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Sources of Data of Stochastic Effects of Radiation

Michael K O'Connor, Ph.D.
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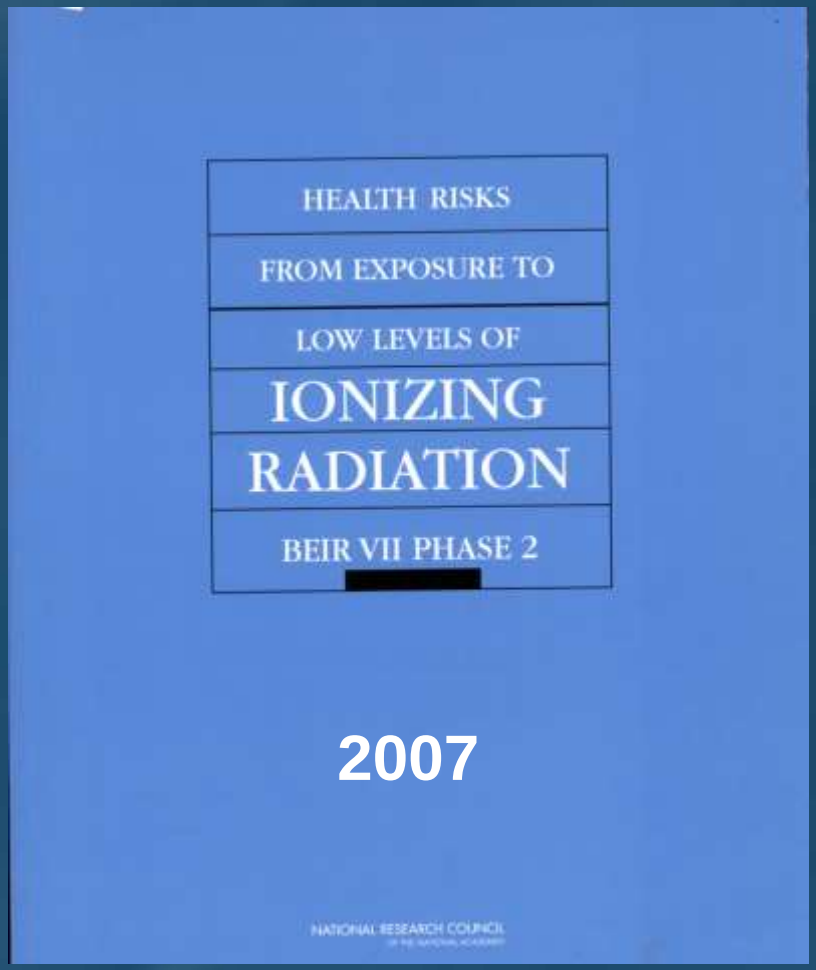
Biological Effects of Ionizing Radiation (BEIR)



National Academy of Science – National Research Council

Sources of data

- Environmental Radiation Studies
- Occupational Radiation Studies
- Medical Radiation Studies
- Atomic bomb survivor Studies

Sources of Data of Stochastic Effects of Radiation

Environmental Radiation Studies

Populations living near nuclear facilities

"..no increased risk…with radiation exposure"

Populations exposed to atomic bomb testing

"..some studies (4 out of 10) show some effect"

Chernobyl

High incidence of thyroid cancer

"..no evidence of an increase in any solid cancer type to date"

Natural background (China / India)

"..did not find higher disease rates in geographical areas with high background levels.."

Cancer Mortality in Moderate/High Background Radiation Area of Yangjiang, China, 1979-1995

- Background radiation
  6.4 mSv / year
- 20-year study in 125,079 subjects
- Risk estimate was negative
  i.e. radioprotective effect
- Conclusion: lower mortality, but <u>not statistically significant</u>

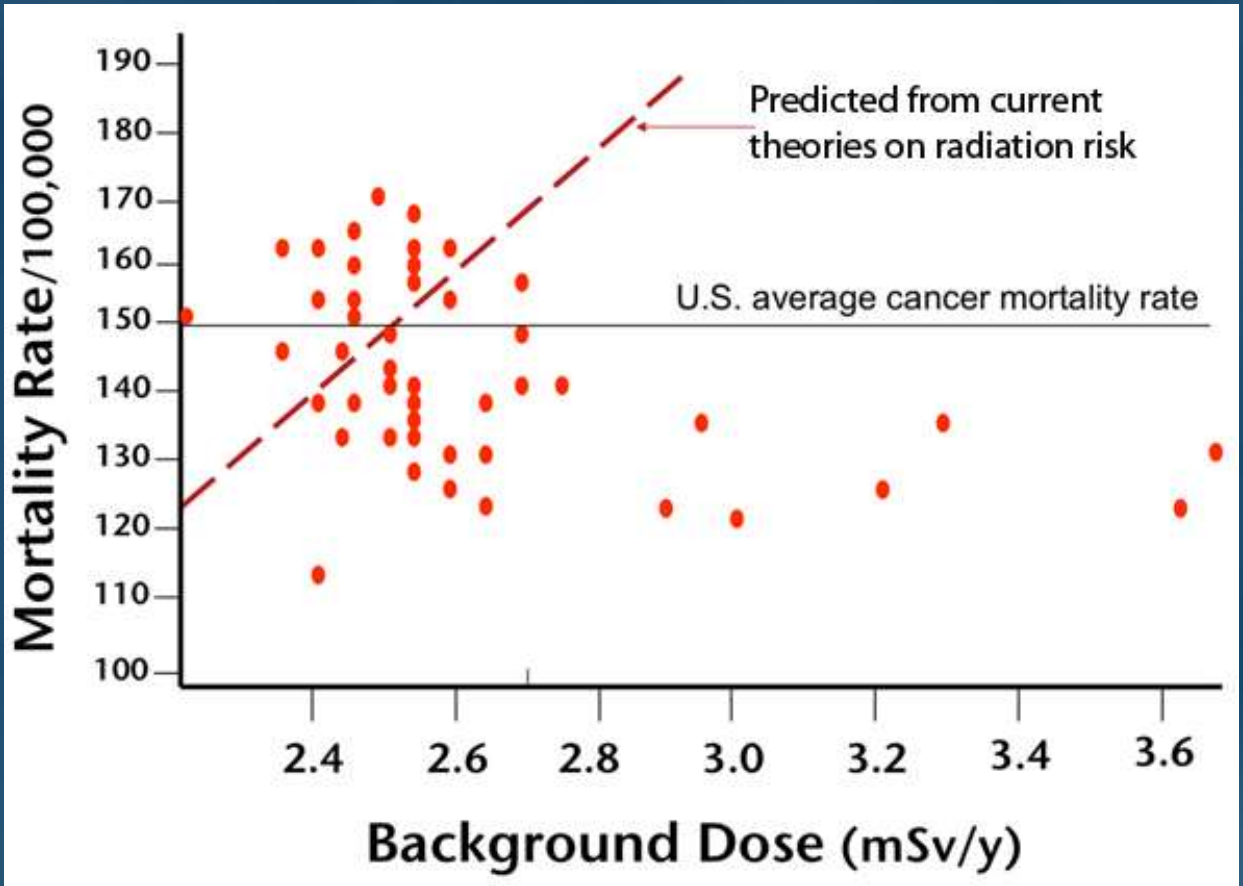
(Tao et al, Zhonghua Yi Xue Za Zhi, 1999; 79: 487-492)

Most radioactive place in the world - Ramsar, Iran (due to Radium-226)
Background radiation = 100 – 260 mSv / year

No epidemiological evidence of adverse affects

Lymphocytes from residents demonstrate fewer induced chromosome aberrations

Background Radiation: Differences on Annual Cancer Mortality Rates/100,000 for each U.S. State over a 17-Year Period



States with significantly higher doses (e.g. Colorado), have lower cancer rates than States with much lower average doses like Georgia, and vice versa. (Frigerio and Stowe, 1976)

Sources of data

- Environmental Radiation Studies
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- Atomic bomb survivor Studies

Occupational Radiation Studies on Workers in the Nuclear Power Industry

U.S. – 9 studies
U.K. – 6 studies
Canada – 1 study
France – 1 study

Six large combined cohort studies
Combined study population > 500,000 subjects with 30- 40 years of follow-up

Cumulative dose levels: 30-60 mSv

Occupational Radiation Studies on Workers in the Nuclear Power Industry

"….in most cases, rates for all causes and all cancer mortality in the workers were <u>substantially lower</u> than the reference populations."

Findings explained as "healthy worker effect"

(U.S. Academy of Science, BEIR VII, 2007)

Participants 407 391 workers individually monitored for external radiation with a total follow-up of 5.2 million person years.

