

# **Radiation Risk Modeling**

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# Objectives of this Session

- Provide background to help understand presentations this week

## Will discuss

- Basic measures of risk
  - Commonly used radiation risk models
- 
- Not a “how to do it” session

# Analyzing data from radiation epidemiology studies

- What is the design of the study?
- What kind of data do we have?
- What do we want to learn?

# **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
  - LET

# **What do we want to learn from radiation epidemiology studies?**

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

# Outline

- **Basic definitions and concepts**
- **Radiation risk modeling**
  - **General comments**
  - **Examples**

# 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



# Incidence rate

- **Risk per unit of time:**
  - Expressed as cases per population and time period
- **Examples:**
  - Number of newly diagnosed cases of cancer expressed per 10,000 person-years
  - Number of deaths from cancer expressed per 10,000 person-years

# Comparing Incidence Rates

- **Compare disease incidence rates in an exposed population to rates in an unexposed population (referent group)**
- **Measures used for this purpose**
  - **Ratio of rates (relative effect)**
  - **Difference in rates (absolute effect)**

# Comparing Incidence Rates

- $R_e$  = Rate in “exposed” population
- $R_u$  = Rate in “unexposed” population
  
- **Relative risk (RR) =  $R_e/R_u$** 
  - Unitless measure
- **Excess absolute risk (EAR) =  $R_e - R_u$** 
  - Expressed per population and time period (e.g. per 10,000 person-years)

# Comparing Incidence Rates

**Excess absolute risk (EAR) =  $R_e - R_u$**

**Excess relative risk (ERR) =**

$$\mathbf{RR - 1 = R_e/R_u - 1}$$

**$R_u$  often referred to as baseline risk**

**Risk in exposed = Baseline risk + EAR**

**Risk in exposed = Baseline risk (1 + ERR)**

# Relative Risk

- **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

- Cancer sites receiving “high” radiation doses:  $RR = 3.5$
- Cancer sites receiving “low” radiation dose:  $RR = 1.4$
- Supports radiotherapy as contributing to excess risk

# Relative Risk

- **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 interventions/treatments**
  - **Counseling exposed subjects**
- **More difficult to evaluate than the RR**
  - **Requires cohort data**

# Examples from International Hodgkin Lymphoma Study<sup>1</sup>

	# cases	RR	EAR*
AML	169	21.5	6.3
All solid cancer	1726	2.0	33.1

\*Excess cases per 10,000 person-years

<sup>1</sup>Dores G, et al., JCO 20:3483-94, 2002. HL = Hodgkin lymphoma

# Reality

- **Epidemiologic studies are not controlled experiments**
- **Can't 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 unexposed)
- **Example: Studying lung cancer risk from radiation**
  - Smoking increases the risk of lung cancer
  - 30% of unexposed group smoke
  - 60% of exposed group smoke

# Confounding

**Risk in exposed = Baseline risk + EAR**

**Risk in exposed = Baseline risk (1 + ERR)**

- **If data available on potential confounders, can adjust analyses by including confounders in modeling the baseline risk**

# Confounding: Adjustment for demographic variables

- Analyses nearly always adjusted for attained age, sex, and often birth cohort
- Express baseline risk as a function of these variables
  - 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**

# Effect Modification

- **Measures of radiation risk (RR and EAR) can depend on other risk factors**
- **Modification can be different for RR than for EAR**

# Effect Modification

	Abs. Risk per 10 <sup>4</sup> person- year
<b>Non-smoker, no radiation</b>	<b>1.5</b>
<b>Non-smoker, radiation</b>	<b>3.0</b>
<b>Smoker, no radiation</b>	<b>10.0</b>
<b>Smoker, radiation</b>	<b>14.0</b>

# Effect Modification

	Abs. Risk per 10 <sup>4</sup> person-year	RR for radiation
<b>Non-smoker, no radiation</b>	<b>1.5</b>	<b>1.0</b>
<b>Non-smoker, radiation</b>	<b>3.0</b>	<b>2.0</b>
<b>Smoker, no radiation</b>	<b>10.0</b>	
<b>Smoker, radiation</b>	<b>14.0</b>	

**Radiation RR for non-smoker =  $3.0/1.5 = 2.0$**

# Effect Modification

	Abs. Risk per 10 <sup>4</sup> person-year	RR for radiation
Non-smoker, no radiation	1.5	1.0
Non-smoker, radiation	3.0	2.0
Smoker, no radiation	10.0	1.0
Smoker, radiation	14.0	1.4

Radiation RR for non-smoker =  $3.0/1.5 = 2.0$

Radiation RR for smoker =  $14.0/10.0 = 1.4$

# Effect Modification

	Abs. Risk per 10 <sup>4</sup> person-year	RR for radiation	EAR for Radiation per 10 <sup>4</sup> person-year
Non-smoker, no radiation	1.5	1.0	0.0
Non-smoker, radiation	3.0	2.0	1.5
Smoker, no radiation	10.0	1.0	
Smoker, radiation	14.0	1.4	

Radiation RR for non-smoker =  $3.0/1.5 = 2.0$

Radiation RR for smoker =  $14.0/10.0 = 1.4$

Radiation EAR for non-smoker =  $3.0 - 1.5 = 1.5$  per 10<sup>4</sup>

# Effect Modification

	Abs. Risk per 10 <sup>4</sup> person-year	RR for radiation	EAR for Radiation per 10 <sup>4</sup> person-year
<b>Non-smoker, no radiation</b>	<b>1.5</b>	1.0	<b>0.0</b>
<b>Non-smoker, radiation</b>	<b>3.0</b>	2.0	<b>1.5</b>
<b>Smoker, no radiation</b>	<b>10.0</b>	1.0	<b>0.0</b>
<b>Smoker, radiation</b>	<b>14.0</b>	1.4	<b>4.0</b>

Radiation RR for non-smoker =  $3.0/1.5 = 2.0$

Radiation RR for smoker =  $14.0/10.0 = 1.4$

Radiation EAR for non-smoker =  $3.0 - 1.5 = 1.5$  per 10<sup>4</sup>

Radiation EAR for smoker =  $14.0 - 10.0 = 4.0$  per 10<sup>4</sup>

# Outline

- **Basic definitions and concepts**
- **Radiation risk modeling**
  - **General comments**
  - **Examples**

# 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**

# Objectives of radiation risk modeling

- Quantify the ERR and EAR as functions of exposure (dose if available)
- Evaluate how the ERR and EAR depend on variables such as
  - Age at diagnosis of first cancer
  - Attained age
  - Time since exposure
  - Sex
  - Other risk factors

# Why do we need radiation risk models?

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

# Examples

- **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

- **International cohort of 40,576 1-year survivors**
  - Population-based cancer registries in Denmark, Finland, Norway, Sweden, Ontario, US (SEER)
- **Focused on second solid cancers in 20,987 10-year survivors**
  - 1694 second solid cancers
- **Mean age at diagnosis = 35 years**

# Testicular Cancer Study

- Cohort study
- Follow subjects over time
- Person-year can be considered as unit of analysis

## Example

- Patient diagnosed with TC in 1975 at age 35
- Becomes 10-year survivor in 1985 at age 45

# Example: Subject diagnosed with TC in 1975 at age 35

Calendar year	Attained age	Time since TC diagnosis	Age at TC diagnosis
1985	45	10	35
1986	46	11	35
1987	47	12	35
1988	48	13	35
1989	49	14	35
1990	50	15	35
1991	51	16	35
...	...	...	...

# **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**

# **Cohort Study Analyses: Cox regression**

- **Analyses based on individual subjects**
- **At each time that event occurs, compare exposure (and other variables) of subject experiencing event with exposures of all subjects at risk at that time**
- **Restricted to relative risk**

# Testicular Cancer Study

- **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)**

# Comparisons with the General Population

**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  $(O - E)/\text{person-years}$**

# Comparisons with the General Population

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 first cancer
  - Attained age
  - Time since diagnosis
  - Treatment (limited data)

# Evaluating dependencies of the RR and EAR on age and other variables

- Commonly used approach is to estimate the RR and EAR for each of several categories defined by the variables
- Use simple estimates:
  - $RR = O/E$
  - $EAR = (O-E)/\text{person-years}$

## Number of 2<sup>nd</sup> solid cancers<sup>1</sup>

Attained age(y)	Age at TC diagnosis (y)			All
	<30	30-39	40+	
< 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

<sup>1</sup>Among 10-year survivors of testicular cancer

## Relative risk (O/E)<sup>1</sup>

Attained age(y)	Age at TC diagnosis (y)			All
	<30	30-39	40+	
< 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

