National Cancer Institute

Descriptive Models and Radiation Risk Assessment

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Outline

- General comments on descriptive models
- Radiation risk assessment
  - BEIR VII (2006): Health Risks From Exposure to Low Levels of Ionizing Radiation
- Additional modeling examples
- Accounting for dose measurement error

What is a descriptive model?

- Function that relates disease risk (relative or absolute) to dose and factors that might modify risk
- Models developed by analyzing data from epidemiologic studies
- Objective is to find model that describes the data well

Why do we need descriptive models?

- Increase our understanding of radiation carcinogenesis
- Radiation risk assessment

Descriptive modeling

- Evaluate dose-response relationship
  - Quantify risk as a function of dose
  - Shape of dose-response
- Evaluate patterns of risk by
  - Sex
  - Age at exposure
  - Attained age
  - Time since exposure
  - Other variables

Risk Models

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

  Risk = Baseline risk [1 + ERR]

- **Excess Absolute Risk (EAR):**

  Risk = Baseline risk + EAR

  – **Expressed as excess cases (deaths) per 10,000 person-years**

- **Both models are used in analyzing data from radiation cohort studies**

Modeling the ERR and EAR

- ERR can be modeled
  - Using cohort or case-control data
  - Non-parametric modeling of the baseline risk possible
- Unlike ERR model, EAR modeling requires
  - Cohort data
  - Parametric modeling of baseline risk

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

Linear excess relative risk model

- RR = Relative Risk = $1 + \beta\, d$
  - d is dose (Gy)
  - β is the Excess Relative Risk (ERR) per Gy
- Contrasts with log-linear model: RR = $\exp(\beta\, d)$
  - "Standard" model for analyzing epidemiologic data
- ERR model can be fit with the Epicure software
  - Cohort studies: AMFIT module for Poisson regression

Linear excess relative risk model

- RR = Relative Risk = $1 + \beta\, d\, f(s, e, a)$

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

  Commonly used model:

- RR = Relative Risk =

$$1 + \beta_s\, d \exp[\gamma e + \eta \log(a)]$$

Excess absolute risk model

Risk = Baseline risk + EAR

- Baseline risk is a function of age, sex, and other variables
- EAR = β d f(s, e, a)

  β expressed per 10^4 person-year-Gy

  Commonly used model:

  $$EAR = \beta_s \, d \exp [\gamma e + \eta \log(a)]$$

- Patterns of risk by sex and attained age are often markedly different for the ERR and EAR

s=sex; e = age at exposure; a = attained age; d= dose in Gy

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Radiation Risk Assessment

- Radiation literature periodically reviewed and evaluated by several national and international committees
- Many of these committees develop and recommend models for estimating risks
- These models can then be applied to specific exposure situations

Examples where radiation risk estimates needed

- Risk from exposure received as a result of mammography
- Risk from residential exposure to radon
- Risk from I-131 exposure from atmospheric nuclear tests
- Risk from pediatric CT examinations

Radiation Risk Assessments

- National Research Council of the National Academies of Science (BEIR Reports)

- UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation)
- NCI-CDC Working Group to Revise the 1985 NIH Radioepidemiological Tables (2003)
- NCRP (National Committee on Radiation Protection and Measurements)
- ICRP (International Commission on Radiation Protection)

BEIR VII: Health risks from exposure to low levels of ionizing radiation

- National Research Council of the National Academies of Science
- BEIR = Biological Effects of Ionizing Radiation
  - BEIR V (1990): Low levels of radiation
  - BEIR VI (1999): Radon
  - BEIR VII (2006): Low levels of radiation
- BEIR VII Committee:
  - 18 scientists
  - 11 meetings (6 public)
- Released 6/29/05 (www.nap.edu)

From BEIR VII Statement of Task

"The primary objective is to develop the best possible risk estimate for exposure to low-dose, low energy transfer (LET) radiation in human subjects."

- BEIR VII committee defined "low dose" as
  - < 100 mGy (0.1 Gy) or
  - < 0.1 mGy/min over months or a lifetime

BEIR VII Chapters

Public Summary

Executive Summary

1-4: Biology

5-9: Epidemiology

10: Integration of biology and epidemiology

11: Risk assessment models and methods

12: Estimating cancer risks

13: Summary and Research Needs

Estimating Cancer Risks

- Estimate lifetime risk allowing for dependencies on
  - Dose
  - Sex
  - Age at exposure

Lifetime risk: Risk of developing (fatal) cancer over exposed person's lifespan

BEIR VII Cancer Endpoints

- Cancer mortality
- Cancer incidence
- Separate estimates for
  - leukemia
  - all solid cancers
  - cancers of several specific sites

Cancer sites evaluated by BEIR VII

- Stomach
- Colon
- Liver
- Lung
- Female breast
- Prostate
- Uterus
- Ovary
- Bladder
- Thyroid
- All other solid cancers
- Leukemia

Estimating Lifetime Risk

- Use data from epidemiologic studies to develop risk models
- Apply models to estimate lifetime risk from low-dose exposure to the US population

BEIR VII models: What data were used?

- **Most cancer sites:**
  - A-bomb survivor cancer incidence and mortality data
  - All analyses based on DS02 dosimetry
  - Analyses conducted by BEIR VII Committee

- **Breast cancer:** Pooled analysis of data on A-bomb survivors and medically exposed persons
  - Preston et al. 2002

- **Thyroid cancer:** Pooled analysis of data on A-bomb survivors and medically exposed persons
  - Ron et al. 1995

Strengths of A-bomb Survivor Study for Use in Risk Assessment

- Large population size
- All ages and both sexes
- Long term follow-up for both mortality and cancer incidence
- Whole body exposure
- Well-characterized dose estimates for individual study subjects
- Useful range of doses

A-bomb survivors: Useful range of doses

- 30,000 (62%) exposed survivors with doses 0.005 to 0.1 Sv
- 18,000 survivors with higher does (0.1-4 Sv)
  - allow reasonably precise risk estimates
- Doses lower than in many studies of persons exposed for therapeutic medical reasons

Medical studies

- Huge number of studies
- Radiotherapy for malignant disease

  (cancers of the cervix, breast, ovary, testis, thyroid, Hodgkin disease, childhood cancer)
- Radiotherapy for benign disease in children

  (skin hemangioma, tinea capitis, enlarged tonsils, enlarged thymus)
- Radiotherapy for benign disease in adults

  (ankylosing spondylitis, peptic ulcer, breast and gynecological disease, hyperthyroidism)
- Diagnostic radiation

  (chest fluoroscopy, I-131, scoliosis)

Medical Studies

- Many studies lack individual dose estimates
- Therapeutic doses often very high (10+ Gy)
- Doses usually vary markedly by organ
- Risk estimates often very imprecise
- Data are strongest for thyroid and breast cancer where there are many studies with both
  - Individual dose estimates
  - Doses in a useful range (comparable to A-bomb)

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BEIR VII Models

Models developed for:

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

  Risk = Baseline risk [1 + ERR]

- **Excess Absolute Risk (EAR):**

  Risk = Baseline risk + EAR

- Both ERR and EAR
  - Depend on dose
  - May depend on sex, age at exposure, attained age, time since exposure

BEIR VII Models for Solid Cancers

- Based primarily on cancer incidence data 1958-1998
- Risk expressed as linear function of dose
- Explored many functions for describing the dependency of the ERR and EAR on
  - Age at exposure
  - Attained age or time since exposure

