Radiation Risk Modeling

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(Retired)

DCEG Radiation Epidemiology and Dosimetry Course

NIH NATIONAL CANCER INSTITUTE

www.dceg.cancer.gov/RadEpiCourse

Objectives of this Session

- **Provide background to help understand presentations this week**

Will discuss

  - **Basic measures of risk**
  - **Commonly used approaches to radiation risk modeling**

- **Not a "how to do it" session**

What is a Radiation Risk Model?

- **Function that relates disease risk (relative or absolute) to exposure (dose) and factors that might modify this risk**

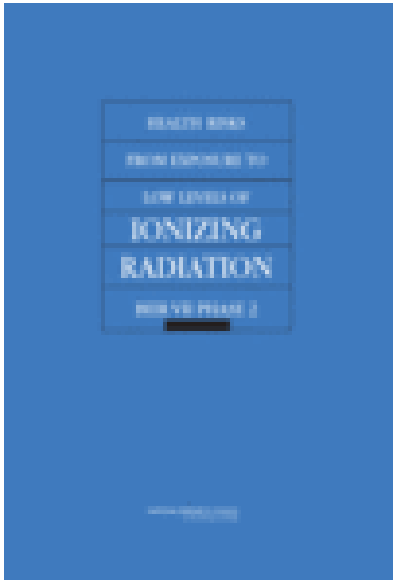
- **Models are developed by analyzing epidemiologic data**

Why Do We Need Radiation Risk Models?

- **Increase our understanding of radiation carcinogenesis**
- **Quantify risks associated with various exposure scenarios**
- **Provide information needed for radiation risk assessment**

Why Do We Need Radiation Risk Models?

Provide the information needed for radiation risk assessment



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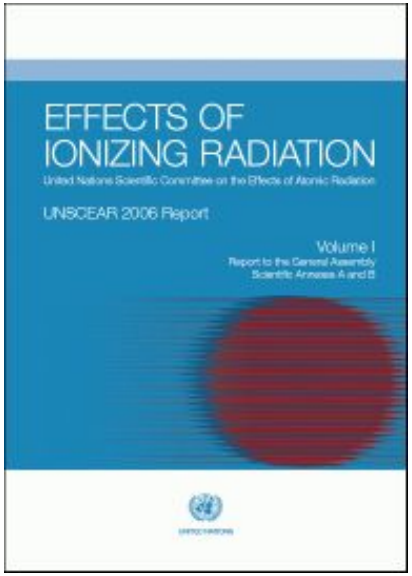
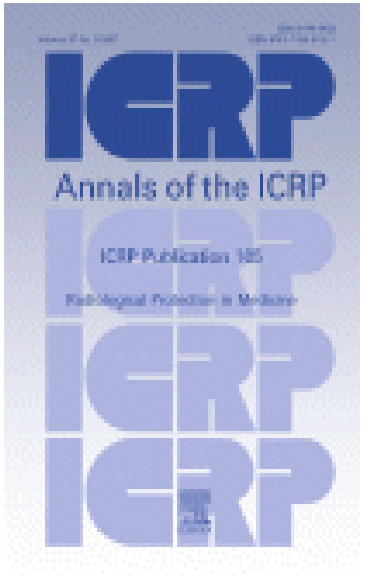


UNSCEAR, United Nations



International Commission on Radiological Protection

Basic Definitions and Concepts

- Make sure that we're all on the same page
- Start with simplest situation of comparing exposed and unexposed subjects
- Move on to studies with doses

Measures of Disease Frequency

- **Many different measures with subtle distinctions among them**

Attributable fraction

Standarized rate

Point Prevalence

Absolute risk

Cumulative incidence

Hazard

Incidence rate

Case fatality rate

Period incidence

Relative risk

Prevalence

Rate Ratio

Odds ratio

Incidence Rate

- **Expressed as cases per population and time period**
- **Example:**
  - **Number of newly diagnosed cases of cancer expressed per year**
  - **Often expressed per 10,000 or 100,000 person-years**

Comparing Incidence Rates (1)

- **Compare disease incidence rates in an exposed population to rates in an unexposed population (referent group)**

Comparing Incidence Rates (2)

- R_e = Rate in "exposed" population
- R_u = Rate in "unexposed" population
  - Often referred to as baseline rate
  - cesselatiris (
- Relative risk (RR) = R_e/R_u
  - Unitless measure
  - Excess relative risk (ERR) = RR – 1
- $R_e = R_u\ RR = R_u\ (1 + ERR)$

Comparing Incidence Rates (3)

- R_e = Rate in "exposed" population
- R_u = Rate in "unexposed" population
  - Often referred to as baseline rate

Excessrelati risk (ERR) = RR - 1

- Excess absolute risk (EAR) = $R_e - R_u$
  - Expressed per population and time period (e.g. per 10,000 person-years)
- $R_e = R_u + EAR$

Relative Risk (1)

- **Easier to evaluate than absolute risk**
  - **Can be estimated from either cohort or case-control studies**

- **Useful for**
  - **Indicating the strength of an association**
  - **Contributes to establishing causation**

Hypothetical Example

Study of survivors of cancer X treated with radiation

- **2nd cancer sites receiving "high" radiation doses: RR = 3.5**

- **2nd Cancer sites receiving "low" radiation dose: RR = 1.4**

- **Supports radiotherapy as contributing to excess risk**

Relative Risk (2)

- **Basis for**
  - **Attributable risk (AR)**
  - **Probability of causation**

$$AR = \frac{\text{excess risk}}{\text{total risk}} = \frac{ERR}{1+ERR}$$

Case-Control Studies

- Can't estimate rates (R_e, R_u)

- Instead of estimating the relative risk, estimate the odds ratio (OR) =

$$\frac{R_e/(1-R_e)}{R_u/(1-R_u)}$$

- If R_e and R_u are small (< 5%), then the OR closely approximates the relative risk = R_e/R_u

Absolute Risk

- Useful for
  - Estimating burden of disease in a population
  - Comparing risks and benefits of exposures
  - Informing exposed subjects
- More difficult to evaluate than the RR
  - Requires cohort data

Examples from International Hodgkin Lymphoma Study[1]

2nd cancer	# cases	RR	EAR*
Acute myeloid leukemia	169	21.5	6.3
All solid cancer	1726	2.0	33.1

*Excess cases per 10,000 person-years

[1]Dores G, et al., JCO 20:3483-94, 2002. HL = Hodgkin lymphoma

Data Available in Radiation Epidemiology Studies

- **Demographic data**
  - **Age, sex, calendar period**
- **Data on other risk factors**
  - **Smoking, diet, family history of cancer**
- **Radiation exposure data**

Radiation Exposure Data

- **Varies tremendously from study to study**
  - **Exposed/unexposed**
  - **Dose estimates for individuals**
- **Timing of exposure(s)**
- **Characteristics of exposure**
  - **Dose-rate**
  - **Internal/External**

Epidemiologic Reality

- **Epidemiologic studies are not controlled experiments**
- **Can’t completely control the make-up of populations available for study**
- **Perfect unexposed comparison group never exists**
- **Exposed and unexposed populations almost always differ in ways other than exposure**

Confounding

- **A risk factor is a confounder if**
  - **It increases or decreases the baseline risk of the disease of interest**
  - **It is related to exposure (e.g. more common in exposed than in exposed)**

- **Example: Studying lung cancer risk from radiation**
  - **Smoking increases the risk of lung cancer**
  - **30% of unexposed group smoke**
  - **60% of exposed group smoke**

Adjusting for Confounding

- **General principle is to compare radiation risks among those who are similar with respect to other variables**
- **Include potential confounders in modeling the baseline risk**
- **Need data on confounding variables to do this**

Confounding: Adjustment for Demographic Variables

- **Analyses nearly always adjusted for attained age, sex, and often birth cohort**
- **Categorical and continuous variables used**
- **Are adjustments adequate?**
  - **Age groups too broad?**
  - **Age effect the same for both sexes?**
  - **Do continuous variables adequately capture effect?**

Confounding: Adjustment for Other Variables

- **Examples: smoking, alcohol consumption, diet, family history**
- **Difficult to obtain data on many life-style risk factors**
- **Available data likely does not reflect full details of exposure**
- **Surrogate measures sometimes used**

Interactions

- What happens when two kinds of exposure occur?

- Do their effects multiply or add?

Interactions/Effect Modification (1)

- **Other risk factors can modify radiation risk (RR and EAR)**

- **Modification can be different for RR than for EAR**

Interactions/Effect Modification (2)

RR_{rad} = RR for radiation

RR_{other} = RR for other factor

RR_{both} = RR for both radiation and other factor

Multiplicative model:

$$RR_{both} = RR_{rad} \times RR_{other}$$

RR_{rad} does not depend on the other factor

Interactions/Effect Modification (3)

$$ERR_{rad} = RR_{rad} - 1$$
$$ERR_{other} = RR_{other} - 1$$
$$ERR_{both} = RR_{both} - 1$$

Additive model:

$$ERR_{both} = ERR_{rad} + ERR_{other}$$
$$(RR_{both} = RR_{rad} + RR_{other} - 1)$$

ERR_{rad} does not depend on the other factor

Interactions (2)

	RR
Non-smoker, no radiation (referent)	1.0
Non-smoker, radiation	2.0
Smoker, no radiation	10.0
Smoker, radiation	?

$$\mathbf{RR_{rad} = 2.0; \quad RR_{smk} = 10.0}$$

Multiplicative Model (1)

	RR	RR
Non-smoker, no radiation (referent)	1.0	1.0
Non-smoker, radiation	2.0	2.0
Smoker, no radiation	10.0	10.0
Smoker, radiation	?	20.0

$$RR_{rad} = 2.0; \quad RR_{smk} = 10.0$$

Multiplicative Model (2)

	RR	RR	RR for radiation
Non-smoker, no radiation (referent)	1.0	1.0	
Non-smoker, radiation	2.0	2.0	**2.0**
Smoker, no radiation	10.0	10.0	
Smoker, radiation	?	20.0	**2.0**

Radiation RR for non-smoker = 2.0/1.0 =2.0
Radiation RR for smoker = 20.0/10.0 = 2.0

Additive Model (1)

	RR	ERR
Non-smoker, no radiation (referent)	1.0	0.0
Non-smoker, radiation	2.0	1.0
Smoker, no radiation	10.0	9.0
Smoker, radiation	11.0	10.0

$$\mathbf{ERR_{rad} = 1.0; \quad ERR_{smk} = 9.0}$$

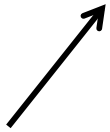
Additive Model (2)

	RR	ERR	ERR for radiation
Non-smoker, no radiation (referent)	1.0	0.0	
Non-smoker, radiation	2.0	1.0	**1.0**
Smoker, no radiation	10.0	9.0	
Smoker, radiation	11.0	10.0	**1.0**

Radiation ERR for non-smoker = 1.0 – 0.0 =1.0
Radiation ERR for smoker = 10.0-9.0 = 1.0

Sub-multiplicative/ Super-additive Model (1)

	RR
Non-smoker, no radiation (referent)	1.0
Non-smoker, radiation	2.0
Smoker, no radiation	10.0
Smoker, radiation	15.0



20.0 for multiplicative; 11 for additive

Sub-multiplicative/ Super-additive Model (2)

	RR	RR for radiation
Non-smoker, no radiation (referent)	1.0	
Non-smoker, radiation	2.0	2.0
Smoker, no radiation	10.0	
Smoker, radiation	15.0	1.5

Radiation RR for non-smoker = 2.0/1.0 =2.0
Radiation RR for smoker = 15.0/10.0= 1.5

Sub-multiplicative/ Super-additive Model (3)

	RR	RR for radiation	ERR	ERR for radiation
Non-smoker, no radiation (referent)	1.0		0.0	
Non-smoker, radiation	2.0	2.0	1.0	**1.0**
Smoker, no radiation	10.0		9.0	
Smoker, radiation	15.0	1.5	14.0	**5.0**

Radiation ERR for non-smoker = 1.0 – 0.0 =1.0
Radiation ERR for smoker = 14.0-9.0 = 5.0

Examples of Radiation Risk Modeling

- **Testicular cancer patients (no doses)**
- **A-bomb survivors (single acute dose)**
- **Mayak nuclear workers (chronic external and internal exposure)**
- **Case-control study of lung cancer following Hodgkin lymphoma (interactions of radiation, chemotherapy, and smoking)**

Testicular Cancer Study (1)

- International cohort of 40,576 1-year survivors
  - Population-based cancer registries in Denmark, Finland, Norway, Sweden, Ontario, US (SEER)
- Followed for up to 40 years
- Focused on second solid cancers in 20,987 10-year survivors
  - 1694 second solid cancers

Travis LB, Fossa SD, Schonfeld SJ, et al. J Natl Cancer Inst 97:1354-1365, 2005.