<sup>1</sup>Among 10-year survivors of testicular cancer

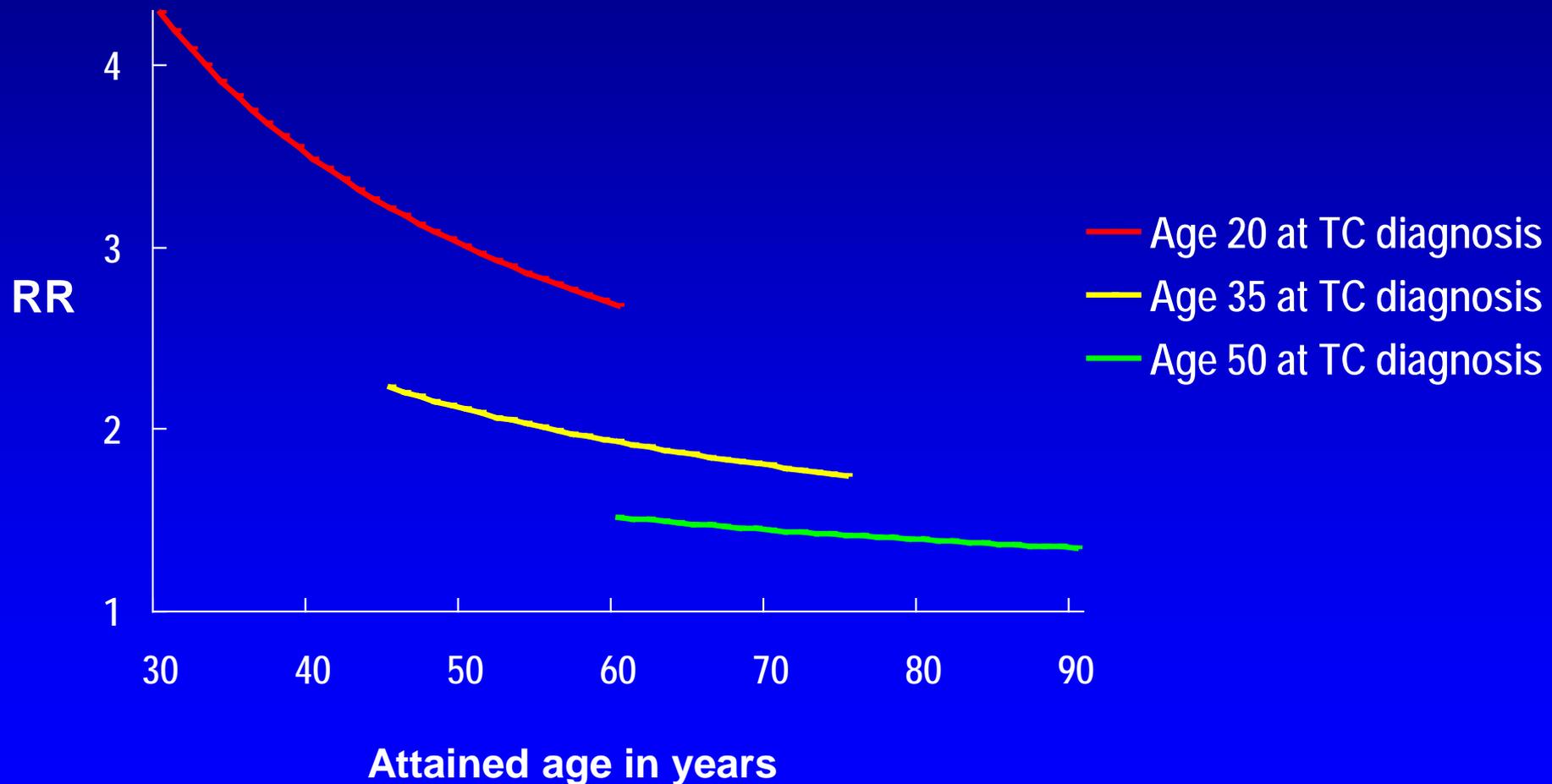
# Limitations of Categorical Approach

- **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**

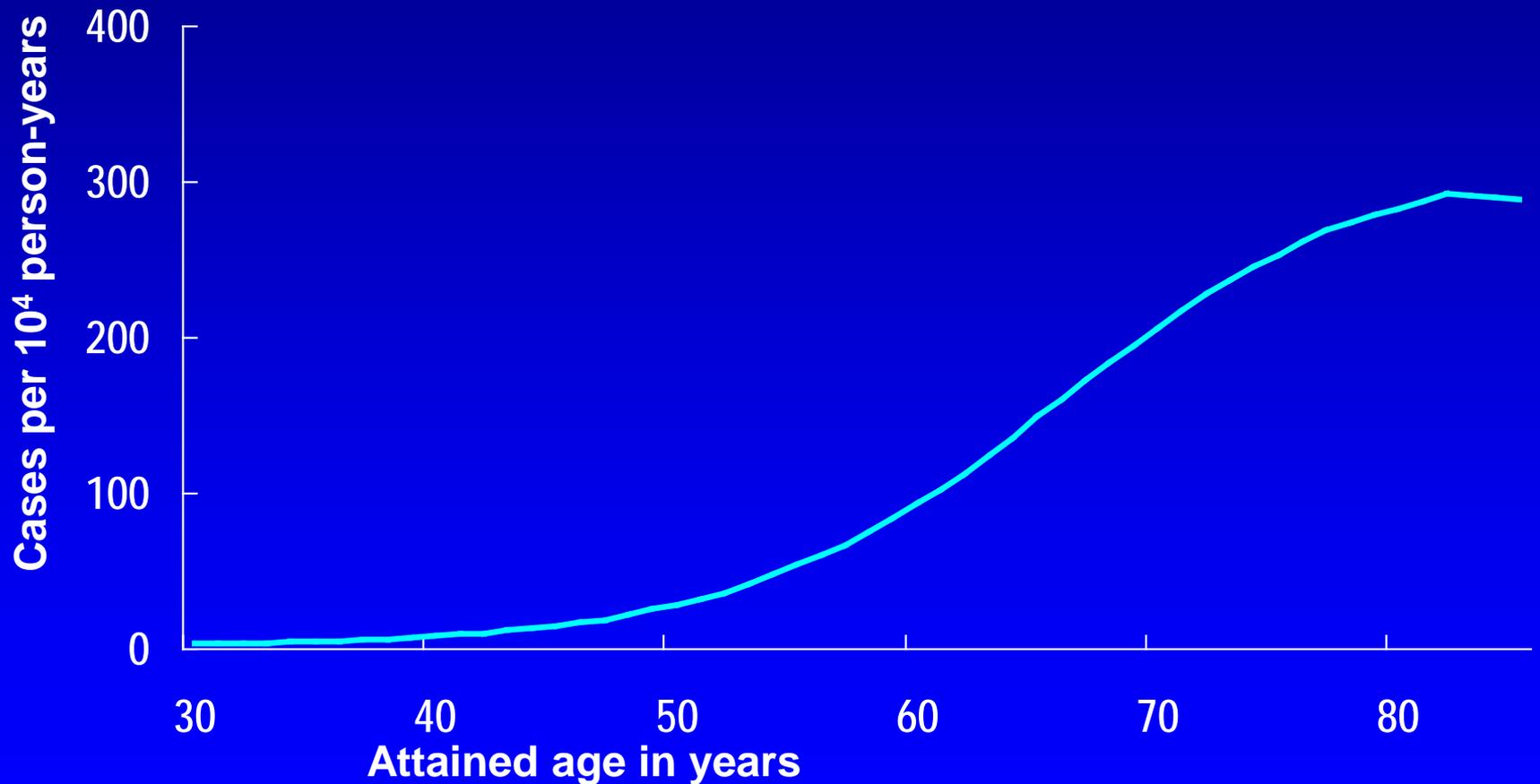
# Modeling RR and EAR

- Express RR and EAR as continuous functions of
  - age at diagnosis (*agedx*)
  - attained age (*age*)
  - other variables
- Example: Use ERR and EAR of the form
$$\beta \exp(\gamma \textit{agedx}) \textit{age}^\eta$$

# Relative risk of 2<sup>nd</sup> solid cancer in 10-year survivors of testicular cancer (TC)



# Baseline rate of solid cancer for males in in general population



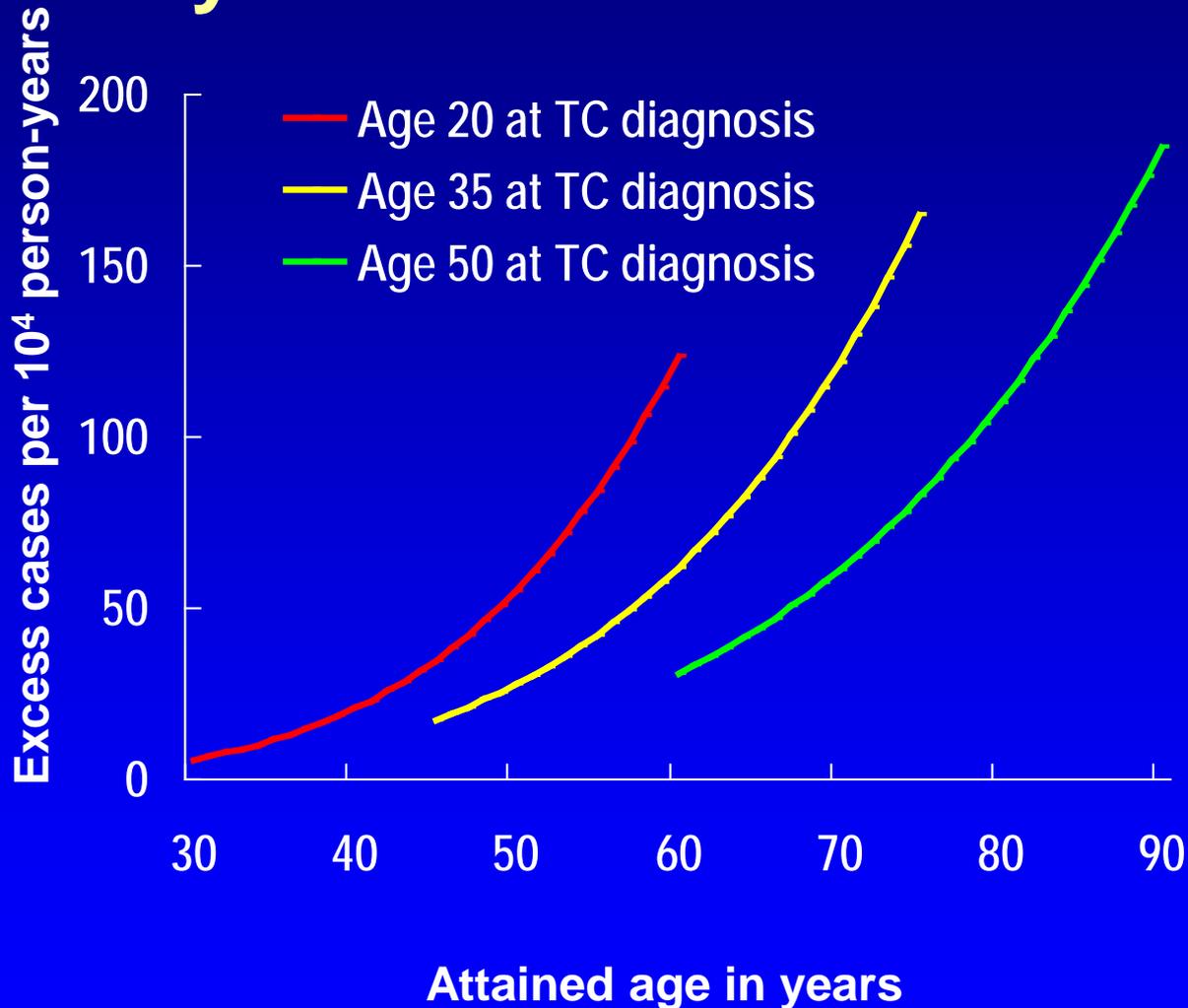
# Excess Absolute Risk (O–E)/10<sup>4</sup> pyr<sup>1</sup>

Attained age(y)	Age at TC diagnosis (y)			All
	<30	30-39	40+	
< 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