BMJ Helping doctors make better decisions

PAPER

Risk of cancer after low doses of ionising radiation: retrospective cohort study in 15 countries

BMJ 2005; 331 doi: 10.1136/bmj.38499.599861.E0 (Published 7 July 2005)
Cite this as: *BMJ* 2005;331:77

Risk of cancer after low doses of ionising radiation: retrospective cohort study in 15 countries

E Cardis, M Vrijheid, M Blettner, E Gilbert, M Hakama, C Hill, G Howe, J Kaldor, C R Muirhead, M Schubauer-Berigan, T Yoshimura, F Bermann, G Cowper, J Fix, C Hacker, B Heinmiller, M Marshall, I Thierry-Chef, D Utterback, Y-O Ahn, E Amoros, P Ashmore, A Auvinen, J-M Bae, J Bernar Solano, A Biau, E Combalot, P Deboodt, A Diez Sacristan, M Eklof, H Engels, G Engholm, G Gulis, R Habib, K Holan, H Hyvonen, A Kerekes, J Kurtinaitis, H Malker, M Martuzzi, A Mastauskas, A Monnet, M Moser, M S Pearce, D B Richardson, F Rodriguez-Artalejo, A Rogel, H Tardy, M Telle-Lamberton, I Turai, M Usel, K Veress

"risk estimate for Canada is the largest…. Only when we excluded Canada was the excess relative risk no longer significantly different from zero (0.58, −0.22 to 1.55)."

"….our estimate of risk of leukemia is not significantly different from zero…"

Canada's Nuclear Regulator

Verifying Canadian Nuclear Energy Worker Radiation Risk:

A Reanalysis of Cancer Mortality in Canadian Nuclear Energy Workers (1957-1994)

SUMMARY REPORT

INFO-0811

June 2011

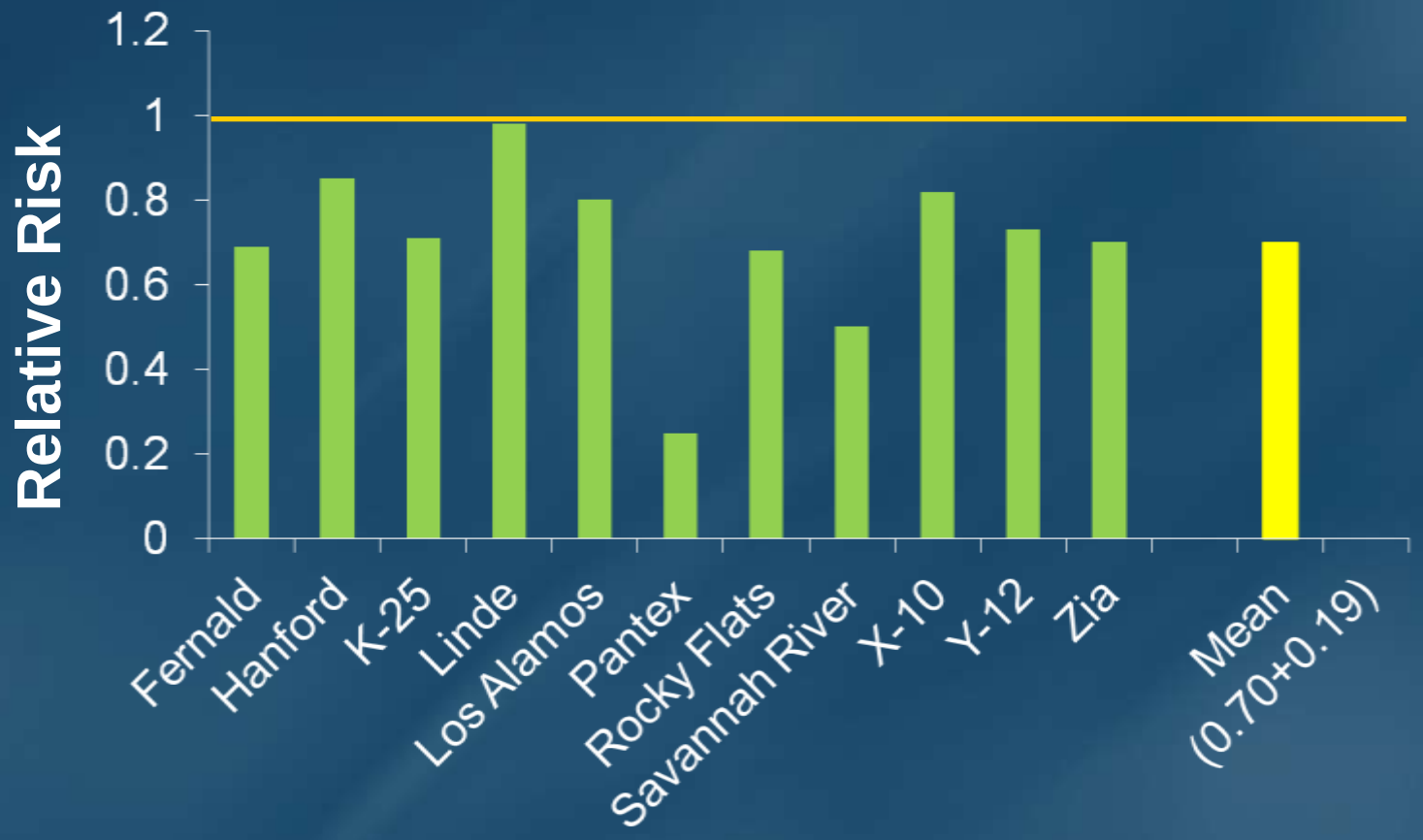
Conclusions and Path Forward

- The CNSC's reanalysis confirms that there is no increased cancer risk among any Canadian nuclear power plant workers for any time period or for AECL NEWs first employed since 1965.
- While the data suggests an increased solid cancer mortality risk for AECL NEWs first employed before 1965 (1956-1964), a comparison using the Canadian Mortality Database shows lower rates of all causes of death and cancer mortality for this group than for the general Canadian population.

Breast Cancer Mortality

Study of 67,979 women who worked with radiation in Nuclear Weapons facilities before 1980 (relative to unmonitored women in same facilities)

Expected mortality = 18,106 deaths / Observed mortality = 13,671 deaths



Wilkinson et al. Nat Inst Occup Safety Health, June 2000

Sources of data

- Environmental Radiation Studies
- Occupational Radiation Studies
- Medical Radiation Studies
- Atomic bomb survivor Studies

Medical Radiation Studies

Focus on therapeutic studies

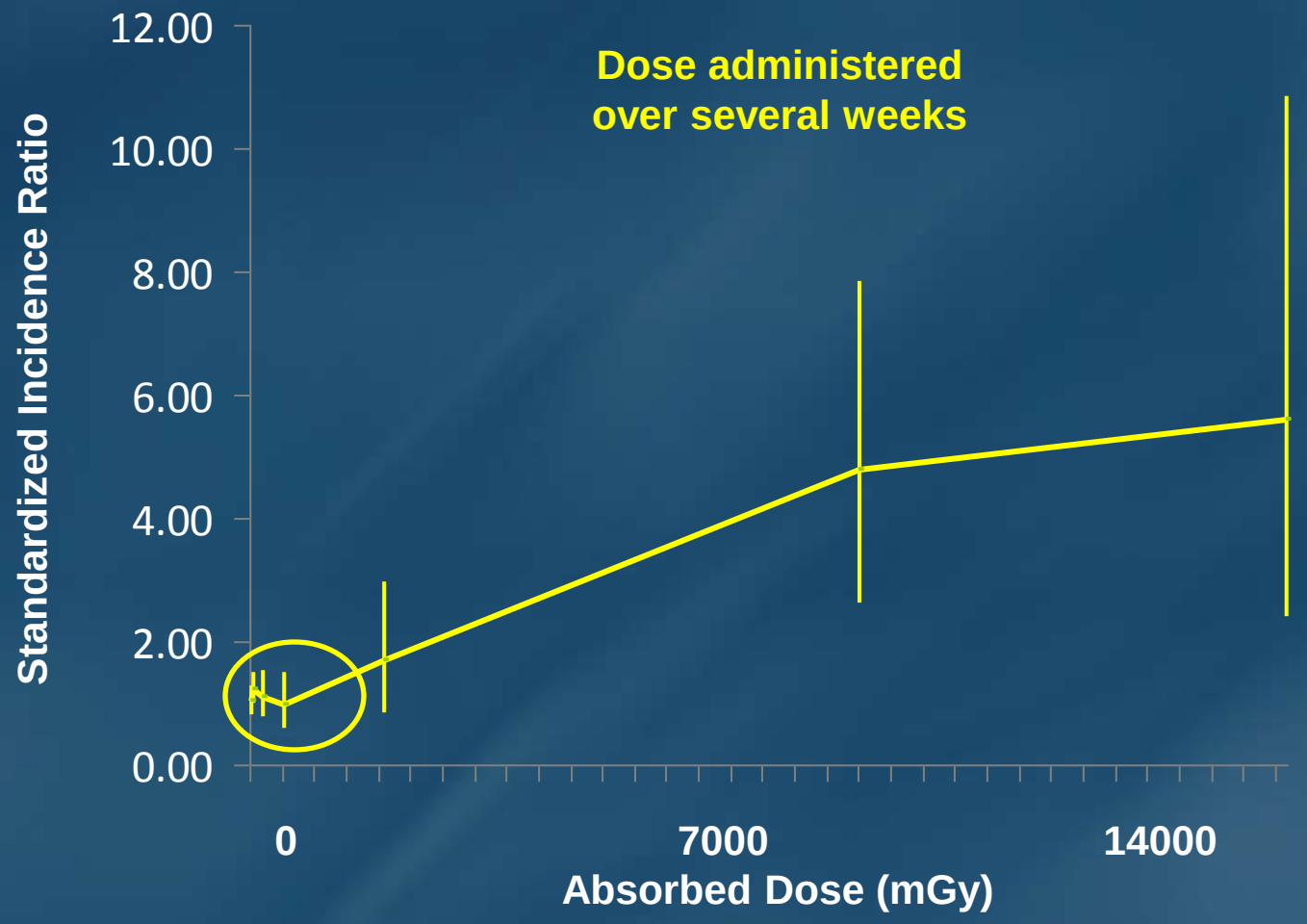
…most of the information comes from studies of populations with medium to high doses

