Texas A&M University
Department of Biology

Radiobiology Laboratory

Brown, S.O., Krise, G.M. and Pace, H.B. (1963) Continuous low-dose radiation effects on successive litters of the albino rat. Radiat. Res. 19, 270-276.

Rats exposed continuously at 20 mSv a day from ^{60}Co had significantly longer lifespans and more robust reproduction than unexposed controls.

Sanders, C.L. S.O.Brown and G.M.Krise. 1963. Effects of continuous low intensity radiation on the cotton rat. Annual Report, Texas A & M Research Foundation, ARMY Project DA-007-49-MD-957, pp. A1-A14.

Cancer mortality in counties surrounding the **Hanford** site was 5%, 11%, and 16% less than expected for all cancer, lung cancer, and thyroid cancer, respectively*. All cancer mortality for **Hanford** workers was 22% less than expected**.

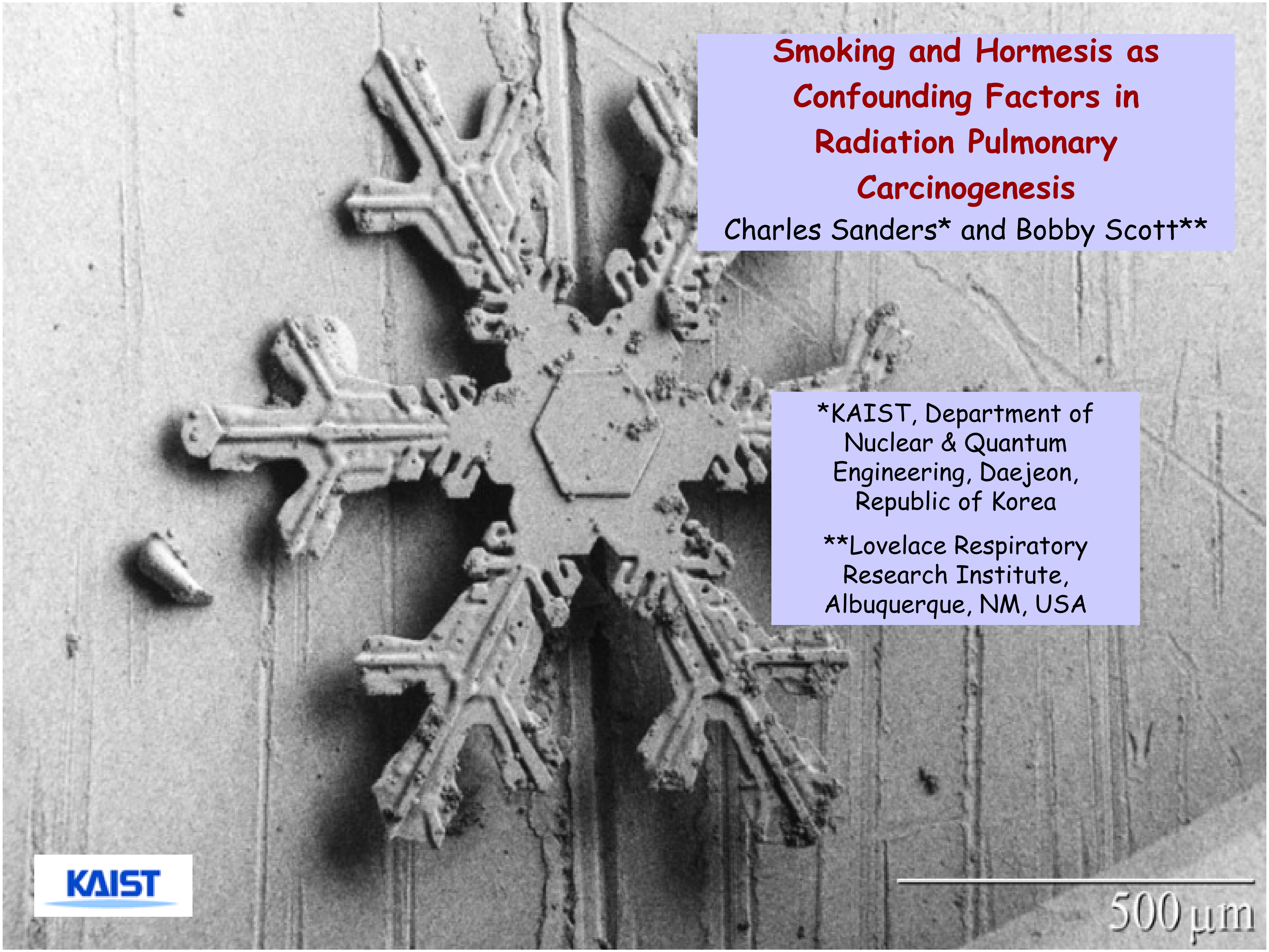
*Boice et al. 2006; **Wilkinson 2000

Smoking and Hormesis as Confounding Factors in Radiation Pulmonary Carcinogenesis

Charles Sanders* and Bobby Scott**

*KAIST, Department of Nuclear & Quantum Engineering, Daejeon, Republic of Korea

**Lovelace Respiratory Research Institute, Albuquerque, NM, USA



Outline

Confounding Factors

- Smoking
- Others

LNT Hypothesis

Hormesis

Populations →

Healthy Worker Effect

Dose-Response

^{239}Pu Human/Rat Studies

Observations

Populations showing evidence of radiation hormesis

Natural	High Background
Residential	Radon
Medical	Radiotherapy
	Fluoroscopy patients
	Radiologists
Occupational	Nuclear utilities
	Nuclear weapons
	Underground miners
	Shipyard workers
	Airline crews
Nuclear incidents	Mayak
	Chernobyl
	Taiwan apartments

There are many confounding factors in lung cancer formation that make it difficult to delineate the <u>harmful</u> or <u>beneficial</u> effects of radiation

Geography and lung cancer rates
(Annual Incidence per 100,000)*

Gender	High Incidence		Low Incidence	
Male	New Zealand	99.7	Peru	11.9
	Canada	90.3	India	12.6
Female	New Zealand	72.9	India	2.4
	Canada	65.6	Spain	2.7

*UNSCEAR 2000 Vol. II.

Cigarette Smoking

duration of smoking

number of cigarettes used per day

type of tobacco

use of a filter

inhalation

number of puffs per cigarette

consumed length of cigarette

time elapsed since cessation

synergism with asbestos

passive smoke exposure

Lung cancer risk and cigarette smoking in Spain and Germany

Smoking Status Duration (years)	*RR*	Smoking Status Cigarettes per day	*RR*
Never Smoker	1.0	Never Smoker	1.0
0-20 pack-years	5.9	1-9	7.3
20-40 pack-years	19	10-19	27
>40 pack-years	37	20-29	31
<2 y ex-smoker	30	30-39	120
>10y ex-smoker	4.5	>39	86

Over 30% of all cancer is due to tobacco.

Up to 20% smokers develop lung cancer

Urban air pollution, passive cigarette exposure and lung cancer in non-smokers

Factor	*RR*
Heavy urban air pollution	~1.5
Passive cigarette smoke exposure	~1.5

Cigarette smoking, asbestos exposure and lung cancer

Group	Smoking	SMR
No Asbestos	No	1.0
Asbestos	No	5.2
No Asbestos	Yes	11
Asbestos	Yes	54

Ann. N.Y. Acad. Sci. 1979: 330:473

Physical exercise, caloric restriction and dietary components produce hormesis-like responses

Lung cancer in women

Frequent Use	Smoking Status	*RR*
Black tea	Never	0.65
Dairy products	Smokers	0.56
Coffee	Smokers	0.47
Wine	Smokers	0.60

Eur. J. Cancer Prevention 2004: 13:471

Lung cancer and diet

High Consumption in Diet	*RR*
Carrots	0.62*
Tomatoes	0.51*
Exclusive use olive oil	0.67**
Use of Sage	0.43**

*compared to low consumption
**compared to no use

Bochicchio et al. 2005: Int. J. Cancer 114:983

Terms for estimating cancer risk or benefit:

Relative Risk (*RR*)