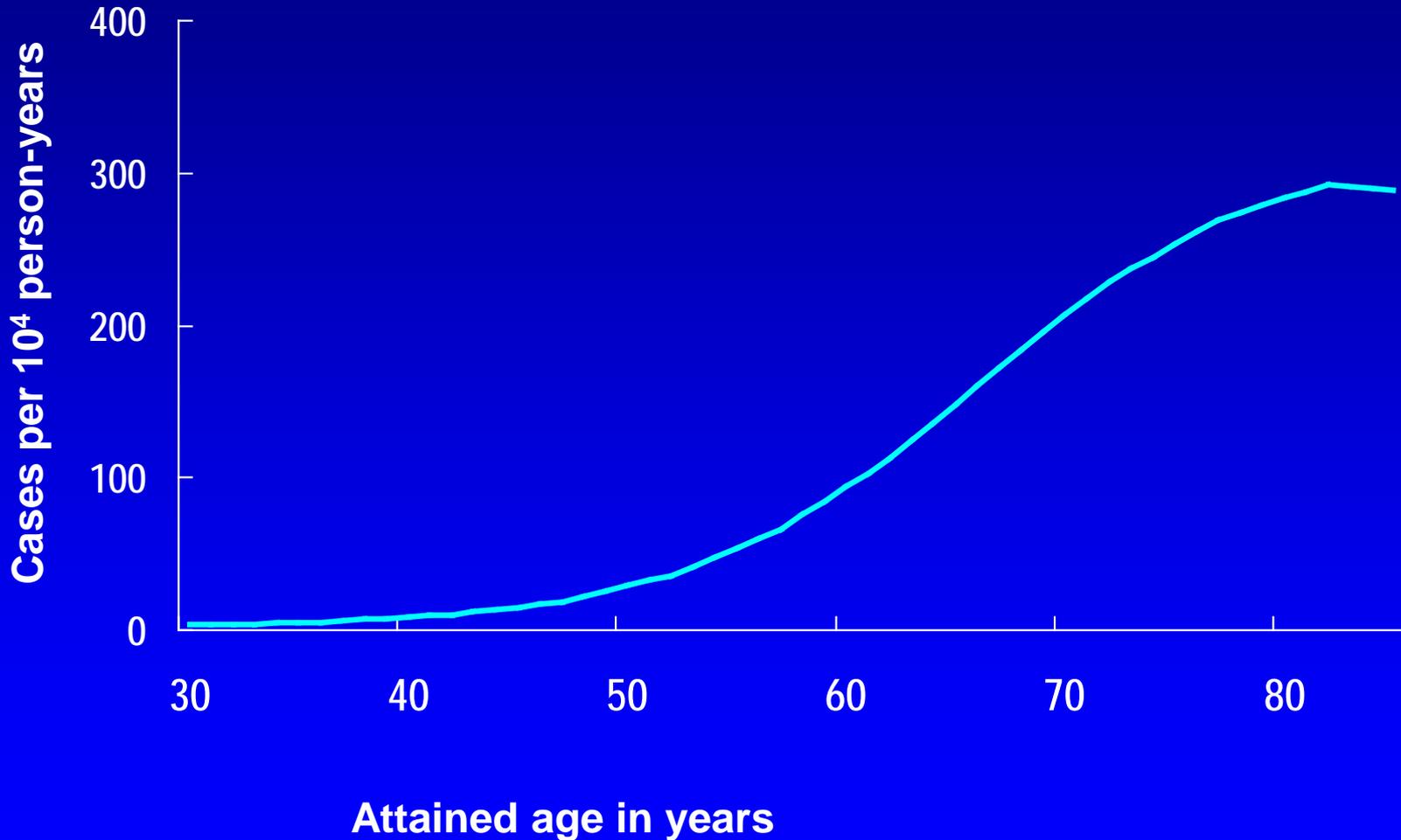
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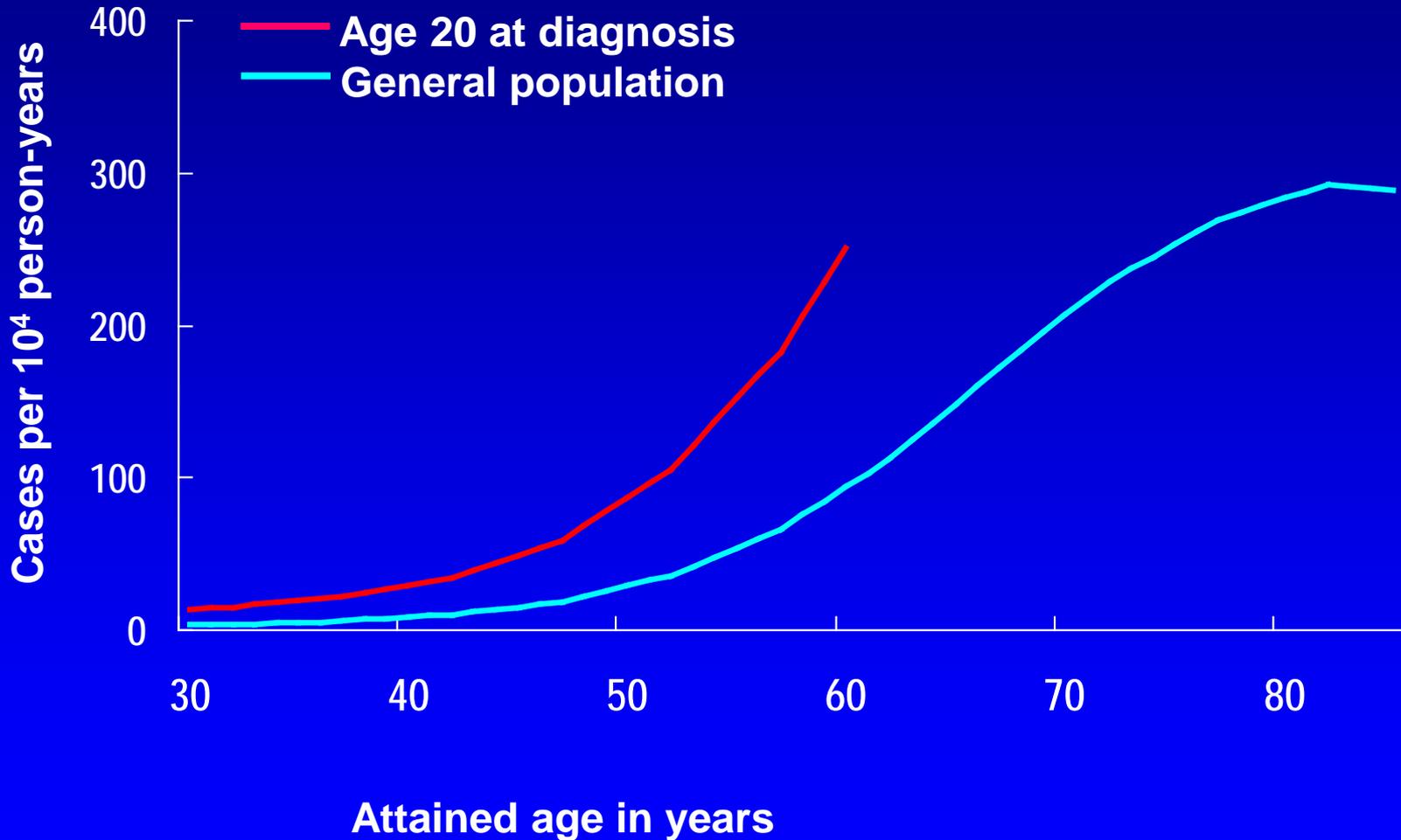
# Excess absolute risk of 2nd solid cancer in 10-year survivors of testicular cancer (TC)



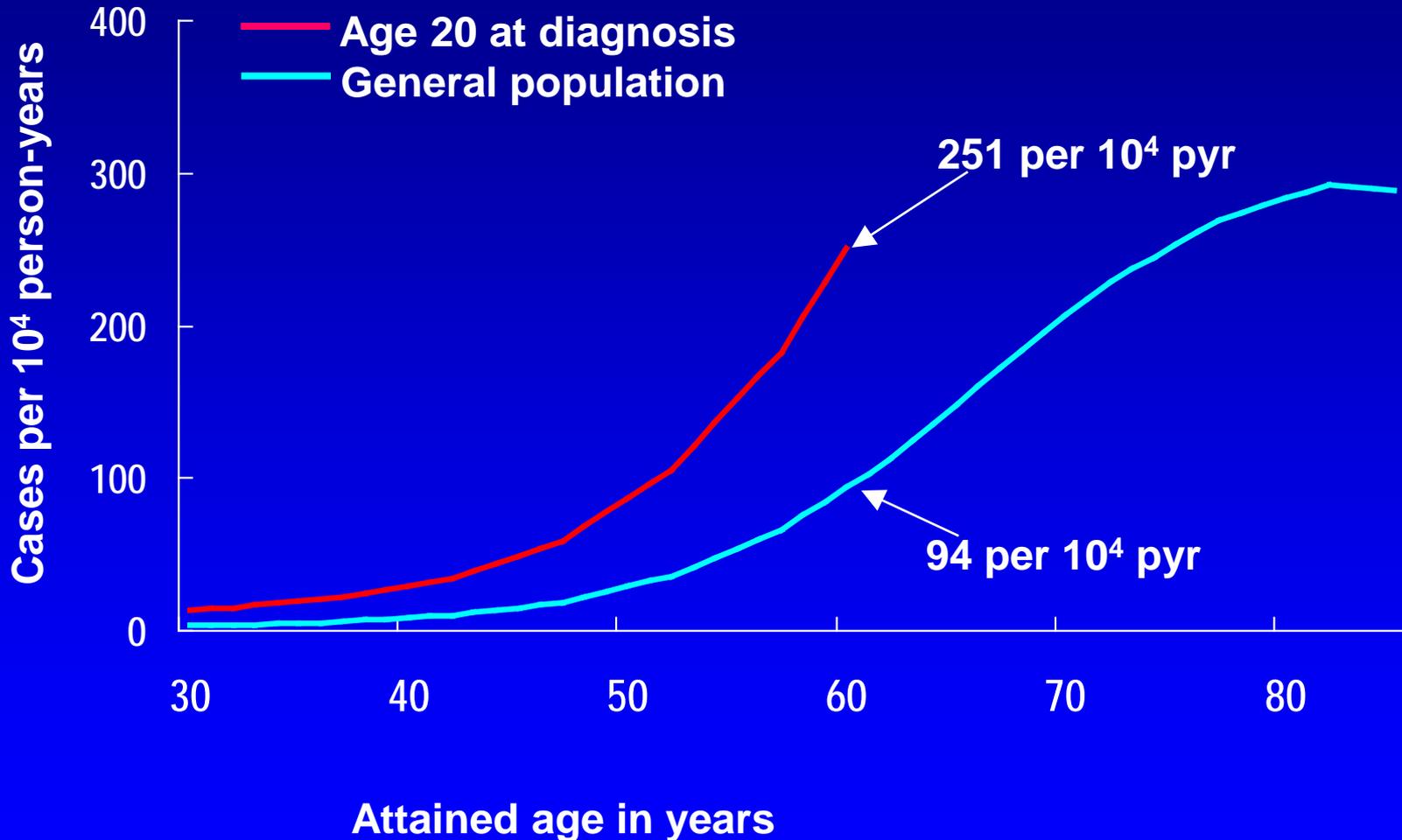
# Second solid cancer rate in testicular cancer patients diagnosed at age 20



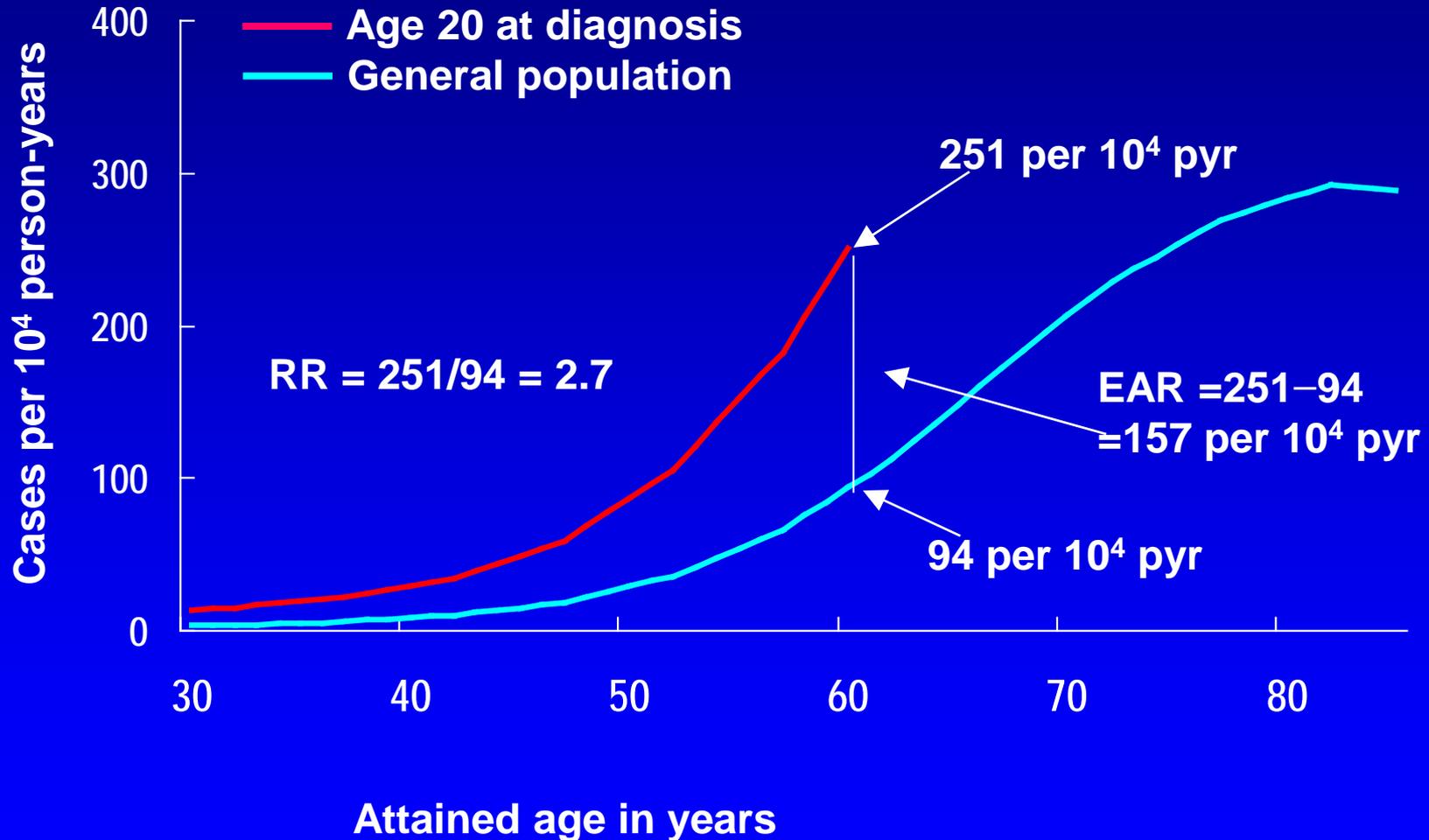
# Second solid cancer rate in testicular cancer patients diagnosed at age 20