Lung Cancer – 9 studies, 40,000 subjects

Breast cancer – 11 studies, 20,000 subjects

Breast Cancer Risk after Radiotherapy for skin hemangioma in infancy (<18 months of age)

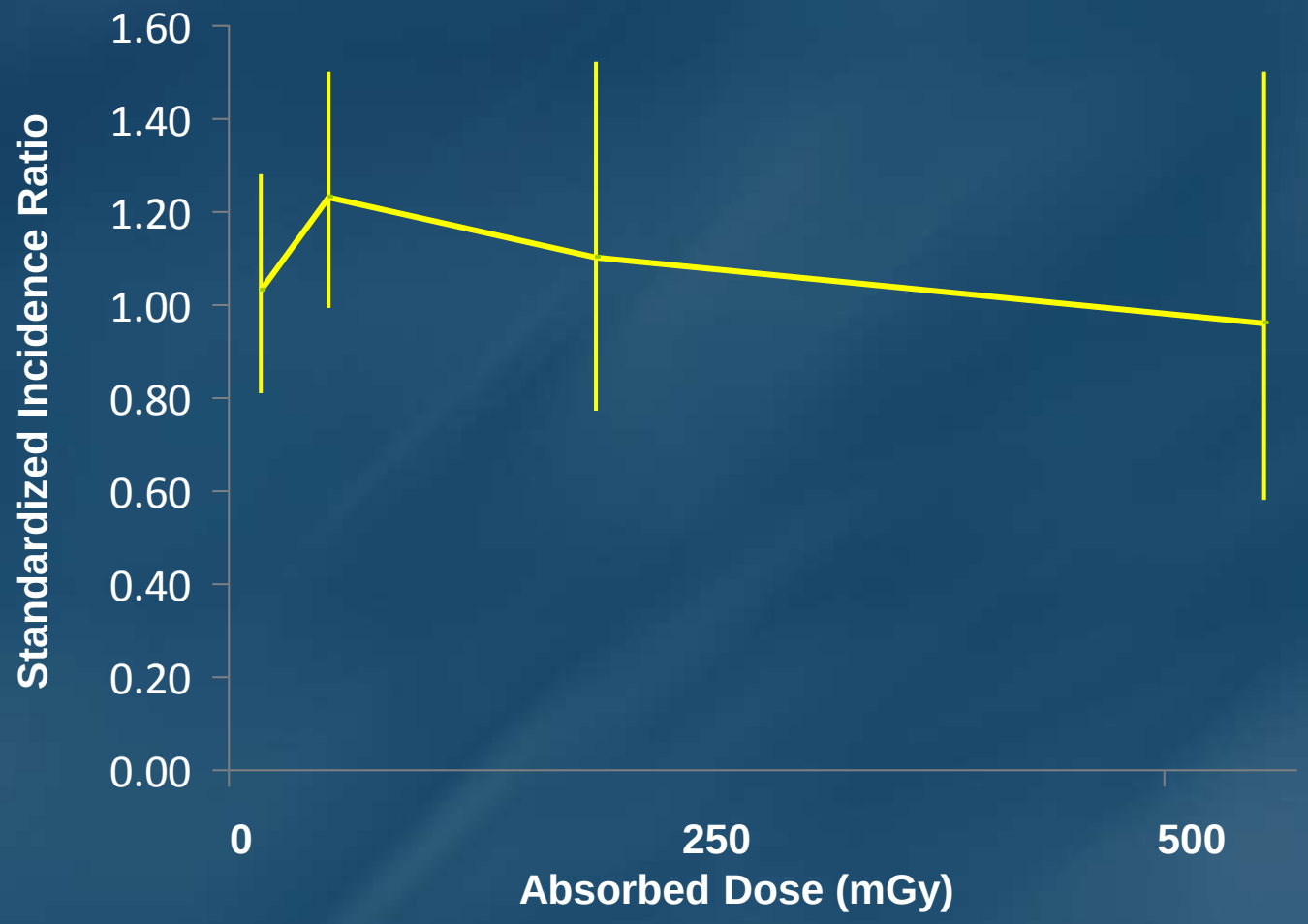
Pooled analysis of 17,202 Infants – Mean follow-up of 45 Years



Lundell et al, Radiation Research 1999; 151: 626-632

Breast Cancer Risk after Radiotherapy in Infancy

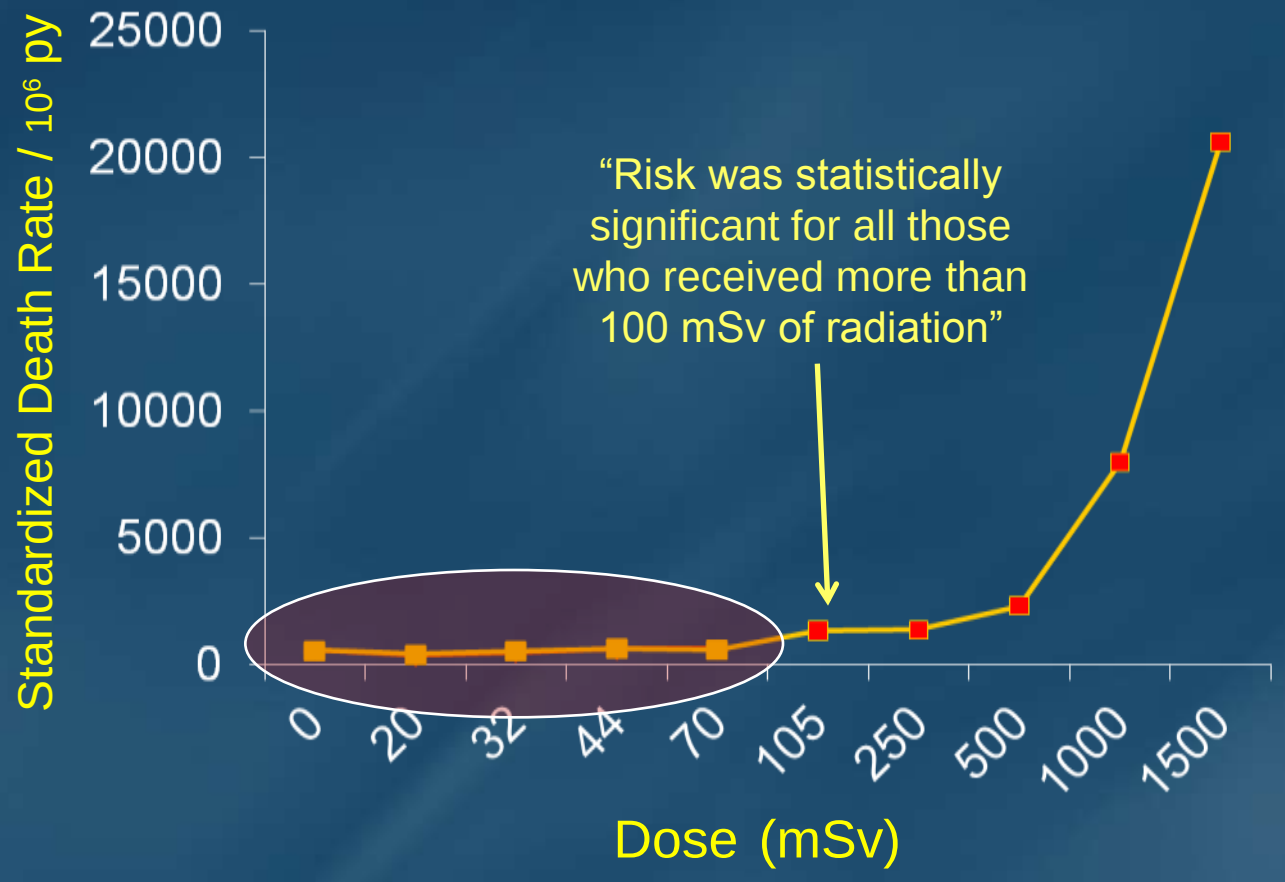
Pooled analysis of 17,202 Infants – Mean follow-up of 45 Years



Lundell et al, Radiation Research 1999; 151: 626-632

Mortality from Breast Cancer after Irradiation during Fluoroscopic Examinations in Patients being treated for Tubercolosis

31,710 women treated between 1930 - 1952
40-year follow-up
Age range 10-40 years



Miller AB et al, NEJM 1989; 321: 1285-1289.