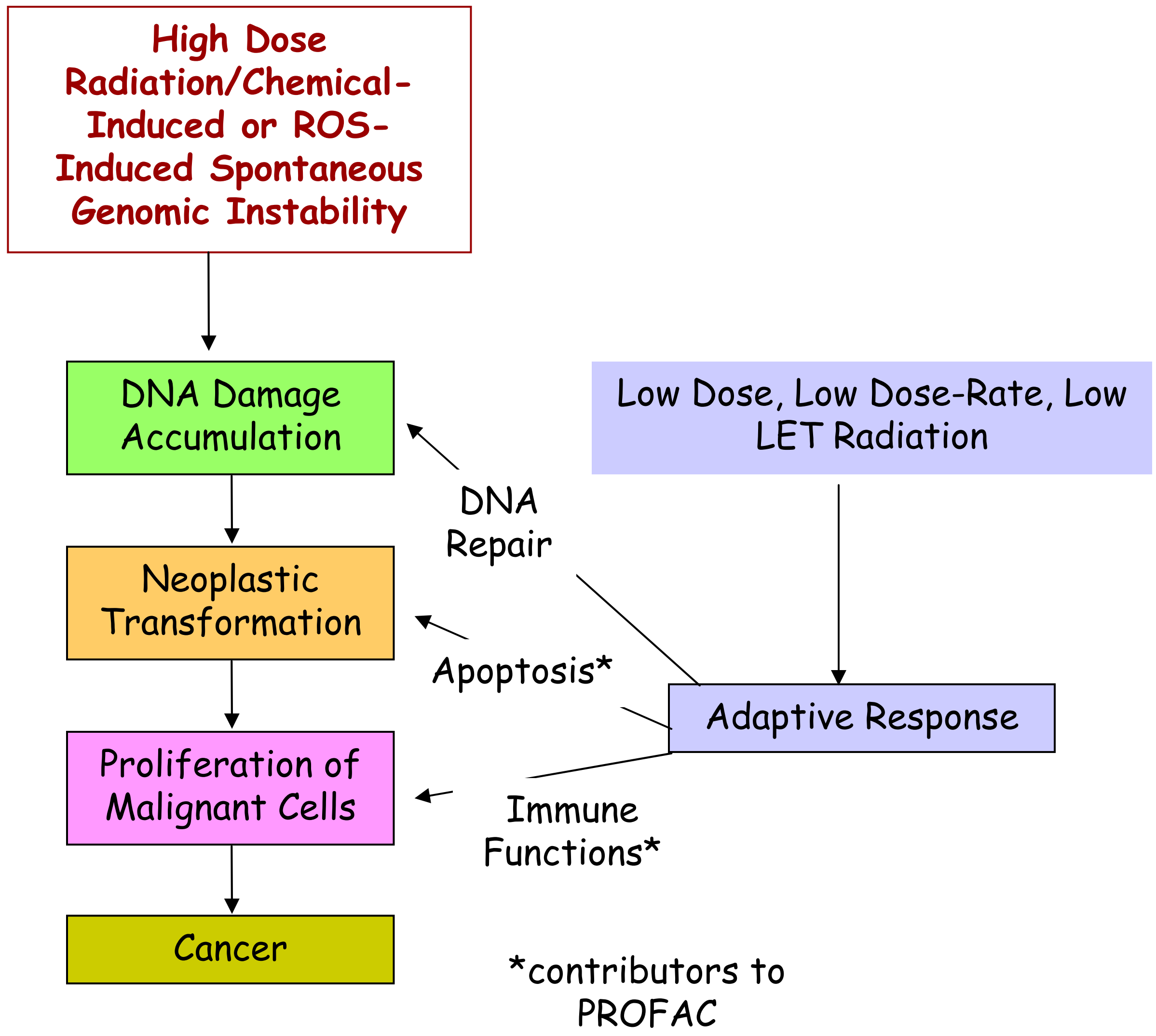
RR – risk after radiation exposure/risk without radiation exposure

Standardized Mortality Ratio (*SMR*)

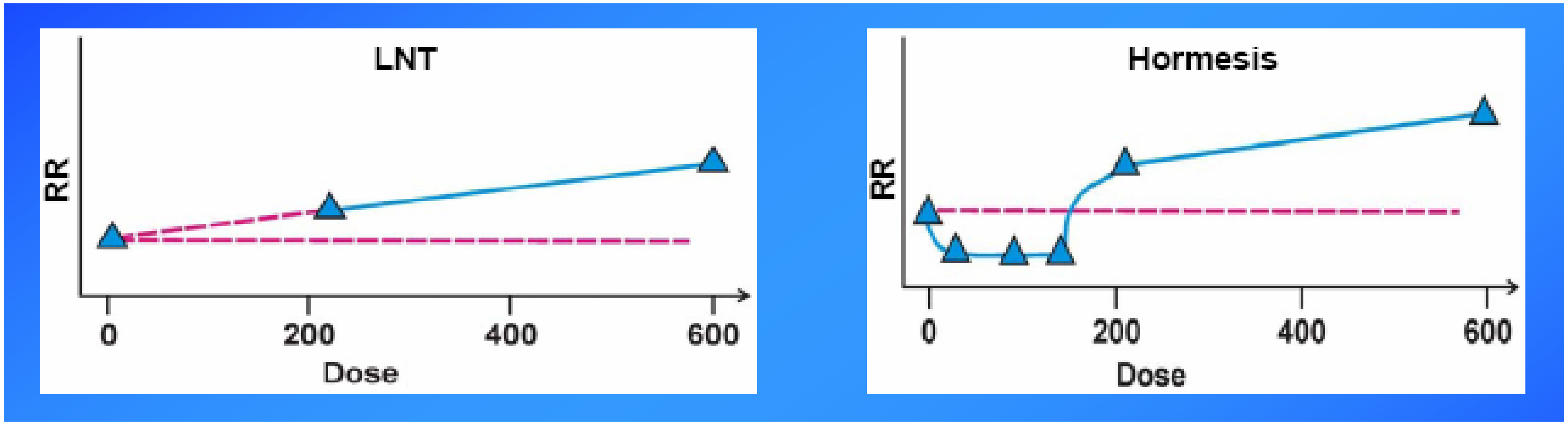
SMR – observed/expected for age-specific mortality

Protection Factor (PROFAC)

PROFAC = 1-*RR* , when RR <1



High Dose Radiation/Chemical-Induced or ROS-Induced Spontaneous Genomic Instability
DNA Damage Accumulation
Neoplastic Transformation
Proliferation of Malignant Cells
Cancer
Low Dose, Low Dose-Rate, Low LET Radiation
Adaptive Response
DNA Repair
Apoptosis*
Immune Functions*
*contributors to PROFAC



The Linear-No-Threshold (LNT) hypothesis denies the presence of a threshold or hormesis processes that decrease cancer risk.

Prevention of radical damage:
Increasing Antioxidants

Repair of damage:
Increasing DNA repair enzymes

Removal of damage:
Stimulating Apoptosis and Immunosurveillance

Approximate human threshold dose for low dose-rate (continuous) low LET radiation exposure*

Effect	Dose-Rate, mSv y^{-1}	Cumulative Dose, Sv
All Cancer	200	-
Lung Cancer	**-**	**15**
Breast Cancer	-	3
Liver Cancer	-	25
Bone Cancer	-	10

*Keirim-Markus, 2002: Atomic Energy 93:836
Parsons, 2003: Biogerontology 4:227.

Lung cancer in German uranium miners

Cumulative WLM	Odds Ratio*
<50	1.00
50-<100	1.23
100-<200	0.91
200-<400	0.94
400-<800	**0.99**
800-<1,600	2.08
1,600-2,911	3.68

← Threshold

*adjusted for age, smoking, asbestos exposure
(Health Phys. 2006: 90:208-216)

CLEAR THRESHOLDS FOR LUNG CANCER

Significantly increased lung cancer is NOT observed at lung doses <1-2 Sv in never smokers

In many cases, radiation appears to protect against spontaneous and smoking-induced lung cancer.

