side by side.
- 200 cases / 397 controls (total 597).
- All were members of same HMO, and resided in Worcester, County.
- Multivariate model employed to control for confounders (smoking, residency, education, income).
- Did not average over wide dose intervals!

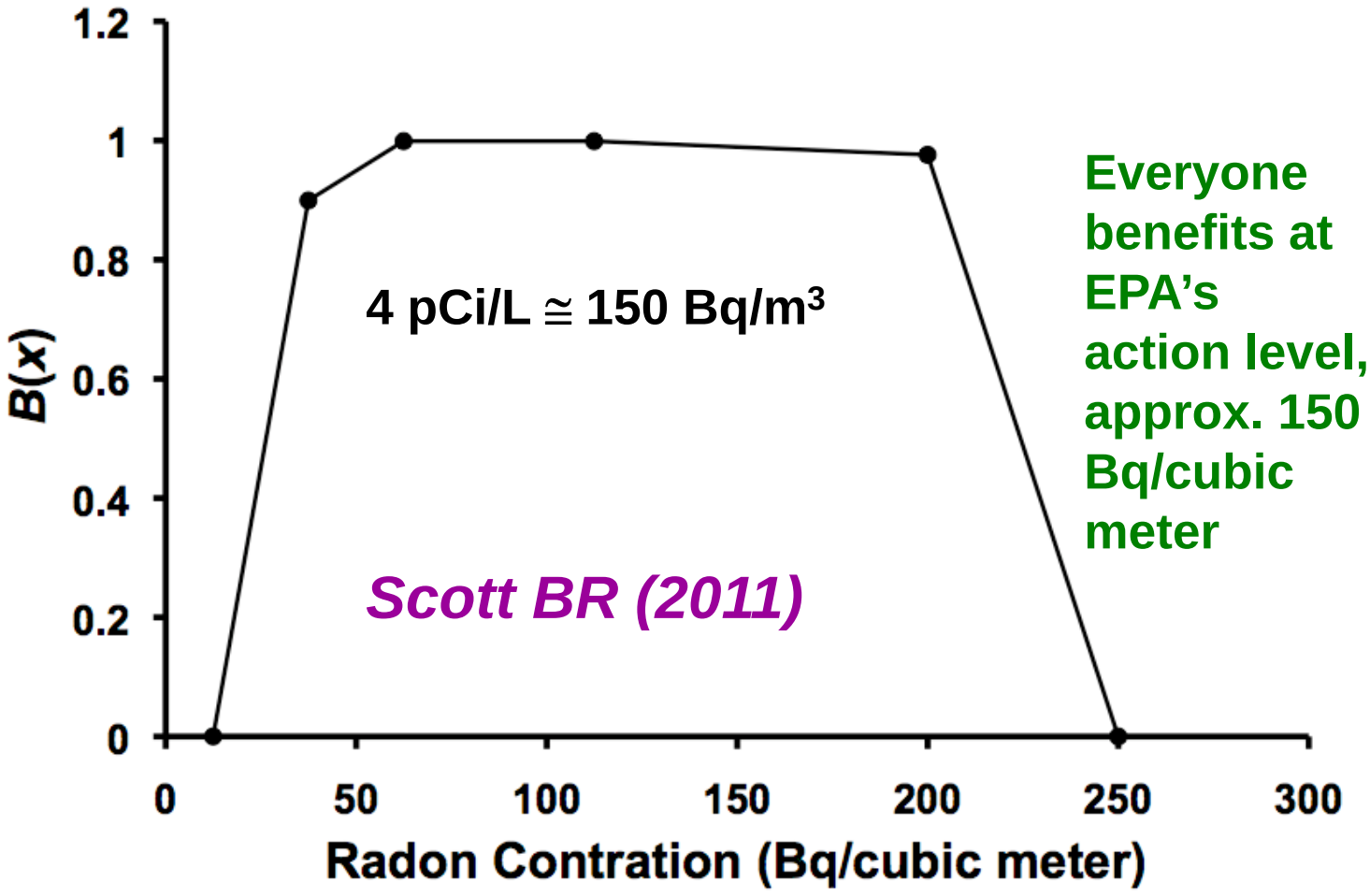
U-shaped Dose-Response for Residential Radon