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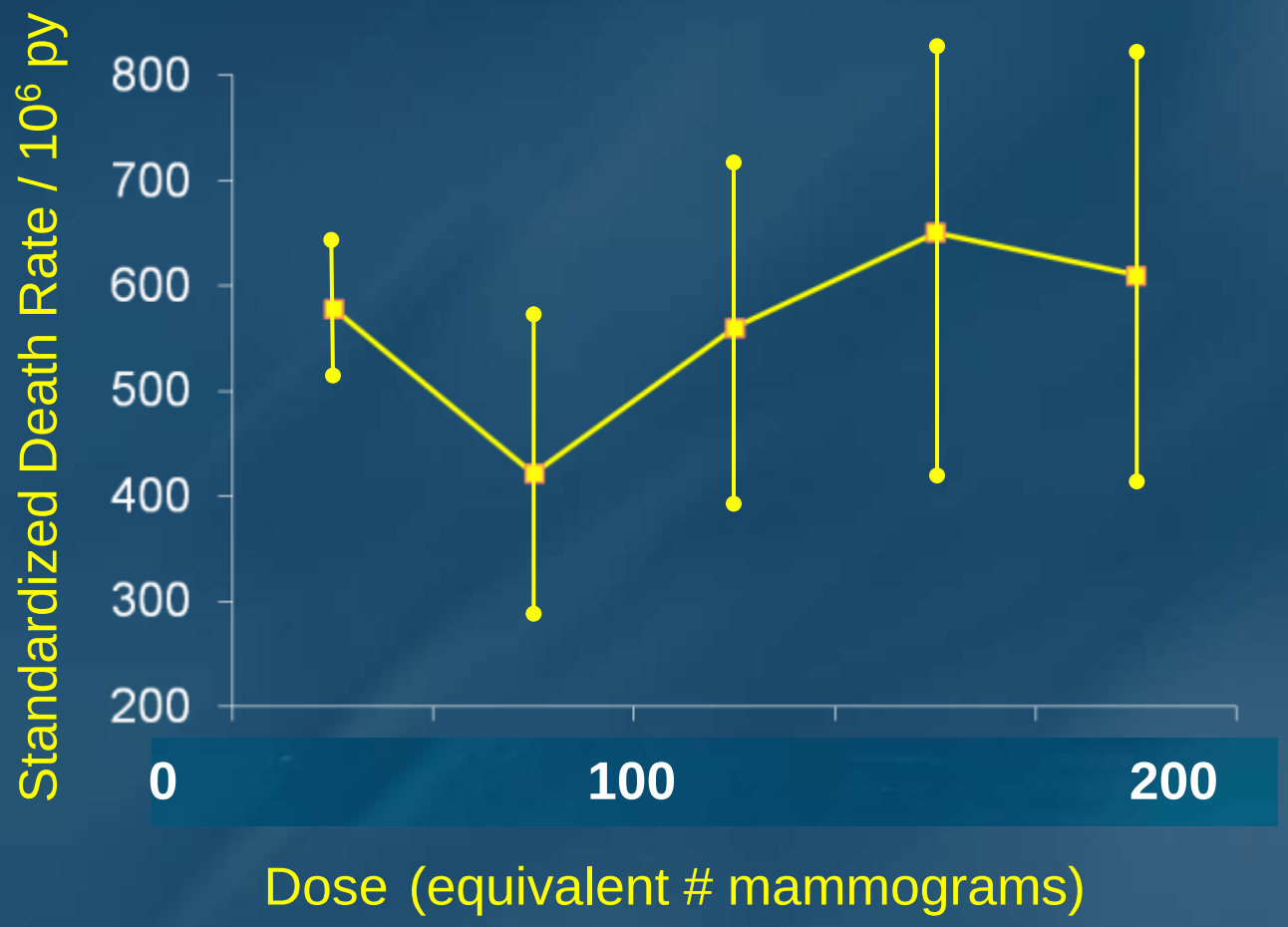


Sources of data

- Environmental Radiation Studies
- Occupational Radiation Studies
- Medical Radiation Studies
- Atomic bomb survivor Studies

Atomic Bomb Survivor Studies

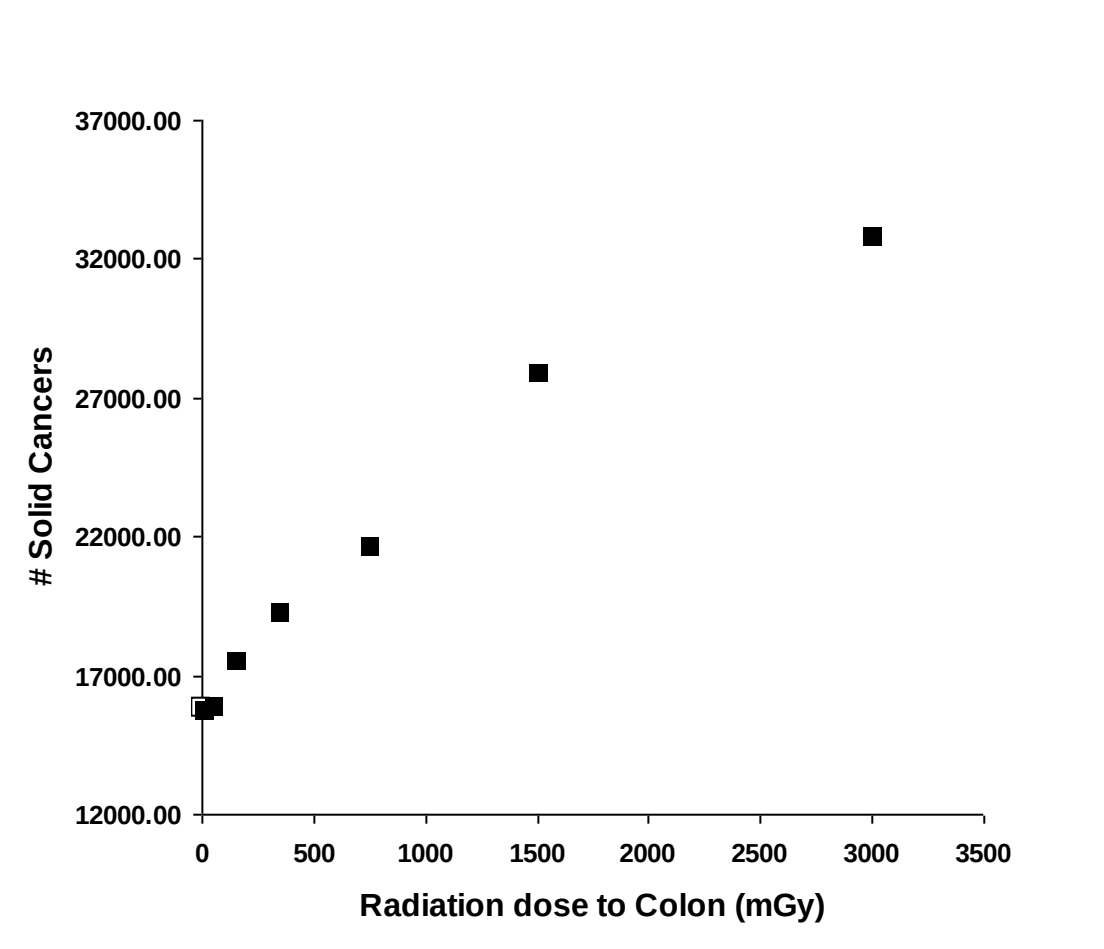
- 120,000 survivors
- Monitored over 60 years
- Dose range

Dose range	37,000	0-5 mSv
	32,000	5-100 mSv
	17,000	100 mSv – 2000 mSv

Sources of data used in BEIR VII
Atomic bomb survivor Studies

Data from Table 4, Preston et al, 2007

 # solid cancers adjusted to per 100,000 people



Preston et al, Rad Res 2007;168: 1-64.
(Radiation Effects Research Foundation)

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Atomic bomb survivor Studies

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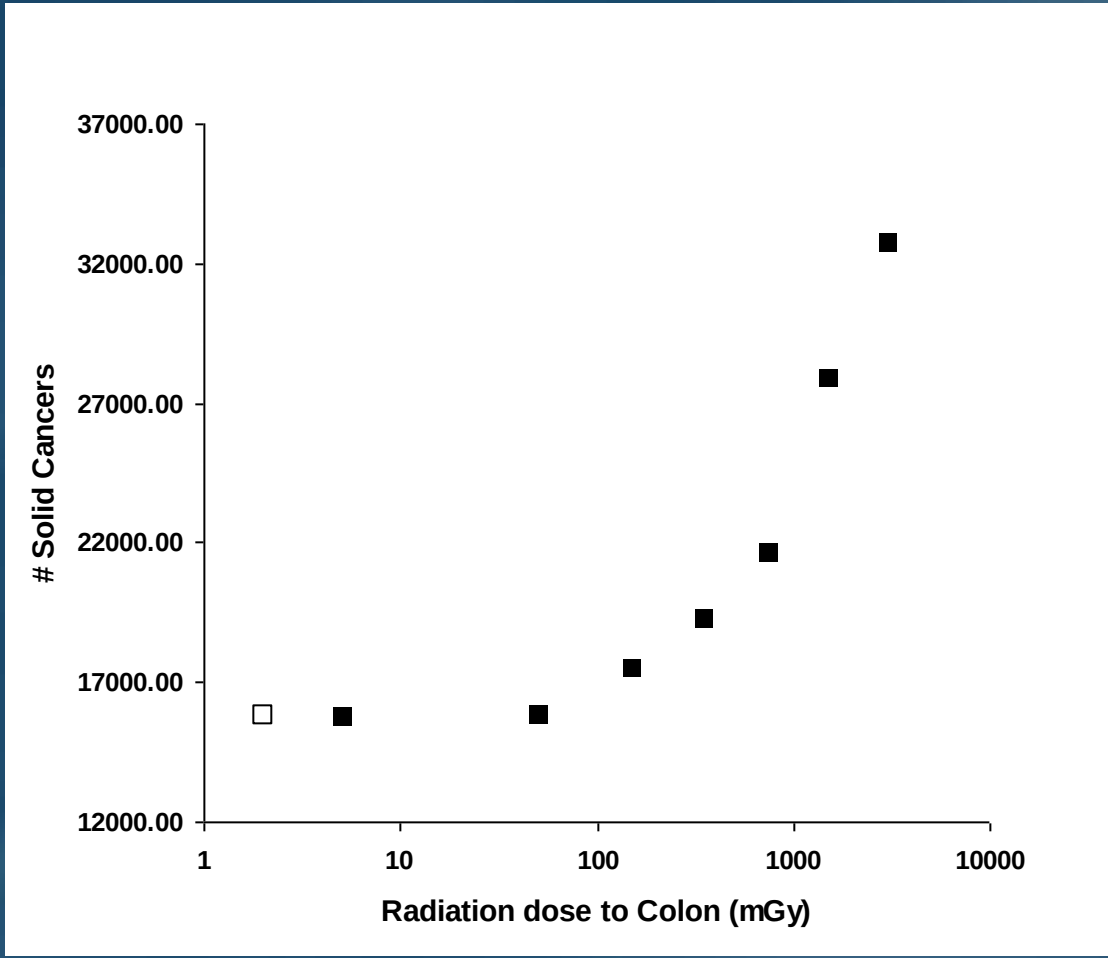


