National Cancer Institute

DIVISION OF CANCER EPIDEMIOLOGY AND GENETICS
Radiation Epidemiology Branch

Solid Cancer Incidence Among Atomic Bomb Survivors

2007 Radiation Epidemiology Course

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

A Second Follow-up: 1958-1998
Radiation Effects Research Foundation

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Data from Preston, Ron, Tokuoka et al. Radiat Res, In press.

Outline

- Life Span Study (LSS) cancer incidence cohort
- Cancer incidence follow-up 1958-1998
- Major results
  - All solid cancers
  - Site-specific risks
- Summary remarks

Objectives of Incidence Report

- Quantify cancer risks attributable to radiation
- Explore the shape of the dose-response
- Assess how the risk is modified by age, time, gender and other factors
- Help clarify site-specific differences in risk patterns
- Highlight issues and cancer sites needing more research

LSS Cohort

- Survivors within 2.5 km of the bombings
- Survivors within 2.5-10 km
- Not-in-city (NIC)

TOTAL PEOPLE 120,321

Strengths of LSS Cohort

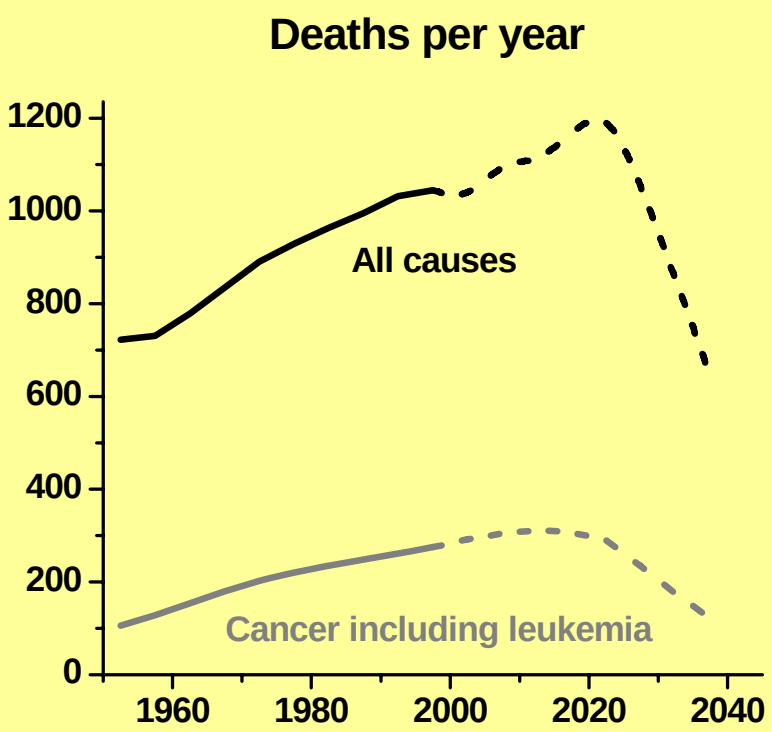
- Large study population
- Basically healthy non-selected population
- All ages and both sexes
- Well characterized dose estimates
- Wide range of doses
- Mortality follow-up virtually complete
- Complete cancer ascertainment in tumor registry catchment areas
- More than 50 years of follow-up