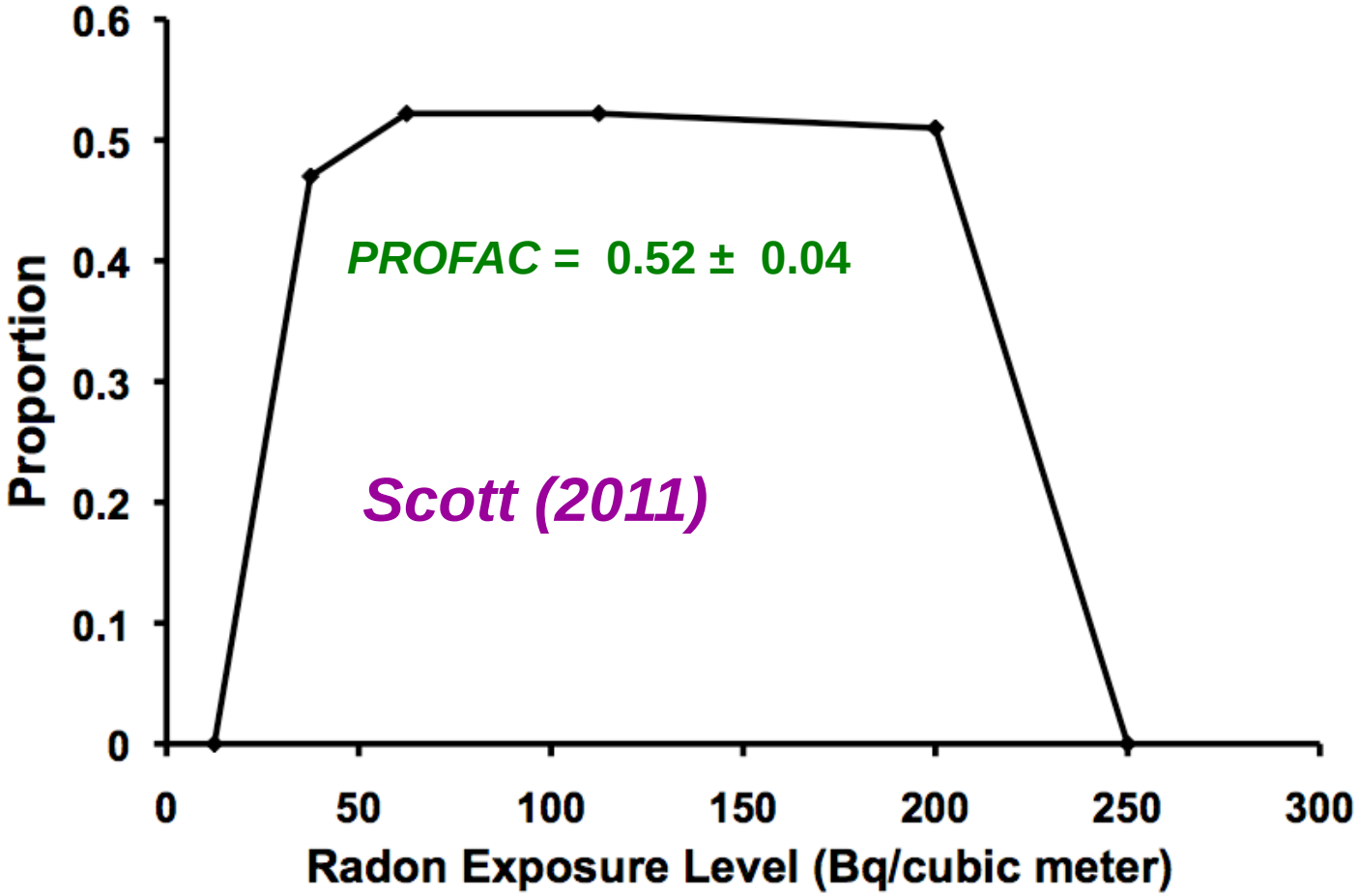
Lung Cancer Adjusted OR (95% C.I.)



