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Radiation Risk Modeling

Radiation Epidemiology & Dosimetry Course

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?

- **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
- Examples of radiation risk modeling
- Additional topics
  - Interpreting data from multiple studies: Pooled analyses
  - Dose measurement uncertainties

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

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

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 relative 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)

Comparing Incidence Rates

R_e = Rate in "exposed" population

R_u = Rate in "unexposed" population

R_u often referred to as baseline rate

Rate in exposed = Baseline rate + EAR

Rate in exposed = Baseline rate (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 exposures
  - Informing exposed subjects
- More difficult to evaluate than the RR
  - Requires cohort data

Examples from International Hodgkin Lymphoma Study[1]

	# 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 add or multiply?

Interactions/Effect Modification

- Other risk factors can modify radiation risk (RR and EAR)
- Modification can be different for RR than for EAR

Interactions/Effect Modification

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

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

Additive model:

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

ERR_{rad} does not depend on the other factor

Multiplicative Model

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

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

Multiplicative Model

	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

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

Multiplicative Model

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

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

Additive Model

	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	?	?

$ERR_{rad} = 1.0$; $ERR_{smk} = 9.0$

Additive Model

	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

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

Additive Model

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

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

20.0 for **multiplicative**; 11 for additive

Sub-multiplicative/ Super-additive Model

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

Sub-multiplicative/ Super-additive Model

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

Sub-multiplicative/ Super-additive Model

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

Sub-multiplicative/ Super-additive Model

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

Outline

- Basic definitions and concepts
- Examples of radiation risk modeling
- Additional topics
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  - Dose measurement uncertainties

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)
- 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