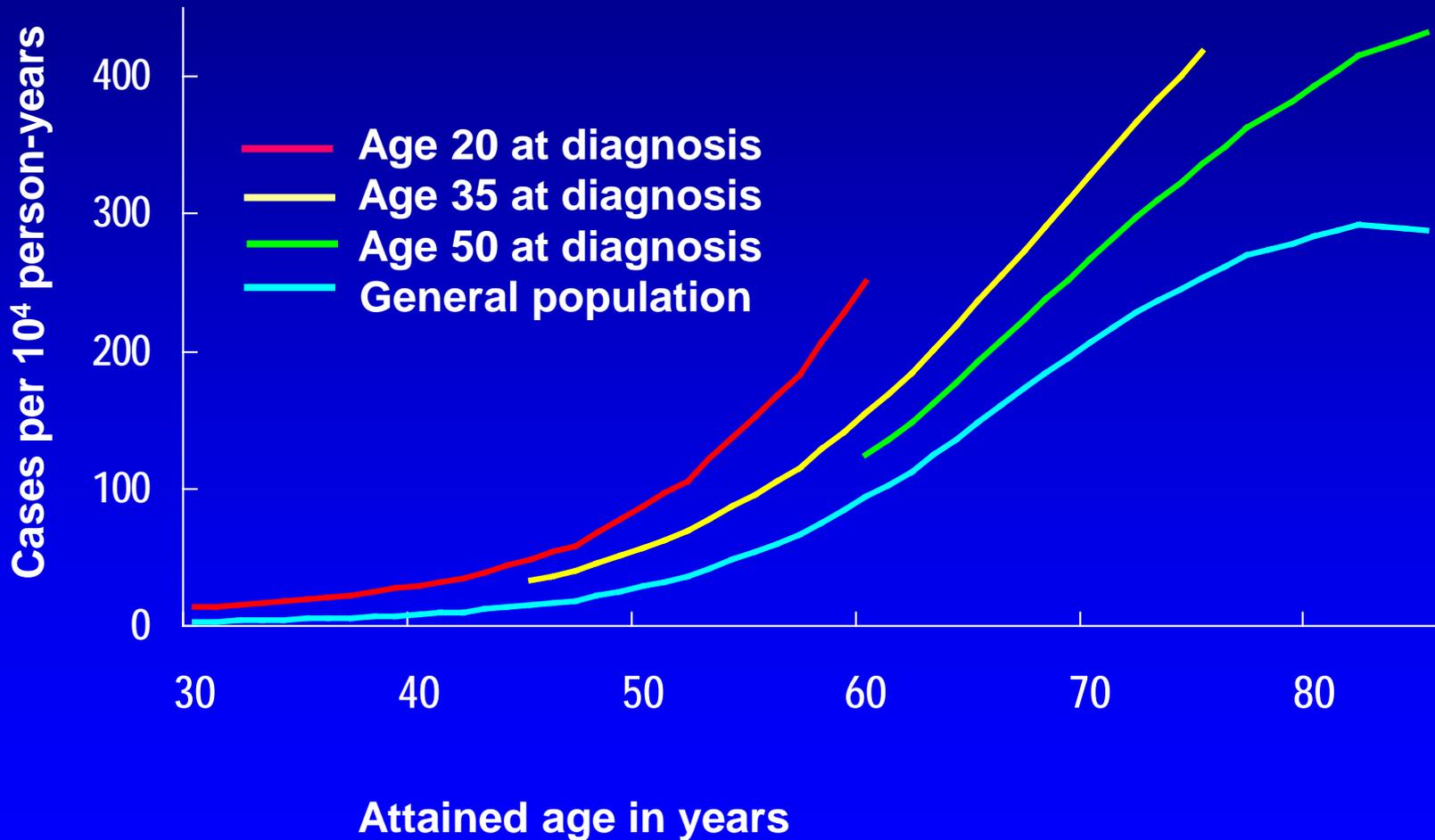
# Second solid cancer rate in testicular cancer patients diagnosed at age 20



# Second solid cancer rate in testicular cancer patients diagnosed at age 20



# 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

**Hypothetical example. Start with 100 patients.  
Assume rate for 2<sup>nd</sup> cancer is 2% per year**

<b>Year of follow-up</b>	<b># free of 2<sup>nd</sup> cancer at start of interval</b>	<b>Expected # of 2<sup>nd</sup> cancers in interval</b>	<b>Cumulative % with 2<sup>nd</sup> cancers by end of interval</b>
<b>1</b>	<b>100</b>	<b>.02x100=2.0</b>	<b>2</b>
<b>2</b>	<b>98.0</b>	<b>.02x98 = 2.0</b>	<b>4</b>
<b>3</b>	<b>96.0</b>	<b>.02x96 = 1.9</b>	<b>5.9</b>
<b>4</b>	<b>94.1</b>	<b>.02x94 = 1.9</b>	<b>7.8</b>
<b>5</b>	<b>92.2</b>	<b>.02x92 = 1.8</b>	<b>9.6</b>

**Competing risk (dying of 1<sup>st</sup> cancer): Assume EAR of 30% in first year, 10% in 2<sup>nd</sup> year, 0% thereafter**

<b>Year of follow-up</b>	<b># free of 2<sup>nd</sup> cancer at start of interval</b>	<b># of 2<sup>nd</sup> cancers in interval</b>	<b>Cumulative % of 2<sup>nd</sup> cancers by end of interval</b>	<b># of deaths from competing risk</b>
<b>1</b>	<b>100</b>	<b>.02x100= 2</b>	<b>2</b>	<b>.3x100=30</b>
<b>2</b>	<b>68</b>	<b>.02x68= 1.4</b>	<b>3.4</b>	<b>.1x68= 6.8</b>
<b>3</b>	<b>60</b>	<b>.02x60= 1.2</b>	<b>4.6</b>	<b>0</b>
<b>4</b>	<b>59</b>	<b>.02x59= 1.2</b>	<b>5.8</b>	<b>0</b>
<b>5</b>	<b>57</b>	<b>.02x56= 1.1</b>	<b>6.9</b>	<b>0</b>

# Cumulative Risk in Testicular Cancer Patients

- Used EAR model for solid cancer risks along with solid cancer rates in the general population