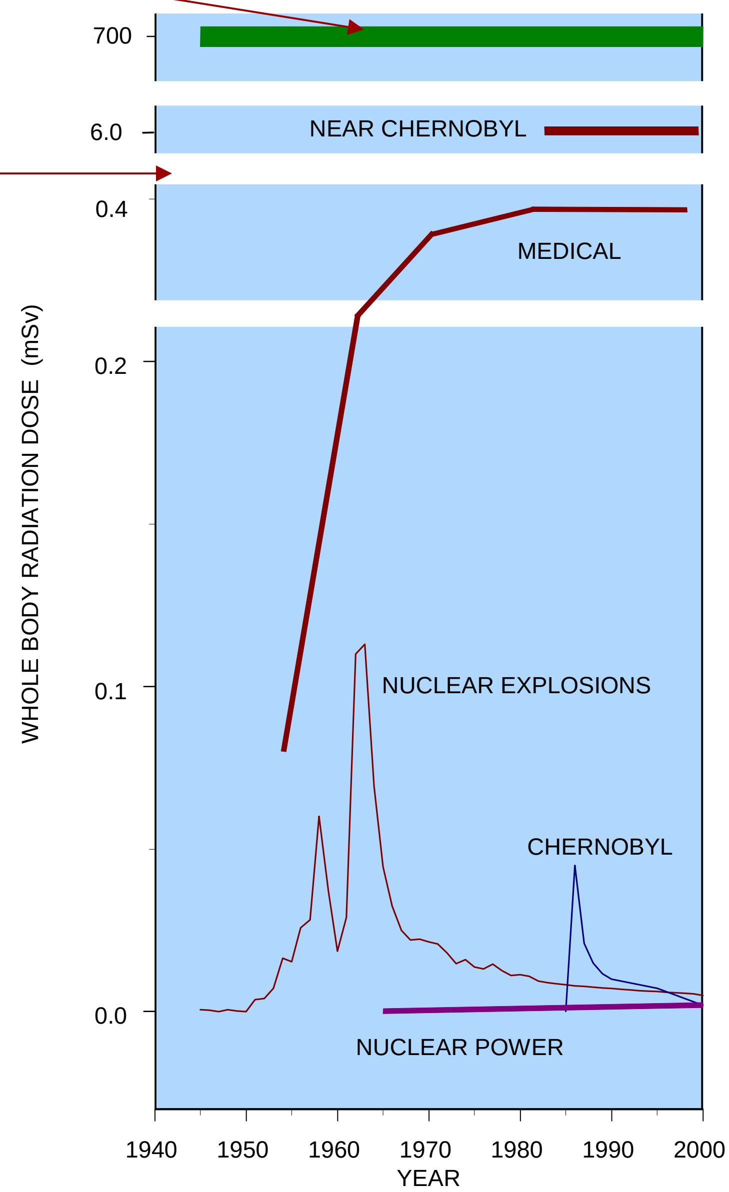
High Dose Background Radiation

Some residents in Ramsar, Iran, 700 mSv/y^{-1}

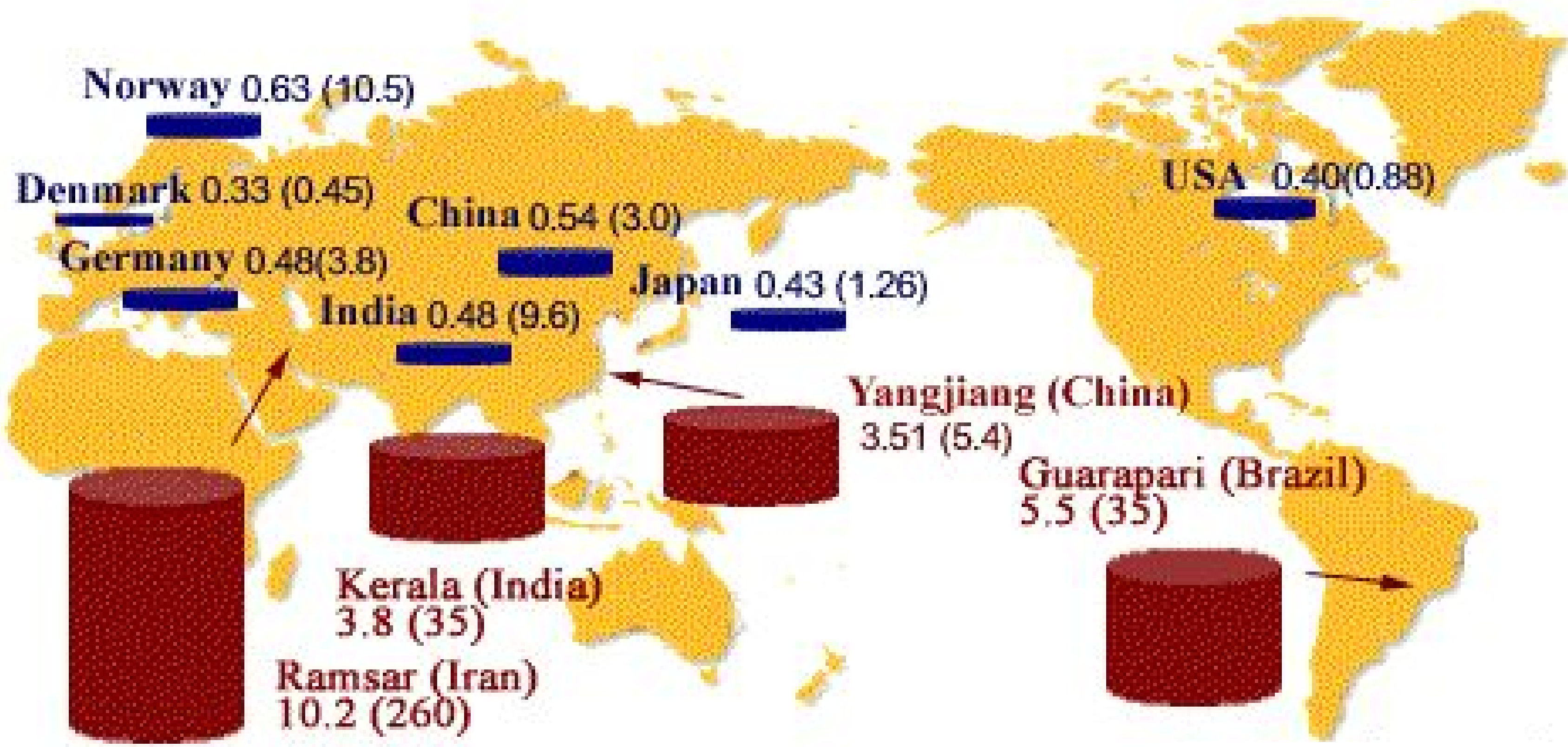
Background global dose average, 2.4 mSv/y^{-1}

Average Global Annual Radiation Doses

(Figure taken from: Jaworowski in 'Entwicklungen im Strahleschutz', 2001)



No increase in lung cancer was found at any of these high background dose regions. PROFAC for lung cancer in Yangjiang, China was 0.19.