Testicular Cancer Study (2)

- **Exposed: 20,987 10-year survivors of testicular cancer**
  - **Commonly treated with radiation**
  - **Some also treated with chemotherapy**

- **Unexposed (referent group): General populations in Denmark, Finland, Norway, Sweden, Ontario, US (SEER)**

Travis et al. 2005

Comparisons with the General Population (1)

O = observed number of cases or deaths from disease of interest

E = expected number of cases or deaths based on general population rates

RR estimated by Observed-to-Expected (O/E) ratio

EAR estimated by (O – E)/person-years

Comparisons with the General Population (2)

RR estimated by Observed-to-Expected (O/E) ratio

O/E ratio also known as

- **Standardized Incidence Ratio (SIR) for incidence data**
- **Standardized Mortality Ratio (SMR) for mortality data**

Testicular Cancer Study: Objectives

- **Quantify the RR and EAR**

- **Evaluate how the RR and EAR depend on variables such as**
  - **Age at diagnosis of testicular cancer**
  - **Attained age**
  - **Time since diagnosis**
  - **Treatment (limited data)**

Evaluating Dependencies of the RR and EAR on Age and Other Variables

- **Common starting point is to estimate the RR and EAR for each of several categories defined by the variables**

- **Use simple estimates:**
  - **RR = O/E**
  - **EAR = (O–E)/person-years**

Number of 2nd Solid Cancers[1]

Attained age (y)	Age at TC diagnosis (y)			
	<30	30-39	40+	All
< 50	141	96	0	237
50-59	92	200	122	414
60-69	49	198	338	585
70+	9	78	371	458
All	291	572	831	1694

[1]Among 10-year survivors of testicular cancer

Travis et al. 2005

Relative Risk (O/E)[1]

Attained age (y)	Age at TC diagnosis (y)			
	<30	30-39	40+	All
< 50	2.6	2.1	--	2.3
50-59	2.8	1.6	1.5	1.7
60-69	2.1	1.9	1.3	1.5
70+	2.4*	1.7	1.2	1.3
All	2.5	1.8	1.3	1.5

*Only 9 cases

[1]Among 10-year survivors of testicular cancer

Travis et al. 2005

Limitations of Categorical Approach

- **Estimates for categories defined by 2 or more variables often based on small numbers**

- **May be difficult to make sense of patterns, particularly if estimates imprecise**

Modeling RR and EAR

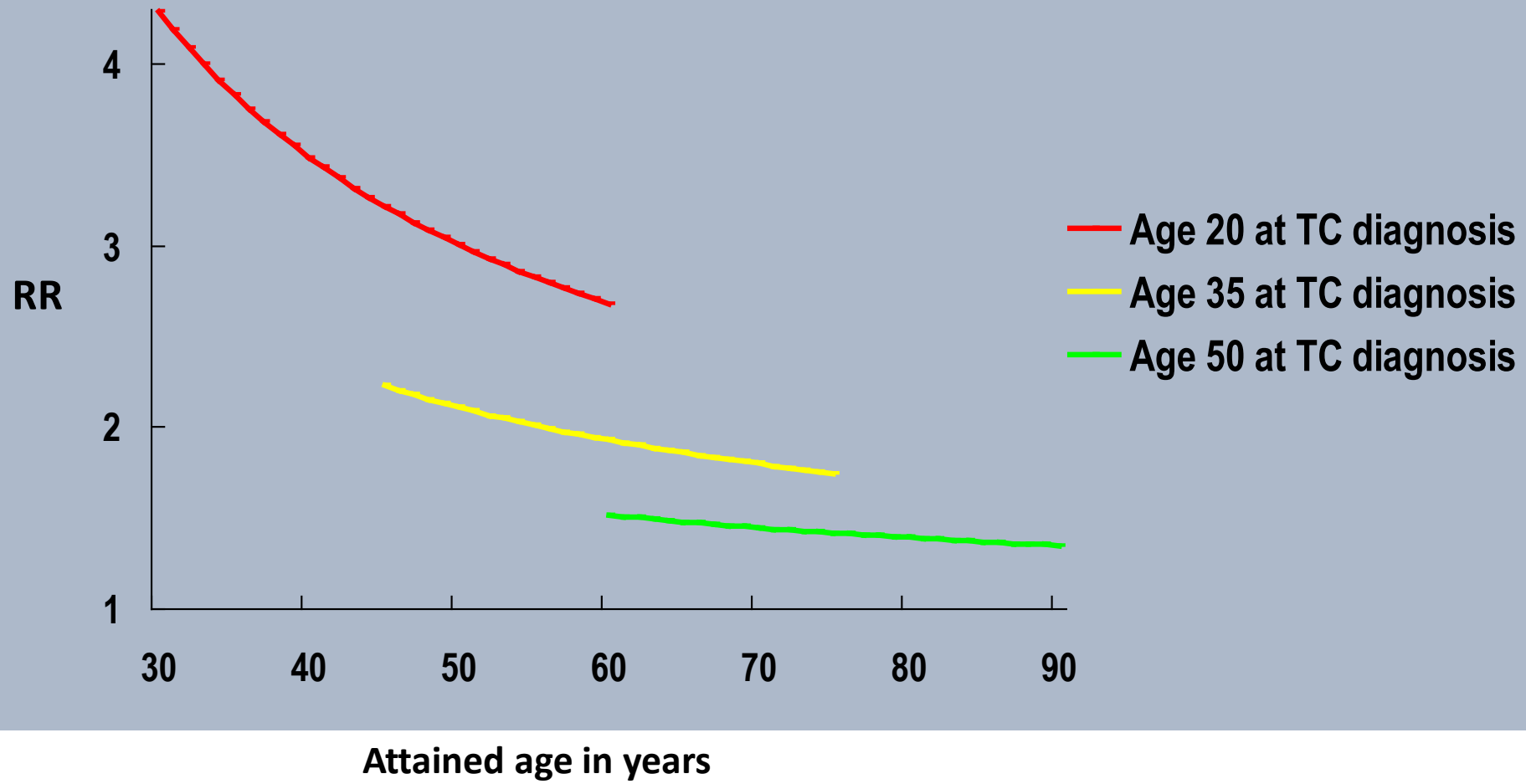
- **Express RR and EAR as continuous functions of**
  - **age at diagnosis (*agex*)**
  - **attained age (*attage*)**
  - **other variables**

- **Example: Use ERR and EAR of the form**

$$\beta \exp(\gamma\, agex)\, attage^{\eta}$$

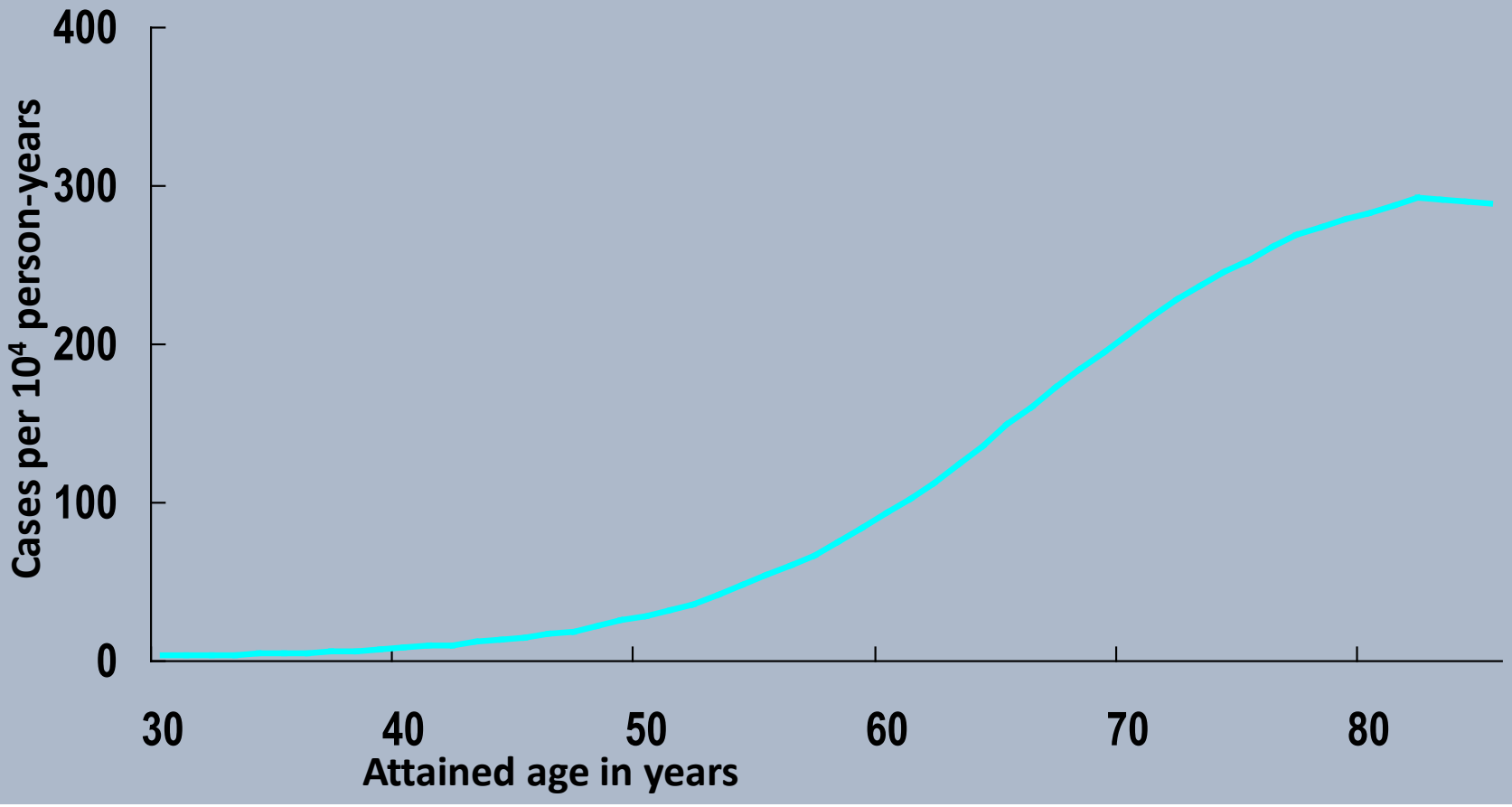
Travis et al. 2005

Relative Risk of 2nd Solid Cancer in 10-year Survivors of Testicular Cancer



Travis et al. 2005

Baseline Rate of Solid Cancer for Males in the General Population



Travis et al. 2005

Excess Absolute Risk (O–E)/10^4 pyr[1]

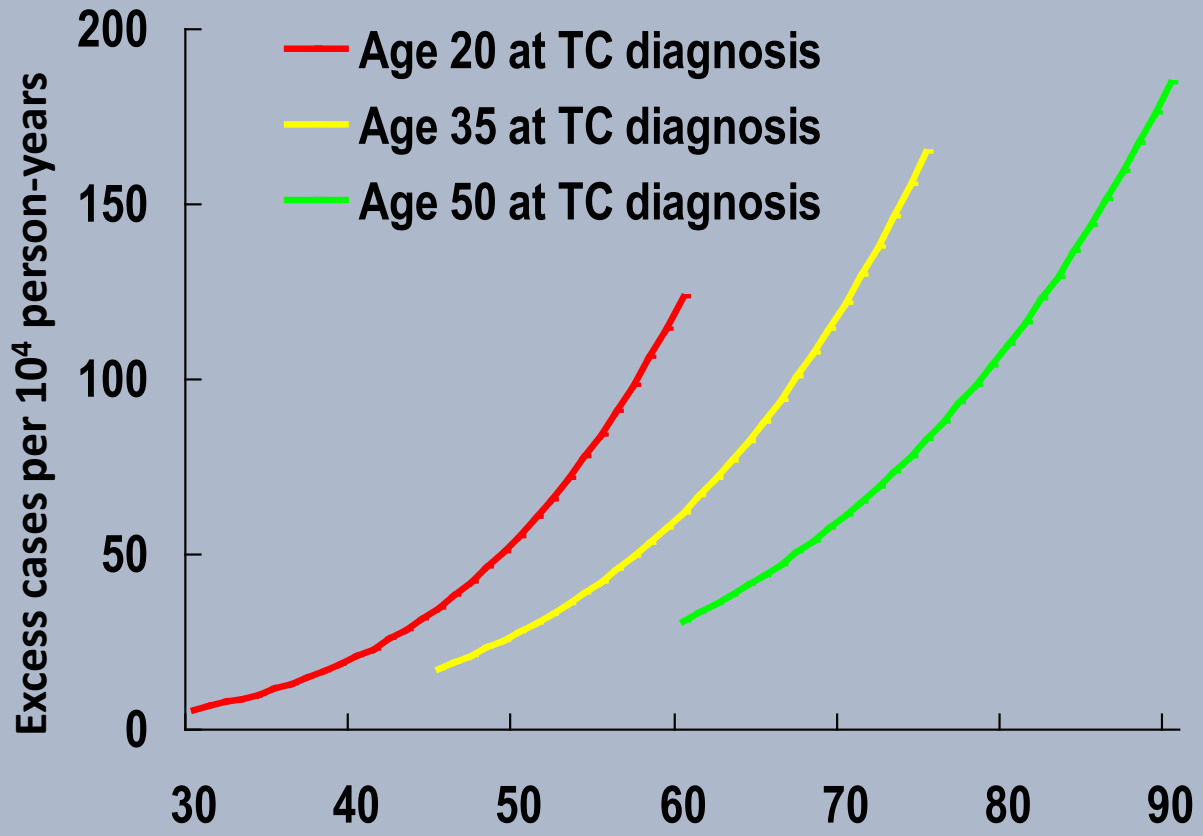
Attained age (y)	Age at TC diagnosis (y) <30	30-39	40+	All
< 50	14	16	--	14
50-59	72	25	25	33
60-69	126	102	34	59
70+	81*	146	56	69
All	23	35	37	31

*Only 9 cases

[1]Among 10-year survivors of testicular cancer

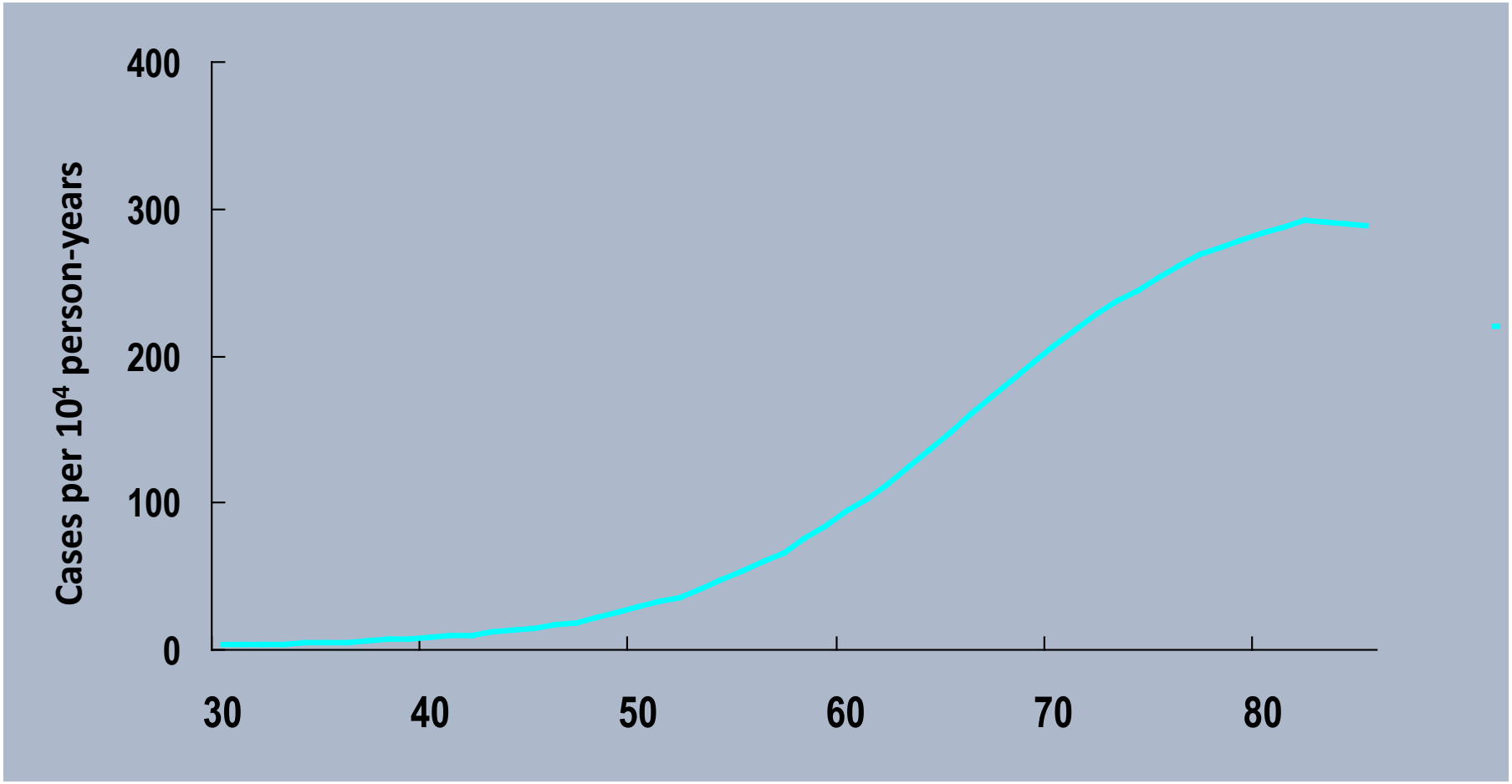
Travis et al. 2005

Excess Absolute Risk of 2nd Solid Cancer in 10-year Survivors of Testicular Cancer