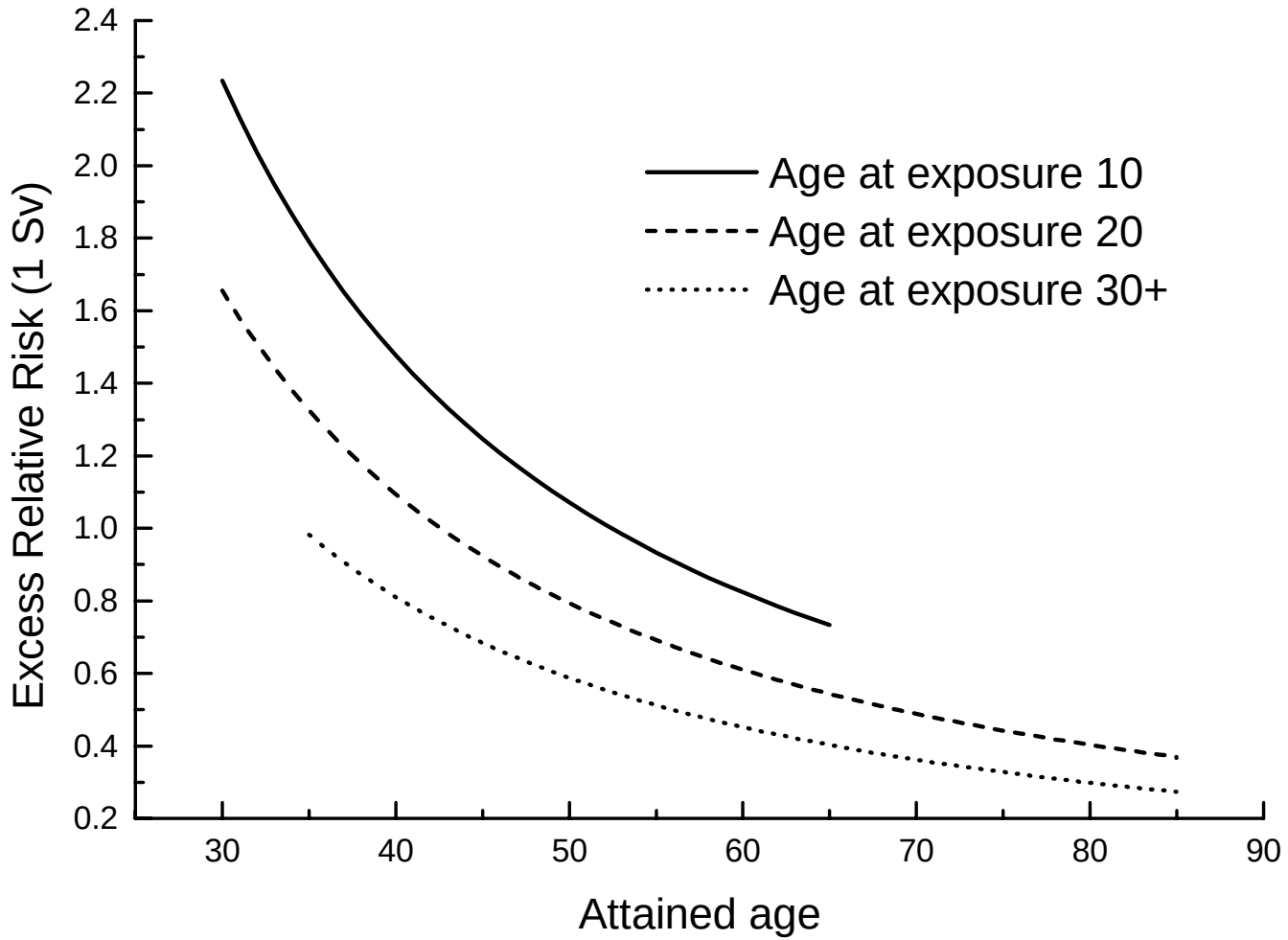
BEIR VII Models for Solid Cancers

Selected Models:

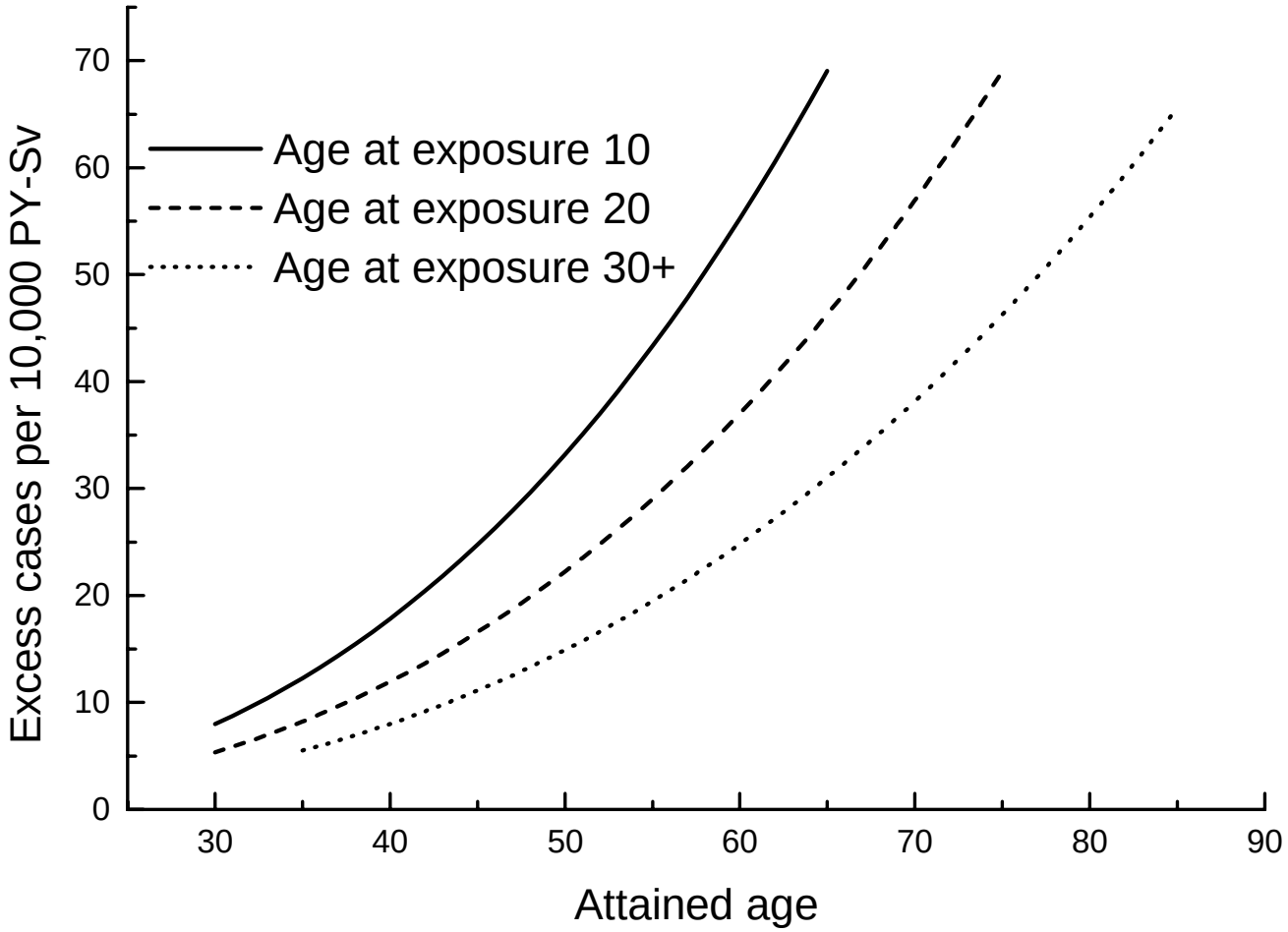
- **Both ERR and EAR decreased with increasing age at exposure over the range 0 to 30 years**
  - **No further decrease after age 30**

- **Both ERR and EAR depended on attained age**
  - **ERR decreased with attained age**
  - **EAR increased with attained age**