Doses are mean (maximum) mGy/y

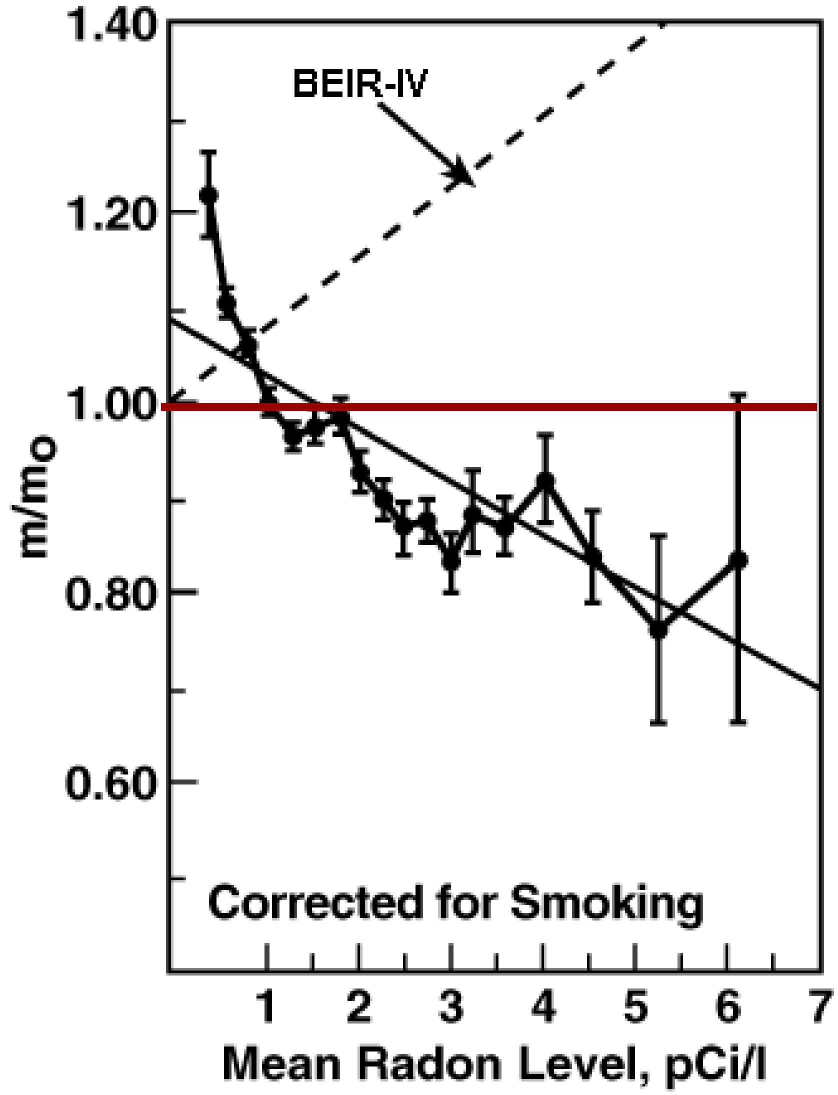
Haynes found a negative correlation between radon and lung cancer in 55 counties of England and Wales; radon levels were highest in Cornwall

Cornwall Districts	SMR	
	Lung Cancer	Other Cancers
Caradon	0.73	1.01
Carrick	0.69	1.00
Kerrier	0.80	0.95
N. Cornwall	0.66	0.92
Penwith	0.77	0.94
Restormel	0.80	1.02

Haynes 1988: Radiat. Prot. Dosim. 25:93

At very low doses, lung cancer incidence is high, decreasing to less than expected in the hormesis dose range, not showing an excess lung cancer risk until about 10 pCi/l.

This is called a U-shaped dose-response curve.



Cohen. 1995. Health Phys. 68:157-174

Radon spa in Misasa, Japan

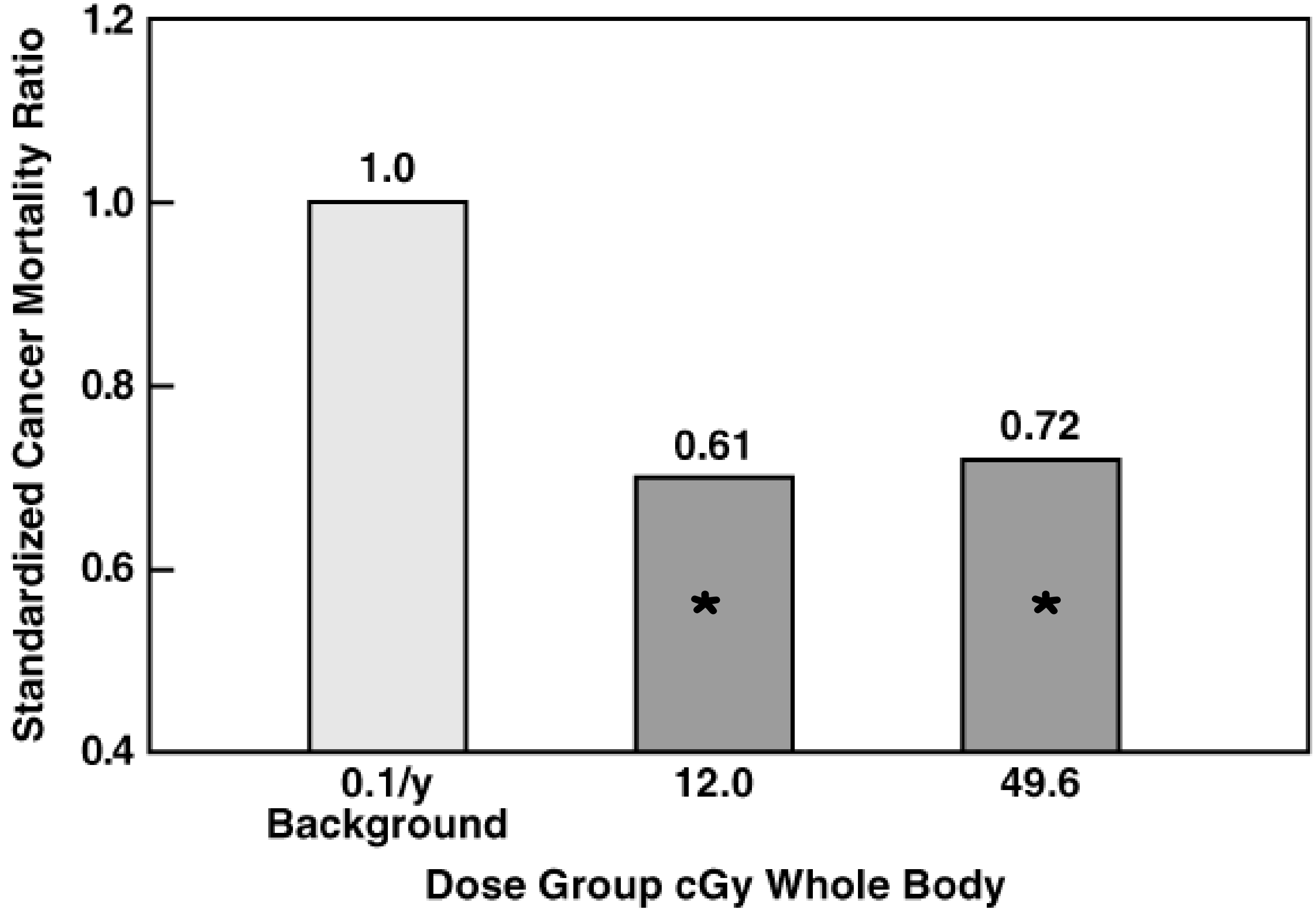
Cancer Site or Type	PROFAC	
	Males	Females
Lung	0.53	0.81

Mifune 1992: J. Cancer Res. 83

PROFAC for lung Cancer at >100 Bq/m^3 was 0.75

Sobue et al. 2000: J. Radiat. Res. 41:81

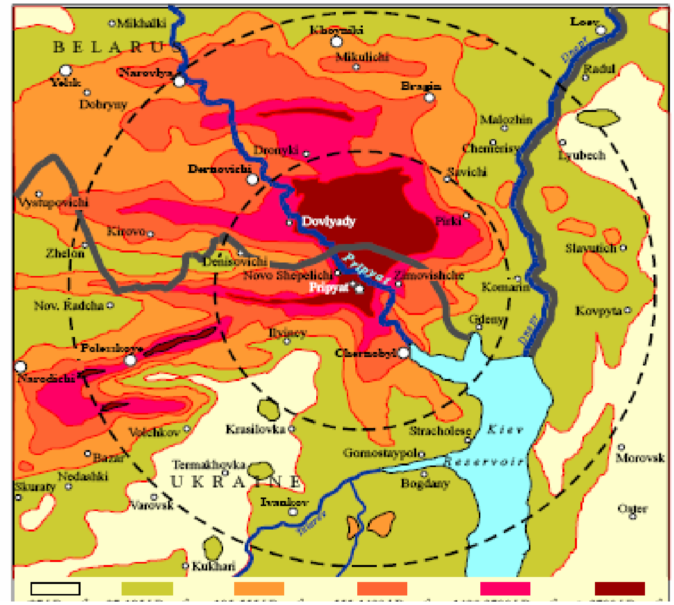
Nuclear Accidents



SMR for cancer in Eastern Urals residents exposed to radiation from a buried waste tank explosion in 1957. *SMR values significantly different ($p < 0.05$)