- **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

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

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

- Commonly 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

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

Modeling RR and EAR

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

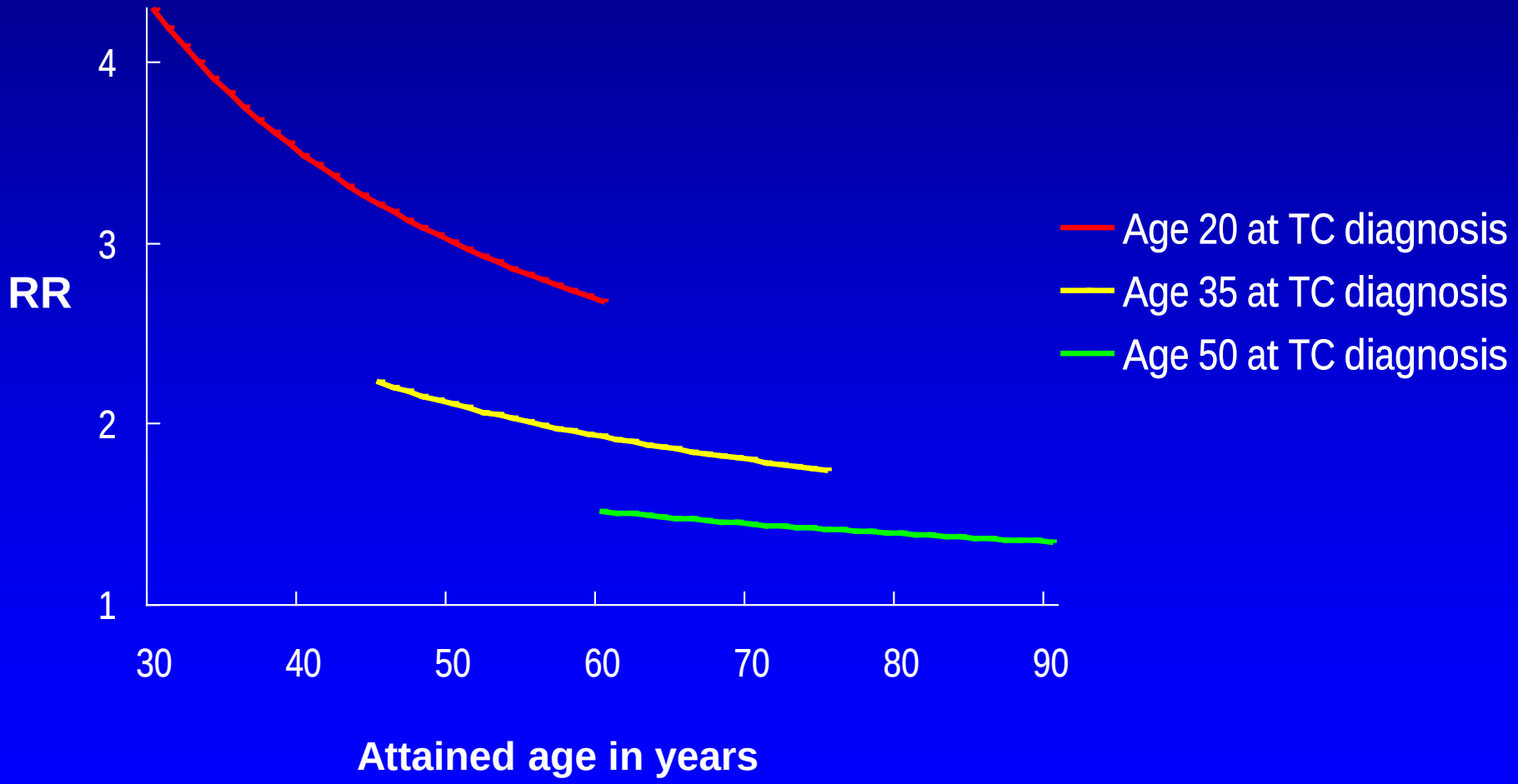
- Example: Use ERR and EAR of the form

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

For ERR, $\gamma = -0.039$; $\eta = -1.0$

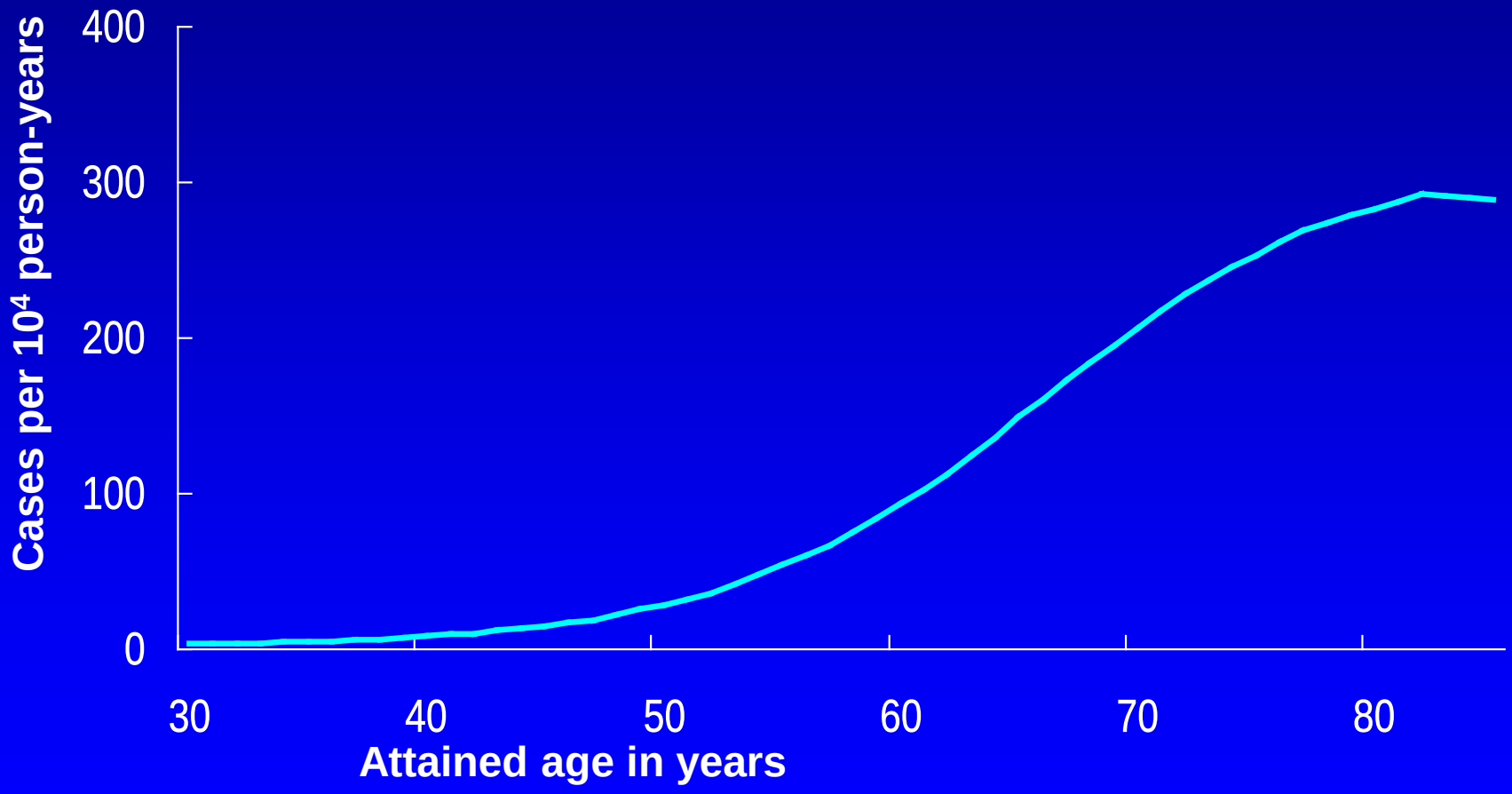
Travis et al. 2005

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

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**

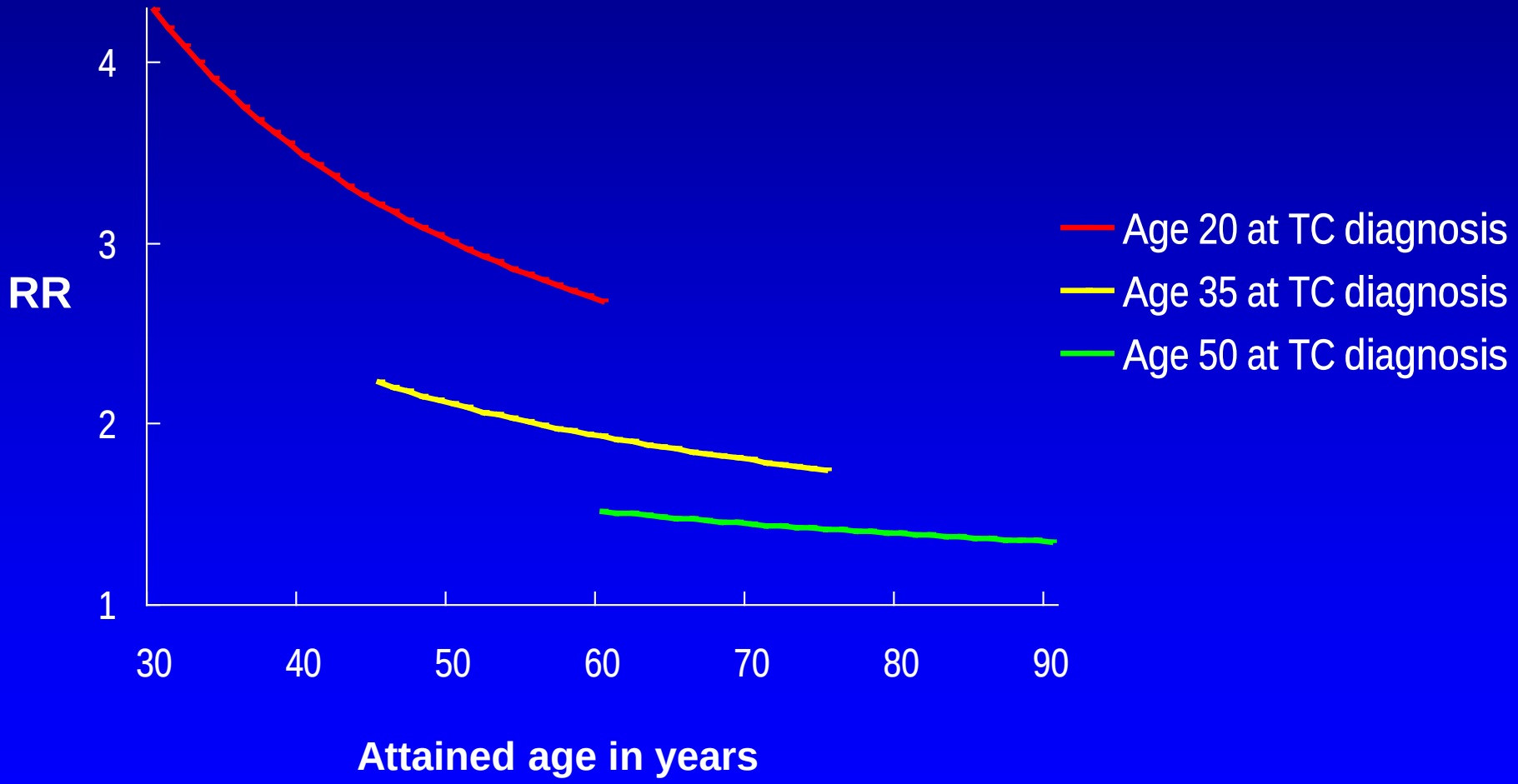
$$\beta \exp(\gamma\, agex)\, attage^{\eta}$$