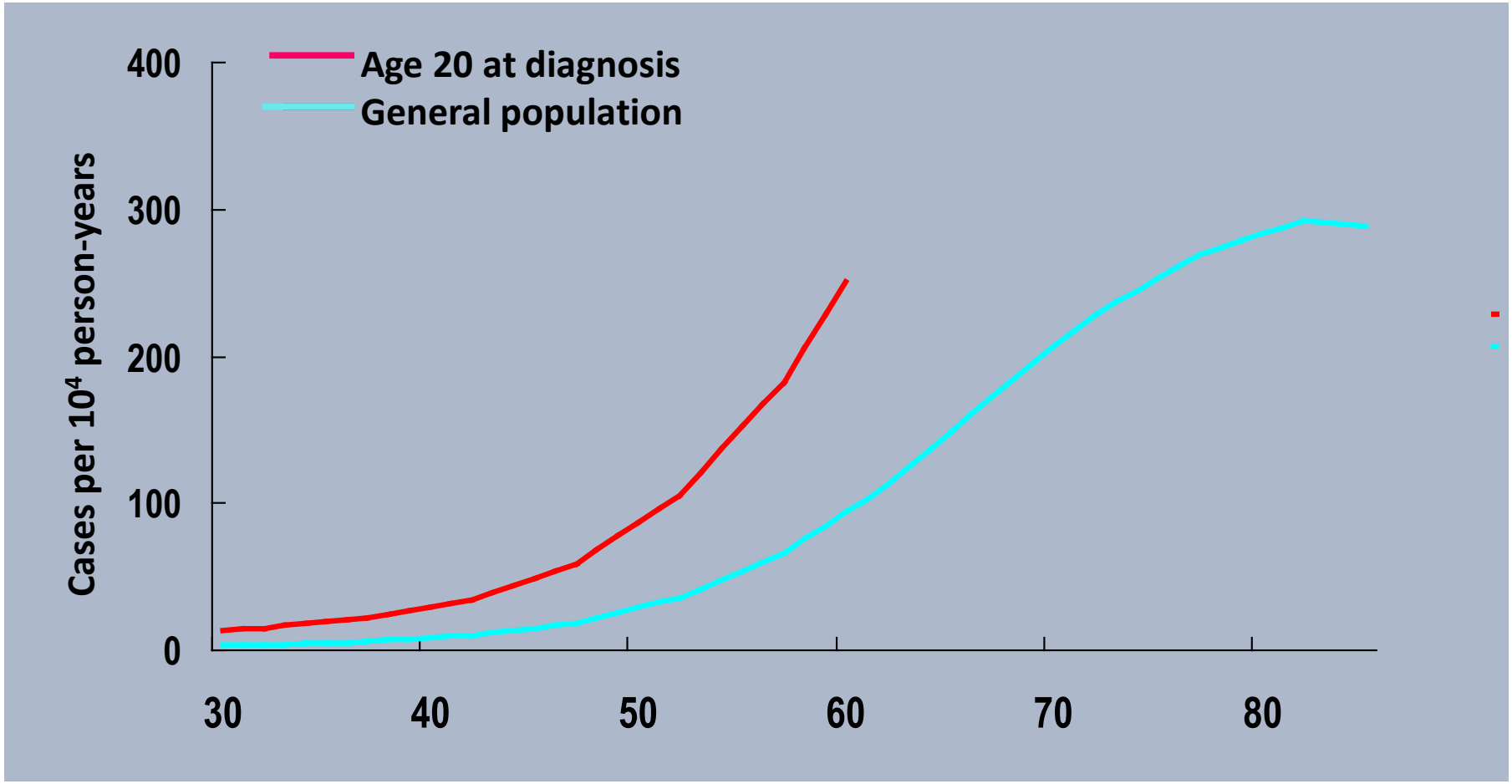


Travis et al. 2005

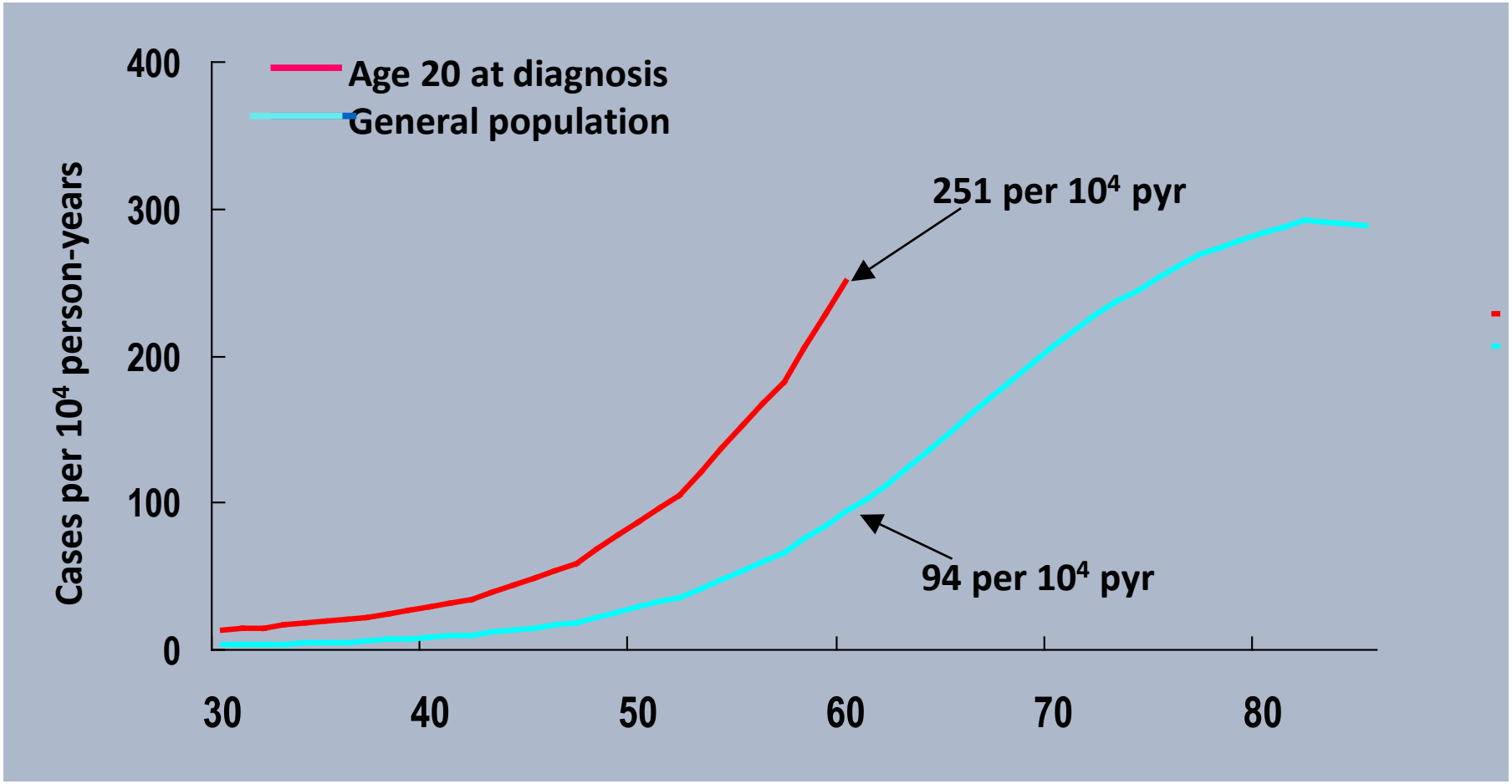
Second Solid Cancer Rate in Testicular Cancer Patients Diagnosed at Age 20 (1)



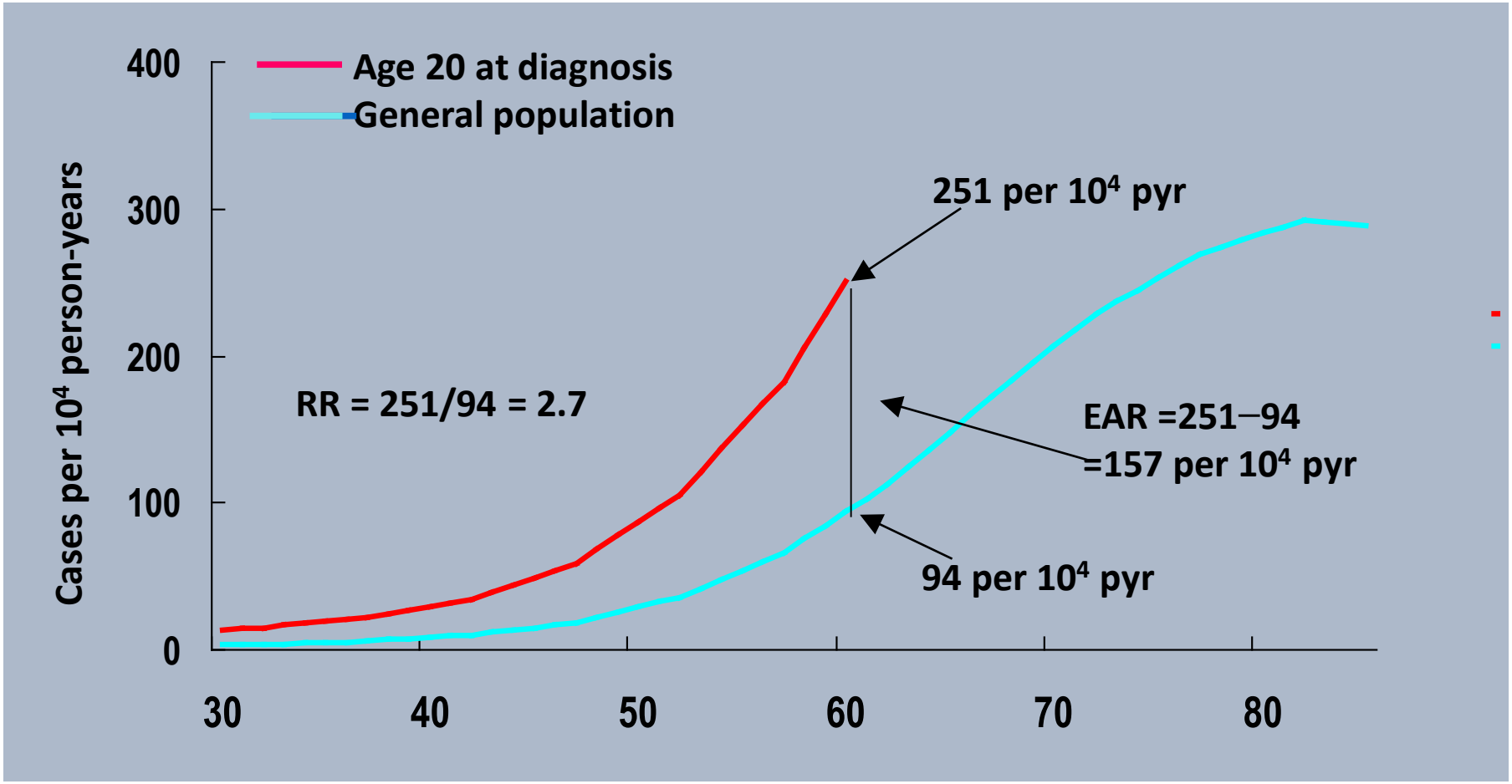
Second Solid Cancer Rate in Testicular Cancer Patients Diagnosed at Age 20 (2)



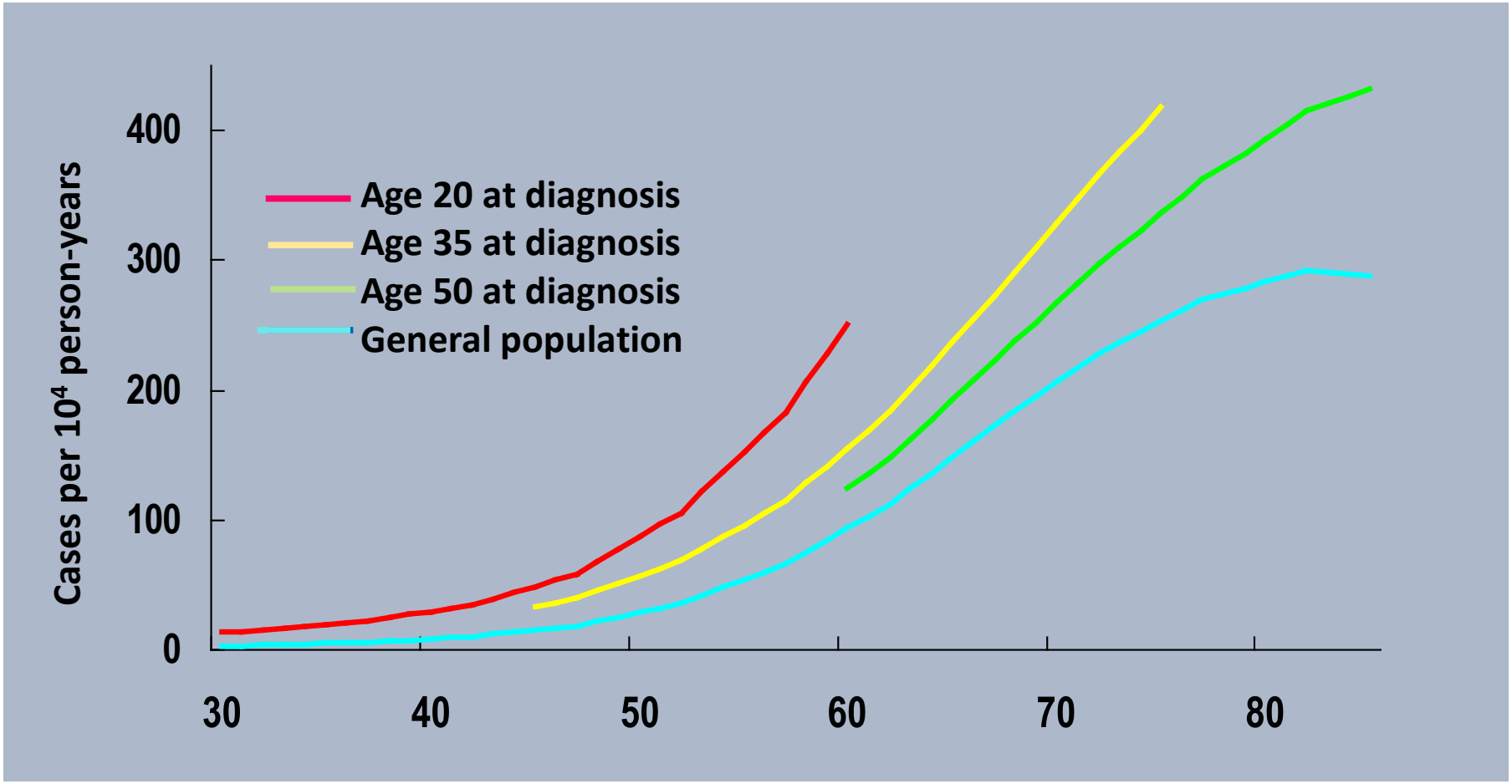
Second Solid Cancer Rate in Testicular Cancer Patients Diagnosed at Age 20 (3)