Chernobyl Fallout Populations

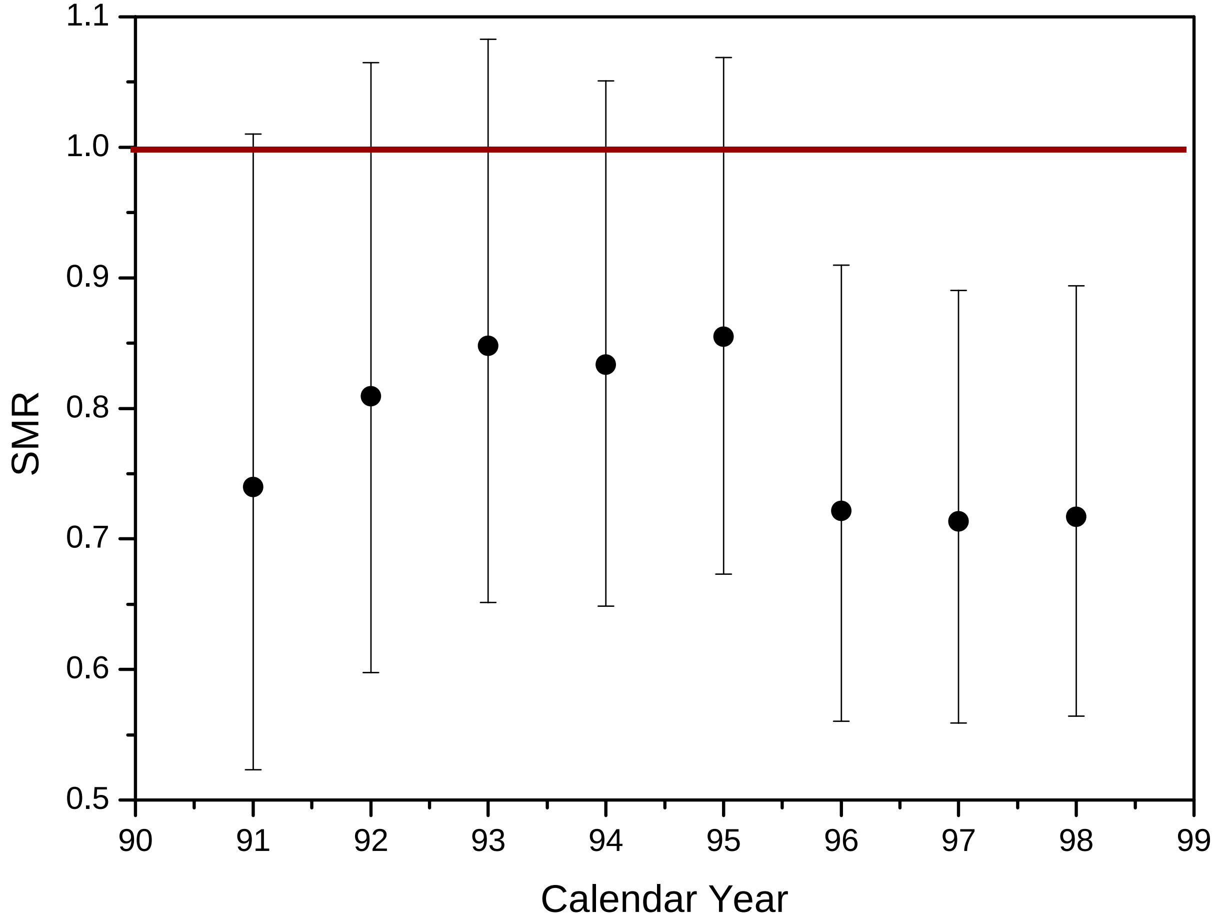
Initially, > 50,000 cancer deaths were predicted over the first 50 years. Current predictions have reduced the risk to 4,000 cancer deaths.



Population	Number of People	Mean Dose (mSv)
Liquidators (1986-1987)	240,000	100
Evacuees (1986)	116,000	33
Low Contaminated Areas	5,200,000	10
High Contaminated Areas	270,000	50

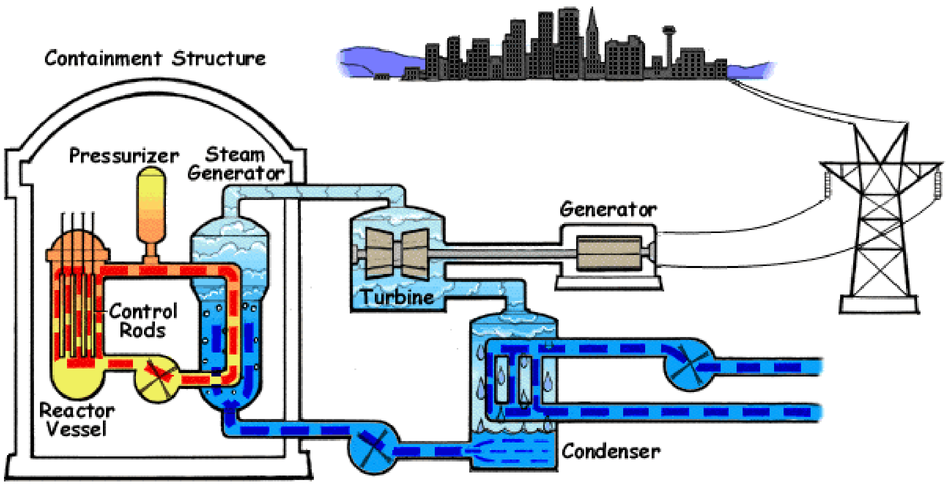
Cardis et al. 2006. J. Radiol. Prot. 26:127-140

Chernobyl alone may have **prevented** thousands of new cancer cases.



SMR for malignant neoplasms among Chernobyl liquidators (redrawn from Health Physics 2001:81:514-521).

Nuclear Worker and Medical Exposure Groups



Nuclear utility workers
(mean cumulative individual doses were <30 mSv)

Epidemiological Study	PROFAC	
	All Cancer	Lung Cancers
US	0.35	0.41
Canada	0.26	0.19-0.60
Japan	0.06	0.28-0.57
UK	0.27	0.35-0.41
Russia	0.07	0.35

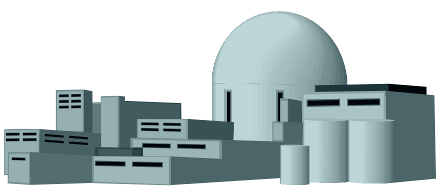
South Korean nuclear workers

Lung Cancer

Dose (mSv)	0	<10	10-50	>50
Number of Workers	6,733	9,193	2,641	1,128
SIR	1.0	0.88	0	1.19
PROFAC	0	0.12	1.00	0

All Cancers

Dose (mSv)	SIR
0	0.95
0-0.1	0.73
0.1-2	0.92
2-10	1.03
10-50	0.66
>50	1.70



The SIR for all cancers and lung cancer was 0.81 and 0.75, respectively.