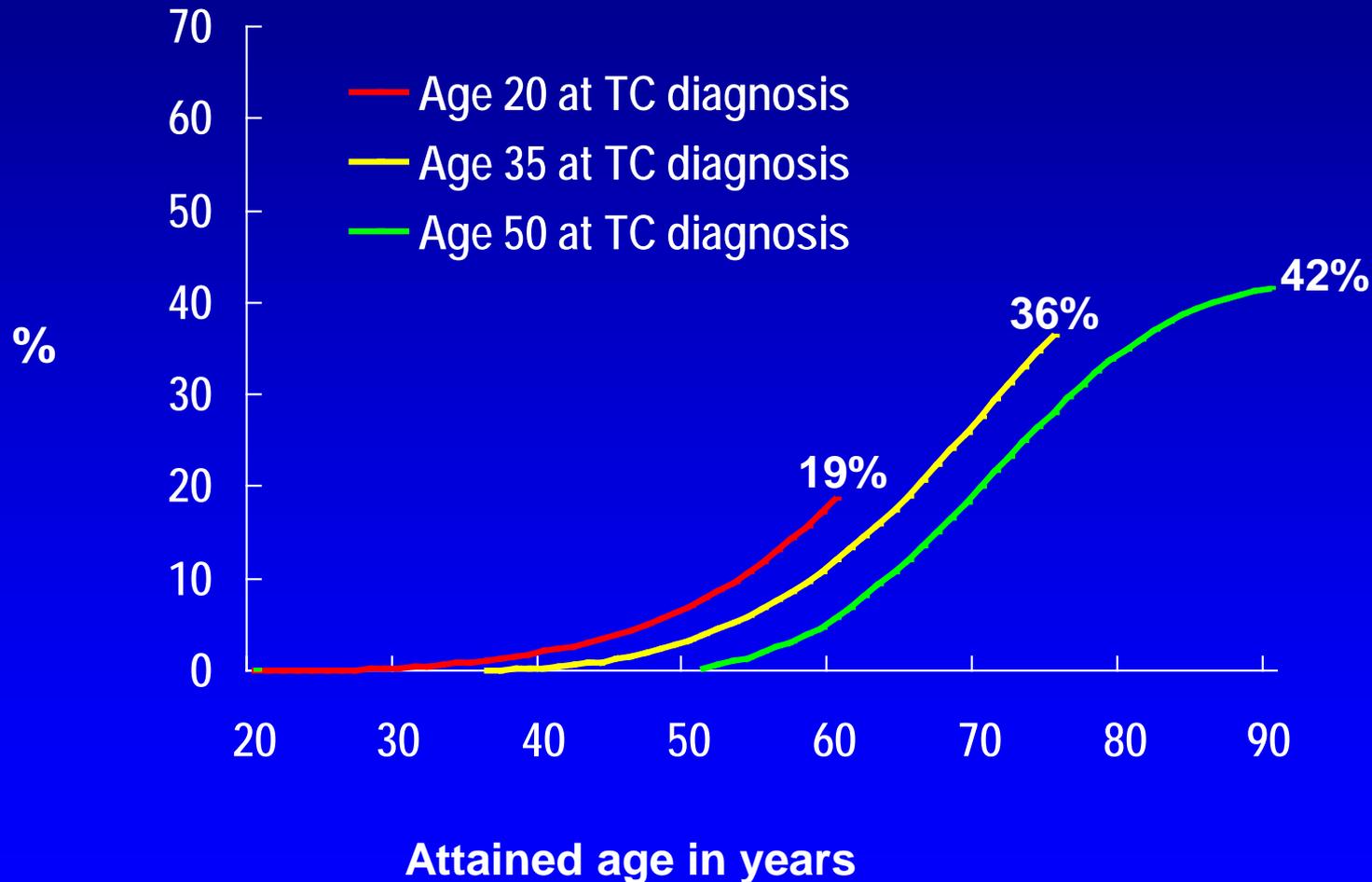
## Competing risks

- 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

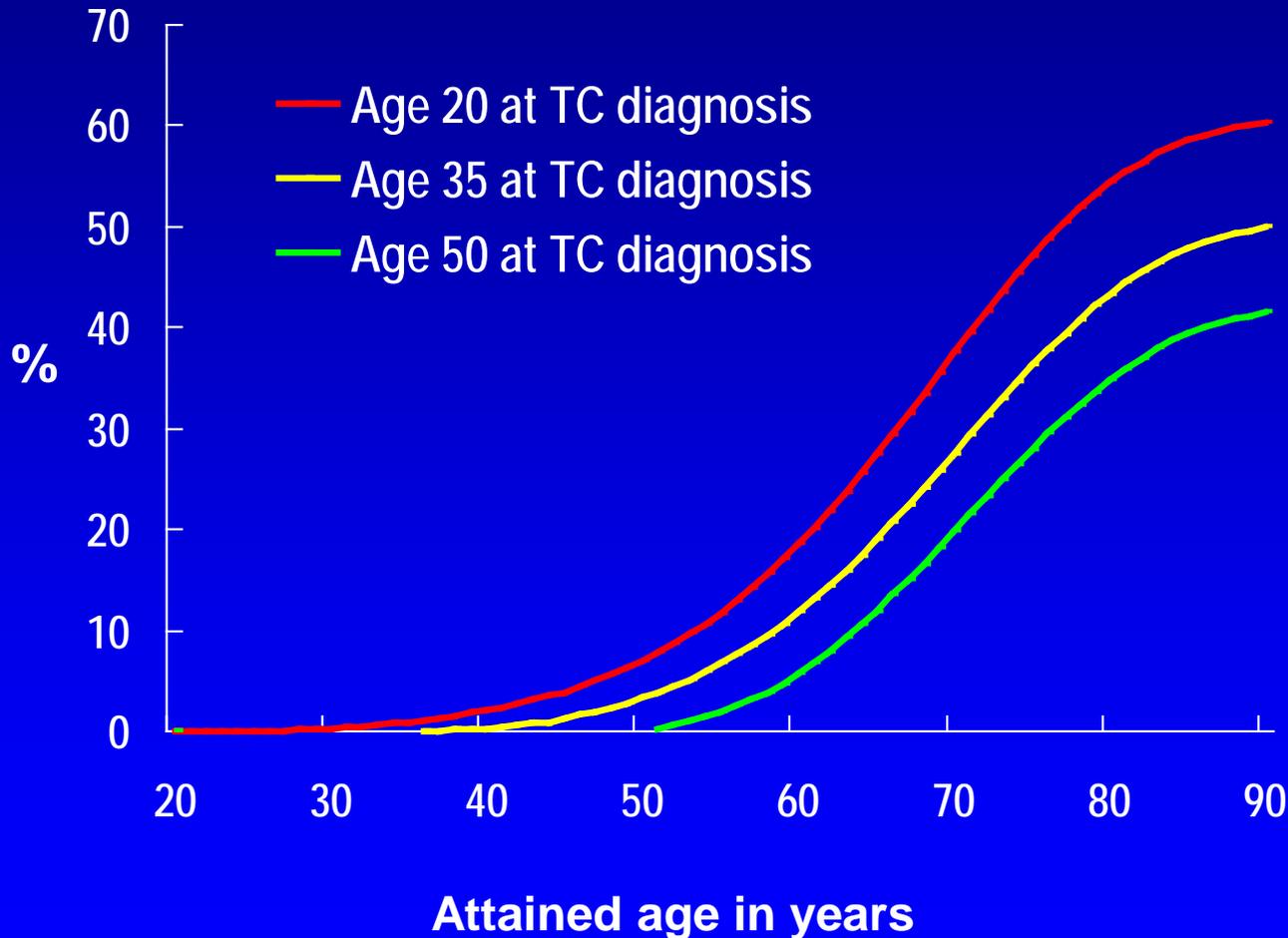
# Cumulative risk (%) for 1-year survivor of seminoma diagnosed at age 35

Attained age	2 <sup>nd</sup> solid cancer	Leukemia	Death from TC	Death from non-cancer	Survival free of 2 <sup>nd</sup> cancer
40	0.3	0.2	1.2	0.9	97
45	1.2	0.3	1.4	2.0	95
50	3.3	0.5	1.6	3.4	91
55	6.7	0.7	1.7	5.4	85
65	19	1.3	1.8	12	66
75	36	2.2	1.9	24	36 <sup>63</sup>

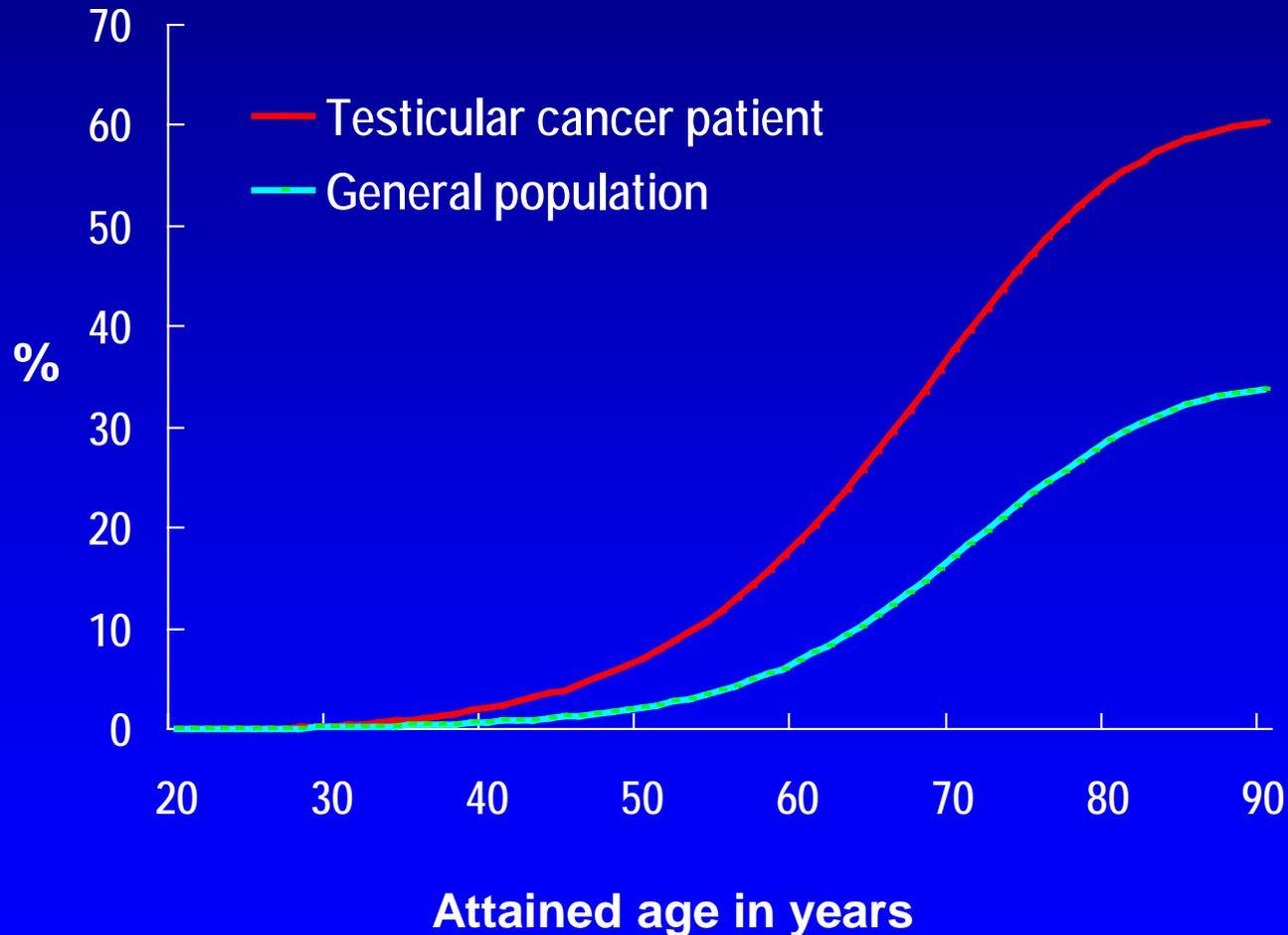
# Cumulative risk (%) of 2nd solid cancer in 1-year survivors of seminoma



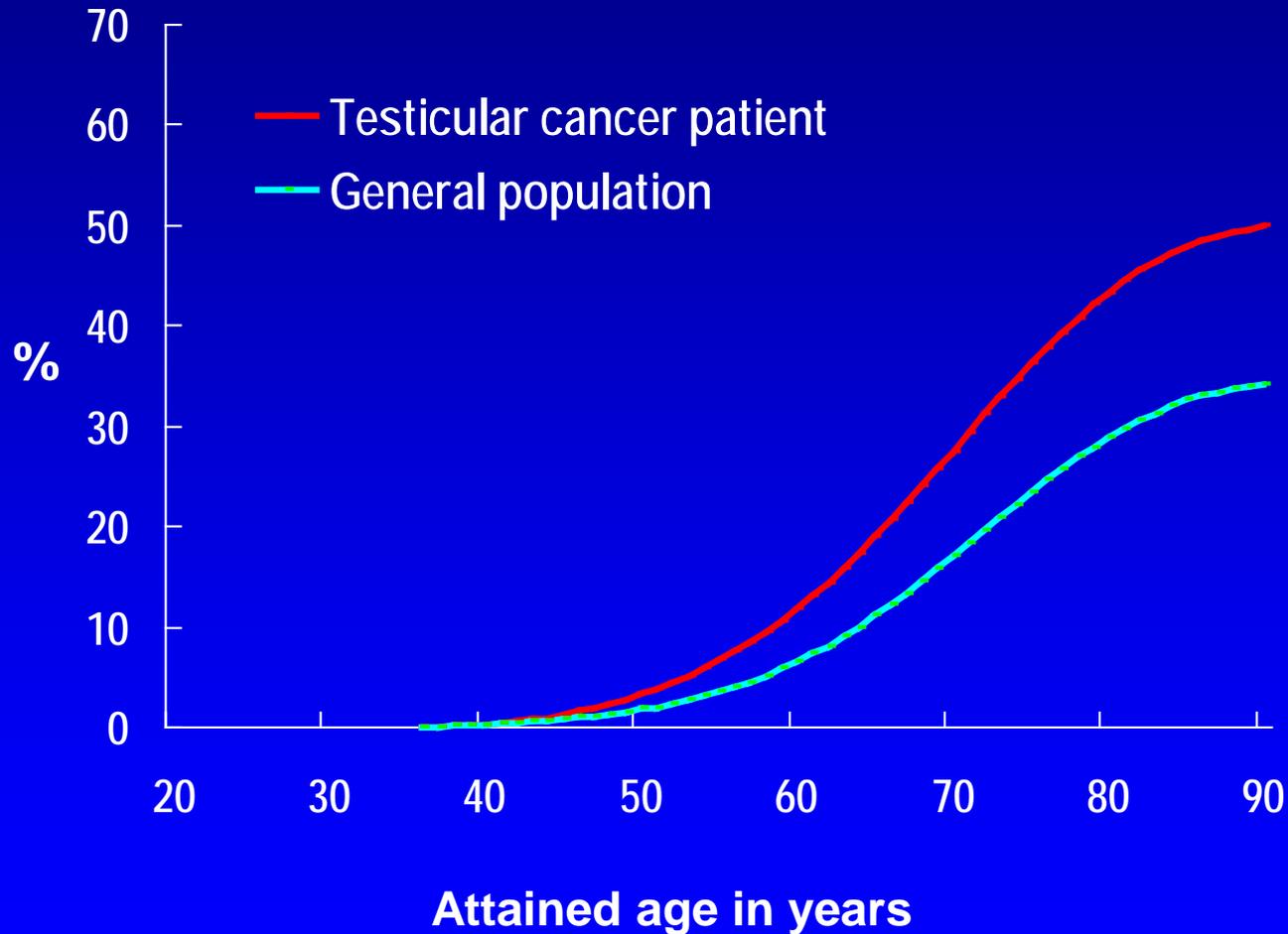
# Cumulative risk (%) of 2nd solid cancer in 1-year survivors of seminoma projected to age 90



# Cumulative risk (%) of solid cancer in seminoma patient diagnosed at age 20



# Cumulative risk (%) of solid cancer in patients diagnosed at age 35



# Cumulative Risk in the General Population

- **Lifetime risk of developing cancer for a person receiving a dose  $d$  at age  $a$** 
  - Lifetime risk is the cumulative risk to the end of life
- **Lifetime risks estimated by various committees concerned with risks assessment (BEIR, UNSCEAR, ICRP)**
  - Most lifetime risk assessments based primarily on A-bomb survivor data