Second Solid Cancer Rate in Testicular Cancer Patients Diagnosed at Age 20 (4)



Second Solid Cancer Rate in Testicular Cancer Patients



Measures of Disease Frequency

- **Incidence rate: Risk per unit of time**
  - **Expressed as cases per population and time period**

- **Can use incidence rates to obtain estimates of cumulative risk**
  - **Probability of developing disease in a specified time period**
  - **Depends on time period but has no units**

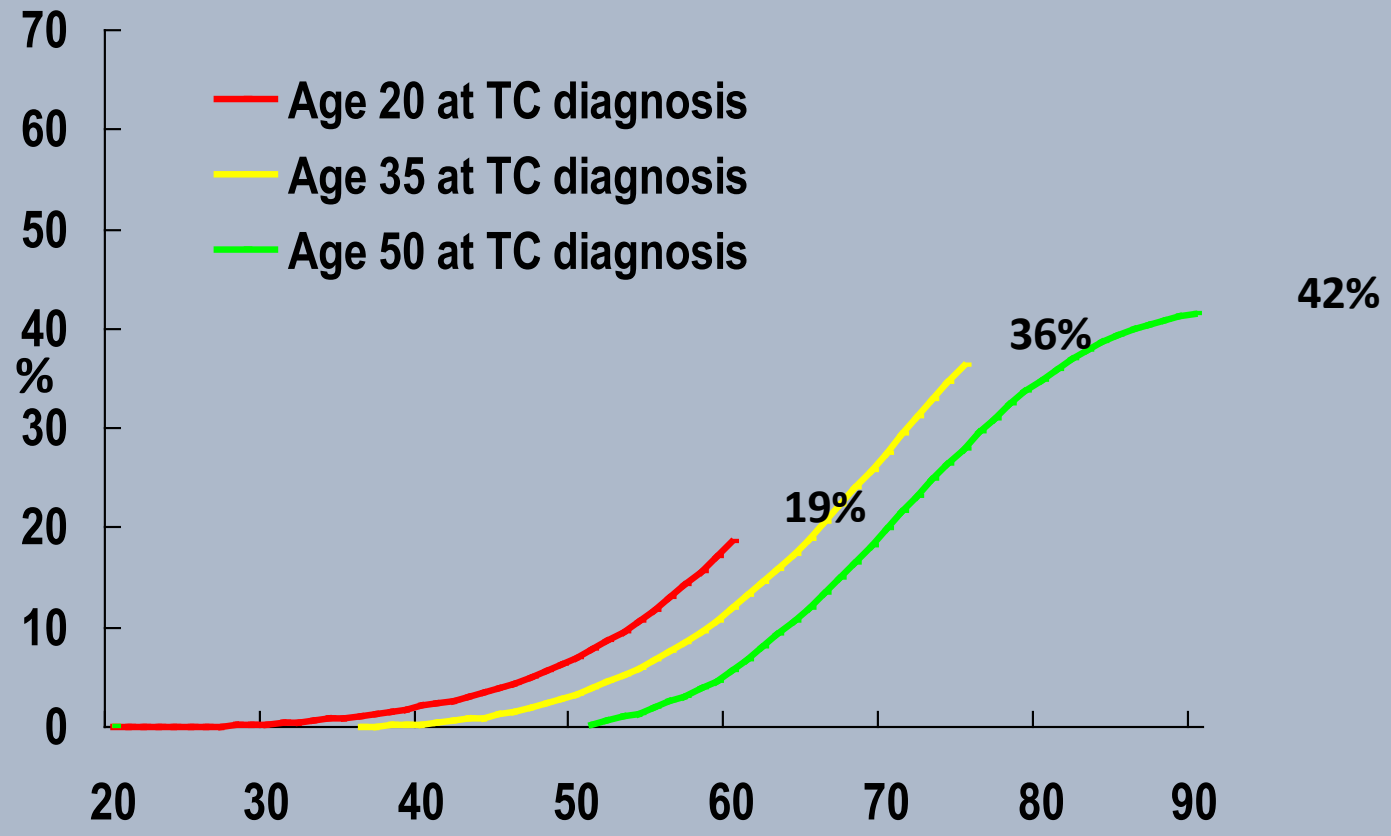
Cumulative Risk in Testicular Cancer Patients

Can use incidence rates to obtain estimates of cumulative risk

Probability of developing disease in a specified time period

- **Death from testicular cancer**
  - **Modeled as a function of age at diagnosis, attained age, and time since diagnosis**
- **Death from non-cancer causes**
  - **Used general population rate**

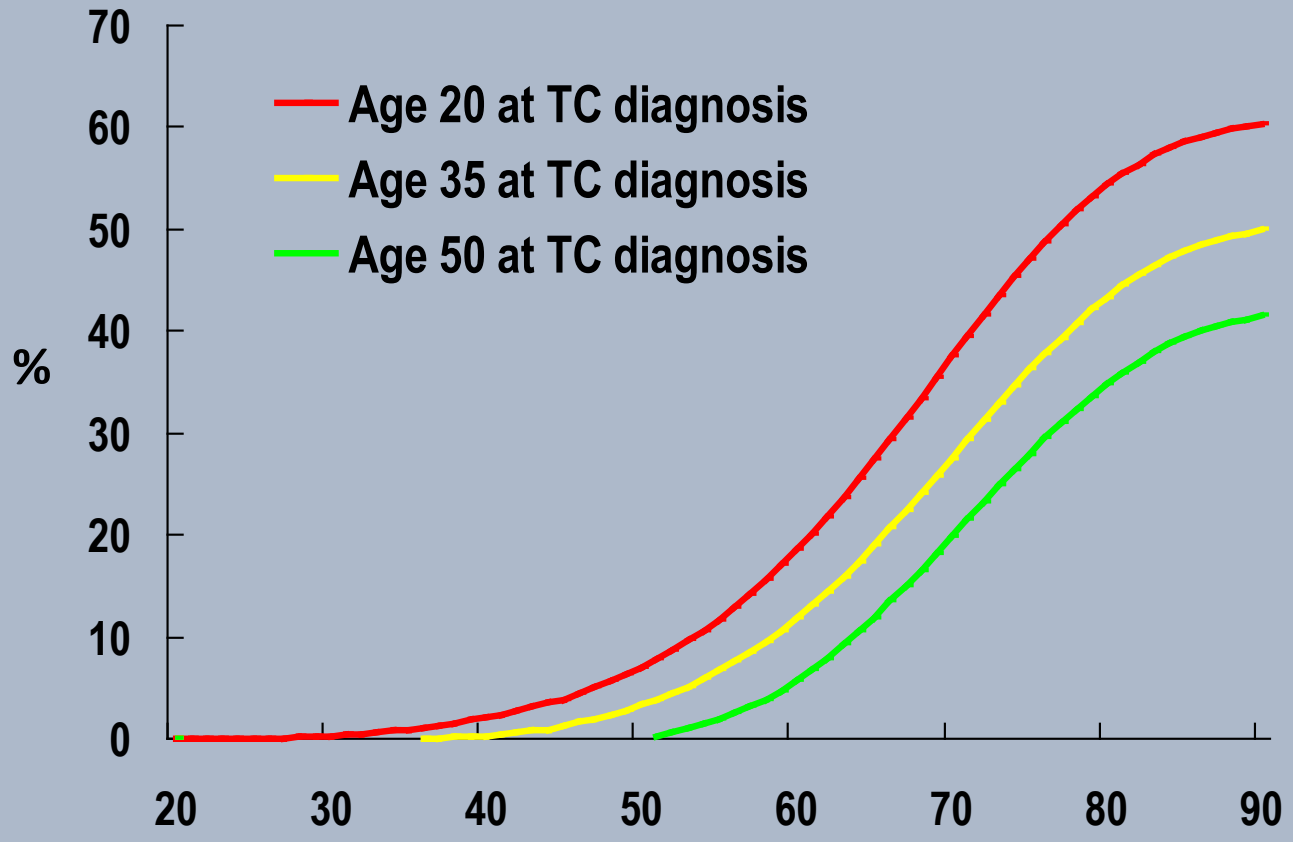
Cumulative Risk (%) of 2nd Solid Cancer in 1-year Survivors of Seminoma



Attained age in years

Travis et al. 2005

Cumulative Risk (%) of 2nd Solid Cancer in 1-year Survivors of Seminoma Projected to Age 90



Travis et al. 2005

Cohort Study Analyses: Poisson Regression

- Allocate person-years for each subject by age, follow-up time, dose, and other variables of interest
- Create a person-year table categorized by variables of interest
  - Grouped data
- Number of events in each cell treated as Poisson variable
- Can model either relative or absolute risk
- Used extensively for radiation risk modeling

Cohort Study Analyses: Cox Regression

- **Analyses based on individual subjects**

- **At each time that event occurs, compare exposure (and other variables) of subject experiencing an event with exposures of all subjects at risk at that time**

Examples

- **Testicular cancer patients (no doses)**
- **A-bomb survivors (single acute dose)**
- **Mayak workers (chronic external and internal exposure)**
- **Case-control study of lung cancer following Hodgkin lymphoma (interactions of radiation, chemotherapy, and smoking)**

Role of Doses in Radiation Epidemiology

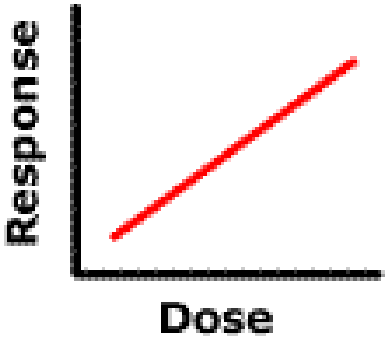
- **Many studies have high quality estimates of dose for individual subjects**
- **Compare risks by level of dose**
- **Explore and quantify dose-response relationship**

Shape of Dose-Response

- **Linear (and linear-quadratic) models used extensively**
- **Can be justified based on radiobiological considerations**
- **Risks at low doses of special interest**
- **Often difficult to distinguish among various dose-response functions**

Excess Relative Risk Model

- RR = Relative Risk = 1 + β d
  - d is dose
  - β d is the excess relative risk (ERR)
  - β is the ERR per unit of dose



- ERR model can be fit with the Epicure software
  - Cohort studies: AMFIT module for Poisson regression

Life Span Study (LSS) Cohort of Japanese A-bomb Survivors (1)

- **Primary source of data for most risk assessments**
- **All ages and both sexes**
- **Long term follow-up for both mortality and cancer incidence**
- **Extensive efforts to estimate doses for individual study subjects**

Life Span Study (LSS) Cohort of Japanese A-bomb Survivors (2)

- Primary source of data for most risk assessments
- All ages and both sexes
- Long term follow-up for both mortality and cancer incidence
- Extensive efforts to estimate doses for individual study subjects

Life Span Study (LSS) Cohort of Japanese A-bomb Survivors (3)

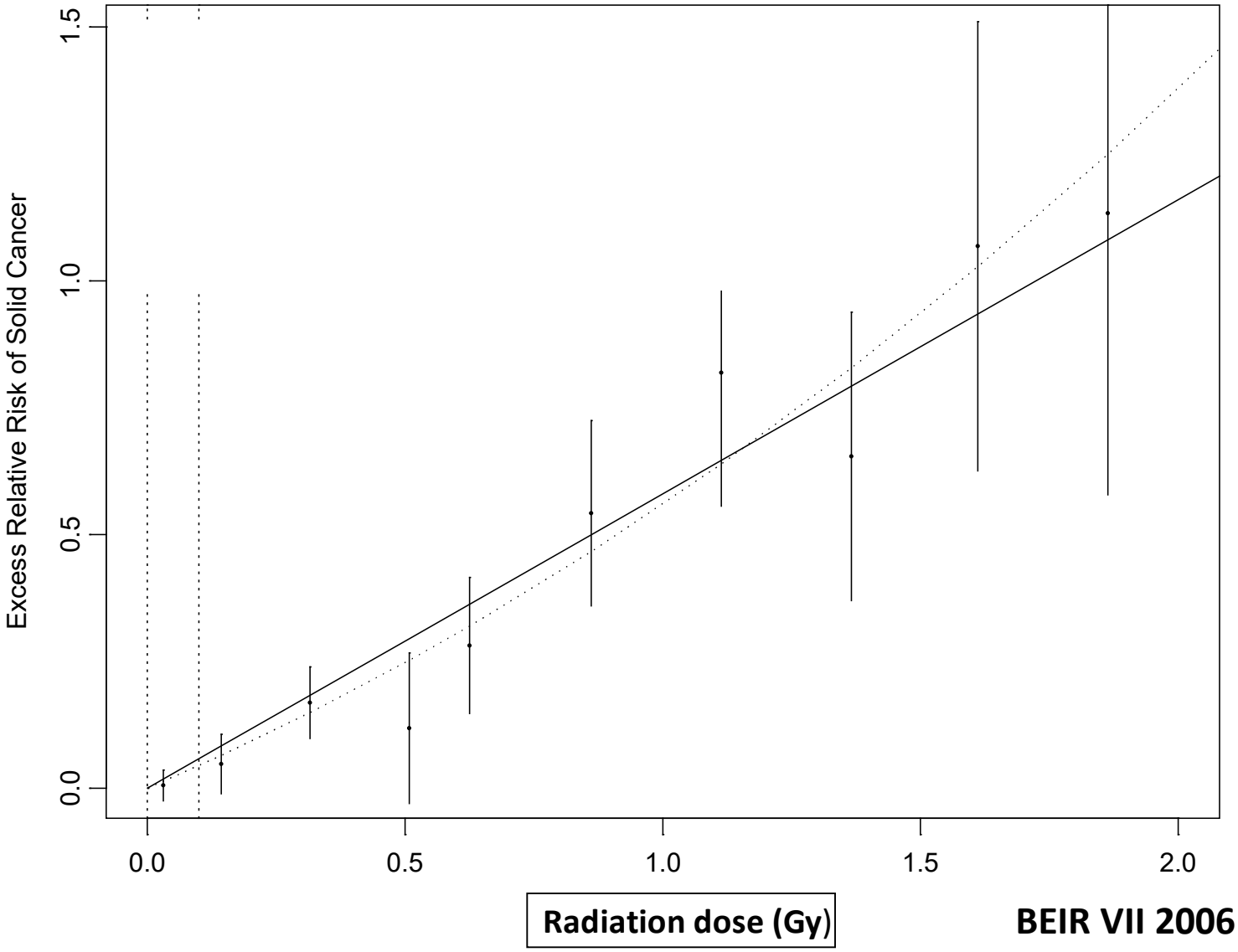
- Primary source of data for most risk assessments
- All ages and both sexes
- Long term follow-up for both mortality and cancer incidence
- Extensive efforts to estimate doses for individual study subjects
- Some results in this in this presentation are old!