For ERR, $\gamma = -0.039$; $\eta = -1.0$

For EAR, $\gamma = -0.046$; $\eta = 4.4$

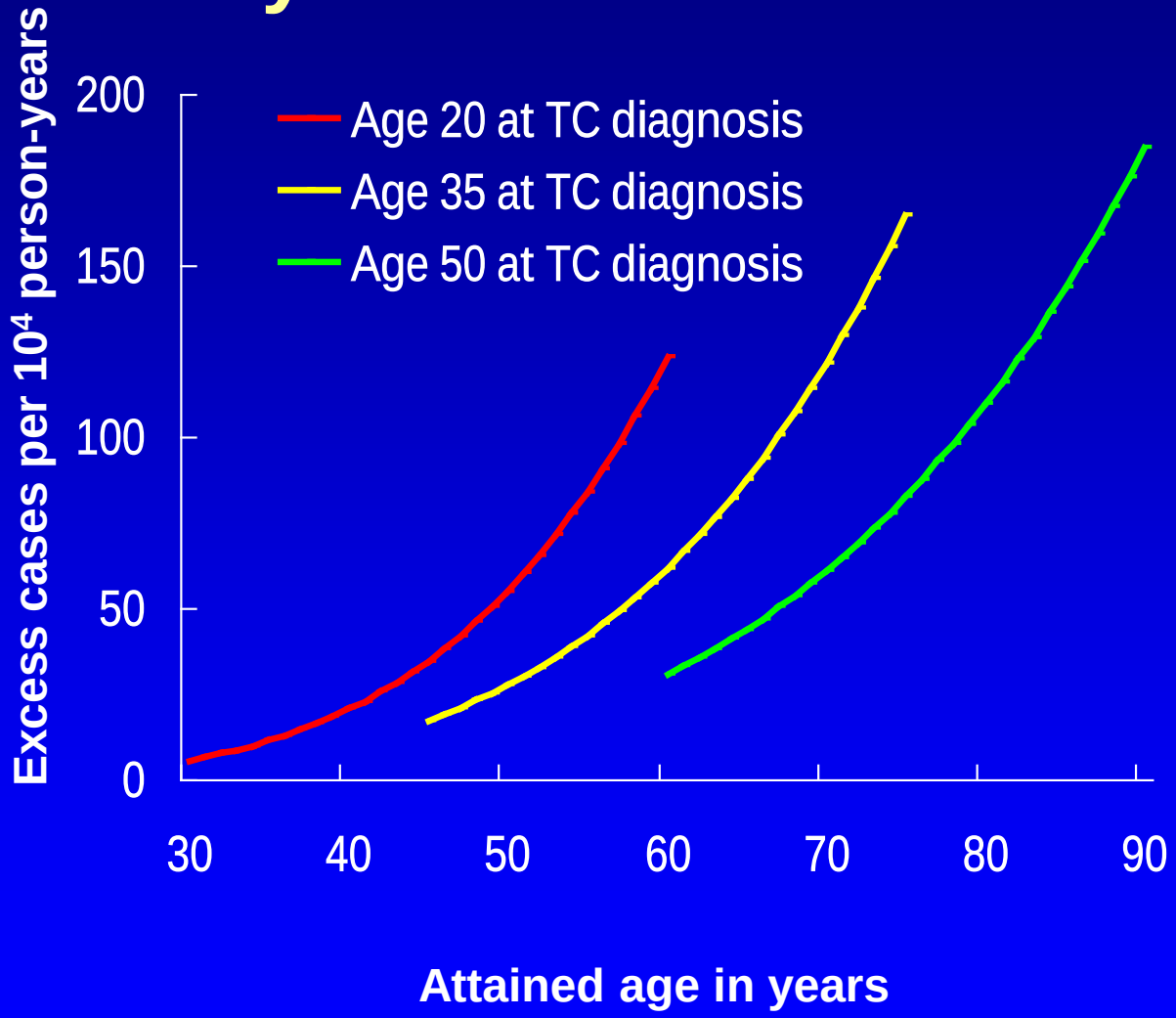
Travis et al. 2005

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



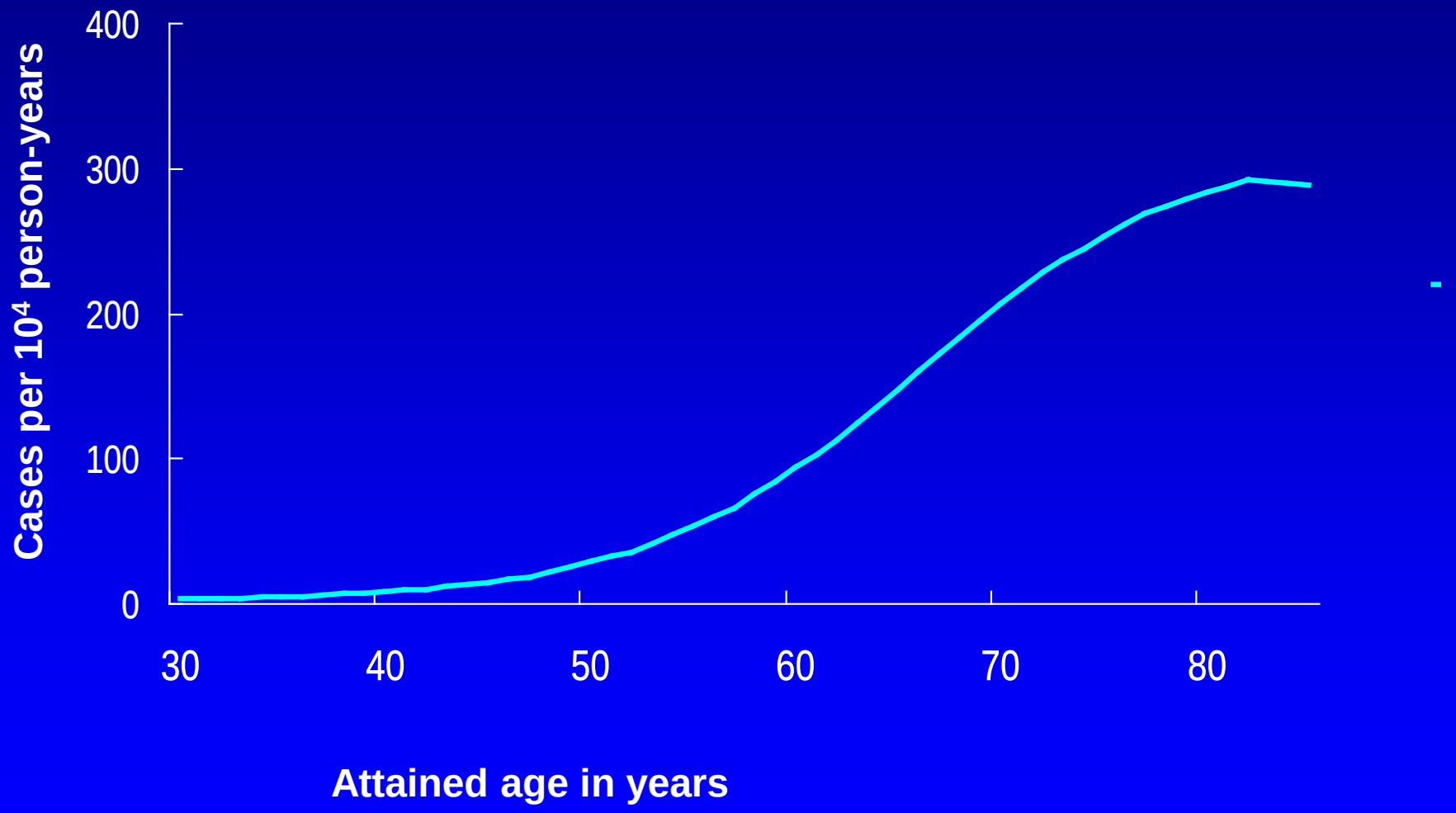
Travis et al. 2005

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