Solid Cancer: ERR per Sv



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



Models for site-specific solid cancers*

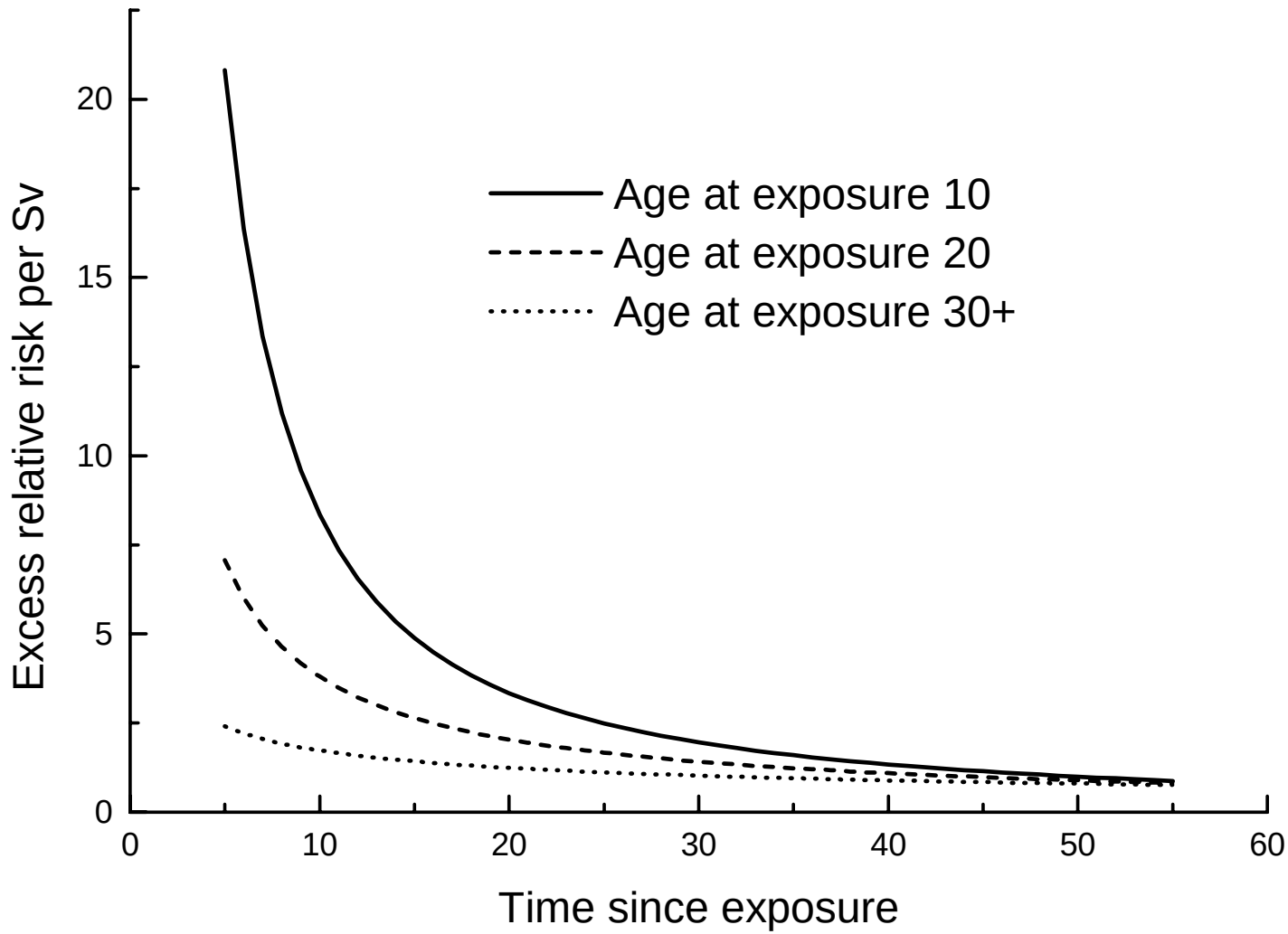
- Both ERR and EAR models developed from A-bomb survivor cancer incidence data
- Patterns with age at exposure and attained age assumed to the same as those for all solid cancer
  - A few exceptions
- All models sex-specific

*Other than breast and thyroid cancer

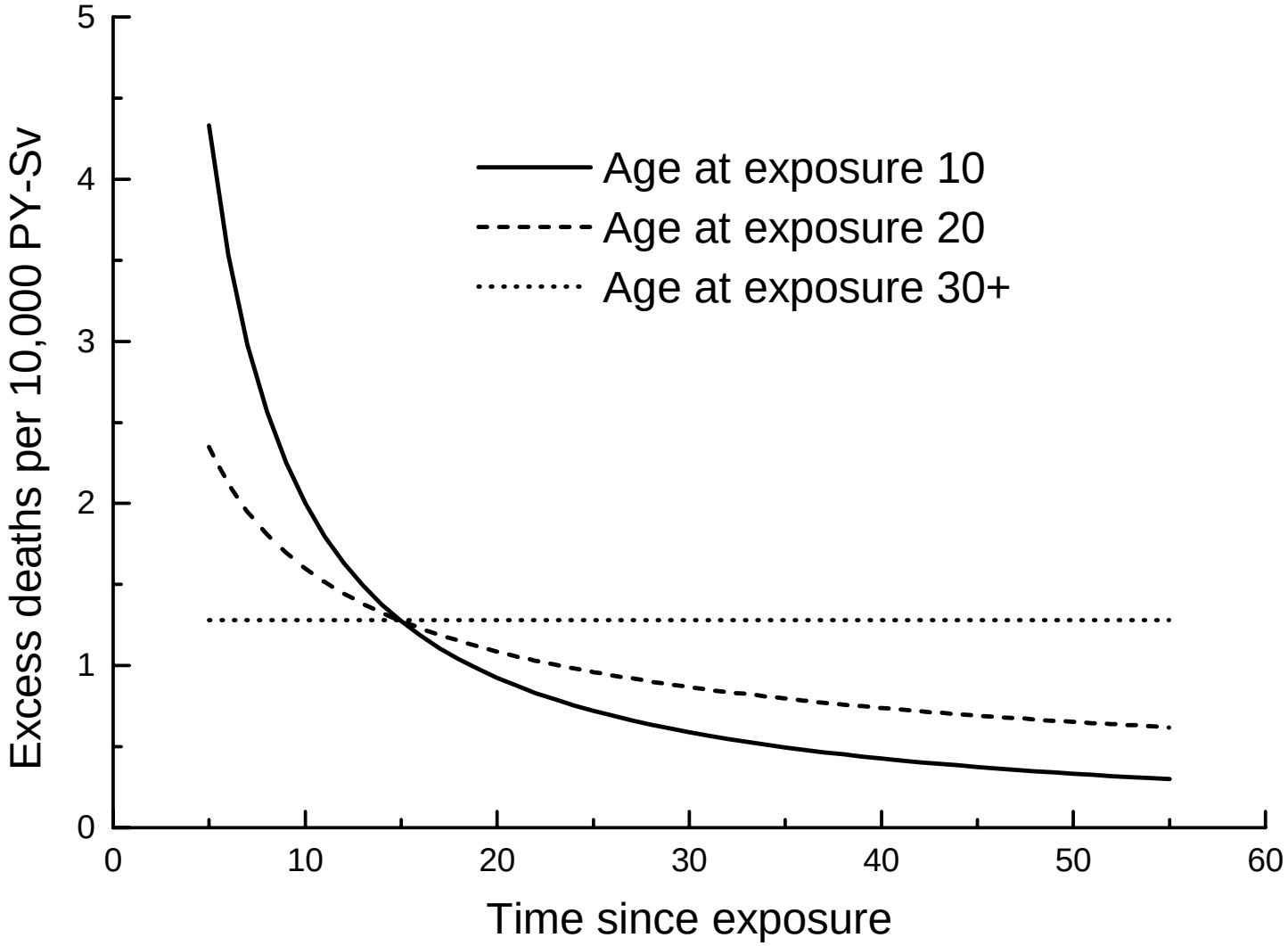
BEIR VII Models for Leukemia

- Based on A-bomb survivor mortality data 1950-2000 (Preston et al. 2004)
- Risk expressed as linear-quadratic function of dose
- Explored many functions for describing the dependency of the ERR and EAR on
  - Age at exposure
  - Attained age or time since exposure
- Final models allowed for dependencies on age at exposure and time since exposure