Atomic Bomb Survivor Dose Distribution

Dose (Gy)	No. of subjects
Not in city	25,239
<0.005	35,978
0.005-	27,511
0.1-	5,594
0.2-	5,926
0.5	3,426
1-	1,565
2+	495

Grant *et al*. Radiat Res 2017

A-bomb Survivor Solid Cancer Incidence: Excess Relative Risk



BEIR VII 2006

ERR Models That Allow for Modification

- **Excess Relative Risk (ERR) =**

$$\beta_s \, d \, f(s, agex, attage)$$

***s*=sex;**

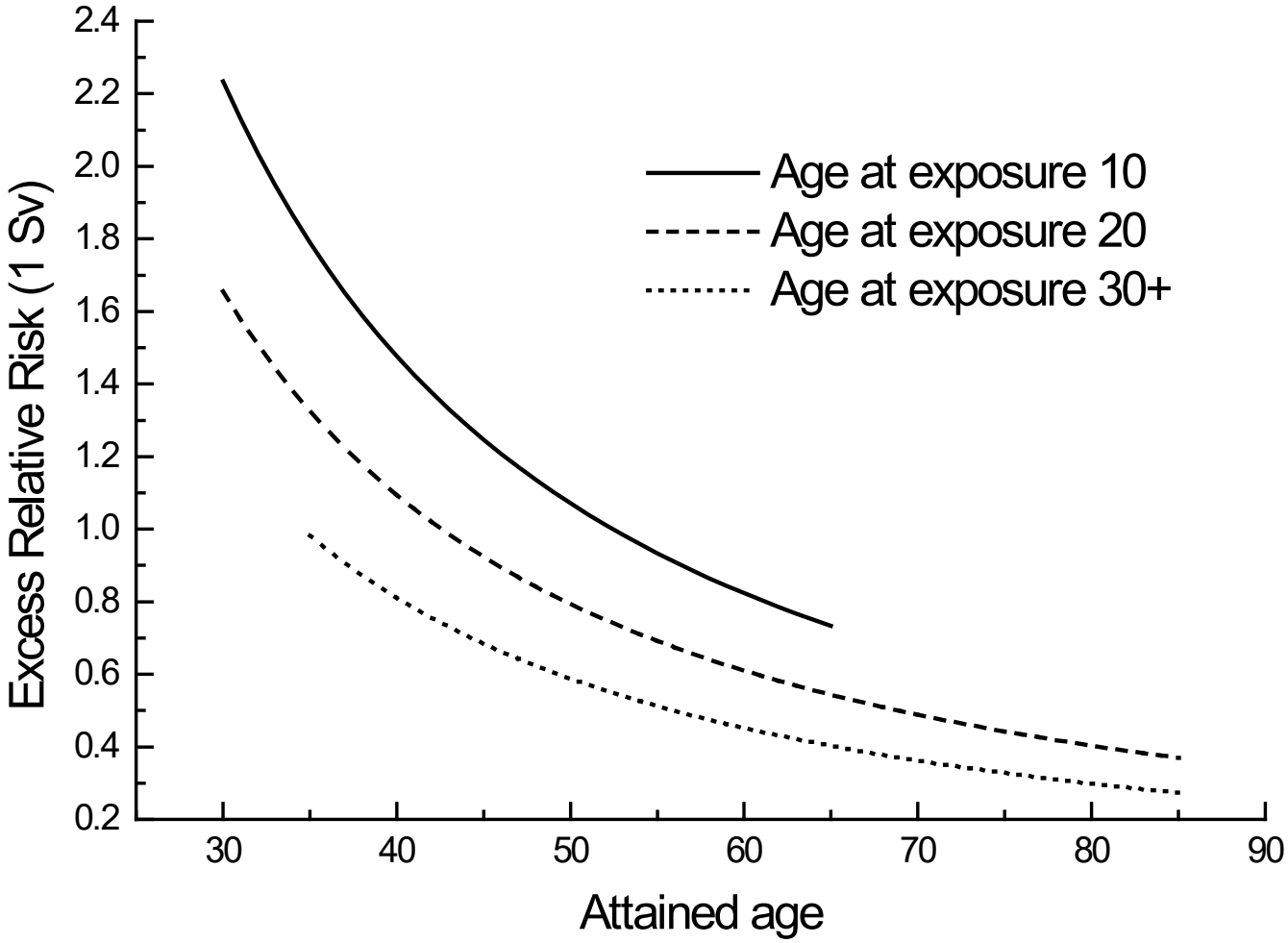
***agex* = age at exposure;**

***attage* = attained age**

Commonly used model:

$$ERR = \beta_s \, d \exp(-\gamma \, agex) \, attage^{\eta}$$

Solid Cancer: ERR per Gy



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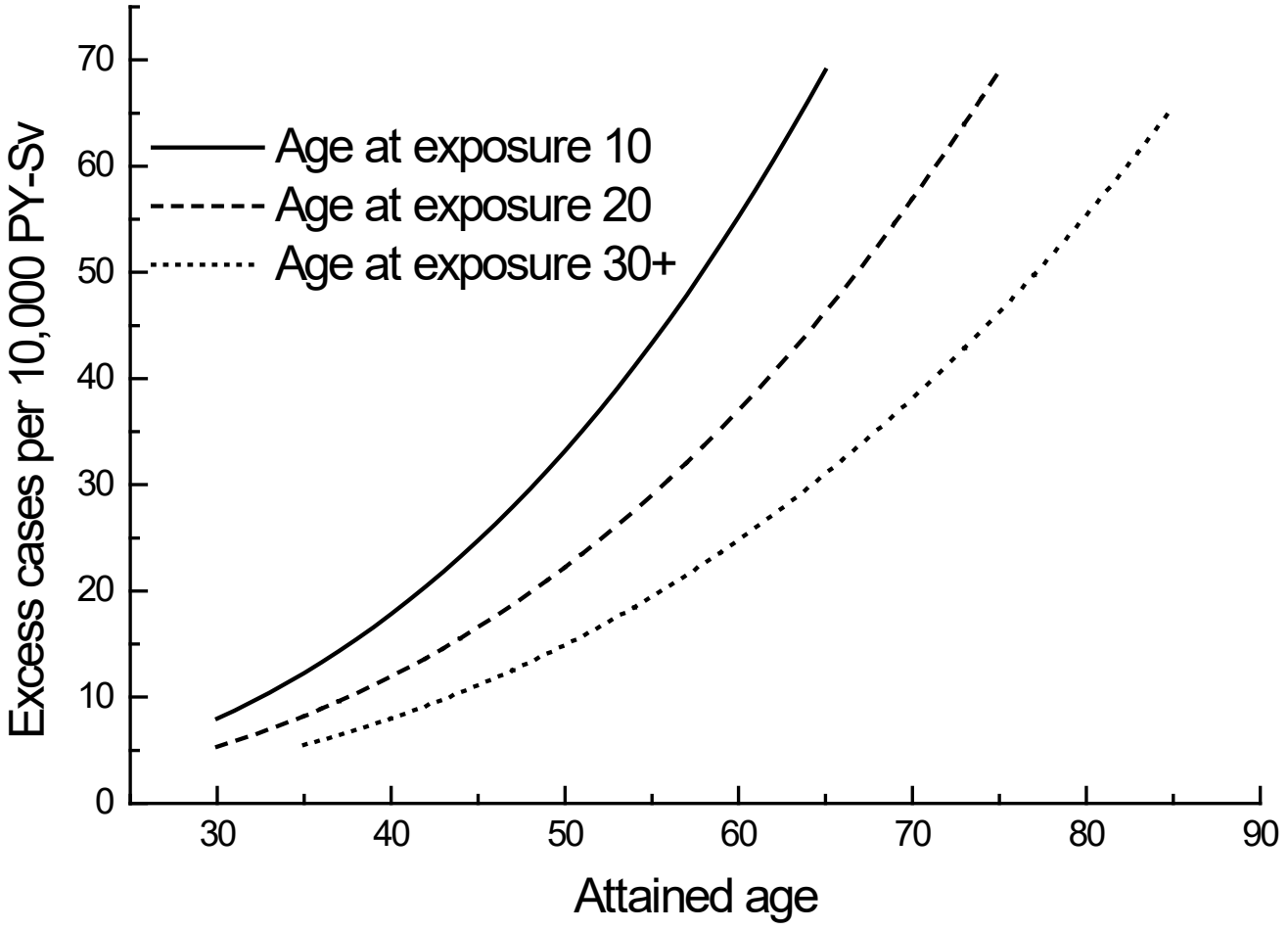
Solid Cancer:
Excess cases per 10,000 PY-Gy



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Life Span Study (LSS) Cohort of Japanese A-bomb Survivors

- **Primary source of data for most risk assessments**
- **For that reason, estimates from other studies are often compared with those from the LSS**
- **Important to consider age, sex, and possibly other variables in making these comparisons**

A-bomb Survivor Risk Estimates

- **Preston et al. (2007) present sex-specific ERR/Gy for exposure at age 30 at attained age 70**

- **Example: All solid cancer**

  Males: 0.35 (0.28-0.43)

  Females: 0.58 (0.43-0.69)

- **For older ages, estimates will be lower**
- **For younger ages, estimates will be higher**

Preston et al. Radiat Res 2007

Examples (1)

- Testicular cancer patients (no doses)

- A-bomb survivors (single acute dose)
- Esophageal cancer after treatment for breast cancer

- Mayak workers (chronic external and internal exposure)

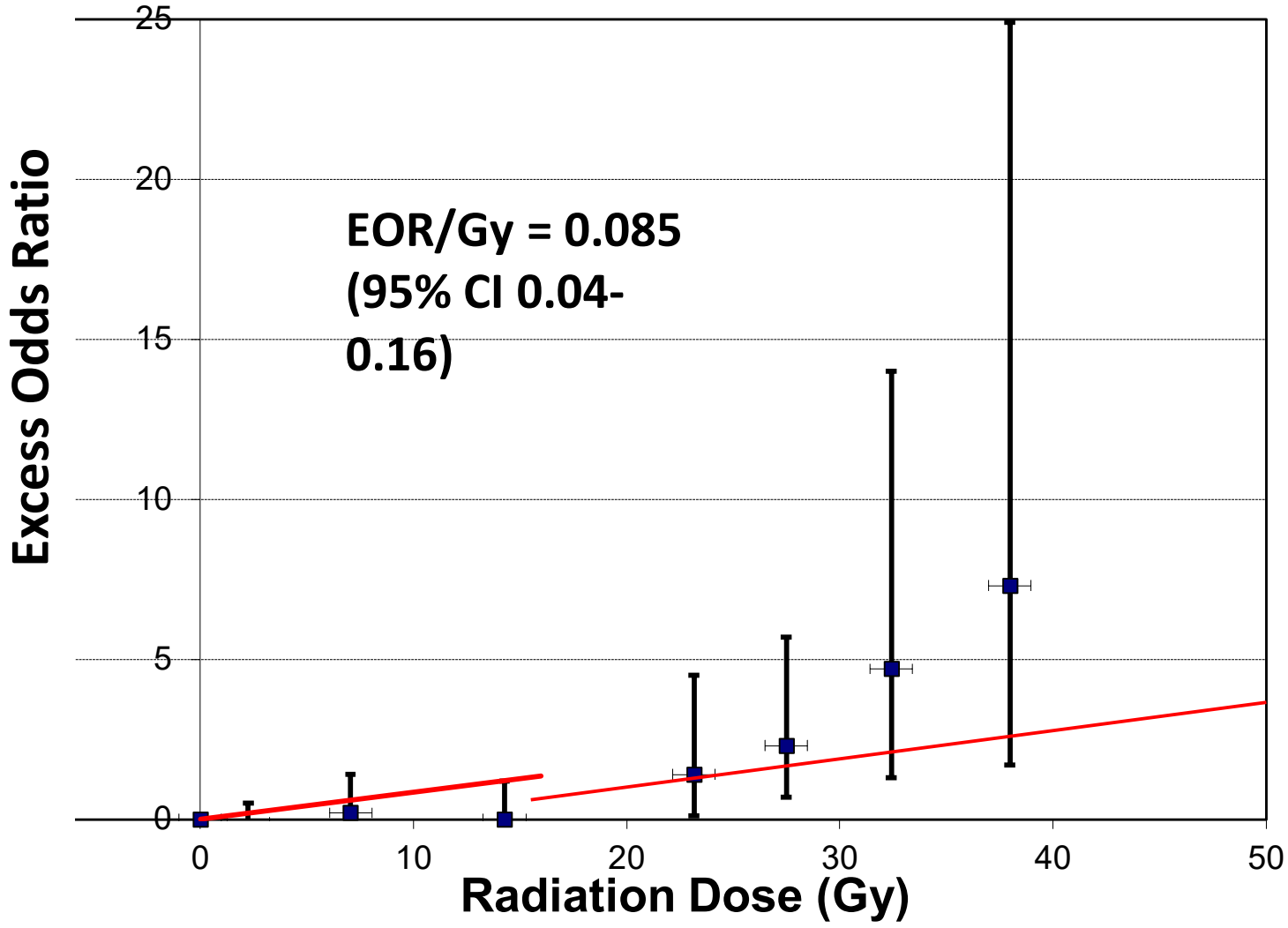
- Case-control study of lung cancer following Hodgkin lymphoma (interactions of radiation, chemotherapy, and smoking)

Esophageal Cancer After Breast Cancer (1)

- **252 cases/488 controls**
- **290,000 ≥5 year survivors of breast cancer**
- **Fractionated exposure received over a period of months**

Morton *et al.*, Annals of Oncology, 2012

Esophageal Cancer after Breast Cancer (2)



Morton *et al.*, Annals Oncol , 2012

Examples (2)

- **Testicular cancer patients (no doses)**
- **A-bomb survivors (single acute dose)**
- **Mayak workers (chronic external and internal exposure)**
- **Case-control study of lung cancer following Hodgkin lymphoma (interactions of radiation, chemotherapy, and smoking)**

Mayak nuclear facility

Mayak Worker Cohort

- 26,000 workers hired 1948-82
- 25% female
- 13,000 deaths
- 3,000 deaths from cancer