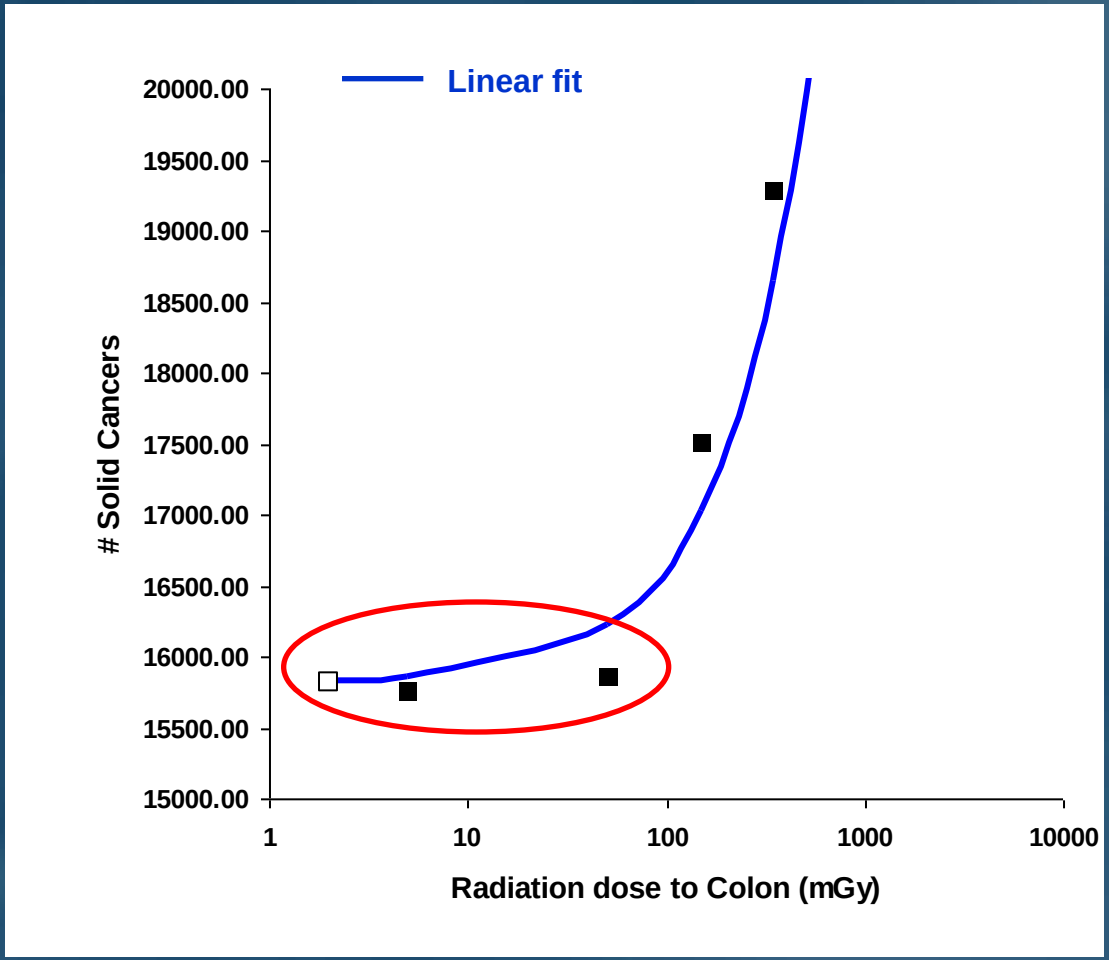
Preston et al, Rad Res 2007;168: 1-64.
(Radiation Effects Research Foundation)

Sources of data used in BEIR VII
Atomic bomb survivor Studies

Data from Table 4, Preston et al, 2007

solid cancers adjusted to per 100,000 people

"Based on fitting with lower threshold, best estimate of threshold was 40 mGy with upper bound of 85 mGy (90% CI) However model not significantly better than LNT"



Preston et al, Rad Res 2007;168: 1-64.
(Radiation Effects Research Foundation)

BRCA1/2 Gene Mutation and Radiation
Are Mammograms safe for these patients?

~50% of studies indicate Yes

MSK Cancer Center – 162 patients
Goldfrank D et al. CEBP

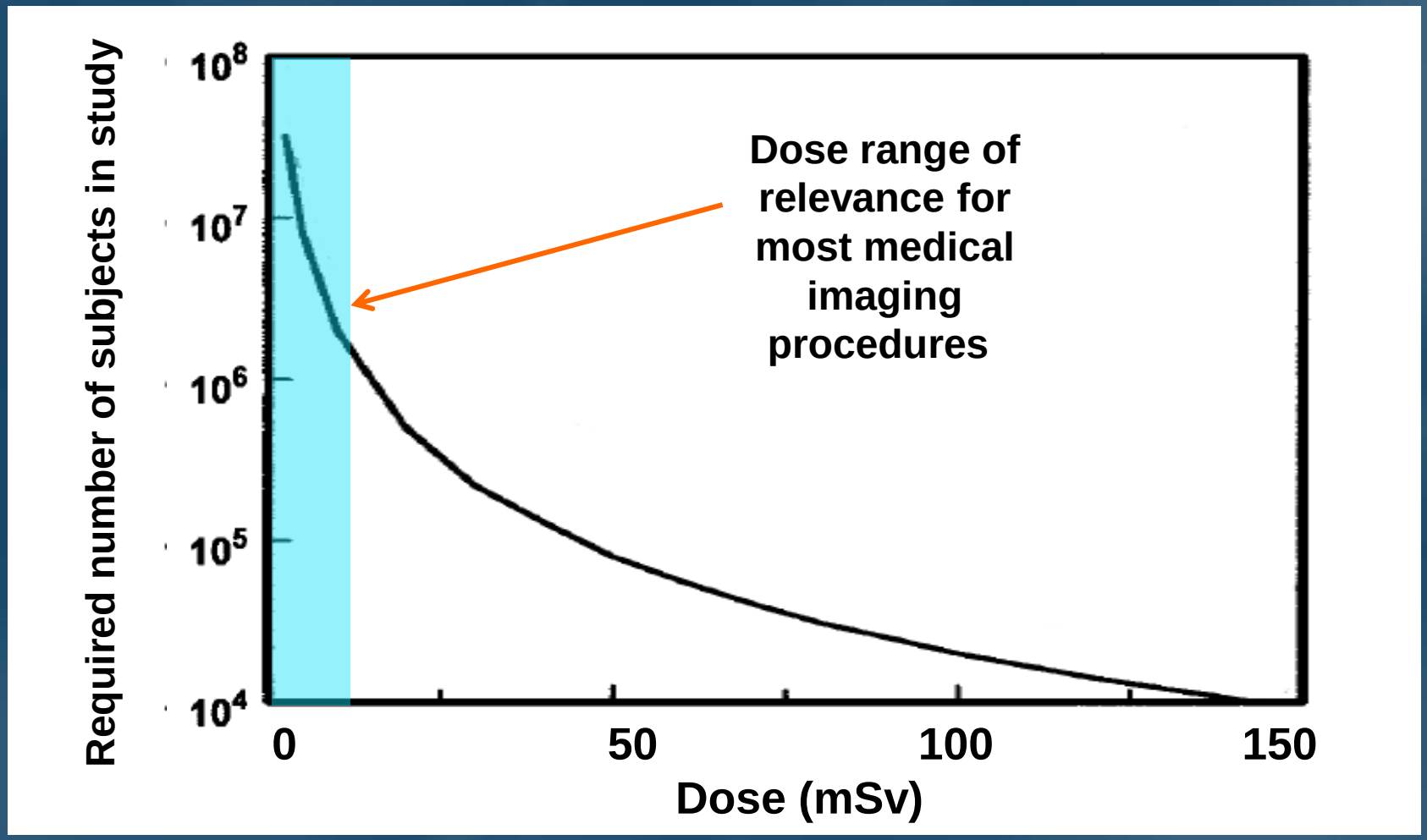
Canadian Study – 1600 patients
Narod SA et al, Lancet 2006; 7: 402-406

~50% of studies indicate No

Combined U.K., France & Netherlands Study – 1993 patients
Pijpe A, et al. BMJ 2012;345:e5660

Polish National Breast Cancer registry – 138 patients
Gronwald J et al, BCRT 2008; 112:581-584.