Leukemia: ERR per Sv



Leukemia: Excess deaths per 10,000 PY-Sv



Estimating Lifetime Risk

- Use data from epidemiologic studies to develop risk models
- Apply models to estimate lifetime risk from low-dose exposure to the US population

Applying Risk Model

- Life-table methods
  - Follow the population forward in time allowing for attrition as the population ages
  - Apply age-specific ERR (EAR) to obtain excess cancers occurring at each age
- Needed information on population of interest
  - Age-sex composition
  - Survival (life-table) data
  - Age- and sex-specific baseline rates for cancer(s) of interest (for ERR models)

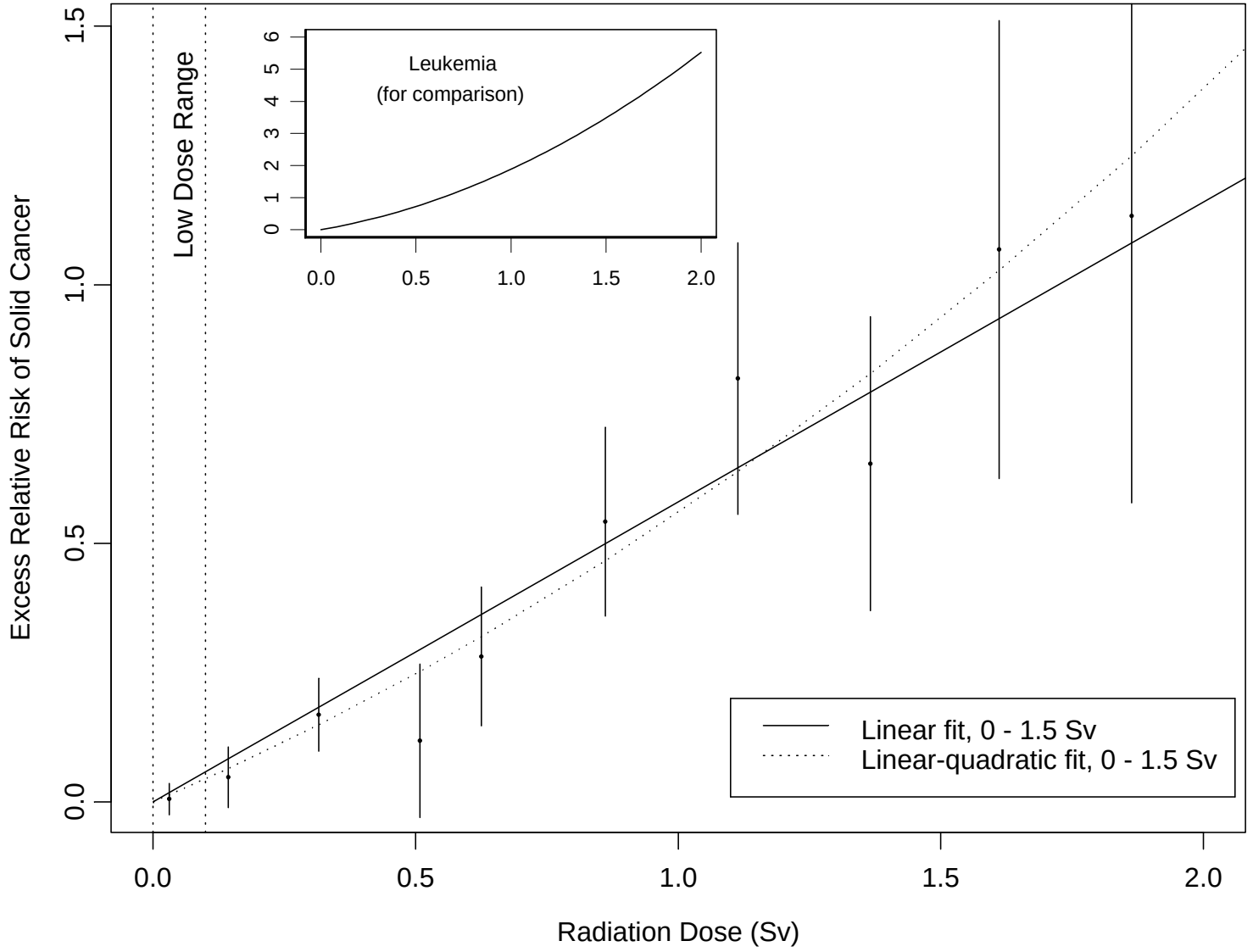
Applying Risk Model : Two Issues of Importance

- Use of model to estimate risk at low doses and dose rates
- "Transporting" risk from Japanese A-bomb survivors to US population
- Both issues discussed in Chapter 10: Integration of Biology and Epidemiology

Use of model to estimate risk at low doses and dose rates

- Radiobiological data support:
  - Linear-quadratic dose-response over the range 0-2 Gy with upward curvature
  - Curvature is ratio of quadratic and linear coefficients
- A-bomb survivor solid cancer incidence data well described by linear model
  - Compatible with small amount of curvature