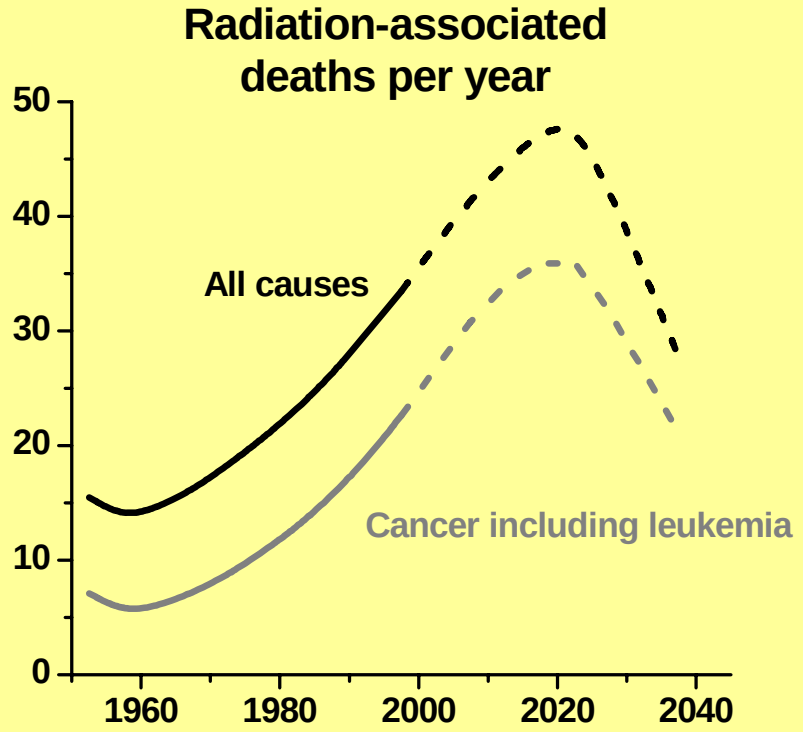
LSS Cohort Endpoints

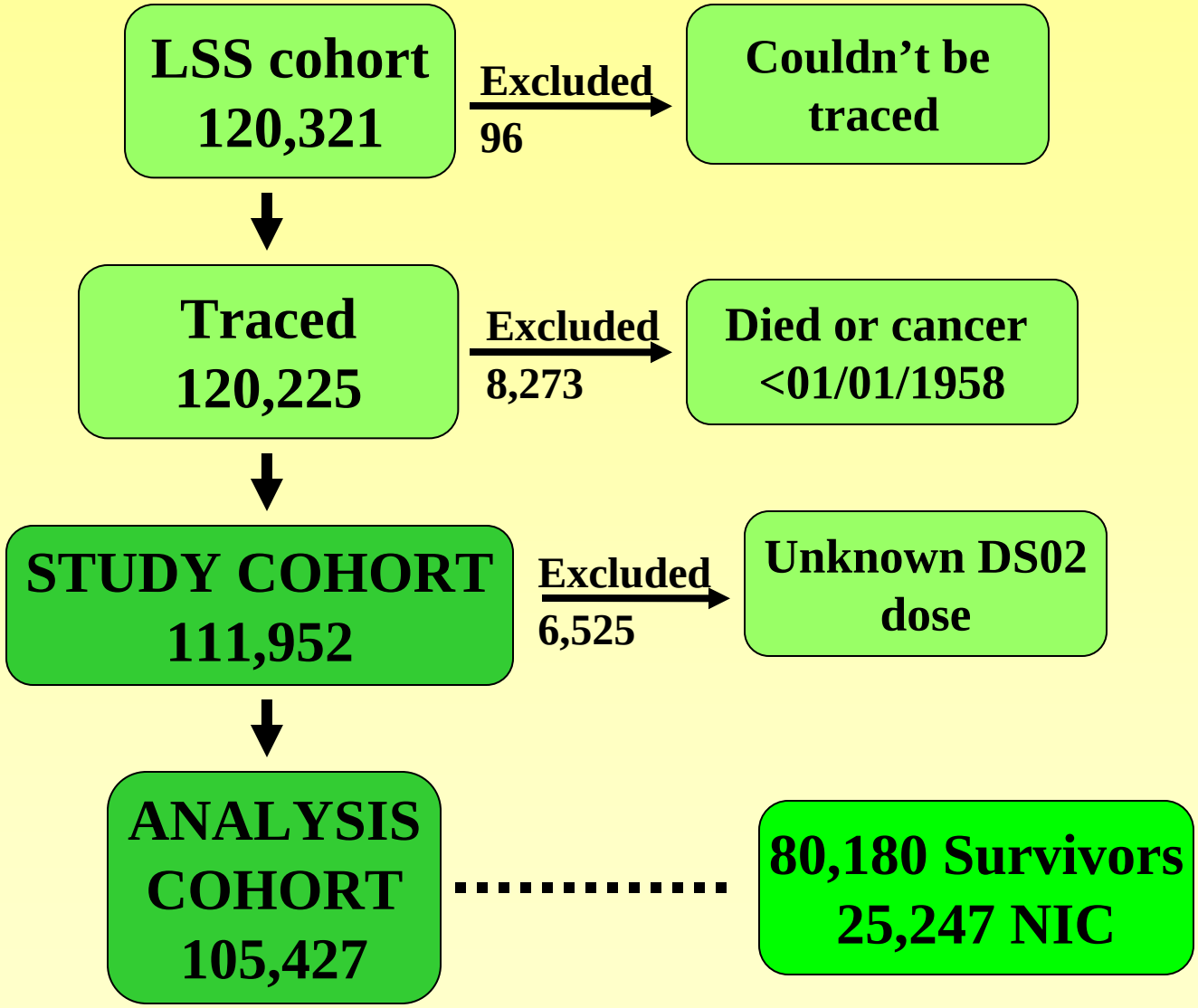
	Incidence	Mortality
Yr. follow-up began	1958	1950
Study population*	105,427	113,186
Mean age at bomb	26.8	29.0
Endpoint	Cancers only	All deaths
Ascertainment	Cancer registry	Family registry
Catchment area	Hiroshima & Nagasaki	All Japan
Most recent follow-up	12/1998	12/2000