# Lifetime risk of developing cancer for person receiving dose $d$ at age $a$

- Use ERR or EAR models for solid cancer risks developed from A-bomb survivor data
- Also need solid cancer rates in the general population

## Competing risks

- Death from other causes
  - Use US vital statistics/life-tables

# 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 =  $1 + \beta d$** 
  - **d is dose**
  - **$\beta d$  is the excess relative risk (ERR)**
  - **$\beta$  is the ERR per unit of dose**
- **ERR model can be fit with the Epicure software**
  - **Cohort studies: AMFIT module for Poisson regression**

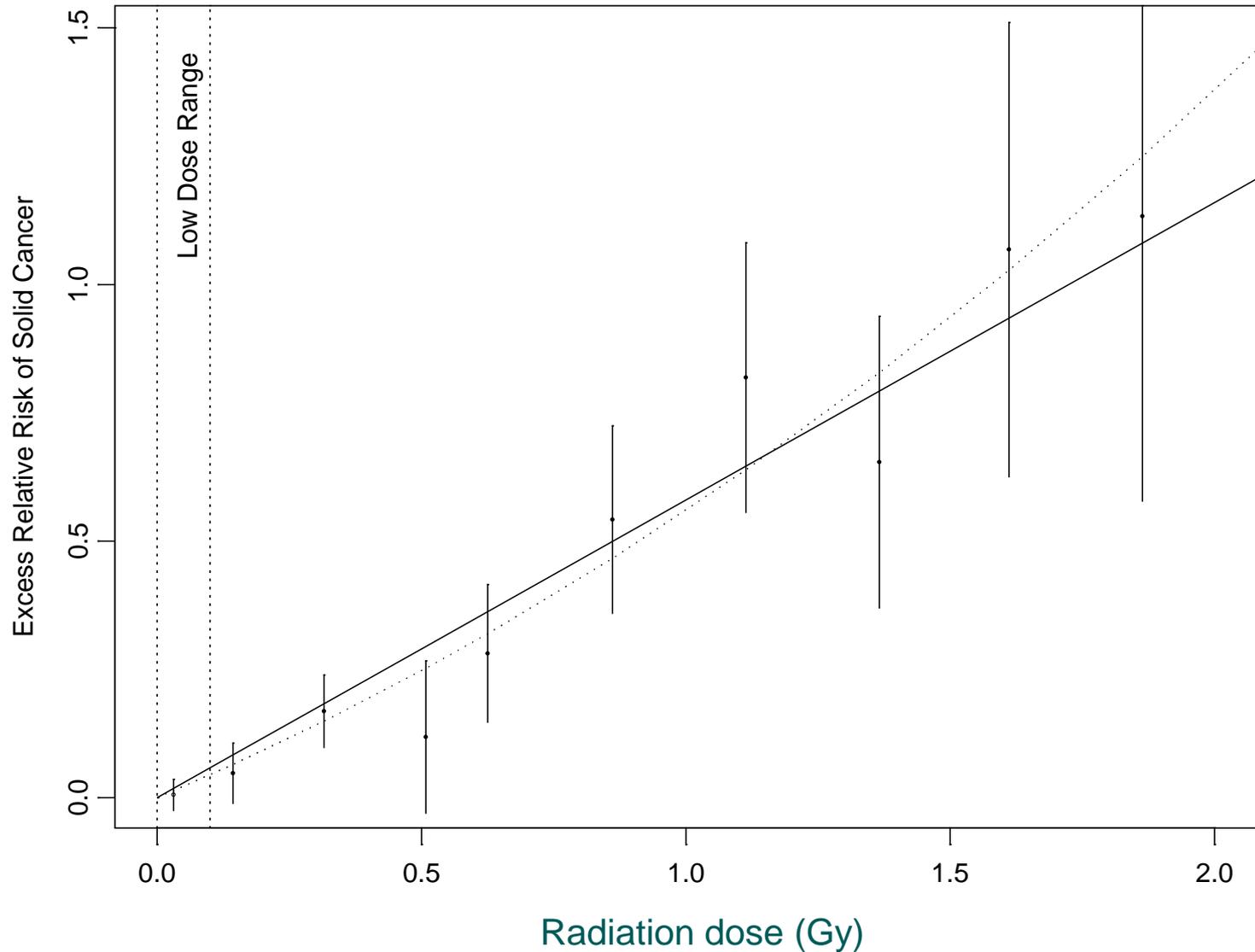
# **Life Span Study (LSS) cohort of Japanese A-bomb survivors**

- **Primary source of data for most risk assessments**
- **87,000 atomic bomb survivors in Hiroshima and Nagasaki with individual dose estimates**
- **All ages and both sexes**
- **Long term follow-up for both mortality and cancer incidence**
- **Well-characterized dose estimates for individual study subjects**

# **A-bomb survivors: Useful range of doses**

- **30,000 (62%) exposed survivors with doses 0.005 to 0.1 Gy**
- **18,000 survivors with higher doses (0.1-4 Gy)**
  - **allow reasonably precise risk estimates**

# A-bomb Survivor Solid Cancer Incidence: Excess relative risk



# ERR models that allow for modification

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

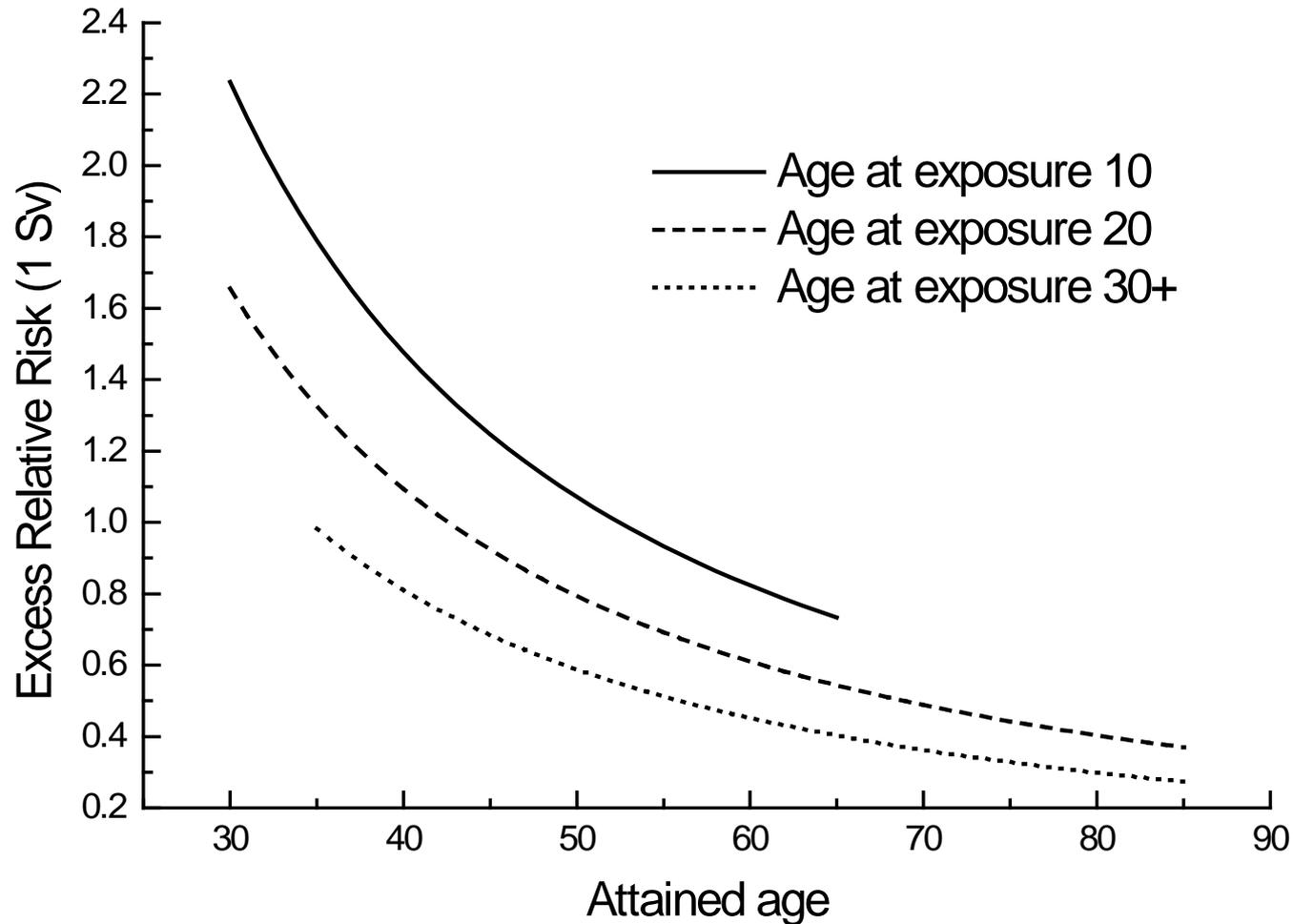
$$\beta_s d f(s, e, a)$$

**s=sex; e = age at exposure; a = attained age**

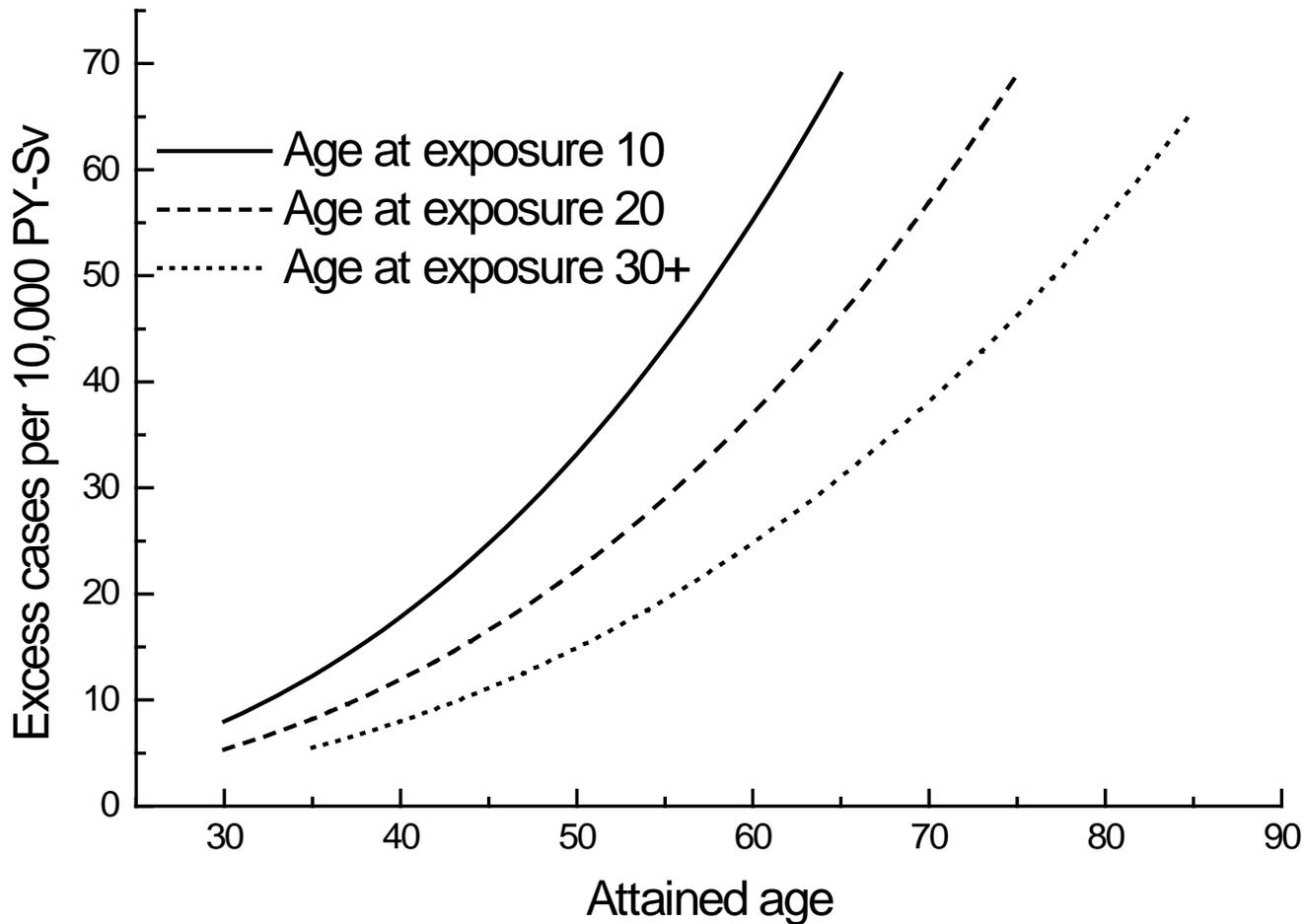
**Commonly used model:**

$$\text{ERR} = \beta_s d \exp(-\gamma e) a^\eta$$

# Solid Cancer: ERR per Sv



# Solid Cancer: Excess cases per 10,000 PY-Sv



# 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)**

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
  
- Protracted low dose rate exposure similar to that of interest for radiation protection