LSS solid cancer incidence: Excess relative risk



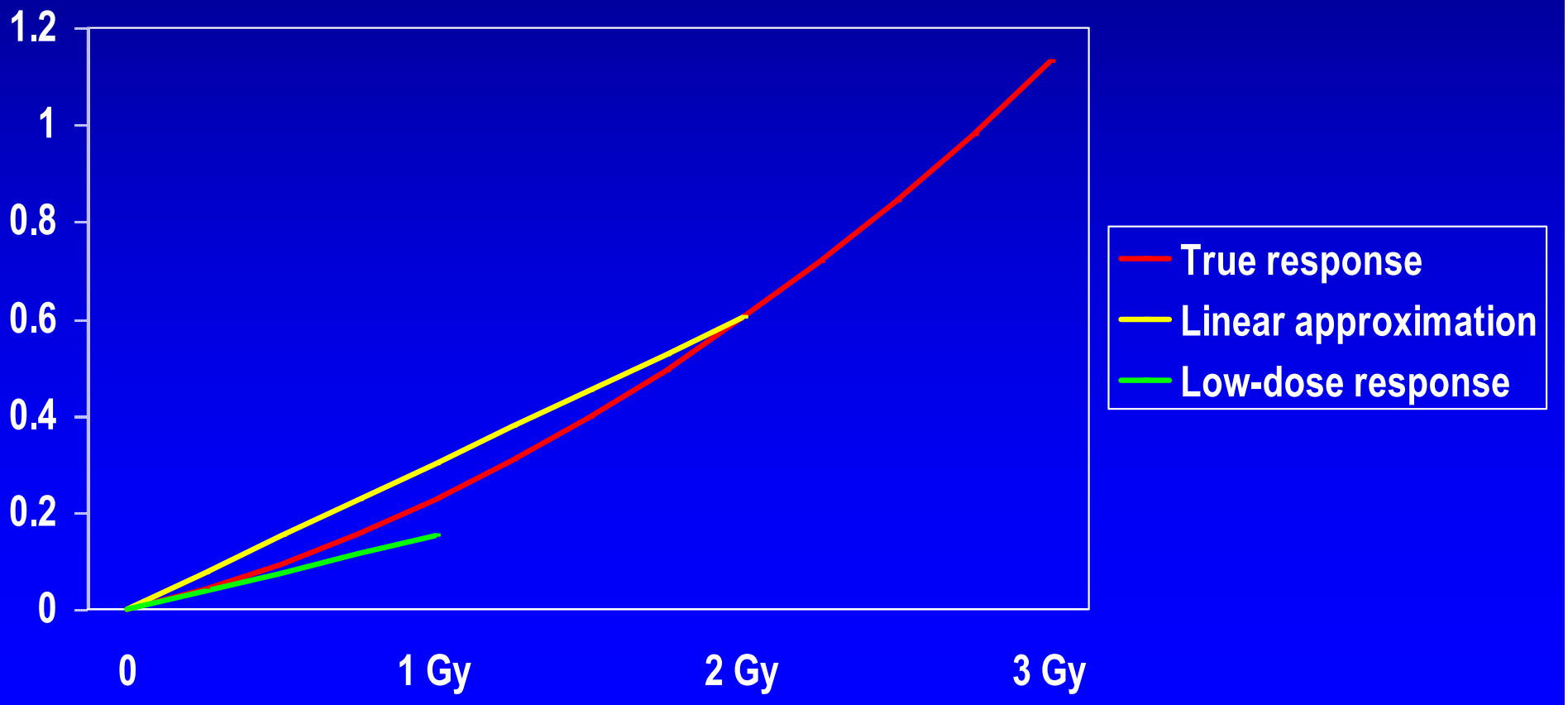
BEIR VII, Fig. ES-1

Use of model to estimate risk at low doses and dose rates

- If true response is linear-quadratic, linear estimates need to be reduced
- Factor used for this is known as the Dose and Dose Rate Effectiveness Factor (DDREF)
- Many past risk assessment have used a DDREF of 2

Dose and Dose Rate Effectiveness Factor (DDREF)

Excess Relative Risk as a function of dose



Dose and Dose Rate Effectiveness Factor (DDREF)

- Not a universal low-dose correction factor
- Depends on what is meant by high dose
- BEIR VII DDREF estimated in a way that is specific for use with the A-bomb survivor solid cancer incidence data

Dose and Dose Rate Effectiveness Factor (DDREF)

- BEIR VII DDREF derived from Bayesian analyses of
  - A-bomb survivor solid cancer incidence data
  - Data from relevant studies in mice
- Estimate with 95% interval: 1.5 (1.1 – 2.3)
- Referred to as "LSS DDREF"

LSS = Life Span Study of A-bomb survivors

Applying Risk Model : Issues

- Use of model to estimate risk at low doses and dose rates
- "Transporting" risk from Japanese A-bomb survivors to the US population

Baseline Cancer Incidence Rates in US and Japan (Females)

	US	Japan
All	280	185
Stomach	3.5	34
Colon	22	17
Liver	1.3	9.8
Lung	34	12
Breast	89	30
Bladder	5.9	2.6

Source: Cancer Incidence in Five Continents, 1997

Approaches for Transporting Risks from Japan to US

- **Absolute risk transport (AR):** Absolute risks the same for Japan and US (BEIR III)
- **Relative risk transport (RR):** Excess relative risks the same for Japan and US (BEIR V)
- Intermediate approaches

  (EPA, NIH Radio-epidemiological Tables)

Model for transporting risks: How do we decide?

- Compare epidemiologic data on non-Japanese populations and A-bomb survivors
- Evaluate interaction of radiation and factors that contribute to differences in baseline risks
- Biological considerations (initiation/promotion)

BEIR VII approach to transport

Breast and thyroid cancer

- Estimates based on pooled analyses that included non-Japanese populations
- Breast cancer: EAR model from Preston et al. 2002
- Thyroid cancer: ERR model from Ron et al. 1995

BEIR VII approach to transport

Sites other than breast and thyroid:

- Provide estimates based on both relative and absolute risk transport
  - Use ERR and EAR models
  - Range reflects uncertainty
- Use weighted mean for point estimates
  - All sites except lung: 0.7 for RR; 0.3 for AR
  - Lung: 0.3 for RR; 0.7 for AR
  - Weighting conducted on logarithmic scale

Example: Lifetime Risk* of Stomach Cancer Incidence in Males

Estimate based on RR transport:	25
Estimate based on AR transport:	280
Weighted mean:	52
Weighted estimate reduced by DDREF of 1.5:	34

*Number of cases per 100,000 persons exposed to 0.1 Gy

RR = Relative Risk transport; AR = Absolute Risk transport

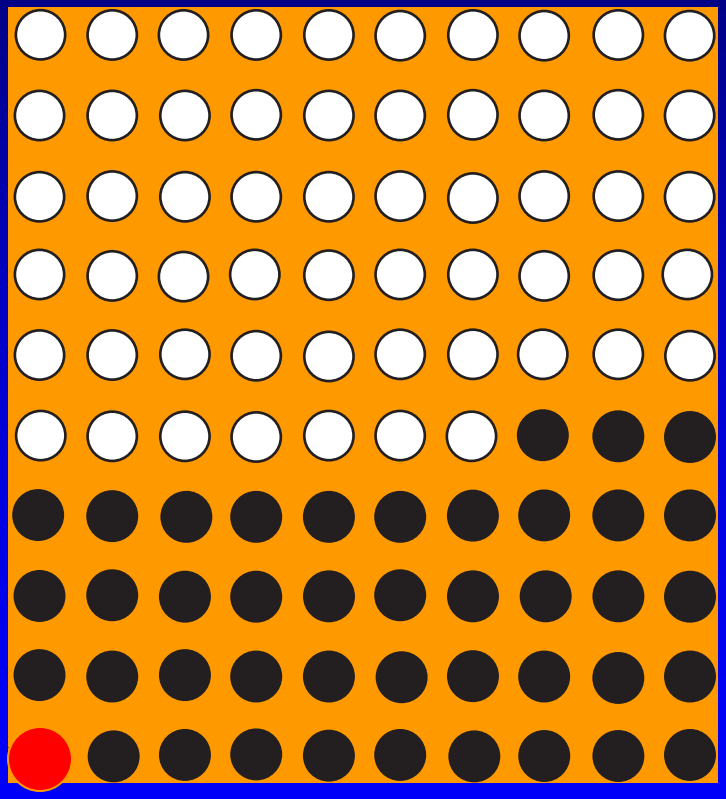
Lifetime risk estimates

- Estimates for “all solid cancers” obtained by summing site-specific estimates.

Lifetime risk for incidence of solid cancer and leukemia

If 100 people exposed to 0.1 Gy (100 mGy), expect

- 1 cancer from this exposure
- 42 cancers from other causes



Sources of Uncertainty Included in Quantitative Assessment

- Statistical uncertainties in estimating model parameters
- Use of model to estimate risk at low doses and dose rates (DDREF)
- Transporting risk from Japanese A-bomb survivors to US population

Lifetime Risk Estimates. Number of cases or deaths per 100,000 persons exposed to 0.1 Gy

	Incidence	Mortality
All solid cancers		
Males	800 (400-1600)	410 (200-830)
Females	1300 (690-2500)	610 (300-1200)
Leukemia		
Males	100 (30-300)	70 (20-250)
Females	70 (20-250)	50 (10-190)

Estimates with 95% subjective confidence intervals

Lifetime Risk Estimates* for Cancer Incidence and Mortality in Females

	Incidence	Mortality
Stomach	43 (5-390)	25 (3-220)
Colon	96 (34-270)	46 (16-130)
Liver	12 (1-130)	11 (1-130)
Lung	300 (120-780)	270 (110-660)
Breast	310 (160-610)	73 (37-150)
Ovary	40 (9-170)	24 (6-98)
Bladder	94 (30-290)	28 (10-81)

Number of cases or deaths per 100,000 persons exposed to 0.1 Gy

BEIR VII Example exposure scenarios

- Single exposure of 0.1 Gy to population of mixed ages
- Single exposure of 0.1 Gy to persons aged 0, 5, 10, 15, 20, 30, 40, 50, 60, 70 and 80
- Exposure of 1 mGy per year throughout life
- Exposure of 10 mGy per year from ages 18 to 65

- Estimates for each scenario shown for
  - Cancer incidence and mortality
  - Each of 12 specific cancer categories

Lifetime risk estimates for solid cancer incidence by age at exposure

	Males	Females
Age at exposure		
10	1330 (660-2660)	2530 (1290-2660)
30	600 (290-1260)	1000 (500-2020)
50	510 (240-1100)	680 (350-1320)
All ages	800 (400-1600)	1300 (690-2500)

Number of cases per 100,000 persons exposed to 0.1 Gy

Comparison of Lifetime Risk Estimates for Solid Cancer* Mortality. Both sexes.