**Excludes people who do not have DS02 doses*

Projections:
Aging of Younger Cohorts






LSS cohort
120,321
Excluded
96
Couldn't be traced
Traced
120,225
Excluded
8,273
Died or cancer <01/01/1958
STUDY COHORT
111,952
Excluded
6,525
Unknown DS02 dose
ANALYSIS COHORT
105,427
80,180 Survivors
25,247 NIC

Strengths of LSS Cancer Incidence Data

- Data on non-fatal cancers
- High level cancer ascertainment
- Accurate diagnoses
- Information on histology
- Includes some benign tumors
- Long follow-up
- Large number of people exposed at young ages

Limitations of LSS Cancer Incidence Data

- Inadequate solid cancer data from 1945-1958
- Inadequate leukemia data from 1945-1950
- Cancer data limited to Hiroshima and Nagasaki area residents
- Limited treatment data

Second Cancer Incidence Report 1958-1998

- 105,427 people with doses
  - 59% female
- 50% alive in 1998
  - ~85% of those <20 ATB
- First primary tumors
- DS02 organ dose estimates

Statistical Methods

- DS02 dose (kerma >4 Gy = 4 Gy)
- Tumor registry catchment area
- Migration adjustment of person years
- General excess relative (ERR) and absolute (EAR) risk models
- Linear dose-response standard model
- Modifying effects of gender and age

LSS Tumor Registry

Hiroshima & Nagasaki catchment area

Active case ascertainment

- *Large hospitals*
- *Tissue registries*
- *Death certificates*
- *Medical associations (small hospitals)*

No dose bias in case ascertainment

LSS Cancer Incidence Cohort

Dose (Gy)	Person Years	Subjects	%
Not in city	680,744	25,247	23.9
< 0.005 in city	918,200	35,545	33.7
0.005 - 0.1	729,603	27,789	26.4
0.1 - 0.2	145,925	5,527	5.2
0.2 - 0.5	153,886	5,935	5.6
0.5 - 1	81,251	3,173	3.0
1-2	41,412	1,647	1.6
2+	13,711	564	0.5

LSS Cancer Incidence

Period	Person Years*	Cases
1958-1998	2,083,988+	17,448+
1958 – 1987	1,655,000	8,613

24% increase in person years and 56% in cases since 1987 follow-up

**Adjusted for migration from catchment area*

+ Includes NIC

Distribution of Solid Cancers

Site	Cases	Mean age at dx.
Stomach	4,730	67.7
Lung	1,759	71 .2
Colon	1,516	69.3
Liver	1,494	67.0
Breast	1,082	59.8
Cervix	859	60.0
Rectum	838	68.0
Bladder	469	70.6
Thyroid	471	60.4
Non-melanoma skin	330	72.4
Nervous system	281	62.6