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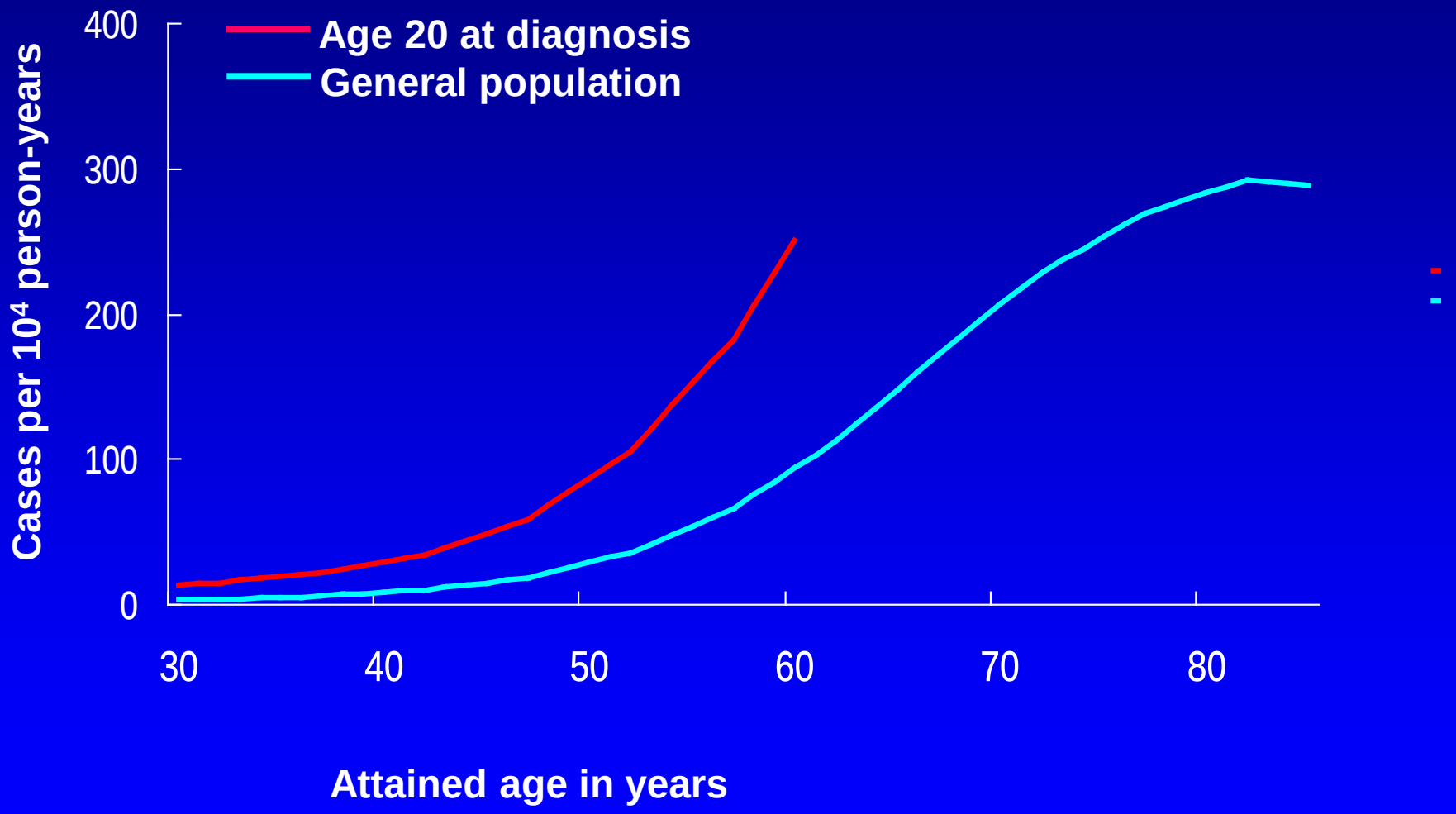
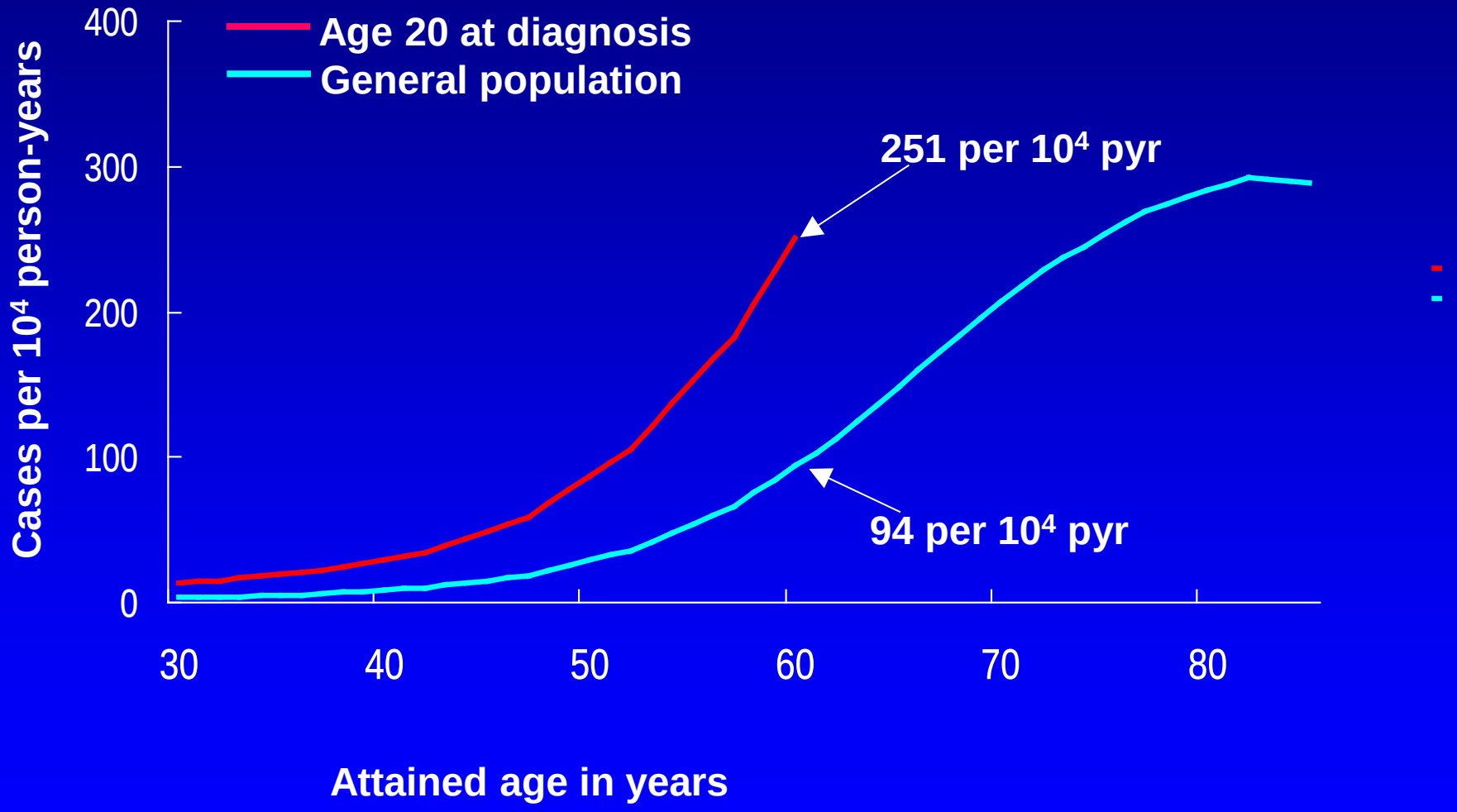
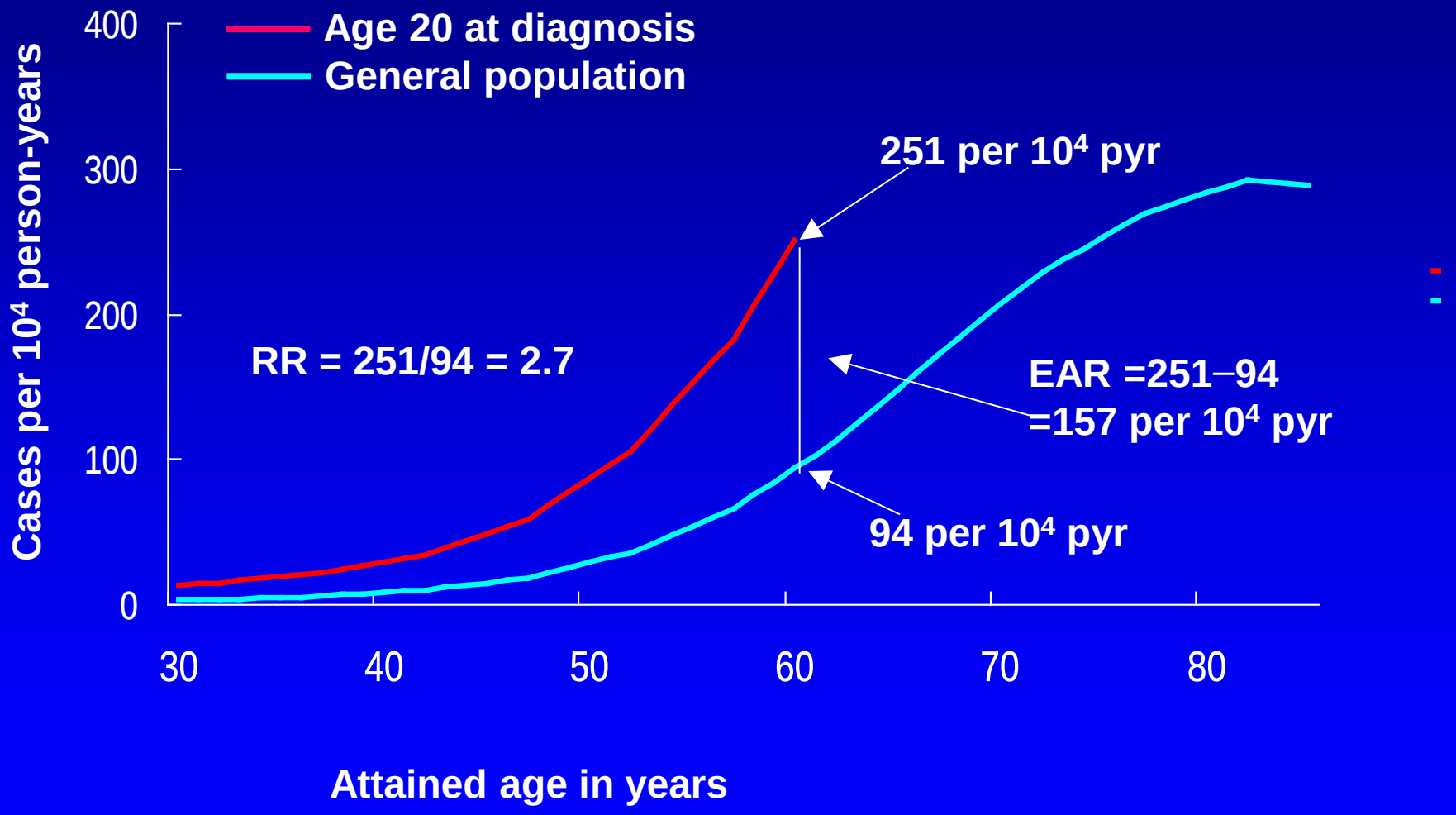


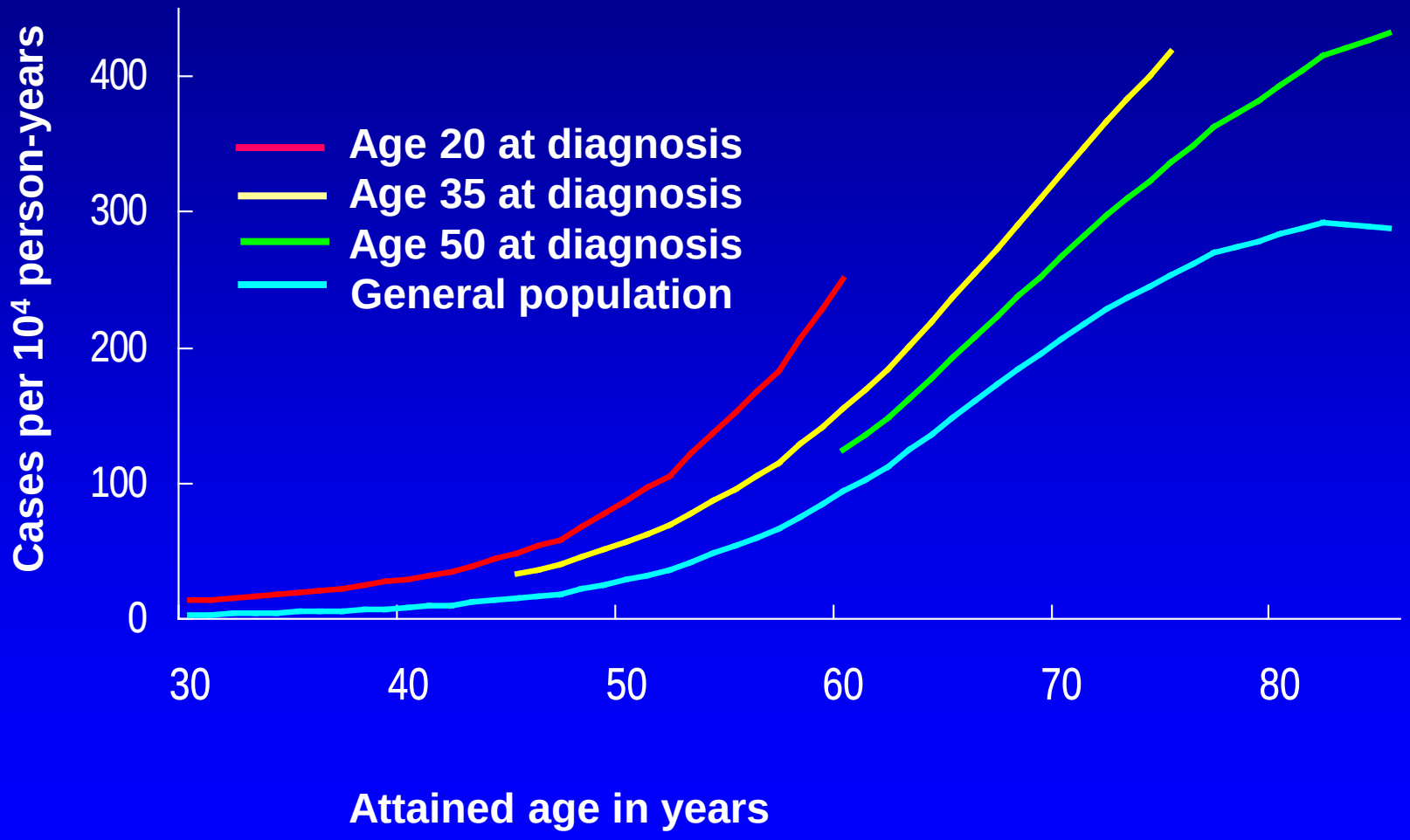
Second Solid Cancer Rate in Testicular Cancer Patients Diagnosed at Age 20