KAIST

Radiological Technologists (compared to general population)

Years Worked (United States)	*SMR* for lung cancer
1926-1939	0.72
1940-1949	0.76
1950-1959	0.83
1960-1982	0.61

Cancer Causes Control 1998: 9:67-75

Years Worked (Japan)	*SMR* for lung cancer
1897-1933	0.62
1934-1950	0.45

J. Epidemiol. 1999: 9:61-72

Others

Epidemiological Study	PROFAC	
	All Cancer	**Lung Cancers**
German & Canadian Airline Crew	0.21-0.29	0.23-0.72
Canadian Dose Registry	0.21	0.31
Breast Cancer Patients	-	0.50
Swedish Benign Breast Disease	-	0.11
Canadian Fluoroscopy	-	0.06-0.13
Massachusetts Fluoroscopy	-	0.16
Radium Ankylosing Spondylitis	-	0.30-0.33

Healthy Worker Effect (workers were selected in better health and had better health care) is Negated by:

Appropriate Internal Controls

Hormesis not Involving Workers

Hormesis in Experimental Animal Studies

PROFAC values among white females at DOE weapons facilities (unbadged and badged workers are compared)

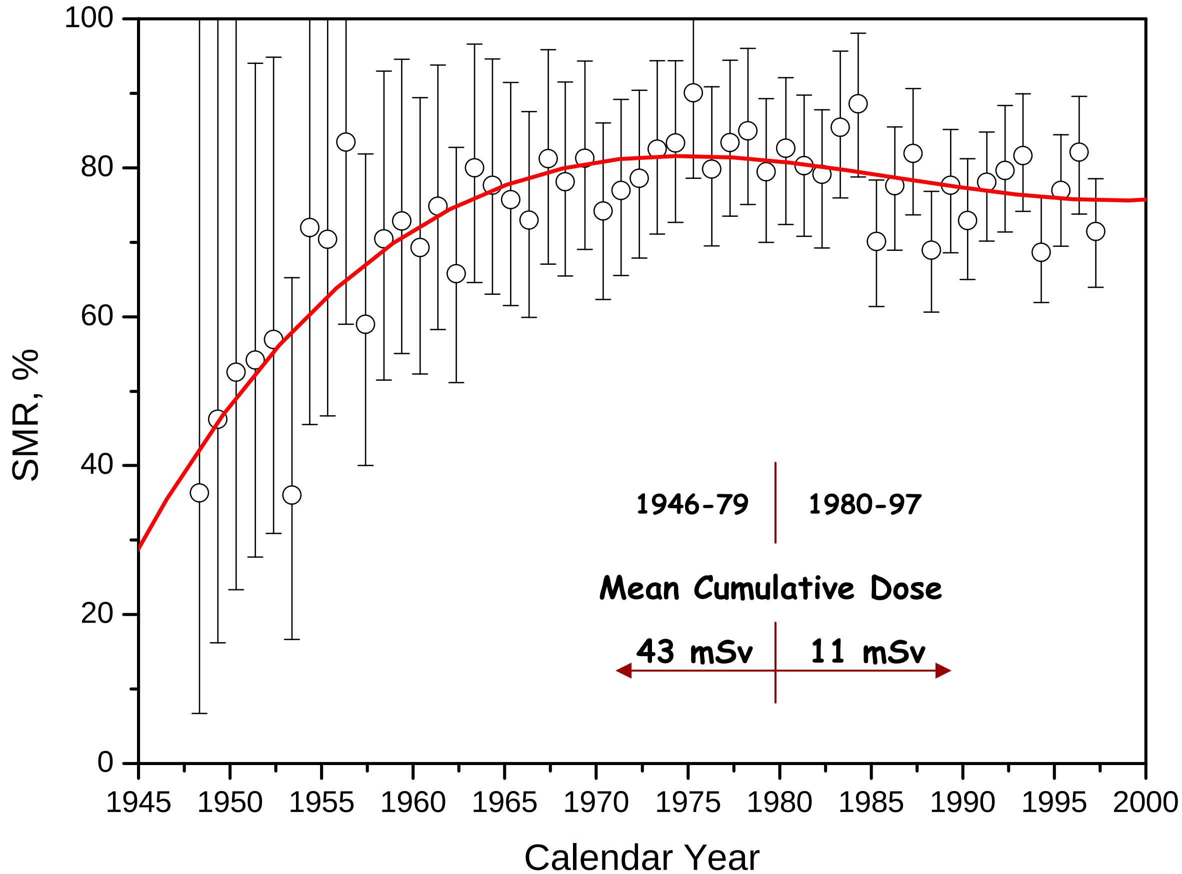
	Cause of Death - PROFAC			
Nuclear Facility	All Causes	All Cancers	Lung Cancer	Breast Cancer
Fernald	0.30	0.23	0.35	0.31
Hanford	0.25	0.22	0.13	0.15
K-25	0.19	0.23	0.20	0.29
Linde	0.03	0.08	0	0.02
Los Alamos	0.33	0.30	0.28	0.20
Mound	0.27	0.11	0.24	0
Pantex	0.35	0.41	0	0.75
Rocky Flats	0.46	0.40	0.30	0.32
Savannah River	0.21	0.27	0.47	0.50
X-10	0.29	0.25	0.20	0.18
Y-12	0.24	0.24	0.05	0.27
Zia	0.26	0.29	0.07	0.30

Wilkinson GS, et al. NIOSH Final Report, 2000

Other epidemiological studies with appropriate internal controls that negate the Healthy Worker Effect

Worker Comparison	PROFAC All Cancer	PROFAC Lung Cancer
UK Radiologists/Physicians	0.29	0.26-1.00
High-Dose/Control Shipyard Workers	0.16	0.07
Monitored/Unmonitored UK Nuclear Utility Workers	0.27	0.39-0.43

Dose-Response



All cause mortality of employees of the United Kingdom Atomic Energy Authority, 1946–97. Radiation workers compared to non-radiation workers (redrawn from *Occupational and Environmental Medicine* 2004;**61**:577-585).

British Radiologists*

Years Joined British Radiological Societies	Tolerance or Exposure Limits	*SMR*	
		All Cancers	Lung Cancer
1897-1920	> 1 Sv $year^{-1}$	1.75	2.46
1921-1935	700 mSv $year^{-1}$	1.24	1.06
1936-1954	70-350 mSv $year^{-1}$	1.12	0.74
1955-1979	<50 mSv $year^{-1}$	0.71	0

*compared to all other UK medical specialties

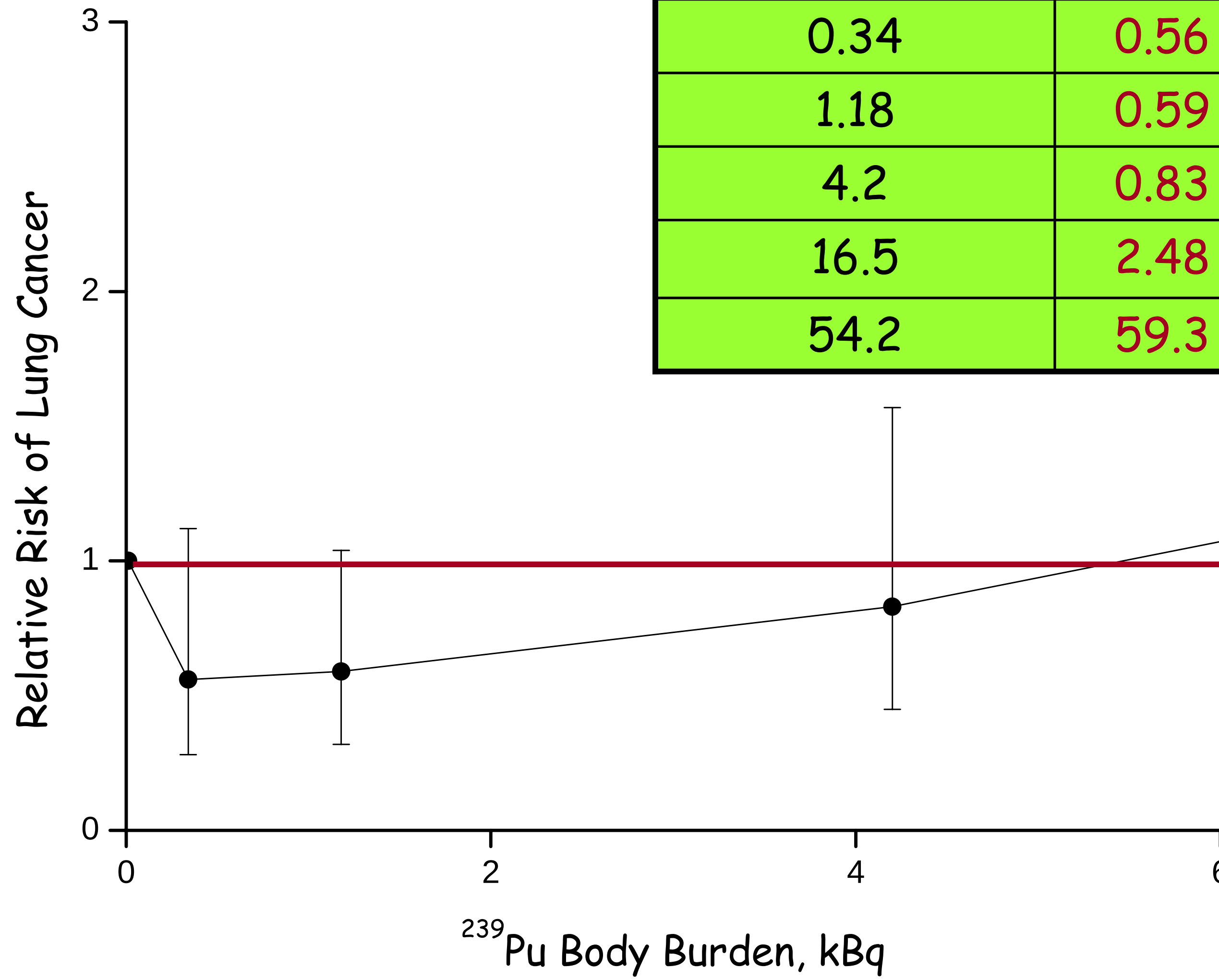
Inhaled $^{239}PuO_2$ in Humans and Rats