# Mayak Dosimetry

## External exposure

- Monitored for external exposure with individual film badges

## Plutonium exposure

- Dose estimates based on urine monitoring
- Analyses restricted to workers for whom plutonium doses could be estimated
  - Urine monitoring data available
  - No potential for plutonium exposure

# 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

Calendar year	Attained age	Annual Pu dose (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

Calendar year	Attained age	Annual Pu dose (Gy)	Cumulative Pu dose (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

Calendar year	Attained age	Annual Pu dose (Gy)	Cumulative Pu dose (Gy)	Cumulative Pu dose 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 both the ERR and EAR
- Evaluate possible modification of the ERR and EAR by sex, attained age, age at hire, and time since exposure

# Model for Mayak Worker Data

ERR and EAR are 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

Internal dose term =  $f(d_{plu}, s, a)$

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

$s$  indicates sex

$a$  indicates attained age

# Plutonium Dose-Response

$$f(d_{plu}, s, a) = f(d_{plu}) \exp [\phi s + \theta \log (a/60)]$$

Evaluated  $f(d_{plu}) =$

$\theta_j$

Categories of dose

$\beta_1 d_{plu}$

Linear

$\beta_1 d_{plu} + \beta_2 d_{plu}^2$

Linear-quadratic

$\beta_1 d_{plu}^n$

Power function

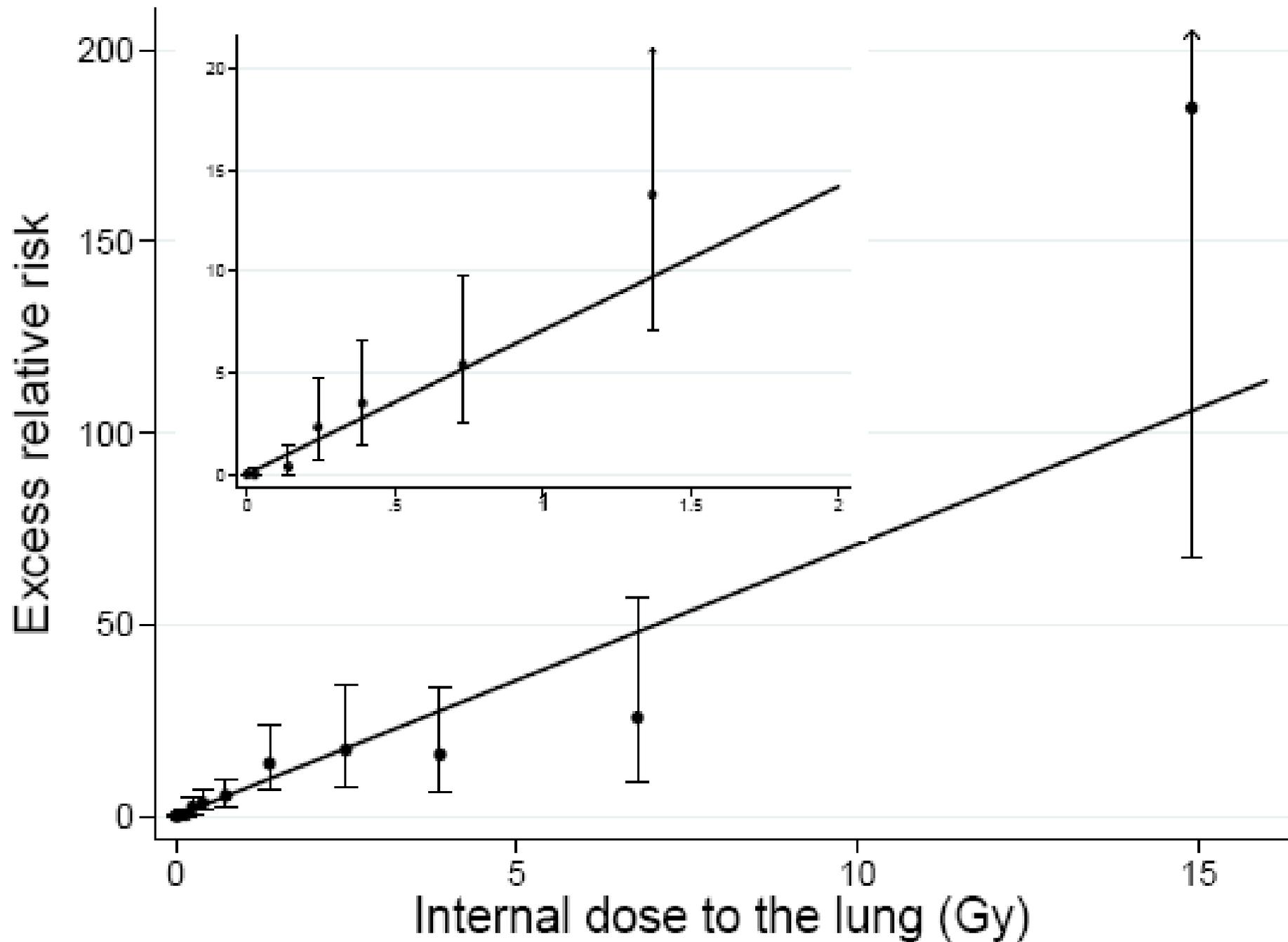
# Lung cancer: Plutonium dose-response

Lung Dose (Gy)	RR (95% CI)	Deaths
0	1.0	139
>0 - .1	0.98 (<1 - 1.3)	111
.1-	1.4 (<1 - 2.4)	16
.2-	3.3 (1.7 - 5.8)	14
.3-	4.5 (2.4 - 7.7)	14
.5-	6.4 (3.5 - 11)	15
1-	15 (8.1 - 25)	16
2-	18 (8.3 - 35)	8
3-	17 (7.1 - 35)	7
5-	27 (10 - 59)	6
10+	186 (69 - 466)	8

Estimates for males.

Estimates for females are a factor of 2.1 higher

Sokolnikov et al. 2008



# 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 ( $\eta$ ) estimated to be 1.01 (0.75 – 1.19)

# 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

# Lung cancer: ERR per Gy for plutonium by age in years

Attained age

<55	11 (5.4 – 20)
55-	6.8 (4.2 – 10)
65-	3.7 (0.9 – 10)
75+	4.1 (0.9 – 10)

P-trend = 0.002

Age at first plutonium dose

< 20	11 (4.5 – 20)
20-	8.0 (5.1 – 12)
25-	4.9 (2.3 – 8.9)
30+	3.4 (1.8 – 5.9)

P-trend = 0.025

# Lung cancer: ERR modifiers

- **ERR/Gy for plutonium**
  - Higher for females than males ( $\theta=0.01$ )
  - Declines with attained age ( $p=0.002$ )
  - Declines with age at first plutonium dose ( $0.025$ )

# 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)**

# Interaction

	RR	Radiation relative risk
Non-smoker, no radiation	1.00	1.0
RR for radiation alone	$RR_{rad}$	Rad risk among non-smokers = $RR_{rad}$
RR for smoking alone	$RR_{smk}$	1.0
RR for both smoking and radiation	$RR_{rad, smk}$	$RR_{rad, smk} / RR_{smk}$

If  $RR_{rad, smk} = RR_{rad} \times RR_{smk}$  then relationship is multiplicative

Radiation RR is the same for smokers and non-smokers

Note:  $RR_{rad, smk} / RR_{smk} = RR_{rad} \times RR_{smk} / RR_{smk} = RR_{rad}$

# Interaction

	RR	ERR= RR-1	Radiation excess risk
Non-smoker, no radiation	1.00	0.00	0.00
Radiation alone	$RR_{rad}$	$ERR_{rad}$	$ERR_{rad}$
Smoking alone	$RR_{smk}$	$ERR_{smk}$	1.0
Both smoking and radiation	$RR_{rad,smk}$	$ERR_{smk,rad}$	$ERR_{smk,rad} -$ $ERR_{smk}$

If  $ERR_{rad, smk} = ERR_{rad} + ERR_{smk}$  then relationship is additive

Note:  $RR_{rad,smk} = RR_{rad} + RR_{smk} - 1$

# Lung Cancer Following Hodgkin Lymphoma (HL)

- **227 lung cancer diagnosed at 1+ years 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**

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

# Lung cancer following Hodgkin disease: Some candidate models

I. Multiplicative interaction for all exposures:

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

II. Additive interaction for all exposures:

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

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

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

# Lung cancer following Hodgkin disease

More general models for radiation and AA therapy

Example:

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

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

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

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

Nearly identical fit to Model III

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

# Lung cancer following Hodgkin disease

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

# Outline

- **Basic definitions and concepts**
- **Radiation risk modeling**
  - **General comments**
  - **Examples**
- **Additional topics**
  - **Interpreting data from multiple studies: Pooled analyses**
  - **Dose measurement uncertainties**

# **Interpreting Data from Multiple Studies**

- **Wealth of epidemiologic data pertaining to radiation risks**
- **Hence, a need to summarize information from more than one study**

# Interpreting Data from Multiple Studies

- **Several studies addressing common issue**

## **Examples:**

- **22 lung cancer case-control studies addressing residential radon exposure**
- **7 studies of thyroid cancer after exposure to external radiation**
- **8 studies of breast cancer after exposure to external radiation**

# Interpreting Data from Multiple Studies

- 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

- **Obtain more precise estimates of risk**
- **Opportunity for understanding differences and similarities in studies**
  - **Comparable statistical methods**
  - **Results in comparable format**
- **Best overview or summary of studies**

# Pooled Analyses

- **Relevant data on thyroid cancer risks available from**
  - **A-bomb survivors**
  - **Several medically exposed cohorts**
- **Thyroid cancer after exposure to external radiation: A pooled analyses of seven studies (Ron et al. Radiat. Res. 1995)**

# Pooled thyroid cancer incidence analyses

- **Estimated ERR and EAR as a function of dose for each individual study**
- **Evaluated comparability of these estimates across studies**
- **Estimated ERR and EAR based on all studies**

# Thyroid Cancer Risk: Childhood External Exposure

Study	Exposed Cases	Mean Dose (Gy)	ERR/Gy (90% CI)
Enlarged thymus	33	1.36	9.1 (3.6-29)
Tinea capitis	44	0.09	32.5 (14-57)
Enlarged tonsils	309	0.59	2.7 (0.6-26)
Childhood cancer survivors	22	12.50	1.1 (0.4-29)
A-bomb survivors	40	0.27	4.7 (1.7-11)