	Estimate	DDREF
BEIR VII (2005)	510	1.5
BEIR V (1990)	695	No DDREF
ICRP (1991)	450	2
EPA (1999)	520	2

*Or all cancers except leukemia

Number of cases per 100,000 persons exposed to 0.1 Gy

Comparison of Lifetime Risk Estimates for Solid Cancer* Mortality. Both sexes.

	Estimate	DDREF	Estimate using DDREF of 1.5
BEIR VII (2005)	**510**	**1.5**	**510**
BEIR V (1990)	695	No DDREF	460
ICRP (1991)	450	2	600
EPA (1999)	520	2	690

*Or all cancers except leukemia

Number of cases per 100,000 persons exposed to 0.1 Gy

Sources of Uncertainty Included in Quantitative Assessment

- Statistical uncertainties in estimating model parameters
- Use of model to estimate risk at low doses and dose rates (DDREF)
- Transporting risk from Japanese A-bomb survivors to US population

Uncertainties in Lifetime Cancer Incidence Estimates for Females

	Percent of variance due to			
	Estimation	Transport	DDREF	95% factor*
All solid	11	6	83	1.9
Stomach	4	89	7	9.2
Colon	54	14	32	2.8
Liver	21	73	6	10.9
Lung	16	44	39	2.6
Breast	25	0	75	2.0
Ovary	79	5	17	4.2

*Ratio of upper 95% bound to estimate

Features of BEIR VII Risk Estimates (1)

- Equal attention to cancer incidence and mortality
- Based on greatly strengthened epidemiologic data
  - A-bomb survivor incidence and mortality data
    - 13,000 incident cases
    - 10,000 solid cancer deaths (5600 for BEIR V)
    - DS02 dosimetry
  - Pooled analyses including several medical studies for estimating breast and thyroid cancer risks

Features of BEIR VII Risk Estimates (2)

- Expanded list of cancer sites
- DDREF estimated using Bayesian analyses
  - A-bomb survivor data
  - Experimental data in mice
- Explicit attention to transport of risks
- Quantitative evaluation of major sources of uncertainty

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Testicular Cancer Study

- International cohort of 40,576 1-year survivors
  - 16 population-based cancer registries
- Focused on second solid cancers in 20,987 10-year survivors
  - 1694 second solid cancers
- Mean age at testicular cancer diagnosis = 35 years

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

Testicular Cancer Study

- Treatment for testicular cancer includes
  - Surgery
  - Radiotherapy
  - Chemotherapy
- Data available on initial treatment
  - Not available for all registries
  - Not detailed
  - Possibly incomplete

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

Simple measures for cohort study

- Compare cancer incidence rates of testicular cancer patients to those of the general population
- Standardized incidence ratio (SIR)
  - A measure of relative risk
  - Estimate by O/E
    - O = observed number of cases or deaths from disease of interest
    - E = expected number of cases or deaths based on general population rates
- Excess absolute risk (EAR)
  - (O – E)/person-years
  - Often expressed per 10^4 person-years

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 calculate the SIR and EAR for several categories defined by the variable of interest
  - SIR = O/E
  - EAR = (O–E)/person-years

Simple measures of RR of 2nd solid cancer[1]

Time since TC diagnosis	# solid cancers	SIR (O/E) (95% CI)
10-19 y	802	1.7 (1.6 – 1.8)
20-29 y	563	1.7 (1.6 – 1.9)
30-34 y	169	1.8 (1.5 – 2.1)
35+ y	160	1.9 (1.6 – 2.2)

[1]Among 10-year survivors of testicular cancer

Modeling RR and EAR

- Express RR and EAR as continuous functions of
  - age at diagnosis ($agedx$)
  - attained age (aa)
  - other variables

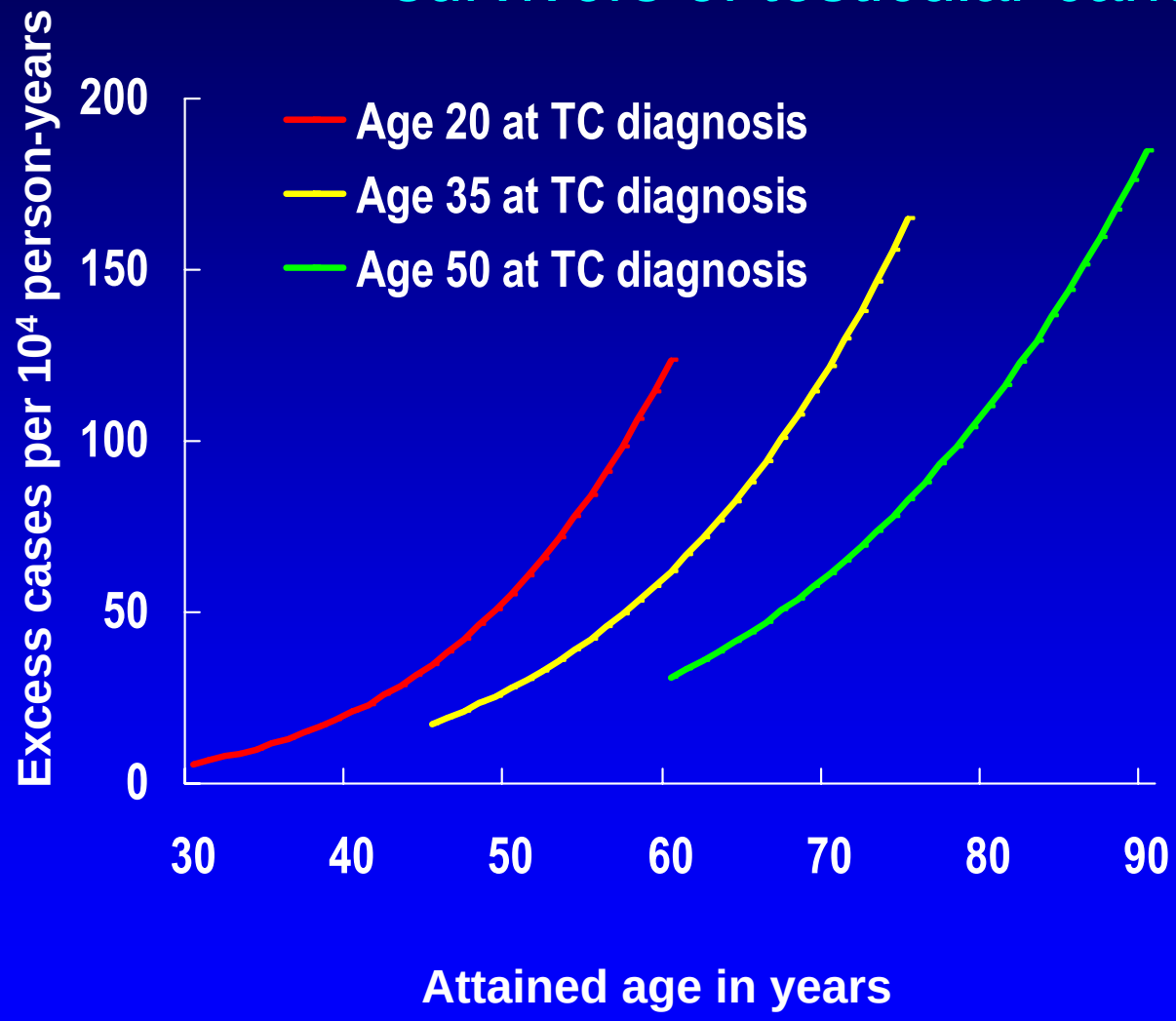
- Example: $RR = 1 + \theta \exp[\beta_1 (agedx) + \beta_2 \ln (aa)]$