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**

Cumulative Risk in Testicular Cancer Patients

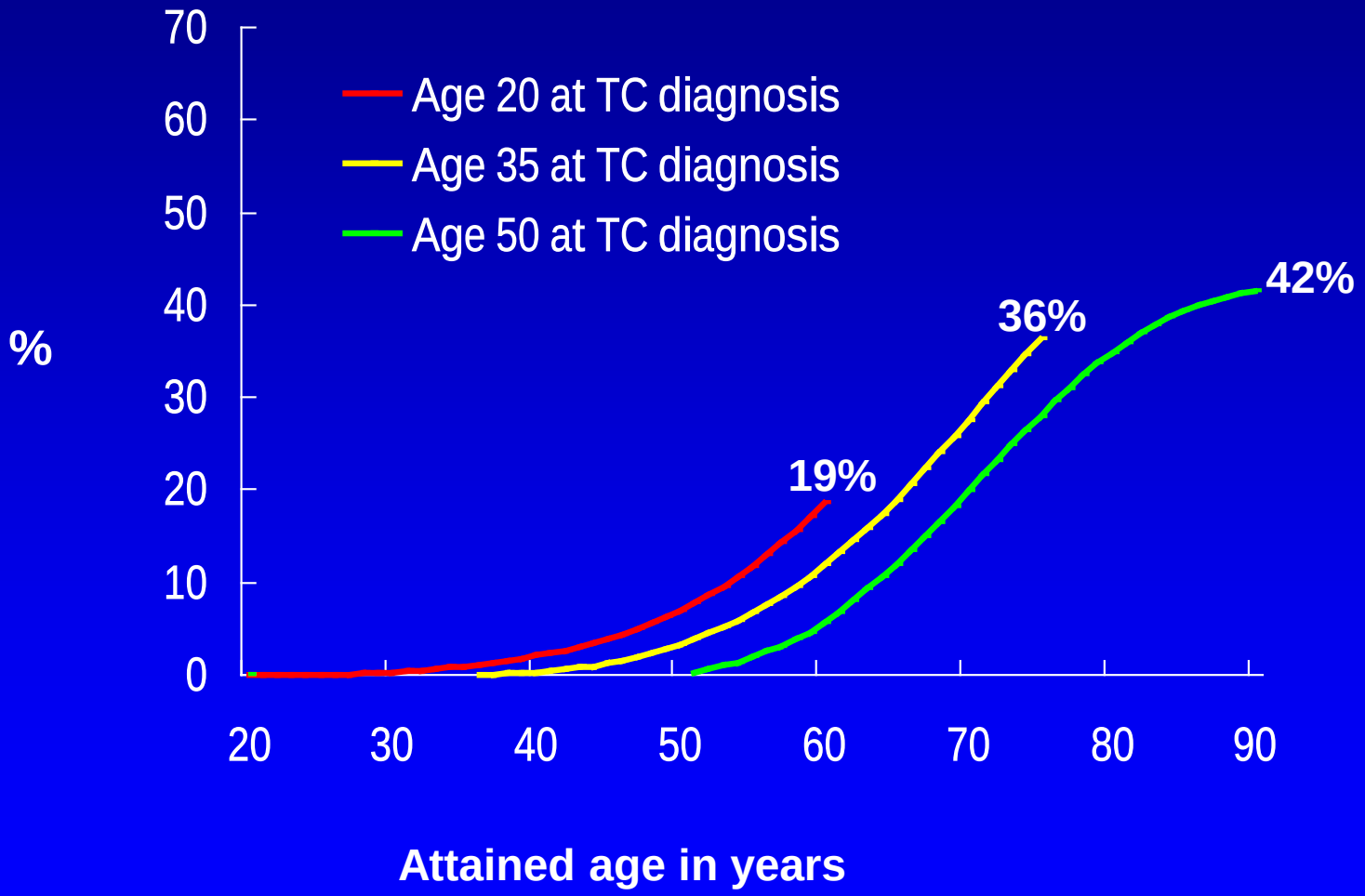
Can use incidence rates to obtain estimates of cumulative risk

Probability of developing disease in a specified time period

Take account of competing risks

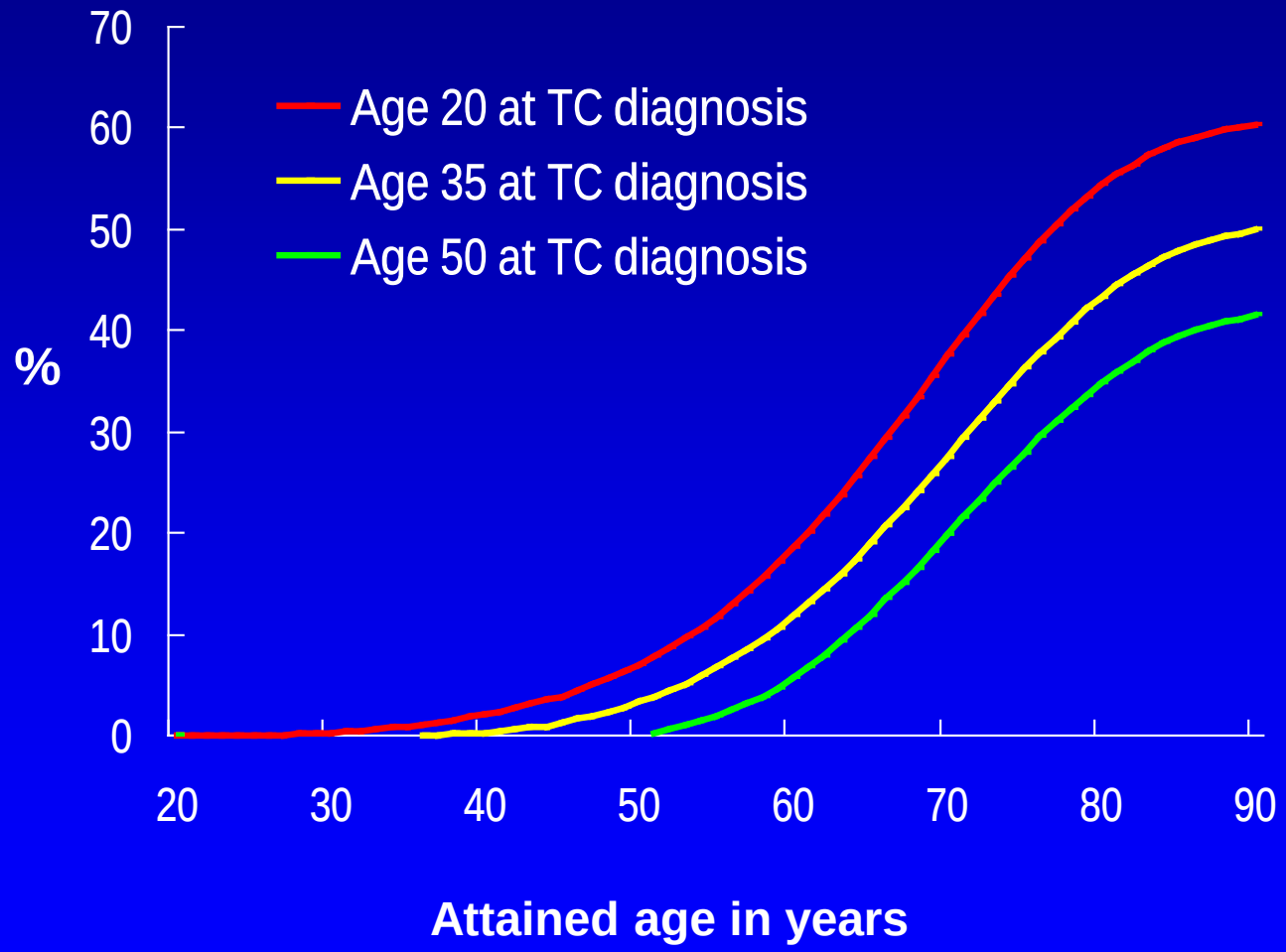
- **Death from testicular cancer**
  - **Modeled as a function of age at diagnosis, attained age, and time since diagnosis**
- **Death from non-cancer causes**
  - **Used general population rate**