Sample size required to detect a significant change in cancer mortality, assuming lifetime follow-up



National Research Council (1995)
Radiation Dose Reconstruction for Epidemiologic Uses

Thank You

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Risk Data and Estimates of Cancer Incidence

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ORIGINAL INVESTIGATION

Projected Cancer Risks From Computed Tomographic Scans Performed in the United States in 2007

Amy Berrington de González, DPhil; Mahadevappa Mahesh, MS, PhD; Kwang-Pyo Kim, PhD; Mythreyi Bhargavan, PhD; Rebecca Lewis, MPH; Fred Mettler, MD; Charles Land, PhD

Estimated that 29,000 future cancers could be related to CT scans performed in the U.S. in 2007 …..and would translate into about 14,500 cancer deaths.

Arch Intern Med. 2009;169(22):2078-2086

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Biological Effects of Ionizing Radiation (BEIR)

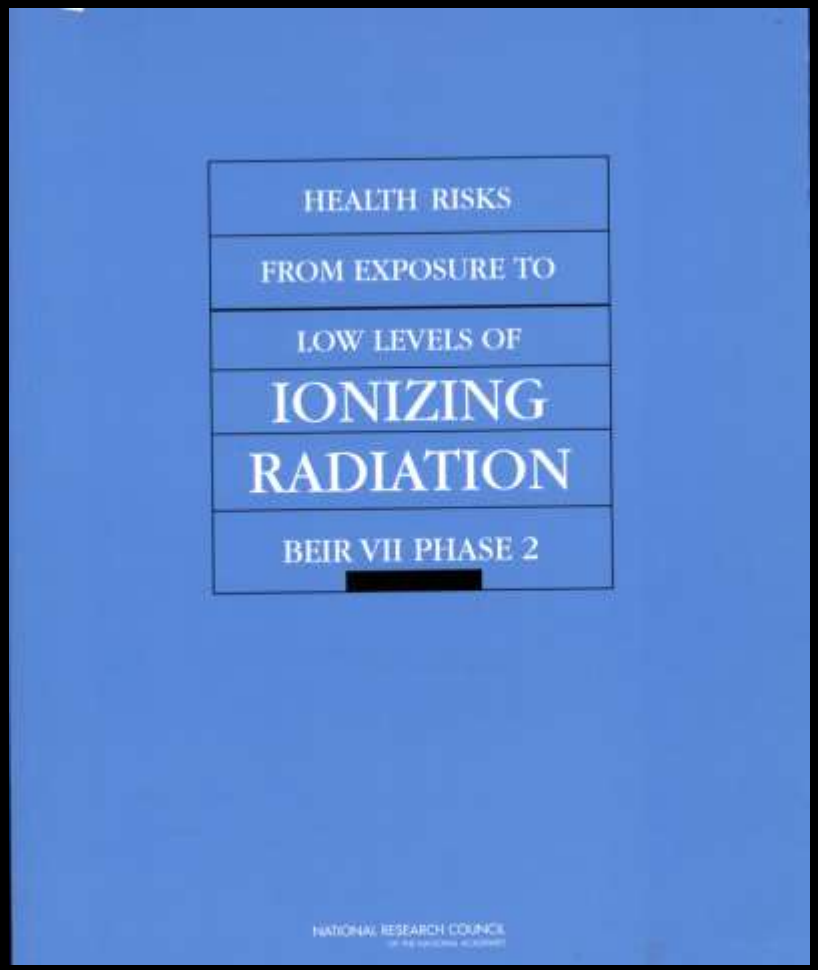

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TABLE 12D-1 Lifetime Attributable Risk of Cancer Incidence[a]

Cancer Site	Age at Exposure (years) 0	5	10	15	20	30	40	[illegible]	[illegible]	[illegible]	80
Males											
Stomach	76	65	55	46	40	28	27	25	20	14	7
Colon	336	285	241	204	173	125	122	[illegible]	[illegible]	[illegible]	30
Liver	61	50	43	36	30	22	21	[illegible]	[illegible]	[illegible]	3
Lung	314	261	216	180	149	105	104	[illegible]	[illegible]	[illegible]	34
Prostate	93	80	67	57	48	35	35	[illegible]	[illegible]	[illegible]	5
Bladder	209	177	150	127	108	79	79	[illegible]	[illegible]	[illegible]	23
Other	1123	672	503	394	312	198	172	[illegible]	[illegible]	[illegible]	23
Thyroid	115	76	50	33	21	9	3	[illegible]	[illegible]	[illegible]	0.0
All solid	2326	1667	1325	1076	881	602	564	[illegible]	[illegible]	[illegible]	126
Leukemia	237	149	120	105	96	84	84	84	82	73	48
All cancers	2563	1816	1445	1182	977	686	648	591	489	343	174
Females											
Stomach	101	85	72	61	52	36	35	[illegible]	[illegible]	[illegible]	11
Colon	220	187	158	134	114	82	79	[illegible]	[illegible]	[illegible]	23
Liver	28	23	20	16	14	10	10	[illegible]	[illegible]	[illegible]	2
Lung	733	608	504	417	346	242	240	[illegible]	[illegible]	[illegible]	77
Breast	1171	914	712	553	429	253	141	[illegible]	[illegible]	[illegible]	4
Uterus	50	42	36	30	26	18	16	[illegible]	[illegible]	[illegible]	2
Ovary	104	87	73	60	50	34	31	25	18	11	5
Bladder	212	180	152	129	109	79	78	74	64	47	24
Other	1339	719	523	409	323	207	181	148	109	68	30
Thyroid	634	419	275	178	113	41	14	4	1	0.3	0.0
All solid	4592	3265	2525	1988	1575	1002	824	678	529	358	177
Leukemia	185	112	86	76	71	63	62	62	57	51	37
All cancers	4777	3377	2611	2064	1646	1065	886	740	586	409	214

NOTE: Number of cases per 100,000 persons exposed to a single dose of 0.1 Gy.

100,000 women aged 30

Single dose of 100 mGy

Over their lifetime

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Sources of data

- Environmental Radiation Studies
- Occupational Radiation Studies
- Medical Radiation Studies
- Atomic bomb survivor Studies

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Estimate of Cancer Incidence based on

Theory:
Linear No Threshold (LNT) Hypothesis

Source of Data:
Based almost exclusively on Atomic Bomb Survivors Study

Risk models:
Excess Relative Risk (ERR)
Excess Absolute Risk (EAR)
Lifetime Attributable Risk (LAR)

Parameters:
Dose & Dose Rate Effectiveness Factor (DDREF)
Relative Biological Effectiveness (RBE)
Latency period

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Risk Models used in LNT

Excess Relative Risk (ERR) model

The ERR is the rate of disease in an exposed population divided by the rate of disease in an unexposed population, minus 1.0.

(This is a useful model if the population under investigation is similar to the population on which the model was based.)

Excess Absolute Risk (EAR) model

The EAR is the rate of disease in an exposed population minus the rate of disease in an unexposed population.

(This model is more suited if there are significant differences (ethnicity, diet, etc) between the population under investigation and that on which the model was based.)

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Risk Models used in LNT

Lifetime Attributable Risk (LAR)

Attributable risk *is the difference in rate of a condition between the exposed population and an unexposed population.*

The LAR is an estimate of the probability of a premature cancer from radiation over the life of the subject

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Risk Models used in LNT

Mrs Smith receives 1 Sv radiation to the breast at age 40

Risk of breast cancer calculated using ERR

At age 45 Risk (age 45) = $\beta * (45/60)^{-2}$

At age 46 Risk (age 46) = $\beta * (46/60)^{-2}$

Lifetime risk $LAR_{ERR} = \sum_{45}^{80} Yearly\ risk\ estimates$

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Modifying Parameters

- Dose & Dose Rate Effectiveness Factor (DDREF)
  - Range of values 1.1 – 2.5 (possible range 1-40)
- Relative Biological Effectiveness (RBE)
  - Range of values 1 - 4
- Latency period
  - Range 2 – 10 years
- Ethnicity, Environment (diet, lifestyle)
  - Convert cancer risk in Japanese subject in 1940's to American subject in 2011 !