$$EAR = \theta \exp[\beta_1 (agedx) + \beta_2 \ln (aa)]$$

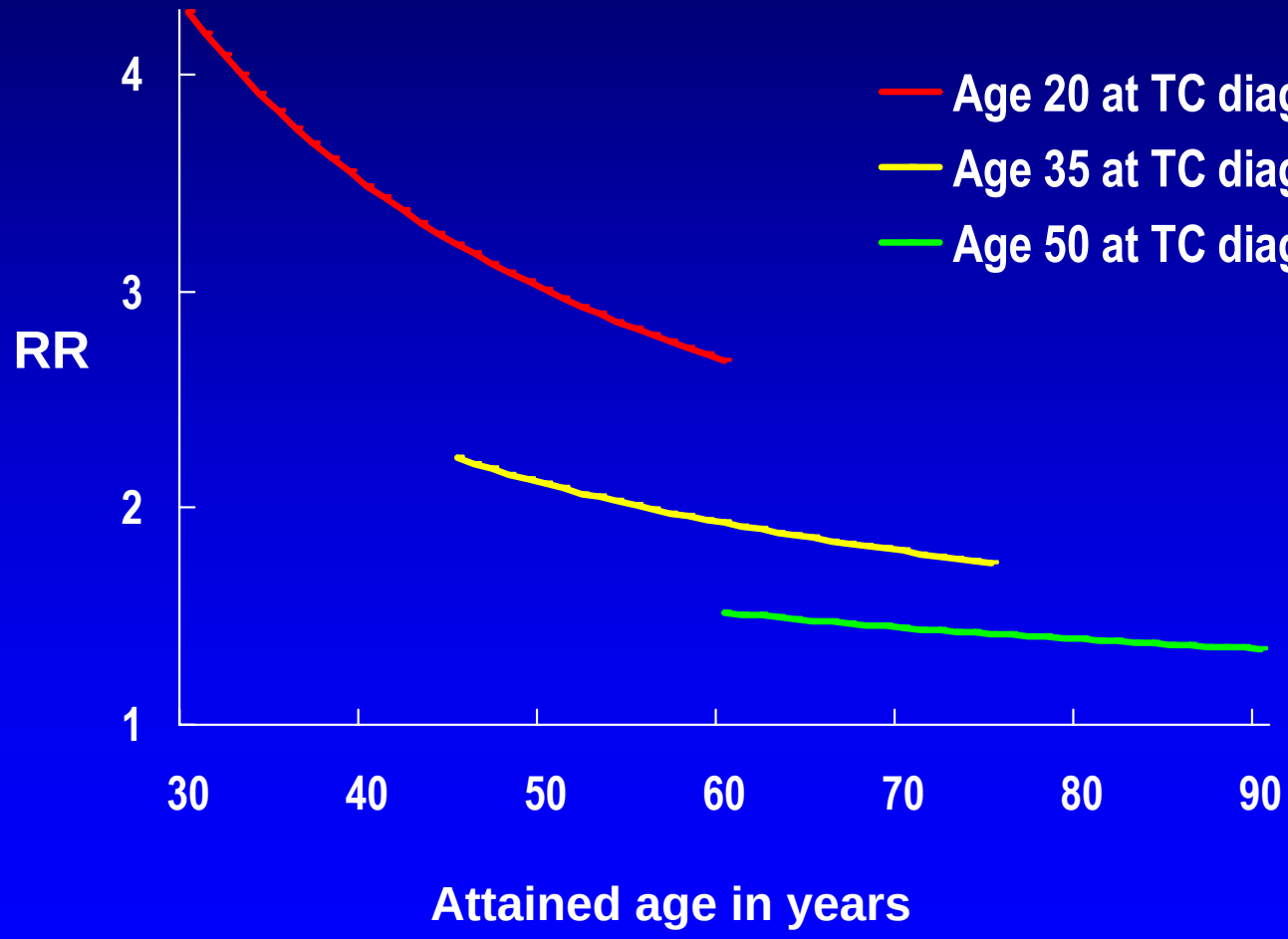
Advantages of modeling

- Allow simultaneous evaluation of several variables (multivariate analyses)
- Use of continuous variables allows estimation of risks at any specified values of these variables

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



Relative risk of 2nd solid cancer in 10-year survivors of testicular cancer (TC)



Adjusted and unadjusted RR of 2nd solid cancer[1]

Time since TC diagnosis	# solid cancers	RR* (95% CI)	RR** (95% CI)
10-19 y	802	1.7 (1.6 – 1.8)	2.1 (1.9 – 2.3)
20-29 y	563	1.7 (1.6 – 1.9)	2.0 (1.8 – 2.2)
30-34 y	169	1.8 (1.5 – 2.1)	1.8 (1.5 – 2.1)
35+ y	160	1.9 (1.6 – 2.2)	1.7 (1.5 – 2.0)

*Not adjusted for attained age

**Adjusted for attained age

[1]Among 10-year survivors of testicular cancer

Cumulative Risk

- Risk of developing event of interest in specified time interval
  - e.g. second solid cancer following testicular cancer
- Depends on length of interval
- Often presented as a function of time
  - e.g. time since diagnosis of testicular cancer
- Need to account for competing risks