- Exposed to both external radiation and to plutonium

Mayak Dosimetry

- **Annual dose estimates (external and plutonium) available for each year exposed**
- **Most analyses based on the assumption that risk depends primarily on cumulative dose received 5 years prior to the time at risk**
- **Cumulative dose increases as workers are followed over time**

Mayak plutonium worker hired in 1950 at age 25 (1)

Calendar year	Attained age	Annual Pu dose to the lung (Gy)
1950	25	3.1
1951	26	2
1952	27	1.5
1953	28	1
1954	29	.9
1955	30	.7
1956	31	.5
1957	32	.5
1958	33	.5
…	…	…

Mayak plutonium worker hired in 1950 at age 25 (2)

Calendar year	Attained age	Annual Pu dose to the lung (Gy)	Cumulative Pu dose to the lung (Gy)
1950	25	3.1	0
1951	26	2	3.1
1952	27	1.5	5.1
1953	28	1	6.6
1954	29	.9	7.6
1955	30	.7	8.5
1956	31	.5	9.2
1957	32	.5	9.7
1958	33	.5	10.2
…	…	…	…

Mayak plutonium worker hired in 1950 at age 25 (3)

Calendar year	Attained age	Annual Pu dose to the lung (Gy)	Cumulative Pu dose to the lung (Gy)	Cumulative Pu dose to the lung with 5-year lag (Gy)
1950	25	3.1	0	0
1951	26	2	3.1	0
1952	27	1.5	5.1	0
1953	28	1	6.6	0
1954	29	.9	7.6	0
1955	30	.7	8.5	0
1956	31	.5	9.2	3.1
1957	32	.5	9.7	5.1
1958	33	.5	10.2	6.6
…	…	…	…	…

Mayak Worker Study

- **The principle sites of plutonium deposition are the lung, liver, and bone**

- **Objective:**

  Evaluate risk of lung, liver and bone cancer as a function of dose from plutonium, external dose, and other factors

Mayak Worker Cohort

Objectives of Lung Cancer Analyses:

- **Evaluate the shape of the dose-response function**
- **Quantify the ERR**
- **Evaluate possible modification of the ERR by sex, attained age, smoking and other variables**

Model for Mayak Worker Data (1)

ERR is the sum of terms for the effects of

- **External dose (d_{ext})**
- **Internal dose from plutonium (d_{plu})**
  - **Only those whose plutonium doses can be estimated contribute**
- **Internal exposure using surrogate categories**
  - **For those whose plutonium doses could not be estimated**

Model for Mayak Worker Data (2)

Internal dose term = f(d_{plu}, *s*, *attage*)

d_{plu} = organ dose from plutonium in Gy lagged by 5 years

***s* indicates sex**

***attage* indicates attained age**

Model for Mayak Worker Data (3)

Internal dose term = f(d_{plu}, *s*, *attage*)

d_{plu} = organ dose from plutonium in Gy lagged by 5 years

***s* indicates sex**

***attage* indicates attained age**

Plutonium Dose-Response

d_{plu} = lung dose from plutonium in Gy lagged by 5 years

ERR(d_{plu}) = excess relative risk as a function of dose

Evaluated ERR(d_{plu}) =

θ_j	Categories of dose
$\beta_1 d_{plu}$	Linear
$\beta_1 d_{plu} + \beta_2 d_{plu}^2$	Linear-quadratic
$\beta_1 d_{plu}^{\eta}$	Power function

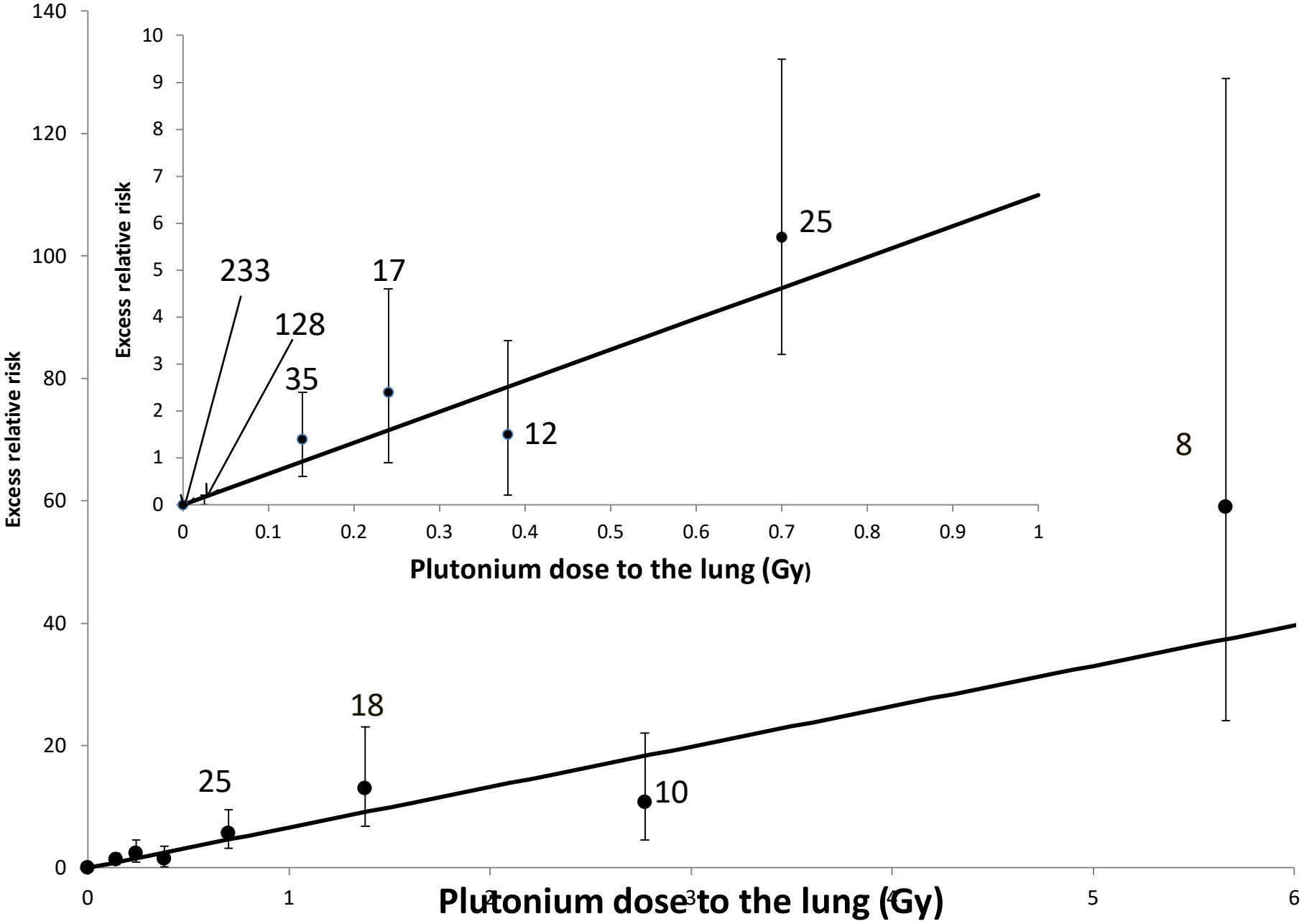
(Also evaluated dependence of ERR(d_{plu}) on age, sex and smoking)

Lung cancer: Plutonium Dose-Response

Lung Dose (Gy)	RR (95% CI)	Deaths
0	1.0	233
>0 - .1	0.99 (<1 - 1.2)	128
.1-	2.4 (1.6 – 3.4)	35
.2-	3.4 (1.9 – 5.6)	17
.3-	2.5 (1.2 – 4.5)	12
.5-	6.7 (4.2 - 11)	25
1-	14 (7.8 - 24)	18
2-	12 (5.5 – 23)	10
4+	60 (25 - 130)	8

Estimates for males at age 60

Gilbert et al. 2013


Excess relative risk
Plutonium dose to the lung (Gy)
233
128
35
17
25
12
8
18
25
10

Lung cancer: Plutonium Dose-Response

- **Dose-response well described by a linear function**
- **Linear-quadratic function did not improve fit over linear function (p > 0.5)**
- **Power function:** $\beta_1 d_{plu}^{\eta}$
  - **Power (η) estimated to be 1.02 (0.84 – 1.23)**

Gilbert et al. 2013

Lung Cancer: Modification by Sex

ERR per Gy for plutonium

Males: 7.1 (4.9 – 10)

Females: 15 (7.6 – 29)

Female/Male ratio = 2.1 (1.0 – 4.3)

Results shown are for attained age 60

Gilbert et al. 2013

Lung Cancer: Modification by Smoking

ERR per Gy for plutonium

Smokers: 6.9 (4.6 – 10)

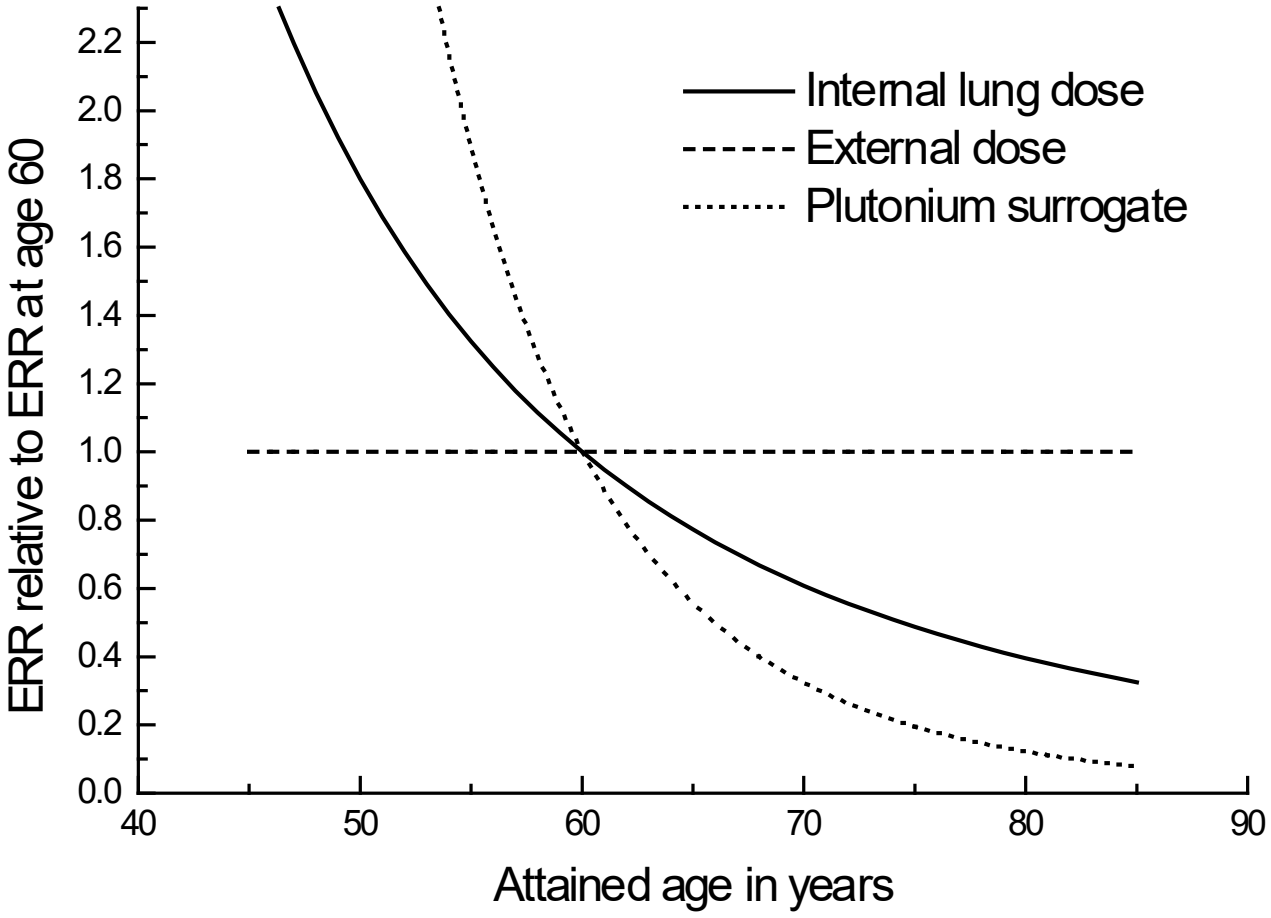
Non-smokers: 29 (9.8 – 83)

Non-smoker/Smoker ratio = 4.1 (1.4 – 12)

Results shown are for attained age 60

Gilbert et al. 2013

ERR/Gy by Attained Age



Gilbert et al. 2003

Examples (3)

- **Testicular cancer patients (no doses)**
- **A-bomb survivors (single acute dose)**
- **Mayak workers (chronic external and internal exposure)**
- **Case-control study of lung cancer following Hodgkin lymphoma (interactions of radiation, chemotherapy, and smoking)**

Lung Cancer Following Hodgkin Lymphoma (HL)

- **227 lung cancer diagnosed at least one year following HL diagnosis**

- **445 controls matched on**
  - **Registry, age, sex, race**
  - **Calendar year of HL diagnosis**
  - **Survival at least as long as case**

- **Data on radiotherapy, chemotherapy, and smoking**

Lung Cancer Following HL

- **Case-control study** (Travis et al. 2002; Gilbert et al. 2003)
- **Investigate interaction of 3 exposures**

Exposure	Measure
Radiation	Dose to site of lung tumor (dose)
Alkylating agents (AA)	Number of cycles (cyc)
Smoking	Pack-years (pks)

Lung Cancer Following HL: Some Candidate Models

I. **Multiplicative interaction for all exposures:**

$$(1 + \beta_{smk}\,pks)(1 + \beta_{rad}\,dose)(1 + \beta_{AA}\,cyc)$$

II. **Additive interaction for all exposures:**

$$(1 + \beta_{smk}\,pks + \beta_{rad}\,dose + \beta_{AA}\,cyc)$$

III. **Multiplicative for smoking and treatment: additive for radiation and alkylating agents**

$$(1 + \beta_{smk}\,pks)(1 + \beta_{rad}\,dose + \beta_{AA}\,cyc)$$

Lung Cancer Following HL (1)

More general models for radiation and AA therapy

Example:

$(1 + \beta_{smk}\, pks)\,(1 + \beta_{rad}\, dose + \beta_{AA}\, cyc + \gamma\, dose*cyc)$

$\gamma = 0$ yields Model III (additive)

$\gamma = \beta_{rad}\, \beta_{AA}$ yields Model I (multiplicative)

Fitted model: $(1 + 0.15\, dose + 0.75\, cyc + .001*dose*cyc)$

Nearly identical fit to Model III

Improved fit over Model I ($p = .017$)

Lung Cancer Following HL (2)

Compared the fits of several models.