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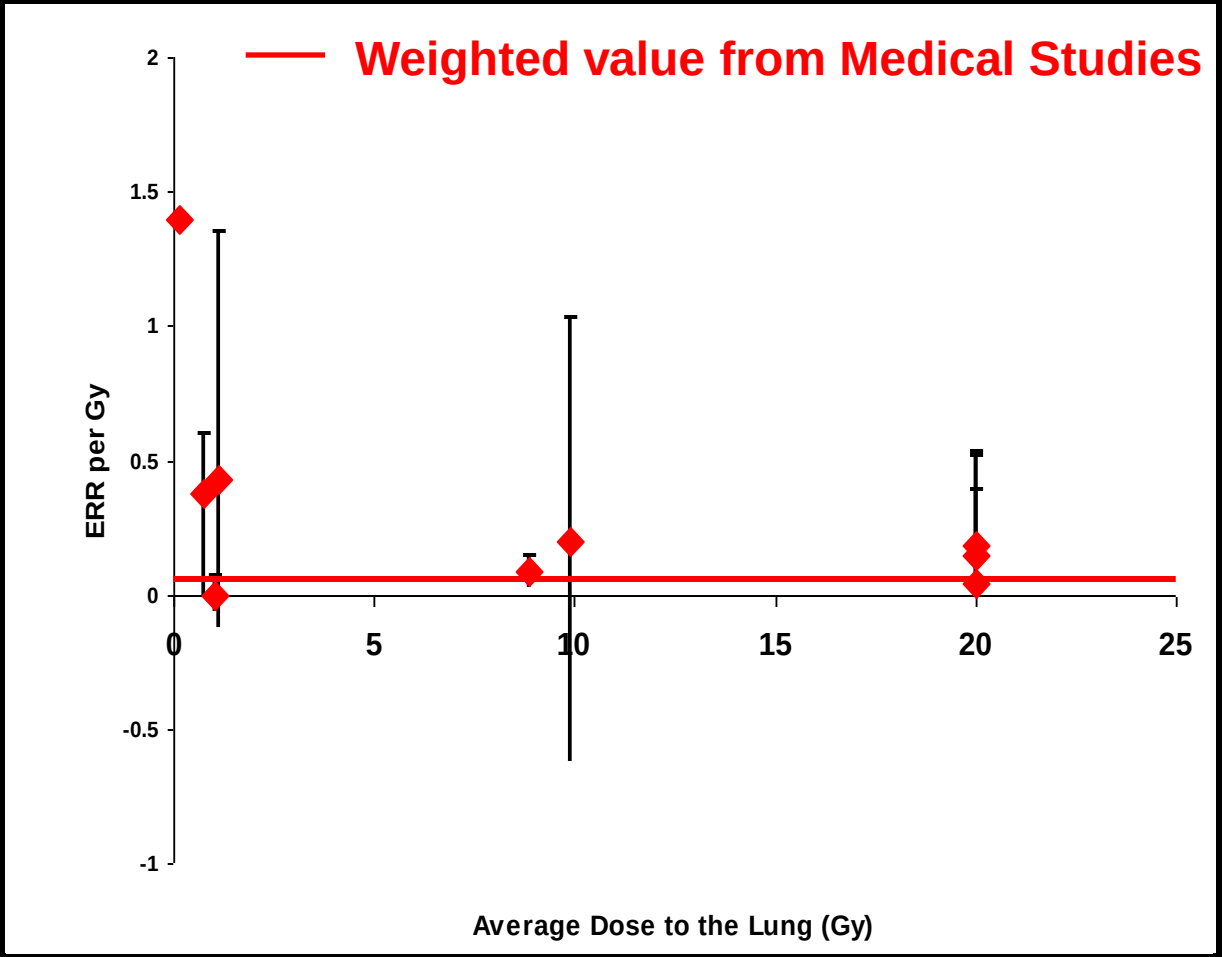
Calculation of ERR - Medical Radiation Studies

Cancer Incidence from radiation exposure to the lungs
9 studies, >40,000 subjects

ERR
Excess risk relative to background risk



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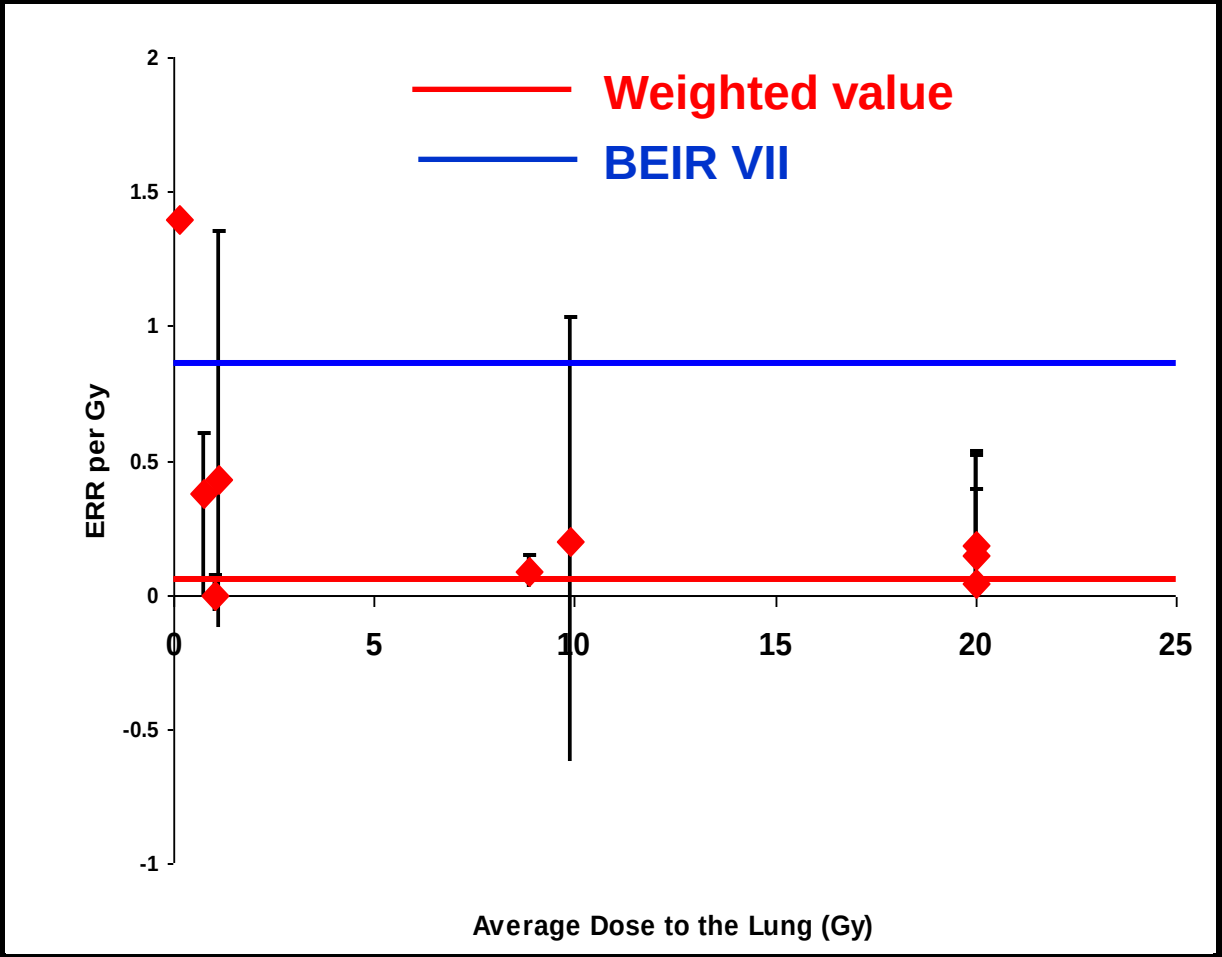