Lung cancer in Mayak plutonium workers

Mean ^{239}Pu Body Burden, kBq	*RR*, Lung Cancer
0.010	1.0
0.34	0.56
1.18	0.59
4.2	0.83
16.5	2.48
54.2	59.3

Threshold α-lung dose was 0.8 Gy.

Workers also exposed to a mean of 1 Gy γ-radiation.



(Tokarskaya: 1997 Health Phys. 73:899-905)

Frequency of lung tumors in female Wistar rats following inhalation of $^{239}PuO_2$. The lowest dose for a lung tumor in exposed rats was **0.05 Gy**.

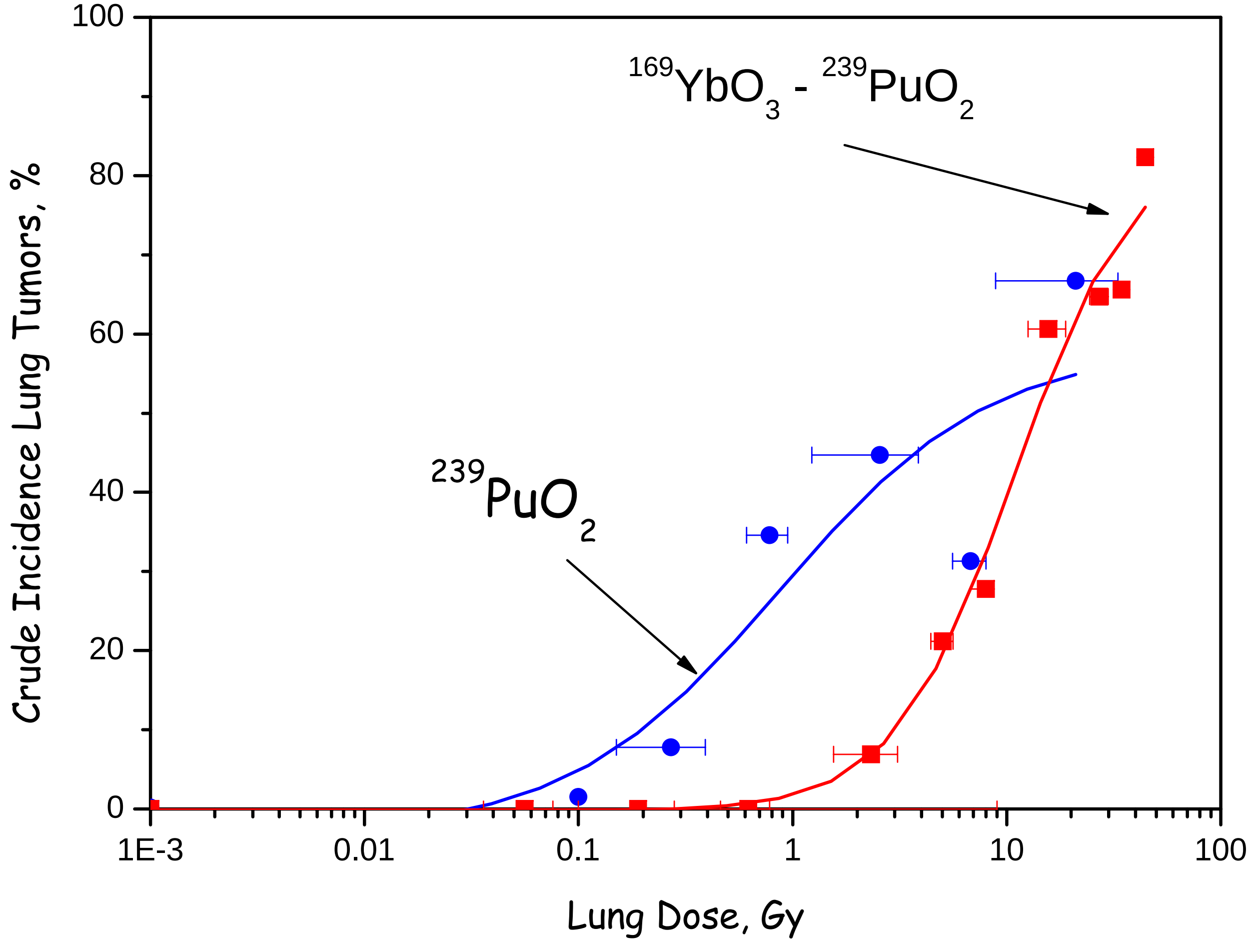
Number Rats	Lung Dose, Gy	Lung Tumors, %
656	0	0.15
131	< 0.10	1.5
51	0.27 ± 0.12	7.8
26	0.78 ± 0.17	34.6
38	2.55 ± 1.32	44.7
16	6.80 ± 1.20	31.3
18	21.0 ± 12.1	66.7

Sanders et al. Radiat. Res. 1976; 68:349

Frequency of lung tumors in female Wistar rats following inhalation of $^{169}YbO_3$-$^{239}PuO_2$. The lowest dose for a lung tumor in exposed rats was **1.5 Gy**. The gamma ray dose to the lung from ^{169}Yb ranged from 0.8-7.0 mGy.

Number Rats	Lung Dose, Gy	Lung Tumors, %
1052	0	0.095
1389	0.056 ± 0.020	0
343	0.19 ± 0.09	0
145	0.62 ± 0.16	0
58	2.32 ± 0.77	6.9
38	5.03 ± 0.60	21.2
18	7.99 ± 0.67	27.8
33	15.7 ± 3.1	60.6
17	27.1 ± 2.7	64.7
32	34.5 ± 2.7	65.6
17	44.4 ± 3.1	82.3

Sanders et al. Intern. J. Radiat. Biol. 1993; 64:417



Crude Incidence Lung Tumors, %
Lung Dose, Gy
$^{169}YbO_3$ - $^{239}PuO_2$
$^{239}PuO_2$
100
80
60
40
20
0
1E-3
0.01
0.1
1
10
100

A low-dose protective apoptosis-mediated (PAM) process, limiting potential cancer formation, may be activated by low-dose, low-LET radiations, which may enhance the elimination of cigarette-induced or alpha irradiation-induced transformed pulmonary cells, thus decreasing lung cancer risk.

Some observations on radio-epidemiological studies of lung cancer

Cigarette smoking is a powerful and complex confounder.

Cessation of smoking would eliminate nearly all radiation-related lung cancer due to low LET radiation.