Residential Radon Benefit, *B*(*x*), for Preventing Lung Cancer



Expected Proportion of Lung Cancers Prevented: *PROFAC*B(x)*



How Risk-Factor Adjustments Can Reintroduce Risk Already Eliminated via Radiation ANP

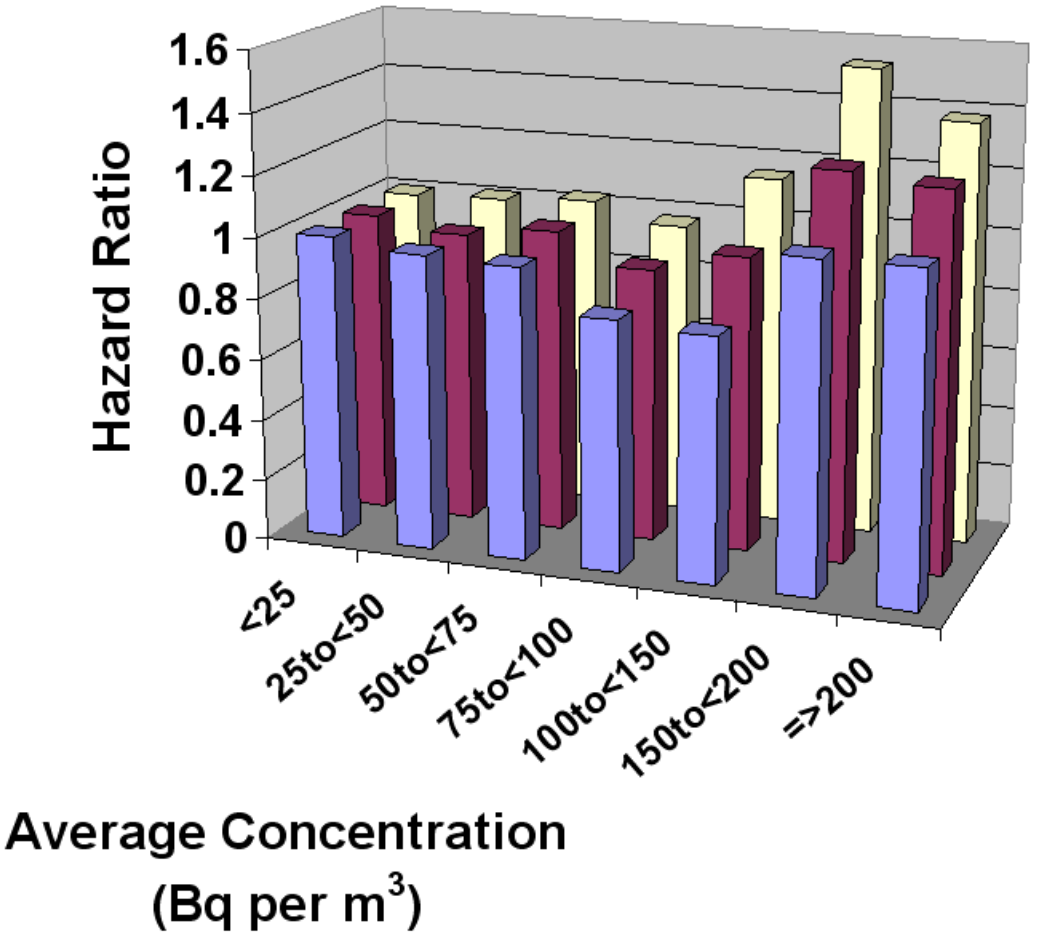
- Excess relative risk (*ERR*) increases as the number of risk factors and their levels increase.
- Adjusting for specific risk factors other than radiation would then be expected to reduce *ERR*.
- For the hormetic zone, *ERR* is negative; thus, reducing its magnitude increases *RR*, since *RR* = 1 + *ERR* (a negative number).