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



Travis et al. 2005

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



Travis et al. 2005

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)

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

- Primary source of data for most risk assessments
- 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 Survivor Dose Distribution

Dose (Gy)	No. of subjects (% of exposed)
0.005-	29,960 (62)
0.1-	5,949 (12)
0.2-	6,380 (13)
0.5	3,426 (7.1)
1-	1,764 (3.7)
2+	625 (1.3)
Total exposed	48,104 (100)
<0.005 (unexposed)	38,507
Total	86,611

Preston et al. Radiat Res 2004

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

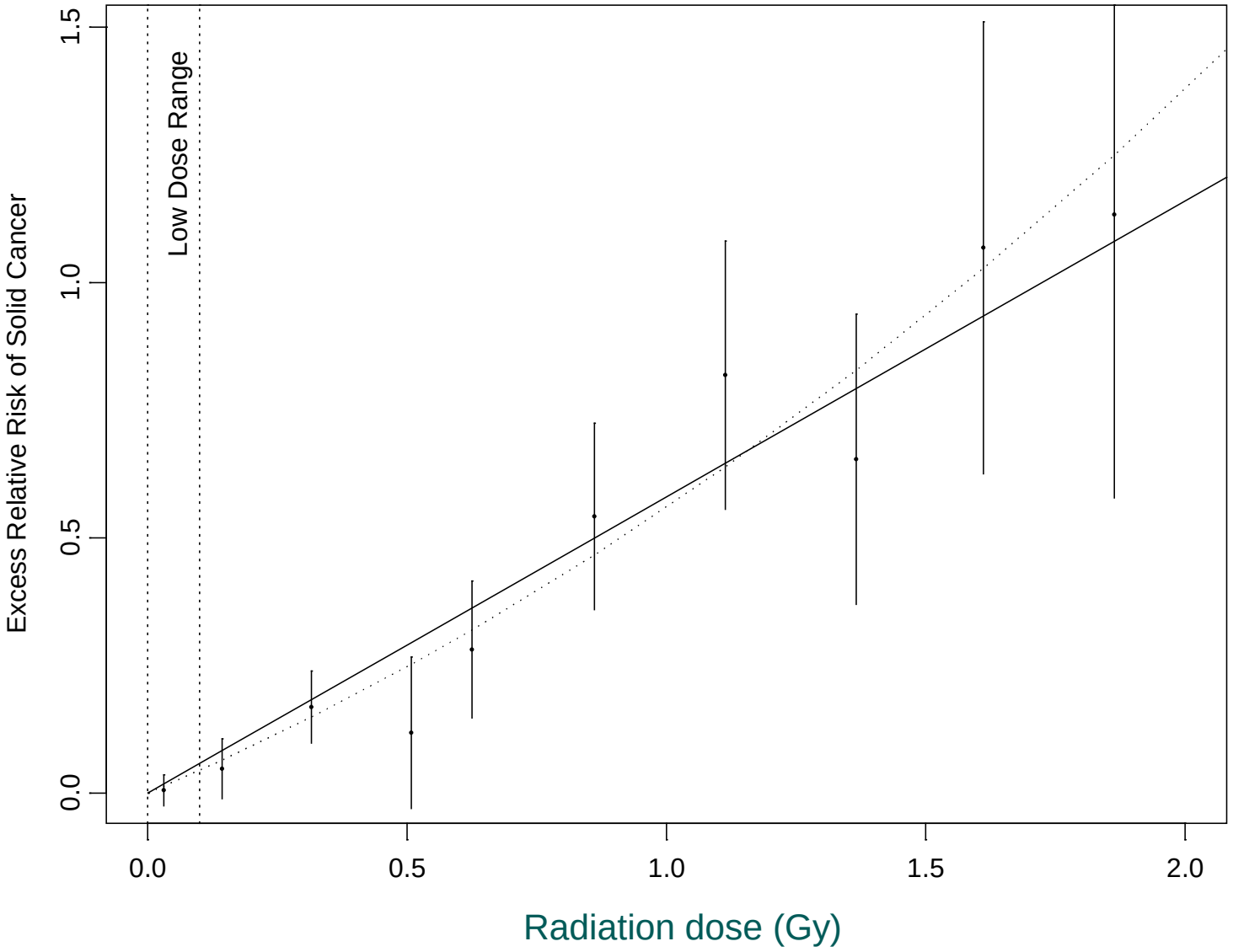
- Linear (and linear-quadratic) models used extensively
- Can be justified based on radiobiological considerations
- Risks at low doses of special interest
- Often difficult to distinguish among various dose-response functions