Conclusions:

- **Interaction of radiation and alkylating agents almost exactly additive; could reject multiplicative model**
- **Interaction of radiation and smoking compatible with multiplicative relationship; could reject additive model**
- **Model III described data well**

Interpreting Data from Multiple Studies (1)

- **Wealth of epidemiologic data pertaining to radiation risks**

- **Hence, a need to summarize information from more than one study**

Interpreting Data from Multiple Studies (2)

- **Several studies addressing common issue**

Examples: Multiple studies of

- **breast cancer after exposure to external radiation**
- **thyroid cancer after exposure to external radiation in childhood**
- **leukemia after exposure to external radiation in childhood**
- **nuclear workers exposed to external radiation**

Interpreting Data from Multiple Studies (3)

- **Several studies addressing common issue**
- **How do we summarize the data?**

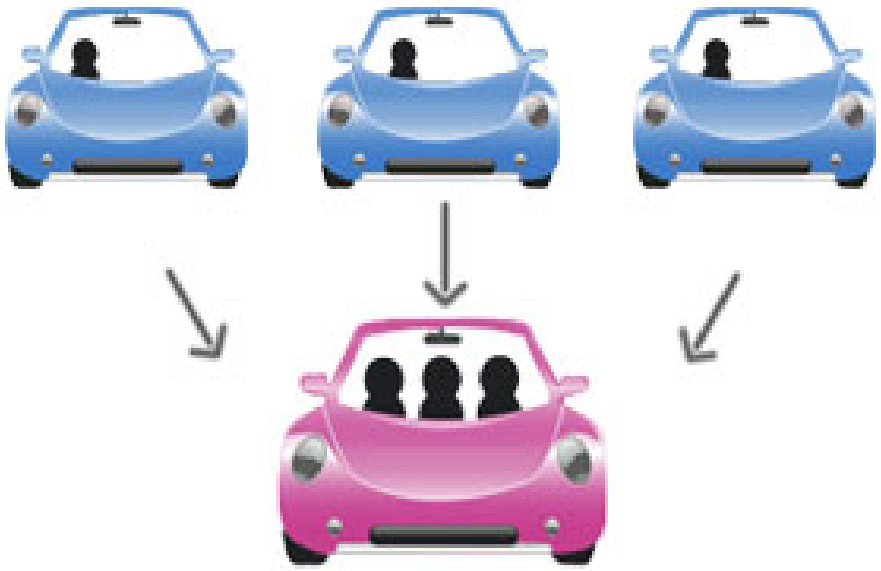
Meta-analyses: Analyze published results from different studies

Pooled analyses: Analyze combined data from individual subjects

- **Pooled analyses more common in radiation epidemiology**

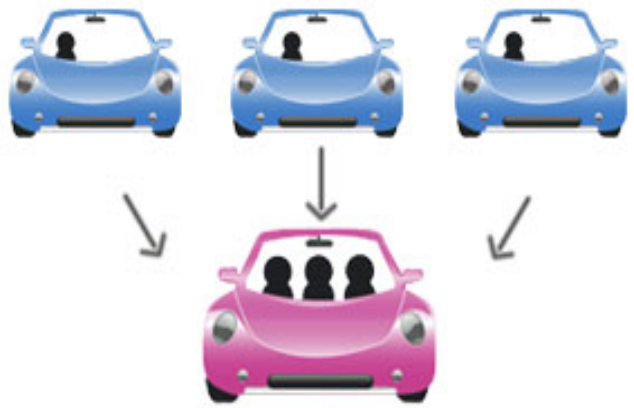
Pooled analyses (1)

- **Analyze combined data from several studies**



Pooled analyses (2)

- **Analyze combined data from several studies**
- **Obtain more precise estimates of risk**
- **Opportunity for understanding differences and similarities in studies**



Pooled analyses (3)

- Analyze combined data from several studies
- Obtain more precise estimates of risk
- Opportunity for understanding differences and similarities in studies
  - Comparable statistical methods
  - Presenting results in comparable format

Interpreting Data from Multiple Studies

- **Several studies addressing common issue**

Examples: Multiple studies of

- **breast cancer after exposure to external radiation**
- **thyroid cancer after exposure to external radiation in childhood**
- **leukemia after exposure to external radiation in childhood**
- **nuclear workers exposed to external radiation**

Studies of Nuclear Workers at Individual Facilities

Population	Country	Publication date(s)
Hanford Site	US	1977, 1978, …, 1993
Oak Ridge Nat'l Lab.	US	1985, 1991
Rocky Flats Weapons Plant	US	1987
Atomic Energy Authority	UK	1985, 1993
Sellafield Plant	UK	1986, 1994, 1999
Atomic Weapons Establish.	UK	1988
Atomic Energy of Canada	Canada	1987
Savannah River Plant	US	1988, 1999
Mound Laboratory	US	1991, 2014
Los Alamos Nat'l Lab.	US	1994
Rocketdyne	US	1999, 2006, 2011
Mallinckrodt Chemical	US	2000

Studies of Nuclear Workers at Individual Facilities (2)

Population	Country	Publication Date
National Dose Registry	Canada	1998, 2001
Nuclear reactor workers	Finland	2002
Nuclear industry workers	Japan	1997, 2003
Nuclear power workers	US	2004
Nuclear power workers	Canada	2004
Atomic Energy Commission	France	2004
National Electricity Co.	France	2005
Nuclear workers	Belgium	2005
Idaho National Engineering and Environmental Lab.	US	2005
Nuclear industry workers	Australia	2005
+ many more studies		

Rationale for studying nuclear workers exposed to low doses of external radiation

- Current risk estimates based on Japanese A-bomb survivors and others exposed at high dose rates
- Uncertainty in extrapolating to low doses and dose rates
- For workers, doses deliberately limited as a protection to the worker
- Provide a direct assessment of risks at low doses and dose rates

Magnitude of Doses

Current risk estimates:

Driven by doses of 0.5+ Gy

Worker-based estimates:

Driven by doses 0.1-0.5 Gy

Of interest for risk assessment:

0 - 0.1 Gy

International Nuclear Workers Study (INWORKS)

- **308,297 workers from the France, UK and US**

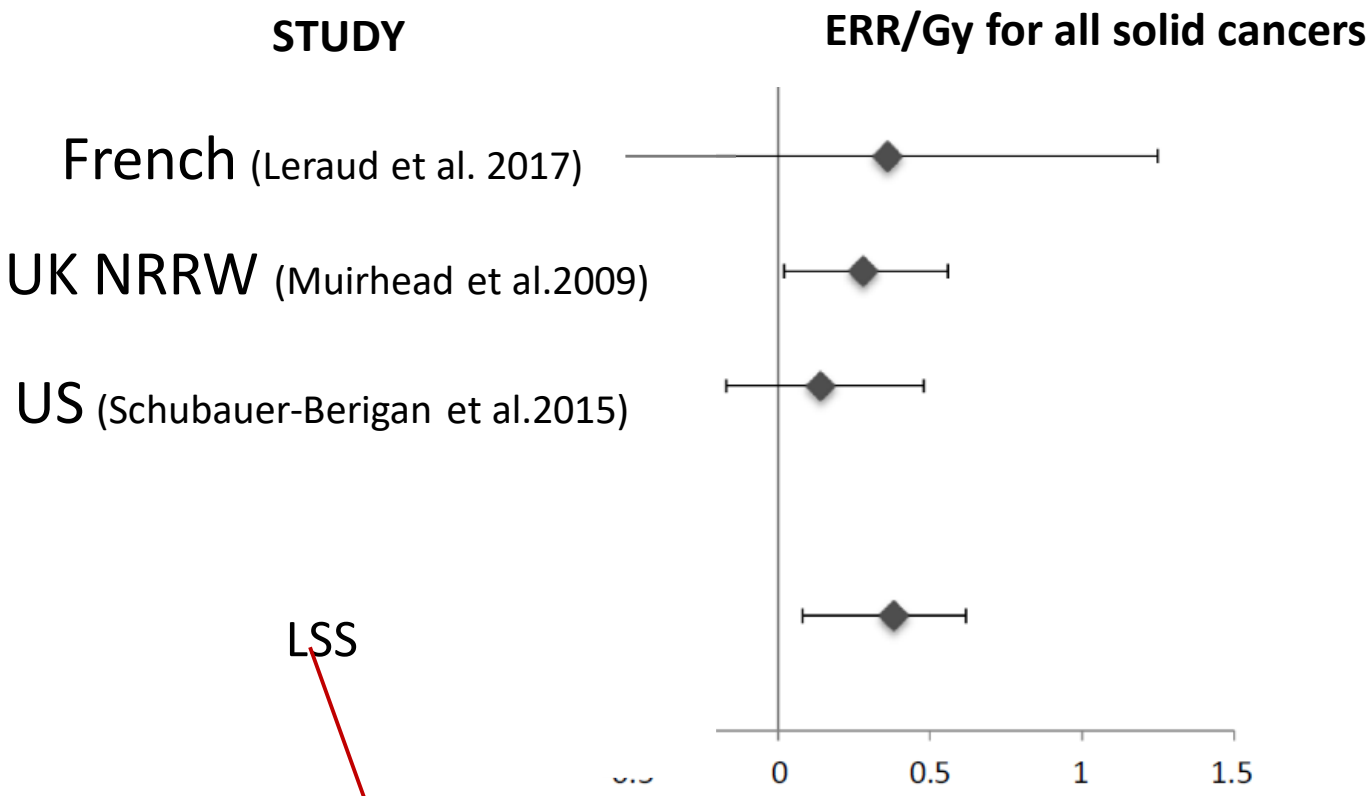
- **17,957 deaths due to solid cancers (Richardson et al. 2015)**

Earlier country specific analyses

Country	Number of workers	Number of cancer deaths
France (2013)	59,021	2,312
UK (2009)	174,541	8,107
US (2015)	119,195	10,877

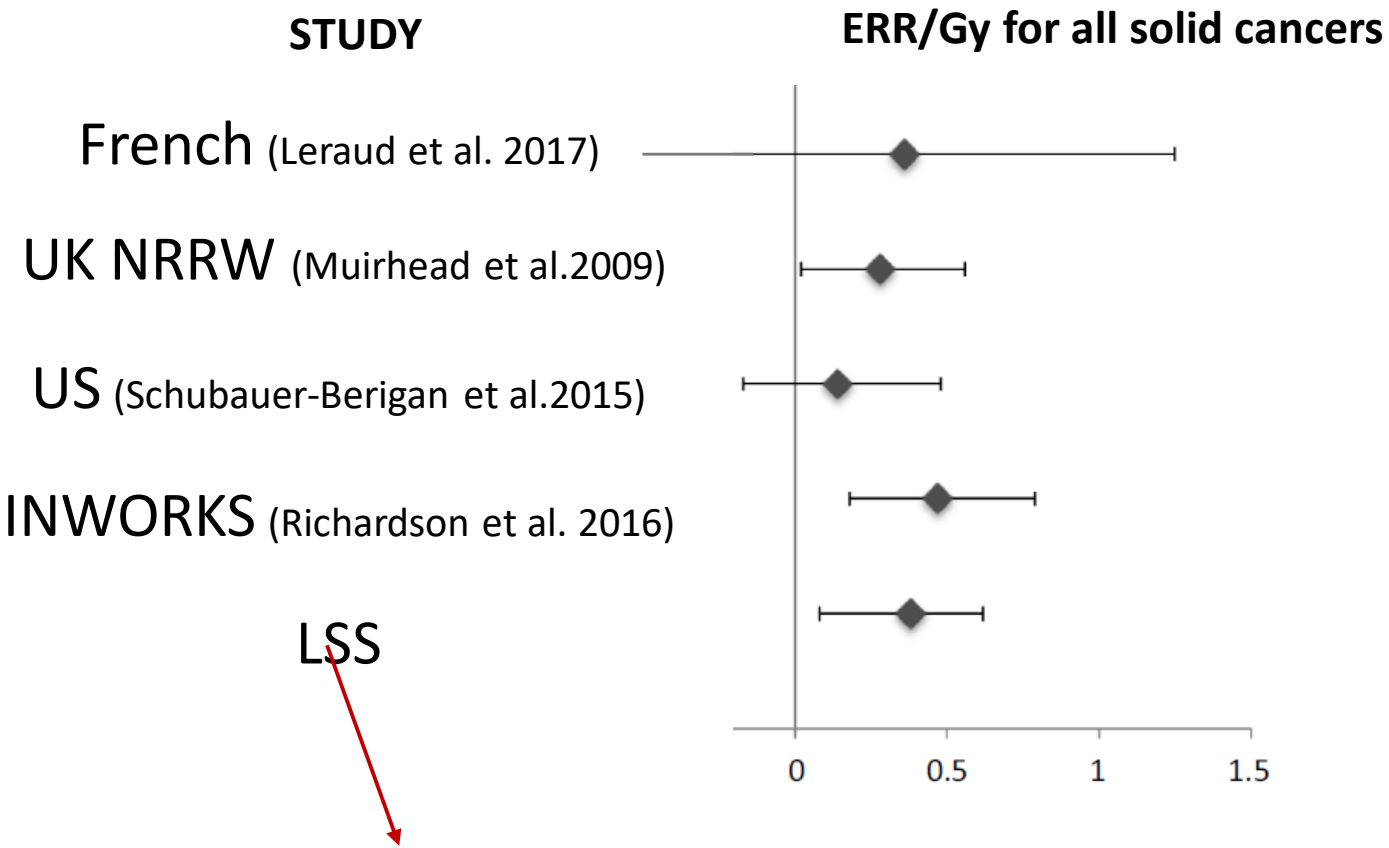
Muirhead et al. 2009
Schubauer-Berigan et al. 2015
Metz-Flamant et al. 2014

ERR/Gy for All Solid Cancers



LSS results based on males exposed at ages 20-65

ERR/Gy for All Solid Cancers



LSS results based on males exposed at ages 20-65

Influence Analyses for All Cancer Excluding Leukemia

	ERR/Gy (90% CI)
INWORKS	**0.48 (0.20, 0.78)**
Exclude	
France	**0.48 (0.19, 0.80)**
UK	**0.39 (-0.03, 0.85)**
US	**0.56 (0.19, 0.97)**

Richardson et al. 2015

Dose Measurement Uncertainties

- **The fact that dose can be measured is a major strength of radiation studies**
- **Dose estimates subject to errors**
- **In most studies, dose estimation is retrospective**
- **Complex systems often needed to estimate dose**

Possible effects of errors in dose estimates

- **Reduction in statistical power for detecting dose-response relationships**
  - **Statistical tests of null hypothesis of no effect are usually not distorted**

- **If errors not accounted for –**
  - **Bias in estimates of linear risk coefficients**
  - **Distortion of the shape of the dose-response function**
  - **Underestimation of uncertainty**

Types of error

- Impact on dose-response analyses depends on distinctions between --
- Classical errors and Berkson errors
- Shared errors and Errors that are independent for different subjects

Classical Error (Measurement Error)