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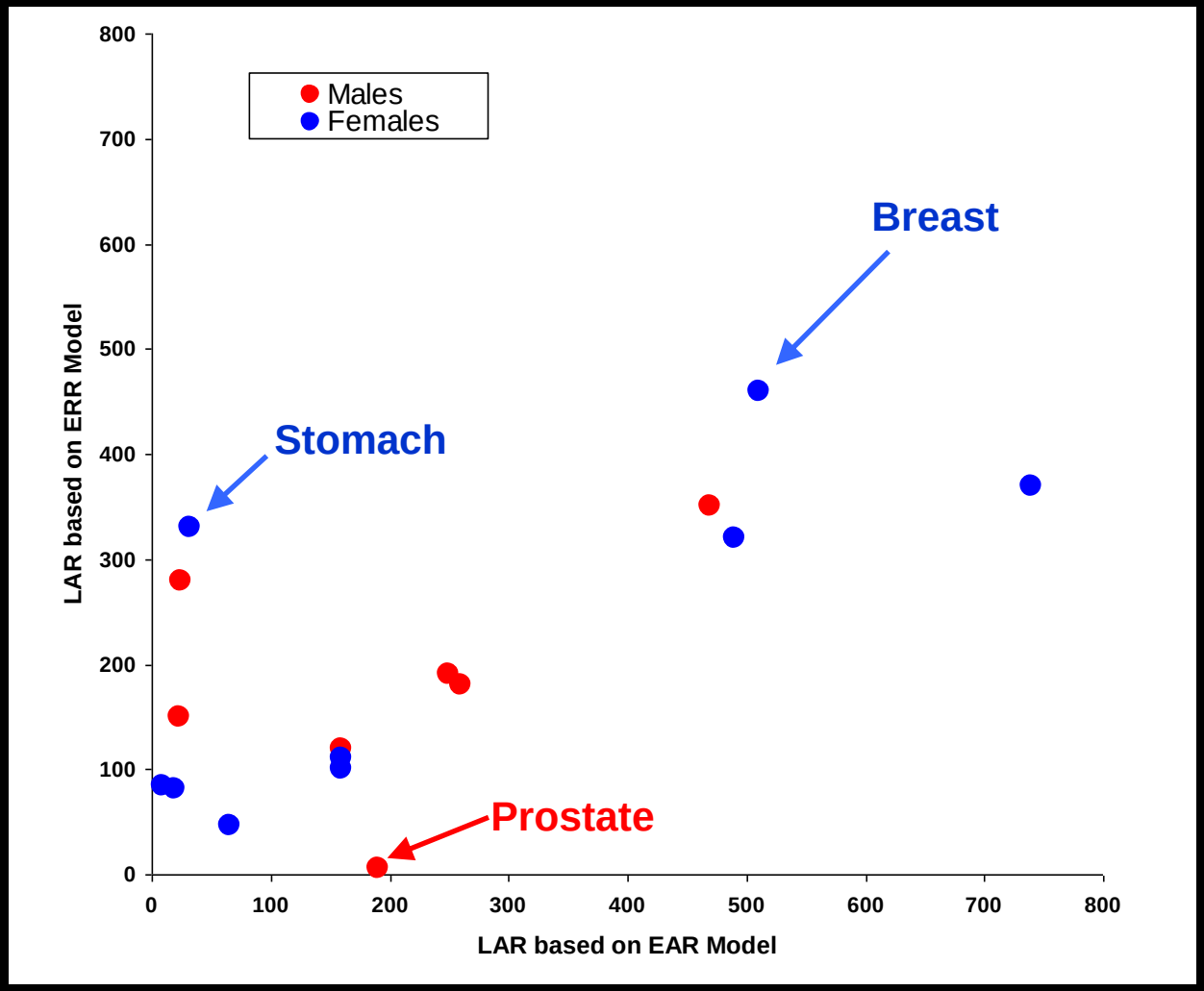
Same Data – 2 different Risk Models

Comparison of LAR using ERR and EAR



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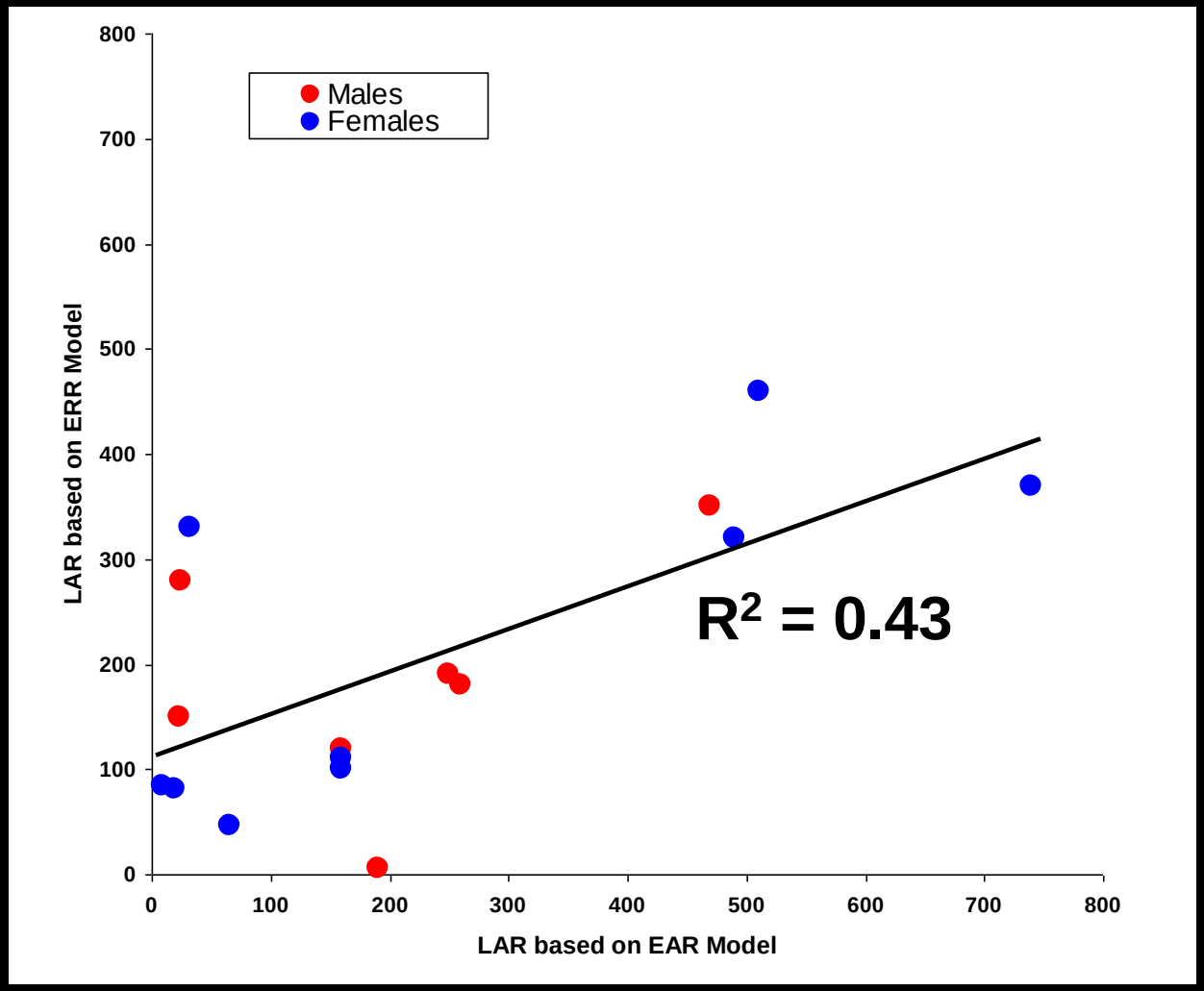

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Risk Models used in LNT

Excess Relative Risk (ERR)

vs.

Excess Absolute Risk (EAR)

Which model is correct ?

Final Risk model = x.ERR + (1-x).EAR
where x is determined by committee !

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Risk Models

Lifetime Attributable Risk (LAR)

- Uses a combination of ERR and EAR
- Uses different combinations for different organs
- Includes additional assumptions about "modifying factors"
- Risk models then applied to cancer rates for U.S. population

- Cancer incidence from ionizing radiation is based on this parameter LAR!

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TABLE 12-5A Lifetime Attributable Risk of Solid Cancer Incidence

Cancer Site	Males: LAR Based on Relative Risk Transport[a]	Males: LAR Based on Absolute Risk Transport[b]	Males: Combined and Adjusted by DDREF[c] (Subjective 95% CI[d])	Females: LAR Based on Relative Risk Transport[a]	Females: LAR Based on Absolute Risk Transport[b]	Females: Combined and Adjusted by DDREF[c] (Subjective 95% CI[d])
Incidence						
Stomach	25	280	34 (3, 350)	32	330	43 (5, 390)
Colon	260	180	160 (66, 360)	160	110	96 (34, 270)
Liver	23	150	27 (4, 180)	9	85	12 (1, 130)
Lung	250	190	140 (50, 380)	740	370	300 (120, 780)
Breast				510 Not used	460	310 (160, 610)
Prostate	190	6	44 (<0, 1860)			
Uterus				19	81	20 (<0, 131)
Ovary				66	47	40 (9, 170)
Bladder	160	120	98 (29, 330)	160	100	94 (30, 290)
Other	470	350	290 (120, 680)	490	320	290 (120, 680)
Thyroid	32	No model	21 (5, 90)	160	No model	100 (25, 440)
Sum of site-specific estimates	1400	1310[e]	800	2310[f]	2060[e]	1310
All solid cancer model[g]	1550	1250	970 (490, 1920)	2230	1880	1410 (740, 2690)

NOTE: Number of cases per 100,000 persons of mixed ages exposed to 0.1 Gy.

…range of plausible values for LAR is labeled a "subjective confidence interval" to emphasize its dependence on opinions in addition to direct numerical observation (BEIR VII, page 278)

Lifetime Attributable Risk (LAR) based on LNT Hypothesis

- "Because of the various sources of uncertainty it is important to regard specific estimates of LAR with a healthy skepticism, placing more faith in a range of possible values" (BEIR VII Report, p278)

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BEIR VII:

What it does say:

- All estimates are based on multiple models and assumptions
- Regard specific estimates with a healthy skepticism
- Confidence intervals are “subjective” and partly based on opinion

Unfortunately many studies quote cancer estimates from BEIR VII as if they were a proven scientific fact !!!

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Future Estimates of Radiation Risk

- LNT based on “single-cell biophysical hit” model and only considers half of the problem!

- Radiation damage appears to increase linearly with dose
- Radiation repair is non-linear and is not considered in the LNT model

- Future models of risk are likely to be based on radiobiology in areas such as DNA repair, bystander effects, adaptive response mechanisms, epigenetics, systems biology, etc.

Dauer LT, et al. review and evaluation of updated research on the health effects associated with low-dose ionizing radiation. Rad Prot Dosim 2010; 140: 103-136.