Residential Radon Study of Turner et al. with 812,000 Participants (2011)

- American Cancer Society Cohort study of association between residential radon an lung cancer.
- Mean county-level residential radon concentration used.
- Minimally-adjusted: age, race, and gender stratified.
- Fully-adjusted-1: age, race, gender, education, marital status, body mass index, cigarette smoking, duration of smoking, and other factors.
- Fully-adjusted-2: Fully-adjusted 1 as well as stratified by state.

Turner MC et al., Cancer Epidemiol Biomarkers Prev 20(3):438-448, 2011.

Adding Back ANP-Eliminated Risk via Risk Factor Adjustments: Data of Turner *et al.* (2011)



Full-2 adjusted

Full-1 adjusted

Min adjusted

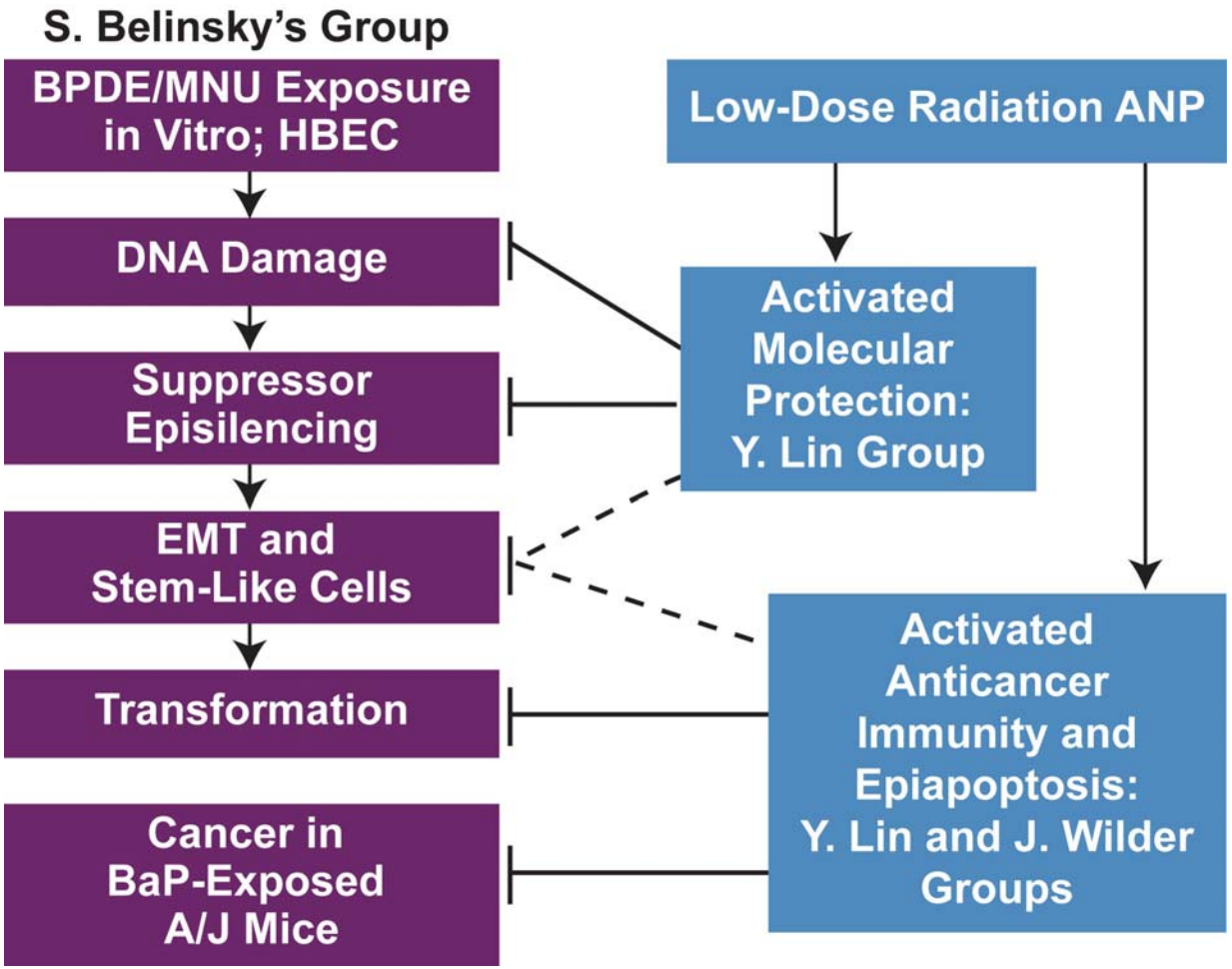
Conclusions of Turner *et al.* (2011)