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

A-bomb Survivor Solid Cancer Incidence: Excess Relative Risk



ERR Models That Allow for Modification

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

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

***s*=sex;**

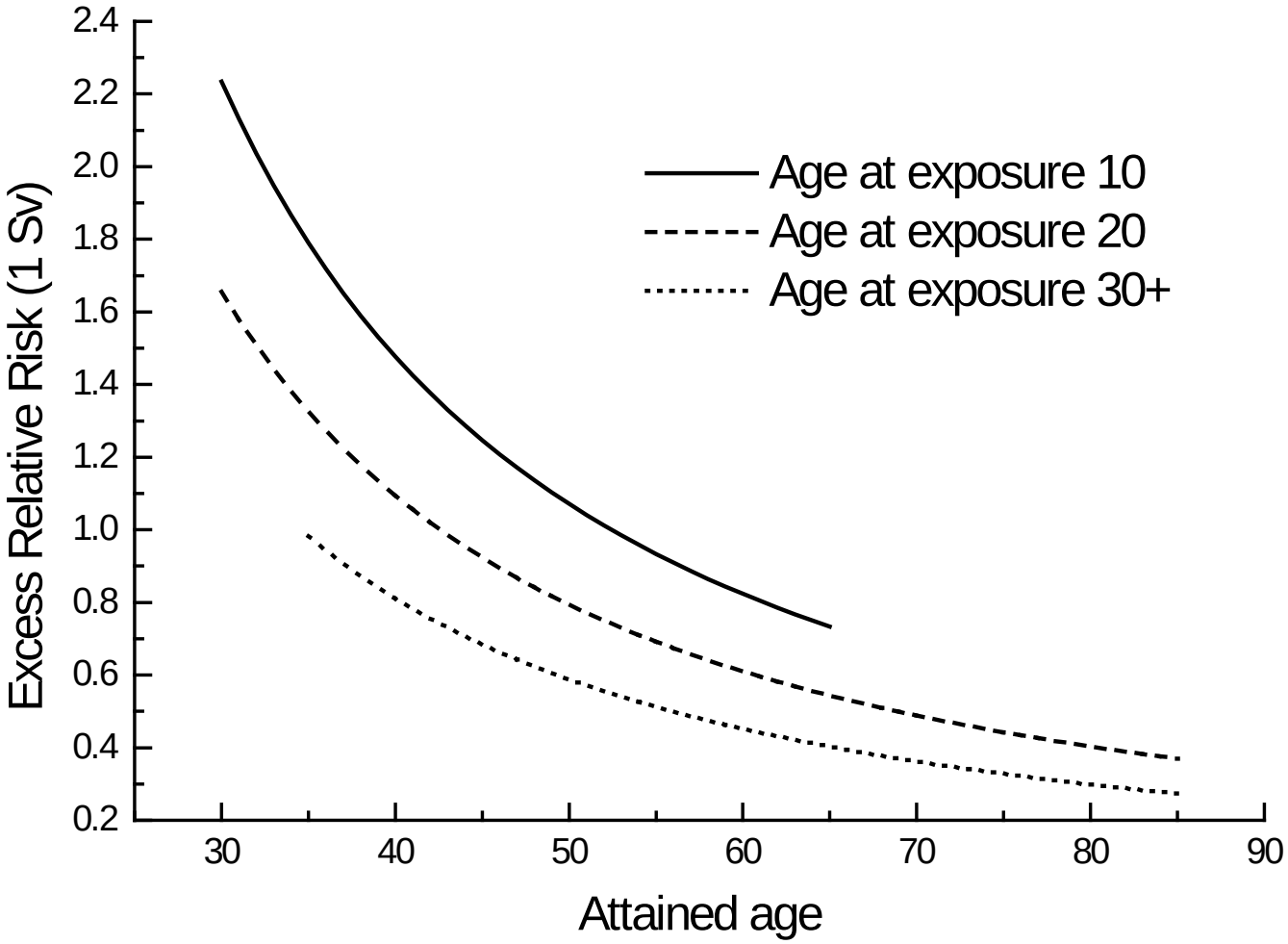
***agex* = age at exposure;**

***attage* = attained age**

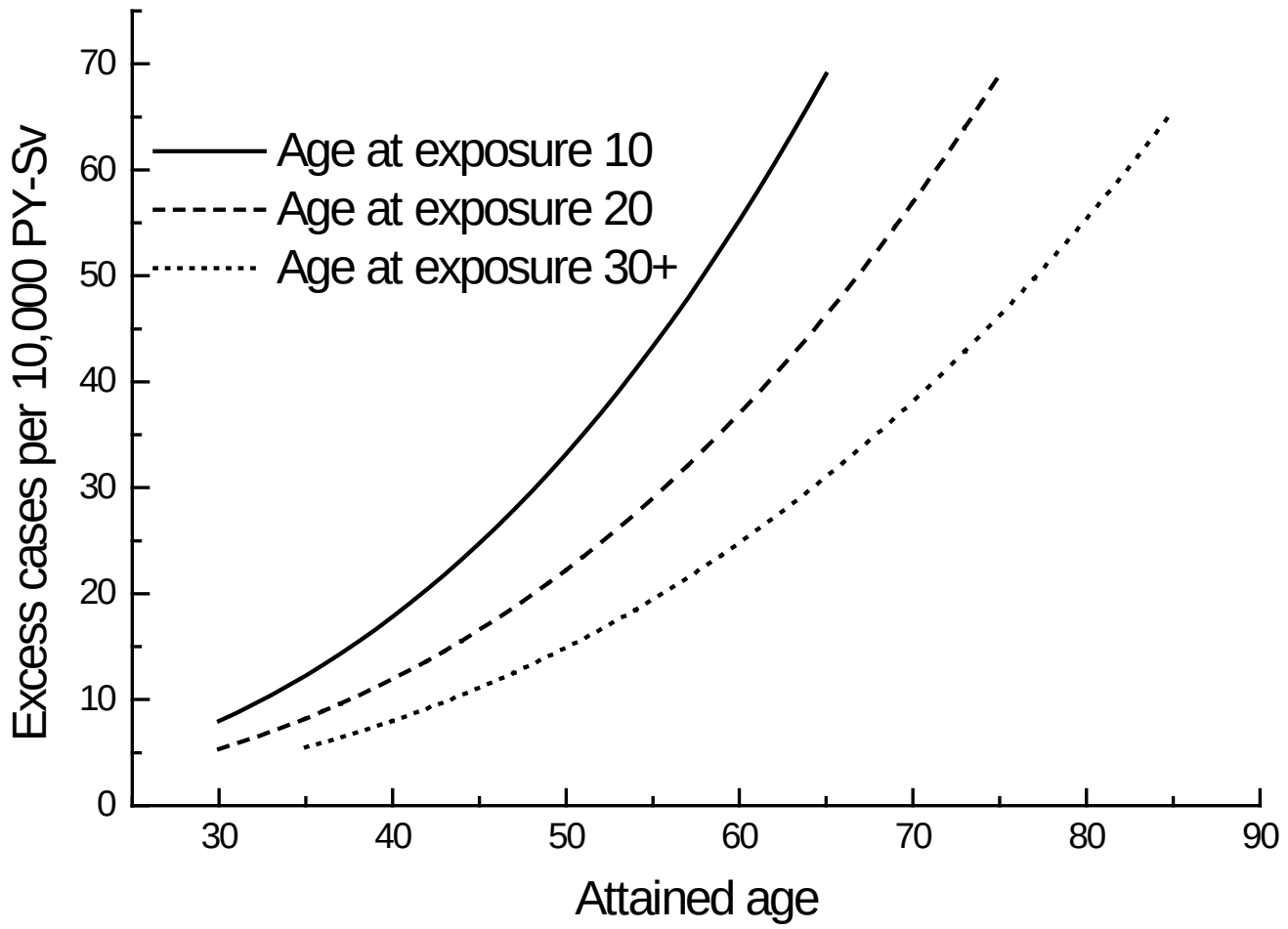
Commonly used model:

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

Solid Cancer: ERR per Gy



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



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**

A-bomb Survivor Risk Estimates

- Recent papers 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

- 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

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

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

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

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*, *attage*)

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

***s* indicates sex**

***attage* indicates attained age**

Plutonium Dose-Response

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

Evaluated $f(d_{plu})$ =

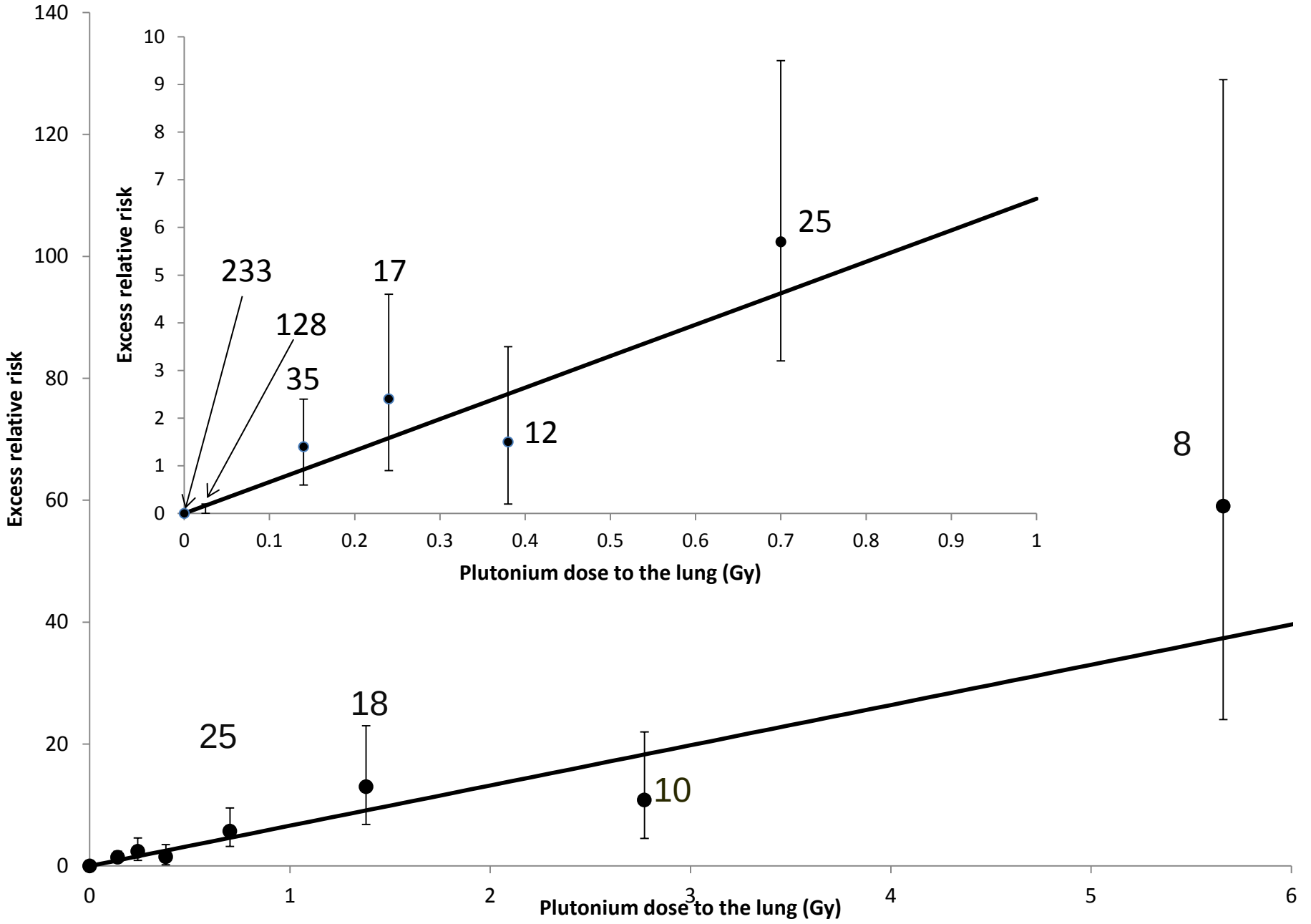
θ_j	Categories of dose
$\beta_1 d_{plu}$	Linear
$\beta_1 d_{plu} + \beta_2 d_{plu}^2$	Linear-quadratic
$\beta_1 d_{plu}^{\eta}$	Power function

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)
140
120
100
80
60
40
20
0
0
1
2
3
4
5
6
25
18
10
8
Excess relative risk
Plutonium dose to the lung (Gy)
10
9
8
7
6
5
4
3
2
1
0
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
233
128
35
17
12
25