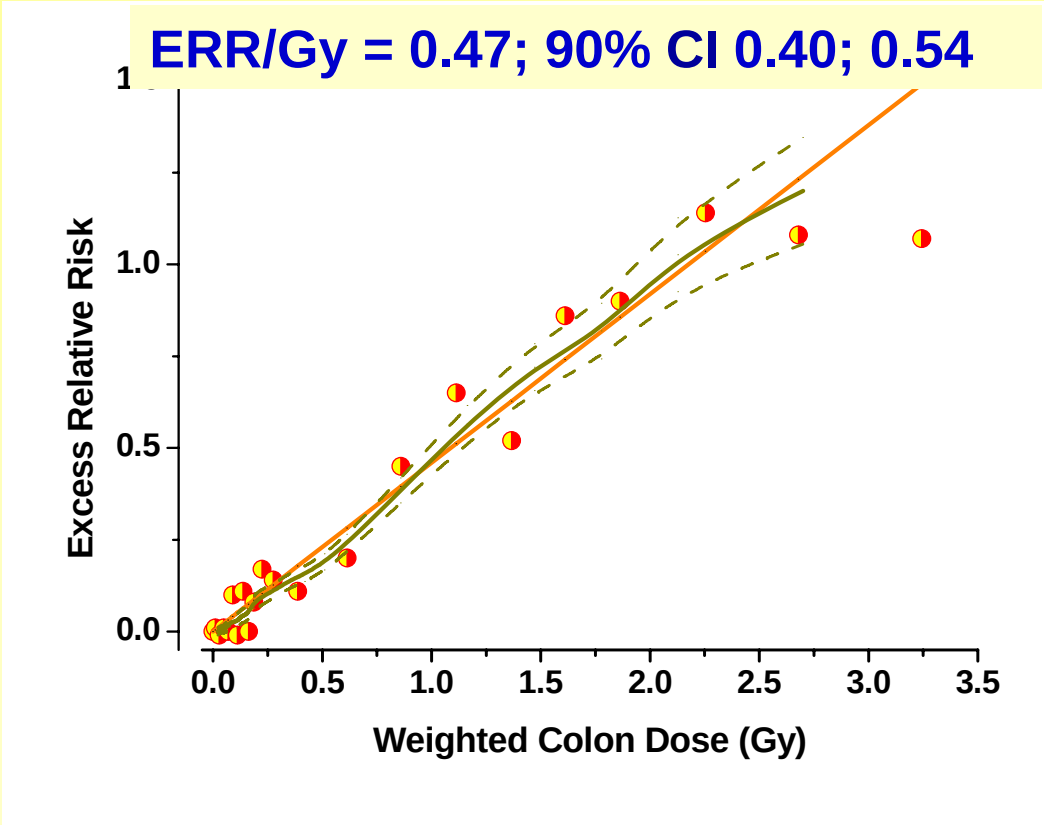
Solid Cancer Incidence

Dose (Gy)	Observed	Excess	AR%
< 0.005	9,597	3	0.0
0.005 - 0.1	4,406	81	1.8
0.1 - 0.2	968	75	7.6
0.2 - 0.5	1,144	179	15.7
0.5 - 1	688	206	29.5
1-2	460	196	44.2
2+	185	111	61.0
Total	***17,448***	***853***	**10.7***