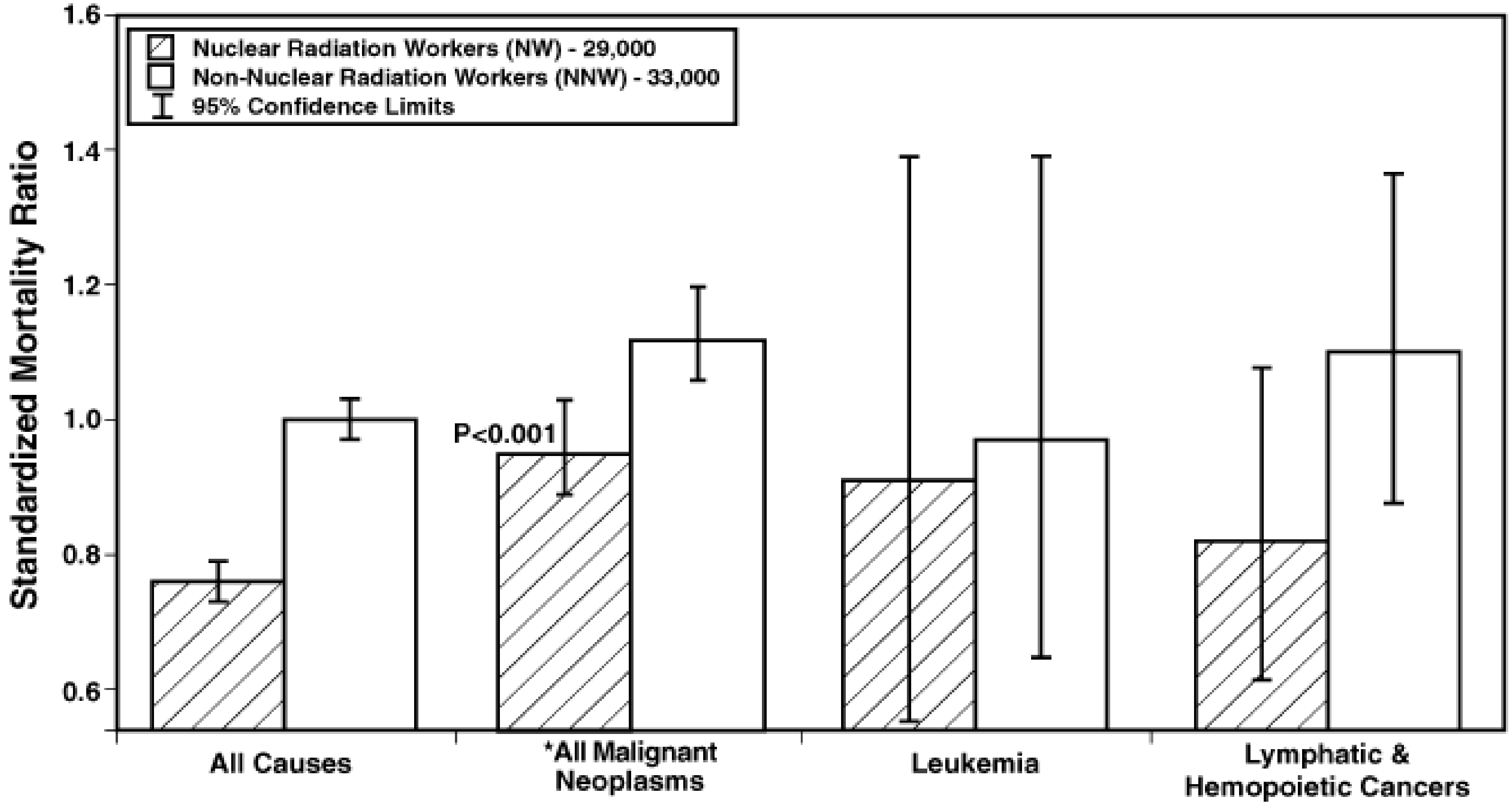
The lack of lung cancer at doses <1 Sv in never smokers or *RR* values <1 in smokers are often not discussed.

Radiation hormesis in the lung is clearly demonstrated in many human populations exposed to ionizing radiation.

The use of the LNT hypothesis, combining of dose groups, and not presenting data for all dose points 'hides' evidence of radiation hormesis.

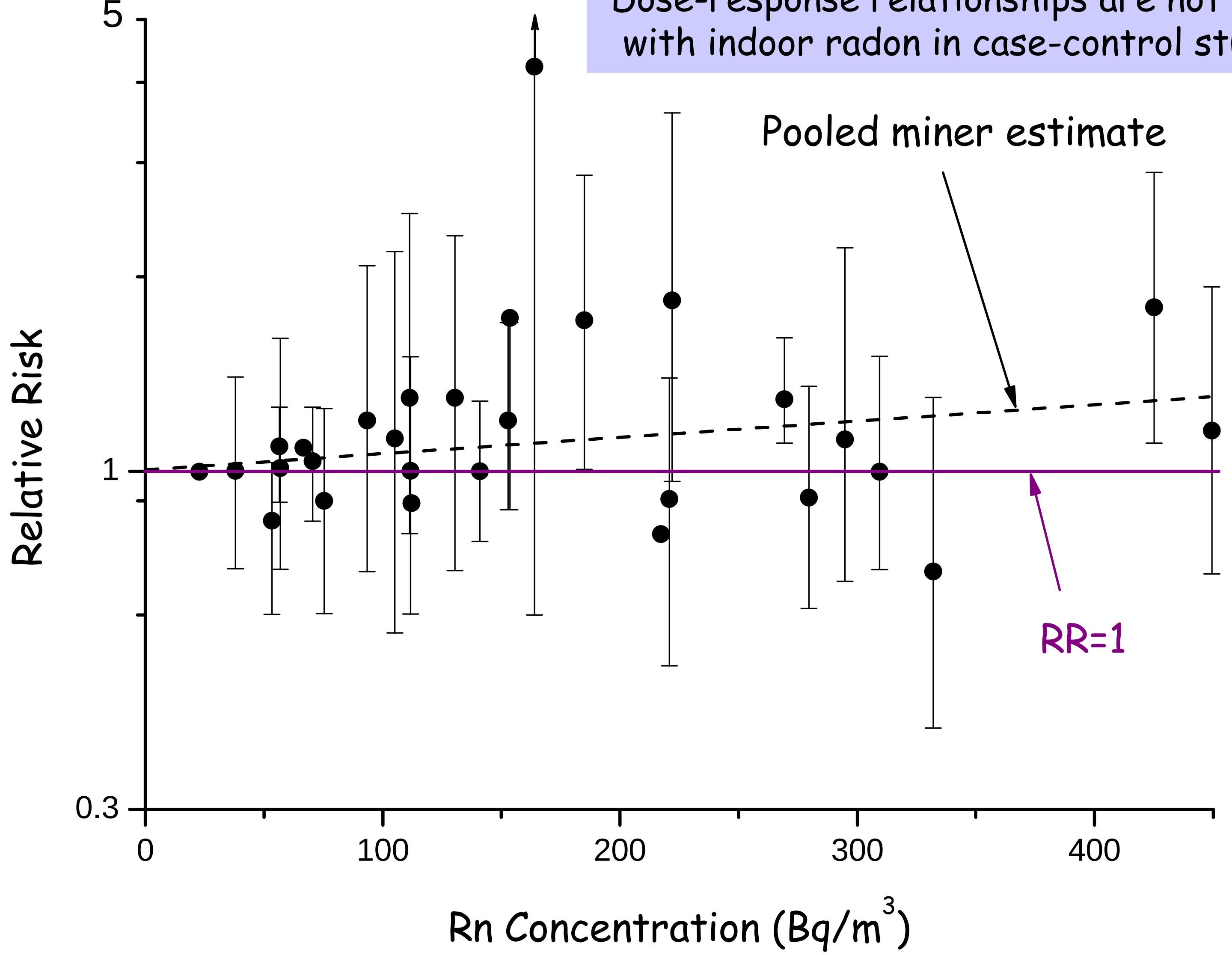
Thanks to Sohn Sukwhun, Ph.D. candidate, Professor Heecheon No and Professor Gyuseong Cho, Department of Nuclear and Quantum Engineering, KAIST, Daejeon, Republic of Korea

Negates HWE



SMR for causes of death among US shipyard workers. Cumulative doses in nuclear workers ranged from 5->400 mSv (Matanoski 2001).

Dose-response relationships are not found with indoor radon in case-control studies



Meta-analysis of lung cancer from studies of indoor radon in Finland, Sweden, China, Canada and the U.S. (redrawn from Lubin et al. 1997. JNCI 89:49).