"A significant positive linear trend was observed between categories of radon concentrations and lung cancer mortality (P = 0.02). A 15% ... increase in the risk of lung cancer mortality was observed per 100 Bq/m^3 increase in radon. Participants with mean radon concentrations above the EPA guideline value (148 Bq/m^3) experienced a 34% …increase in risk for lung cancer mortality relative to those below the guideline value."

Testable Hypothesis Related to Hormetic Response Curve for Radiation Exposure and Lung Cancer

Hypothesis: Low doses and dose rates of low- or low- plus high-LET radiation stimulate a hierarchy the body's natural defenses which together can efficiently protect from lung cancer induction by cigarette smoke carcinogens and other agents.

Our Research Related to Testing the Indicated Hypothesis



Therapy Implications of HRR Model

- Our HRR model is consistent with application of low doses and dose rates of low-LET radiation or low + high-LET radiation (e.g., from radon exposure) in treating inflammatory and proliferative diseases.
- Powerful organizations such as the U.S. Environmental Protection Agency do not support such practices.

U.S. EPA on Radon Therapy

"…radon therapy exists completely outside of the biomedical health care system… As an "alternative therapy" radon's "health" benefits may be more psychological than physiological. People may feel that their arthritis or asthma is temporarily better but in doing so they have increased their long-term lung cancer risk."

http://iaq.supportportal.com/link/portal/23002/23007/Article/21555/What-can-you-tell-me-about-Radon-Therapy

Conclusions: Part A

- Low-dose, low-LET radiation ANP prevents α-radiation-related lung cancer in rodents.
- Low- plus high-LET radiation exposure from residential radon prevents lung cancer in humans caused by cigarette smoke carcinogens and other agents.
- The indicated effects above likely involve a hierarchy of protective mechanisms.

Conclusions: Part B

- Standard risk-factor adjustments in epidemiological and ecological studies may abolish real thresholds and hormetic responses.
- Special considerations need to be given to such issues, otherwise researchers may have insufficient power to reject an invalid LNT hypothesis when it should be rejected.

Participants

Julie Wilder, Yong Lin, Steven Belinsky, Veronica Bruce, Katherine Gott, Wenshu Chen, Shuguang Leng, Julie Hutt, Tom March, Carmen Tellez, and Mabel Padilla

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Dose-Response Special Issue Honoring Zbigniew Jaworowski

- Guest Editors: Bobby Scott and Ludwik Dobrzynski
- Theme: Beneficial effects of low doses and dose rates of ionizing radiation

Backup Slides

Procedures Used in Epi Studies that Remove Thresholds and Hormetic Responses

- Including persons exposed to protective doses in the control group (*Scott et al. 2008*).
- Dose lagging, making smaller doses appear more harmful (*Scott et al. 2008*).
- Averaging over wide dose intervals removing non-linearity (*Scott et al. 2008*).
- Including high-dose data and forcing LNT extrapolation to low doses (Scott et al. 2008).
- Inappropriately attributing adaptive protection to a healthy-worker effect (*Fornalski K and Dobrzynski L, Dose-Response 8(2)125-147, 2010*).

Scott BR et al. J Am Physicians Surg 13(1):5-11, 2008.