***Attributable risk % among people with dose >0.005 Gy.**

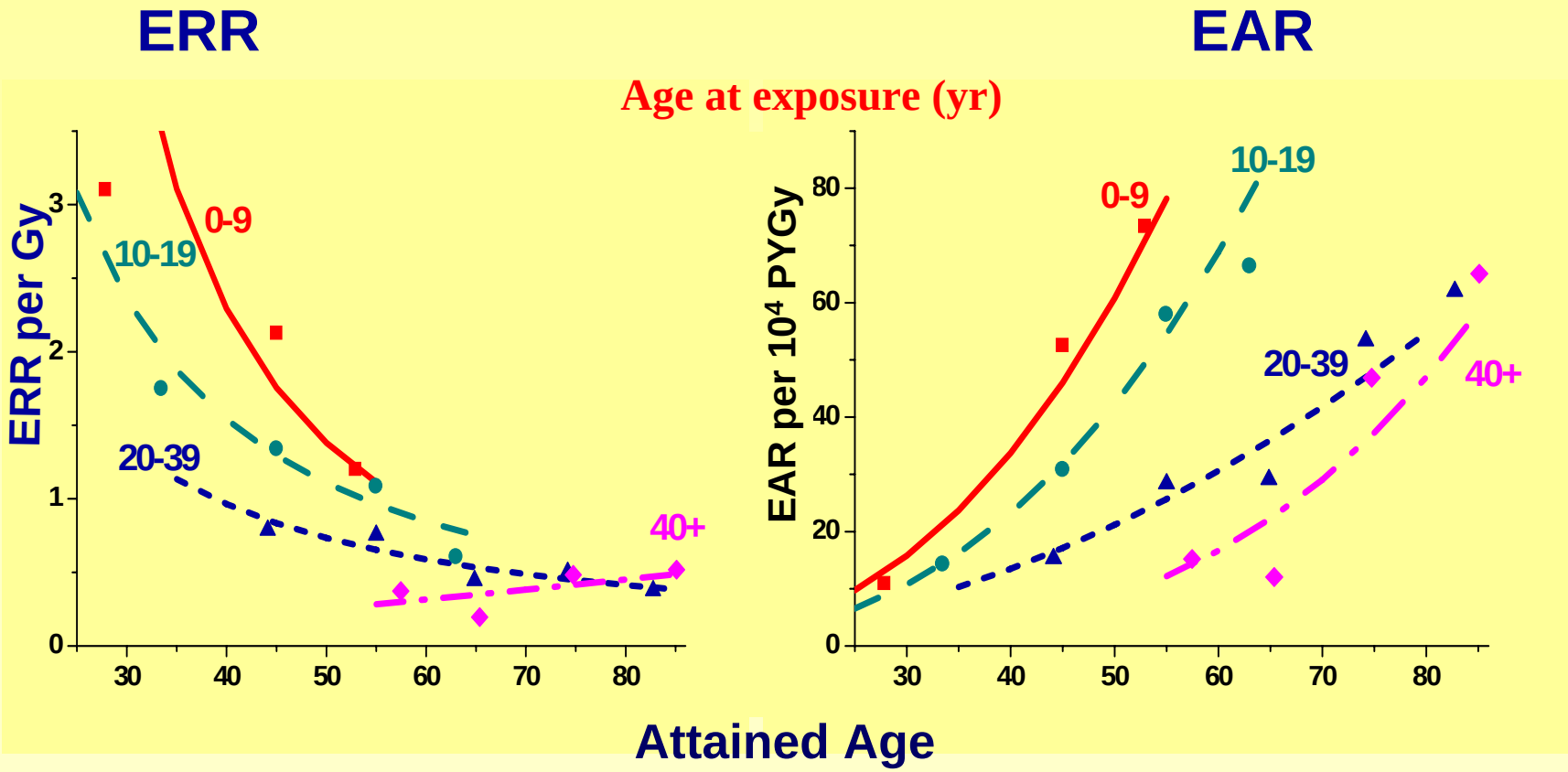
Solid Cancer Incidence Dose Response

- No evidence of non-linearity in the dose response
- Statistically significant trend on 0 – 0.15 Gy range
- Low dose range trend consistent with that for full range