Ron et al. 1995

# Thyroid Cancer Risk: Childhood External Exposure

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Childhood cancer survivors	22	12.50	1.1 (0.4-29)
A-bomb survivors	40	0.27	4.7 (1.7-11)
<b>Combined</b>			<b>7.7 (2.1-29)</b>

Ron et al. 1995

# Pooled thyroid cancer incidence analyses

- Evaluated modification of the ERR by
  - gender
  - age at exposure
  - time since exposure
  - attained age
  - fractionation of exposure

# Pooled thyroid cancer incidence analyses: Ratios of ERR/Gy

## Gender

Male 0.5

Female 1.0\*

$P_{\text{heterogeneity}} = 0.07$

## Age at first exposure

<1 1.0\*

1-4 1.0

5-9 0.5

10-14 0.2

$P_{\text{heterogeneity}} = 0.004$

\*Referent group

# 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
- 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**

# **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)**

# 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

# 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

# Examples where dose estimation errors have been taken into account

- **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)

**Thank you for your attention!**

**Questions?**

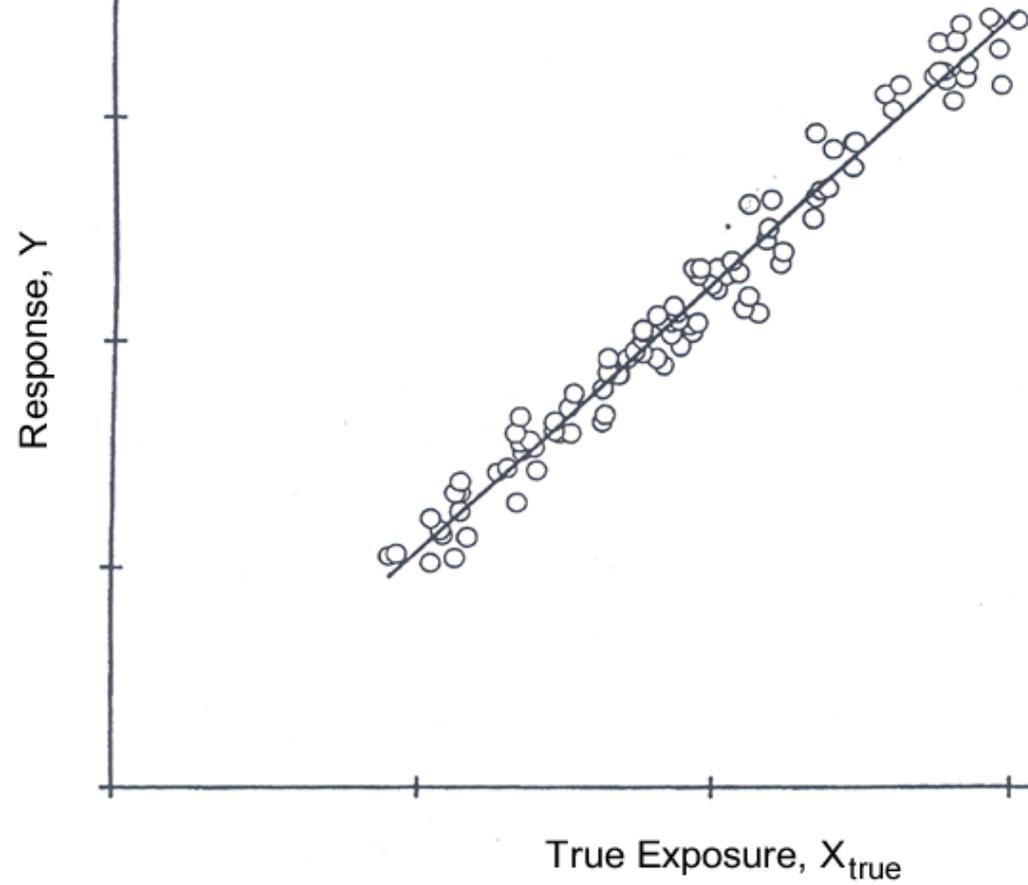
# Examples

**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”**

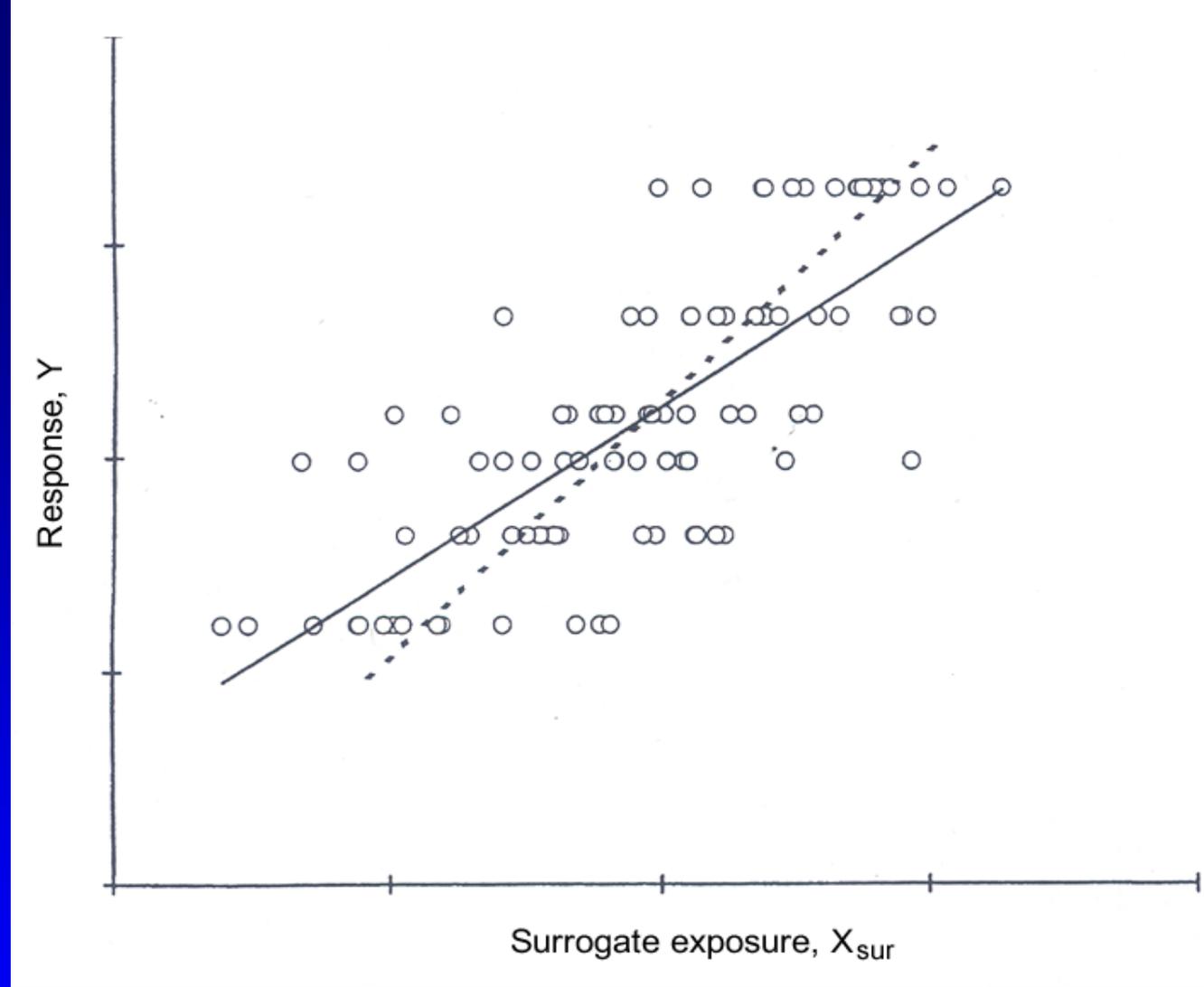
**National Cancer Institute, Publication  
No. 99-4541, 1999.**

No error



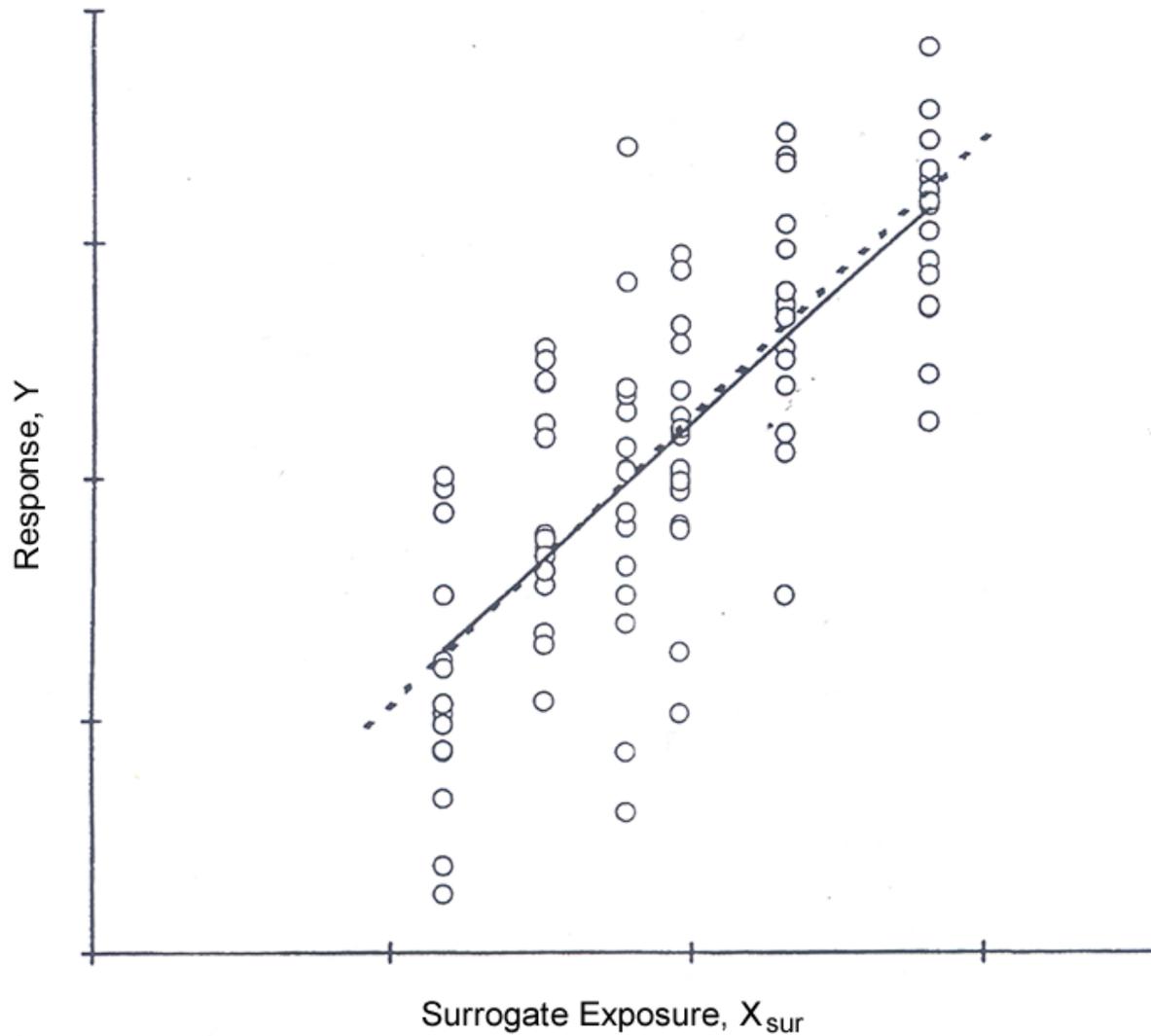
Response versus true dose

# Classical error



————— Response versus estimated dose      True  
- - - - - response

# Berkson error



————— Response versus estimated dose      True  
- - - - - response