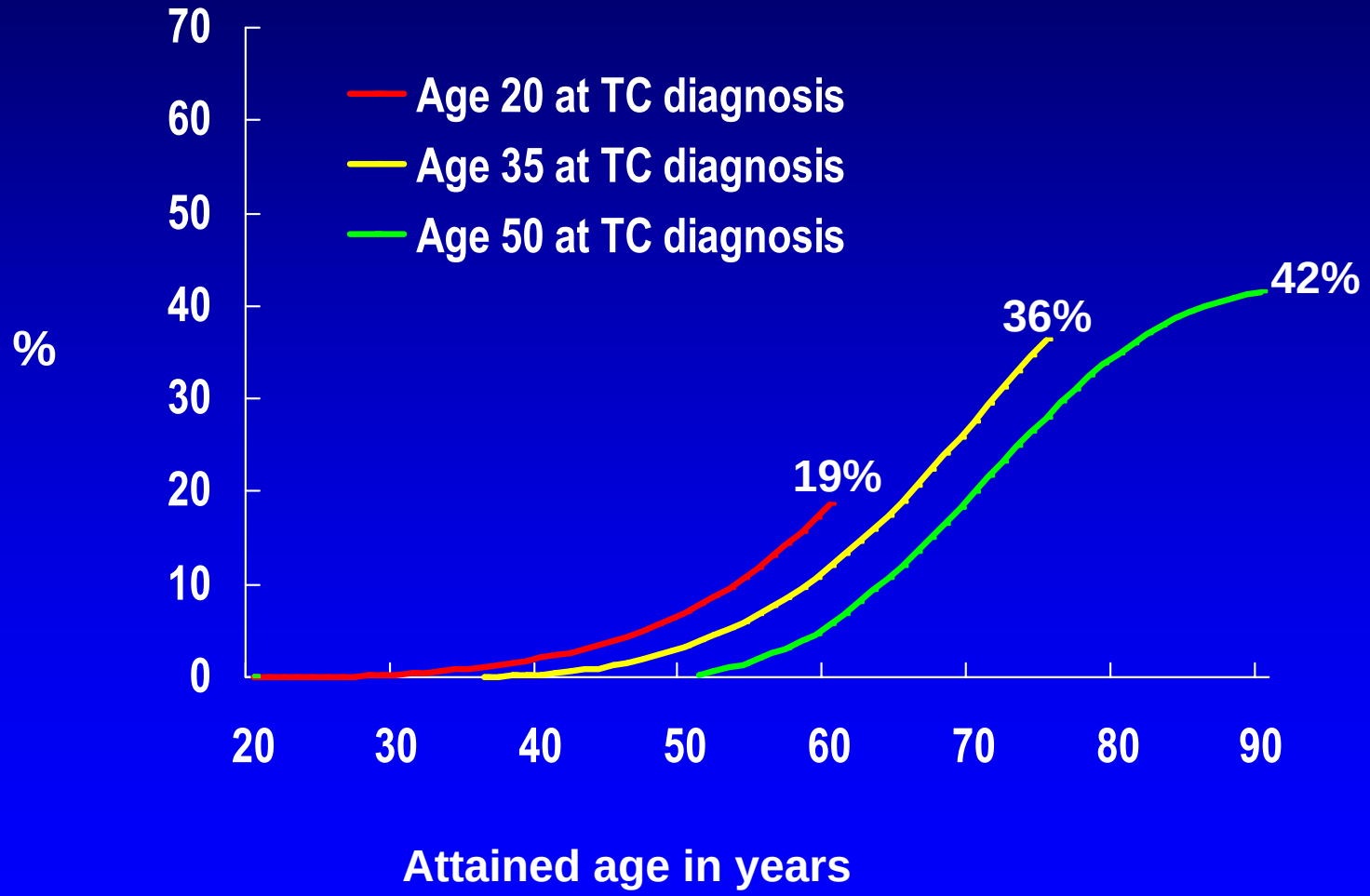
Cumulative Risk in Testicular Cancer Patients

- Used EAR model for solid cancer risks along with data on the the general population

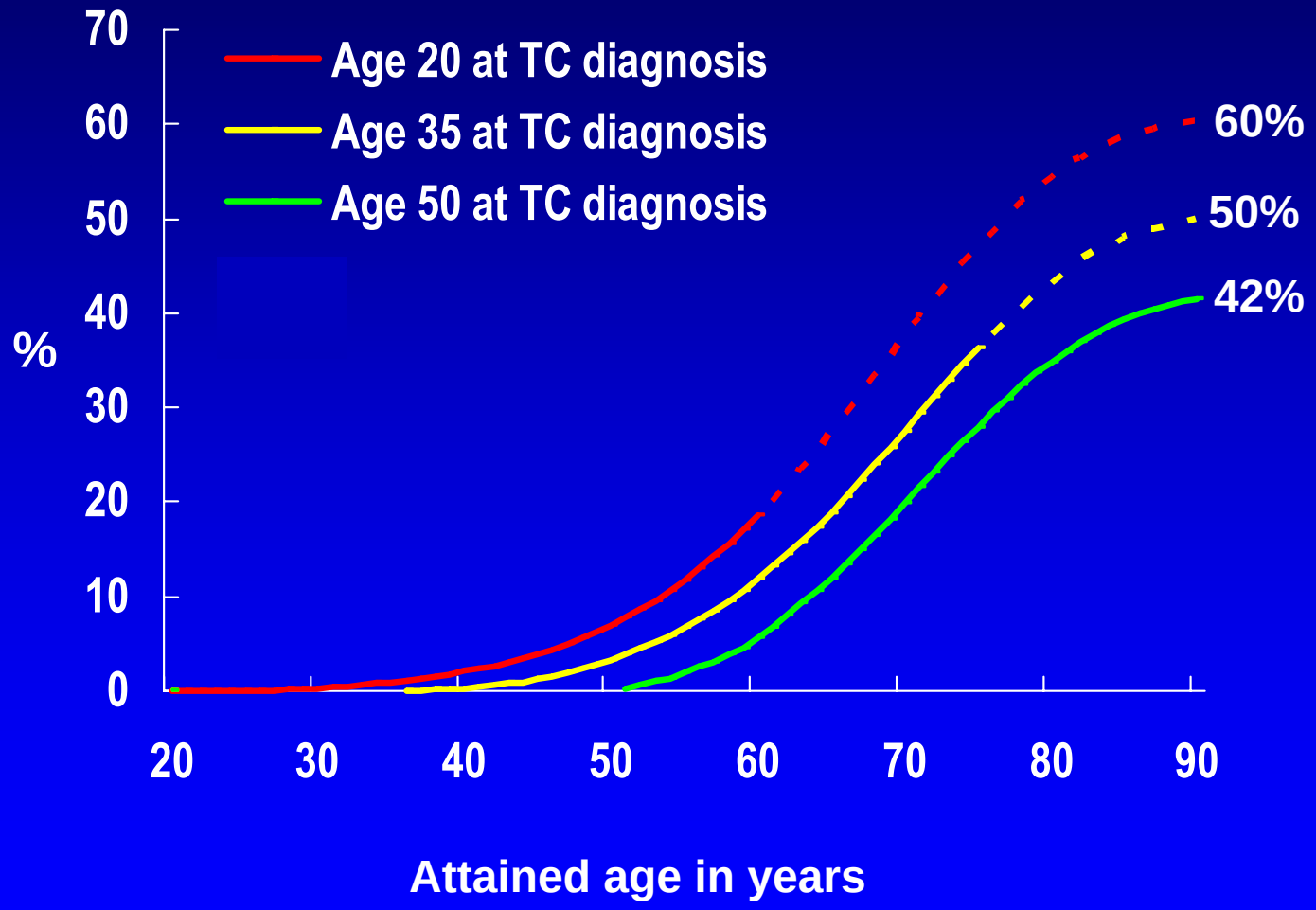
Competing risks

- 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 (%) 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



Lung cancer following Hodgkin disease

- 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 Hodgkin disease: 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 Hodgkin disease

Also evaluated more general models:

Example:

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

$\gamma = 0$ yields Model III

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

$(1 + 0.15\, dose + 0.75\, cyc + .001\, {*}dose{*}cyc)$

Nearly identical fit to Model III

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

Lung cancer following 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

Dose Measurement Error

- 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

Some sources of uncertainty in A-bomb survivor estimates

Uncertainty in

- Yields of the bombs
- Location of individual survivors
- Shielding of individual survivors
- Models for evaluating dependence of dose on distance from epicenter
- Models for evaluating the effects of various types of shielding

Possible Effects of Not Accounting for Errors in Dose Estimates

- **Bias in estimates of risk coefficients**
- **Distortion of the shape of the dose-response function**
- **Biased comparisons across subgroups and studies**
- **Underestimation of uncertainty**

Accounting for Errors in Dose Estimates

- Requires good understanding of error structure
- Shared errors require different treatment than errors that are independent for different subjects
- Classical errors require different treatment than Berkson errors
- Requires lots of communication between dosimetrists and statisticians

Errors in Dose Estimates Used in Epidemiologic Analyses

- Increasingly, errors are being evaluated and considered in radiation dose-response analyses
- A-bomb survivors: Recent analyses calibrated to adjust for random errors

Examples where dose estimation errors have been taken into account

- **A-bomb survivors (Pierce et al. 1996)**
- **Nuclear workers (Gilbert 1998)**
- **Residential radon exposure (Reeves et al. 1998)**
- **Utah fallout study (Thomas et al. 1999)**
- **Underground miners (Stram et al. 1999)**
- **Tinea capitis patients (Schafer et al. 2001; Lubin et al. 2004)**