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)

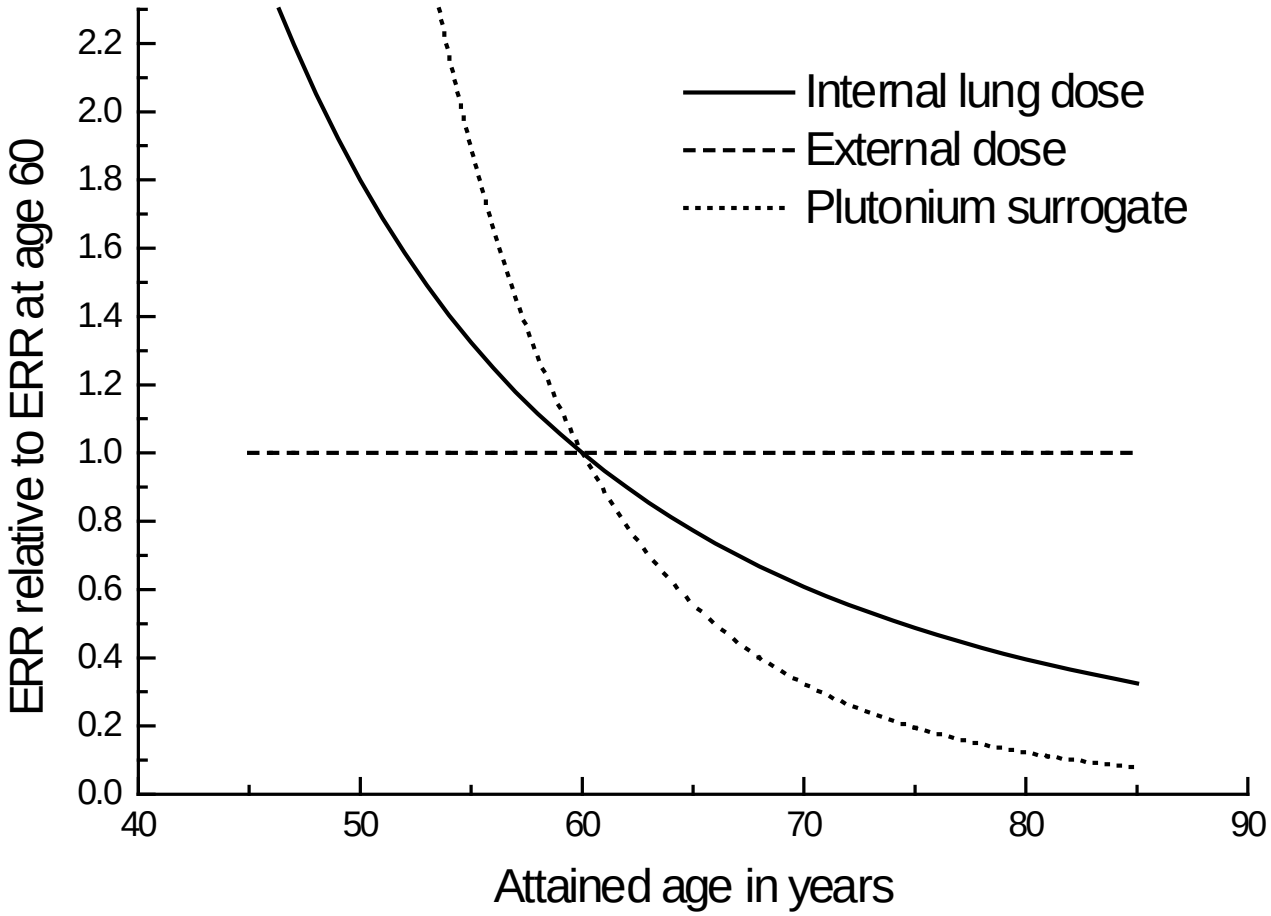
Non-smokers: 29 (9.8 – 83)

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

Results shown are for attained age 60

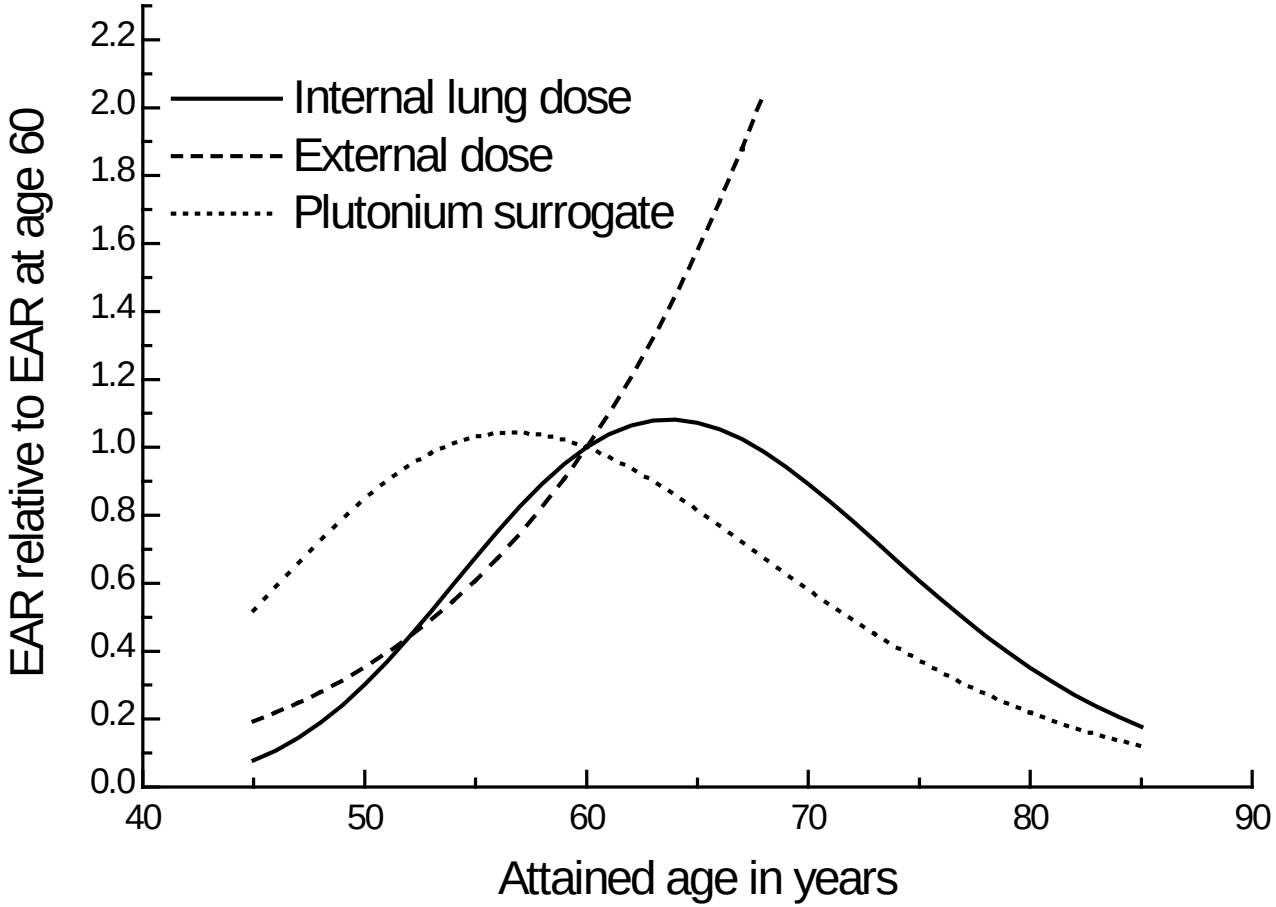
Gilbert et al. 2013

ERR/Gy by Attained Age



Gilbert et al. 2003

EAR by Attained Age



Gilbert et al. 2003

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
-

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
Alkylating agents (AA)	Number of cycles (cyc)
Smoking	Pack-years (pks)

Lung Cancer Following HL: Some Candidate Models

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

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

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

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

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

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

Lung Cancer Following HL

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

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
- Examples of radiation risk modeling
- 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**

Ron et al. 1995

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

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A-bomb survivors	40	0.27	4.7 (1.7-11)
Combined			7.7 (2.1-29)

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**

Ron et al. 1995

Pooled Thyroid Cancer Incidence Analyses: Ratios of ERR/Gy

Gender

Male	0.5
Female	1.0*

$P_{heterogeneity} = 0.07$

Age at first exposure

<1	1.0*
1-4	1.0
5-9	0.5
10-14	0.2

$P_{heterogeneity} = 0.004$

*Referent group

Ron et al. 1995

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 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)

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**

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**

Thank you for your attention!

Questions?

Questions and Answers

U.S. Department of Health and Human Services
National Institutes of Health | National Cancer Institute
www.dceg.cancer.gov/RadEpiCourse
1-800-4-CANCER
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