- **Error that arises from an imprecise measuring device**
- **Adjustment needed to avoid**
  - **underestimation of linear risk coefficients**
  - **distortion of the shape of the dose-response**

Examples:

- **Errors in readings of film badge dosimeters**
- **Errors in bioassay measurements used in estimating internal doses**
- **Errors in questionnaire data used in estimating doses**

Examples (4)

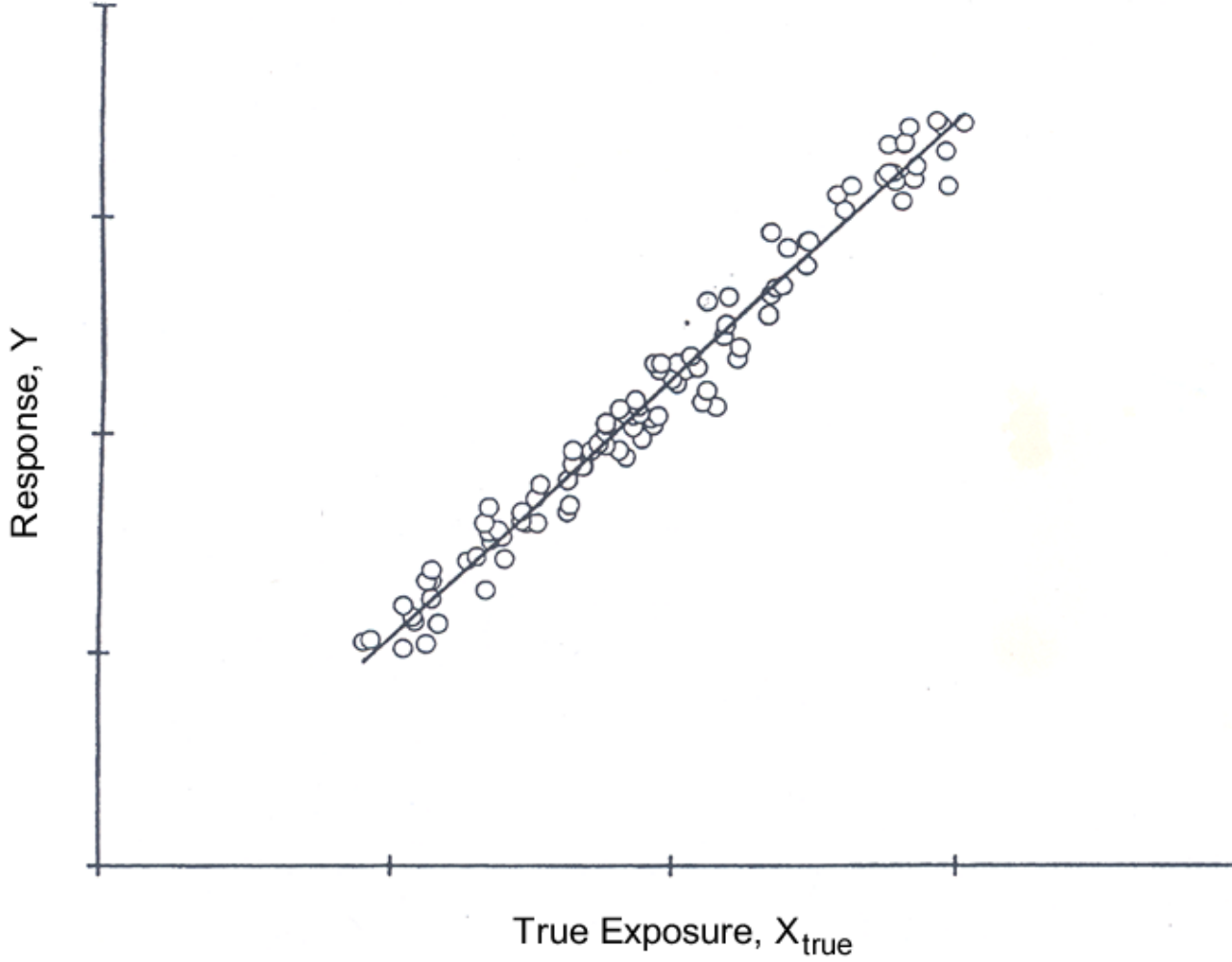
Taken from

DR Cox, SC Darby, GK Reeves, E Whitley,

"The Effects of Measurement Errors with Particular Reference to a Study of Exposure to Residential Radon"

National Cancer Institute, Publication No. 99-4541, 1999.

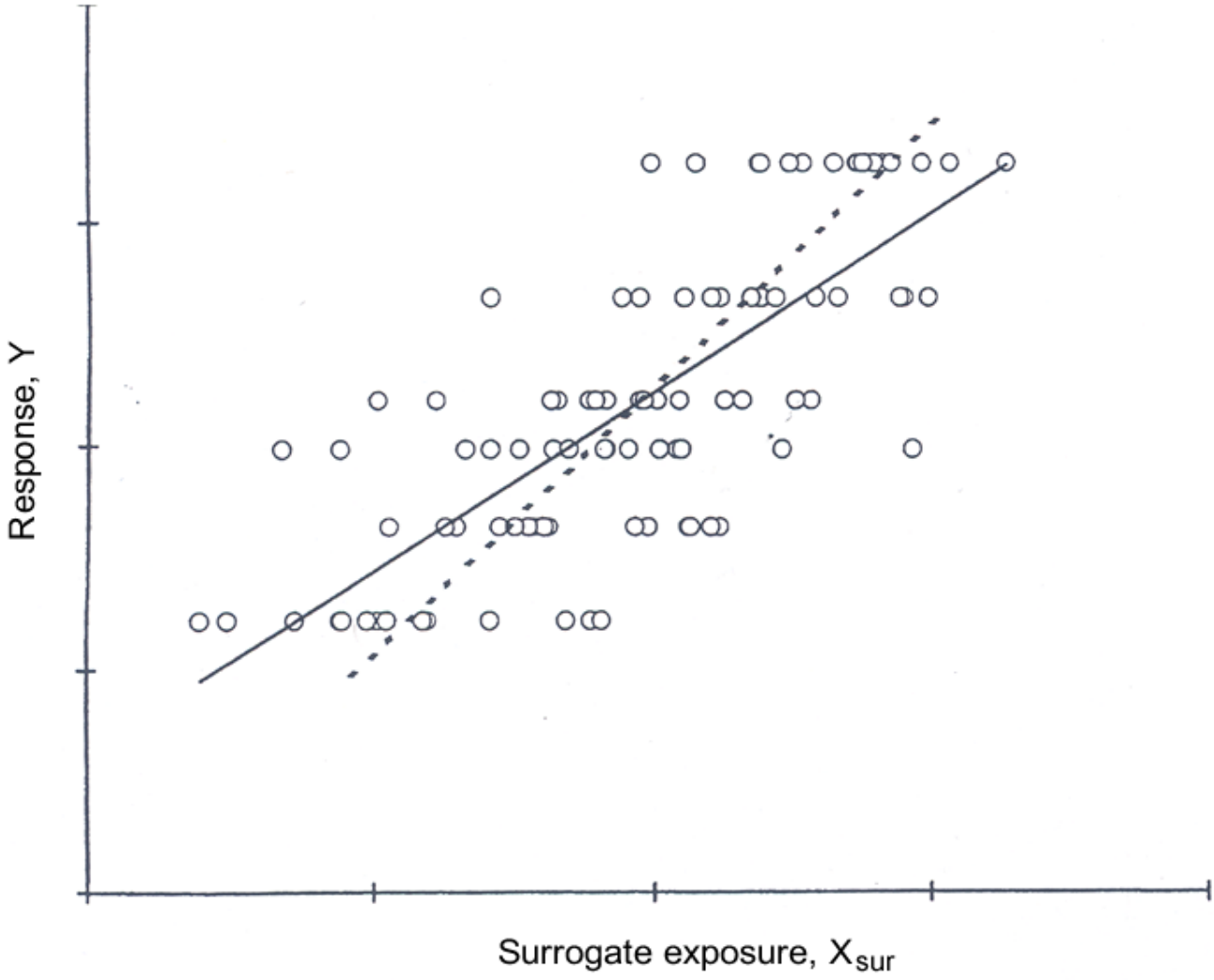
No error



Response versus true dose

Cox et al. 1999

Classical error



Response versus estimated dose

True response

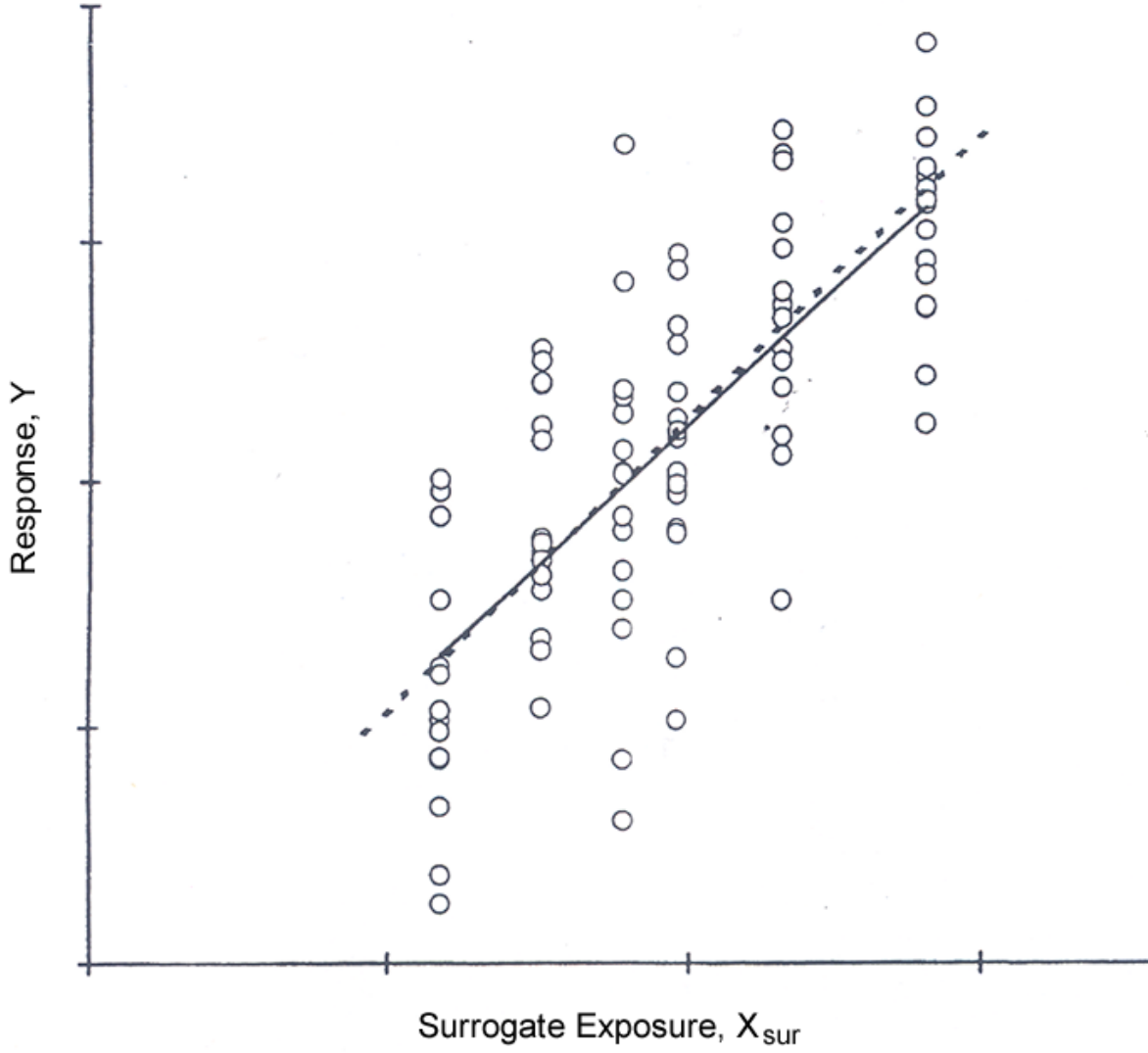
Cox et al. 1999

Berkson Error
(Grouping Error)

- **Error that results when**
  - **Single mean dose used to represent group**
  - **Same model is used to estimate doses for a group**

- **Little distortion in linear dose-response**
  (provided mean doses are correct)

Berkson error



——— Response versus estimated dose

- - - - - - - - - - - - True response

Cox et al. 1999

Shared Errors

- Also known as systematic errors

- Examples
  - Errors in the source term for an environmental exposure
  - Errors in doses assigned to groups of subjects
  - Errors in parameters of models used to convert measurements to doses

Impact of shared errors

Simplest situation:

- **Error shared by all subjects**
- **Expected value of the *estimated dose***

  = K x *true dose*
- **K is unknown**

- **Estimates of linear risk coefficients biased by a factor K**
- **Desirable to include uncertainty in K in confidence intervals**

Statistical Approaches for Accounting for Dosimetry Uncertainties

What they can't do

- **Improve power and precision of estimated risk coefficients**

What they can do

- **Avoid misleading results**
- **Correct biases in risk coefficients**
- **Widen confidence intervals to reflect dosimetry uncertainties**

Error Structure

Need information on --

- **Sources of error**
- **Nature and magnitude of error from each source (distribution functions)**
- **Extent to which errors from various sources are shared (correlated) for different subjects**

Examples Where Dosimetry Uncertainties Have Been Addressed

- **A-bomb survivors** (Pierce et al. 1996; 2008)
- **Residential radon exposure** (Reeves et al. 1998; Fearn et al. 2008)
- **Utah fallout study** (Thomas et al. 1999; Mallick et al. 2002; Li et al. 2007)
- **Underground miners** (Stram et al. 1999)
- **ORNL nuclear workers** (Stayner et al. 2007)
- **Hanford fallout study** (Stram and Kopecky 2003; Hoffman et al. 2007)
- **Tinea capitis patients** (Schafer et al. 2001; Lubin et al. 2004)
- **Chornobyl thyroid study** (Kopecky et al. 2006)

Radiation Risk Modeling (Summary)

- Basic definitions (relative and absolute risk)
- Interactions (multiplicative and additive)
- Dependence of risk on age, sex, and other variables
- Dose-response
- Pooled analyses
- Dose measurement uncertainties

Quiz Question #1

The excess relative risk ERR

A. **Is a commonly used measure in radiation epidemiology**
B. **Is often expressed as a linear function of dose**
C. **Can be allowed to depend on variables such age and sex**
D. **All of the above**

Quiz Question #1

The excess relative risk ERR

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B. **Is often expressed as a linear function of dose**
C. **Can be allowed to depend on variables such age and sex**
D. **All of the above**

Quiz Question #2

If the absolute risk increases with attained age, the relative risk will also increase with attained age

A. **True**

B. **False**

Quiz Question #2

If the absolute risk increases with attained age, the relative risk will also increase with attained age

A. **True**

B. **False**

Thank you for your attention!

- Questions?

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