Sex-averaged at age 70 for exposure at age 30

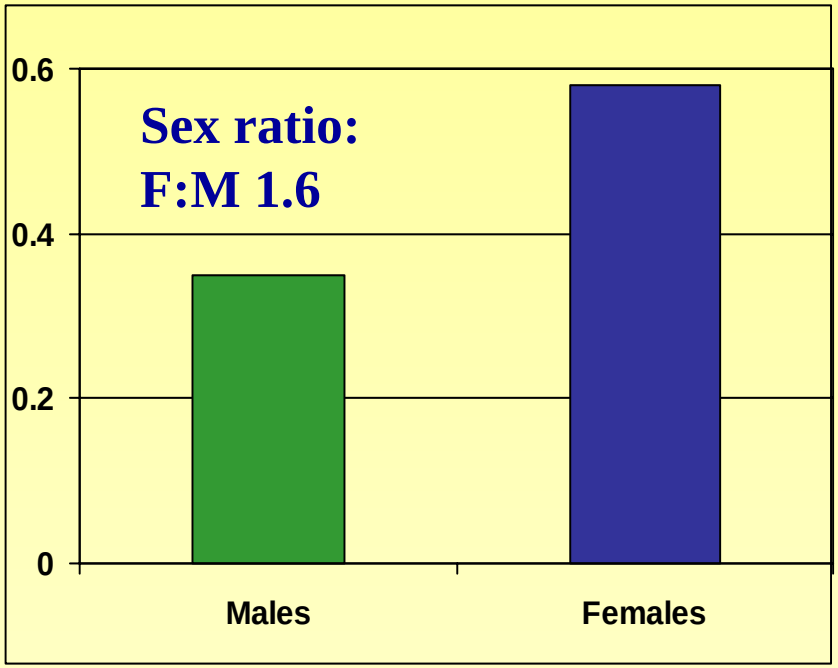
Solid Cancer Temporal Patterns



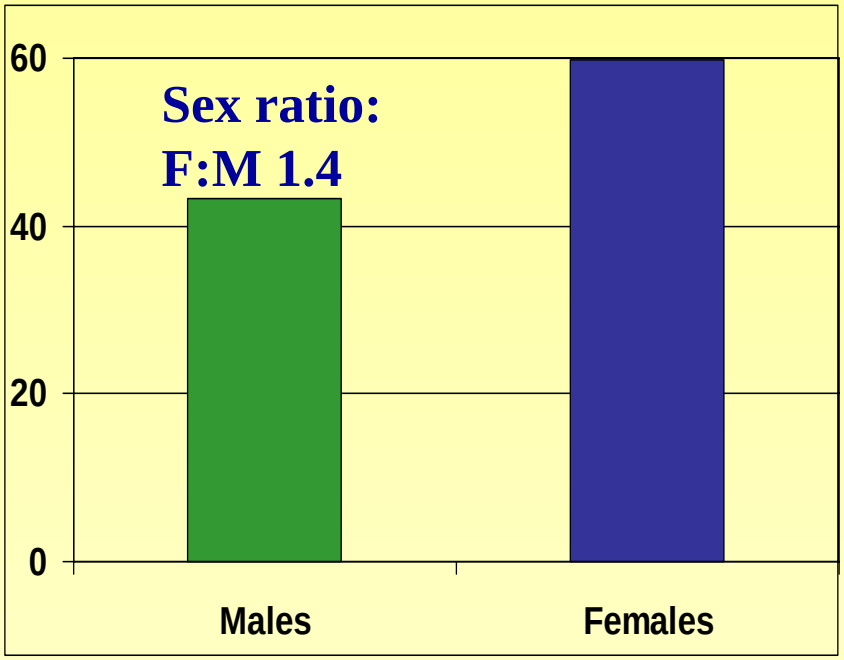
For person age 70 exposed at age 30

Solid Cancer Risks by Gender

ERR per Gy



EAR per 10^4 PYGy



For person age 70 exposed at age 30

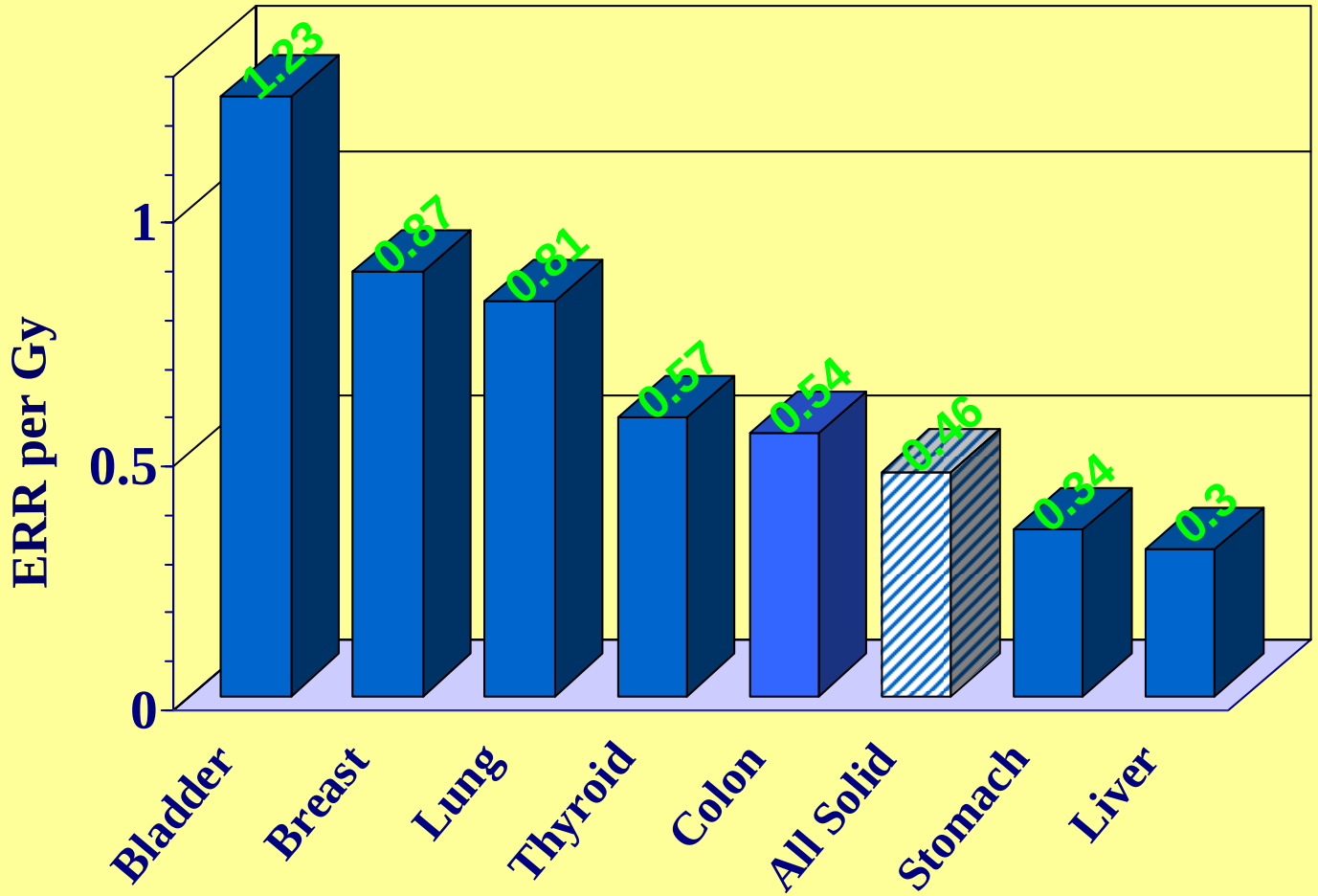
Radiation Risks by Histology

Histology	Cases	ERR/Gy	EAR/10^4PYGY
Adenocarcinoma	10,384	0.46 (0.38; 0.55)	32 (25; 38)
Squamous	2,097	0.41 (0.18; 0.61)	3.8 (1.7; 6.7)
Sarcoma	149	0.48 (0.07; 1.4)	0.20 (0.02; 0.69)
TOTAL	17,448	0.47 (0.40; 0.54)	52 (43; 60)

Site–Specific Risks

- **Site-specific differences likely exist**
  - **But much of observed variability is consistent with random variation**
- **Formal statistical tests generally lack power to detect real differences**
  - **Statistical methods for shrinking estimates toward a central value are likely to lead to improved estimators of risk levels, gender effects and age-time patterns**

Site–Specific Risk Estimates



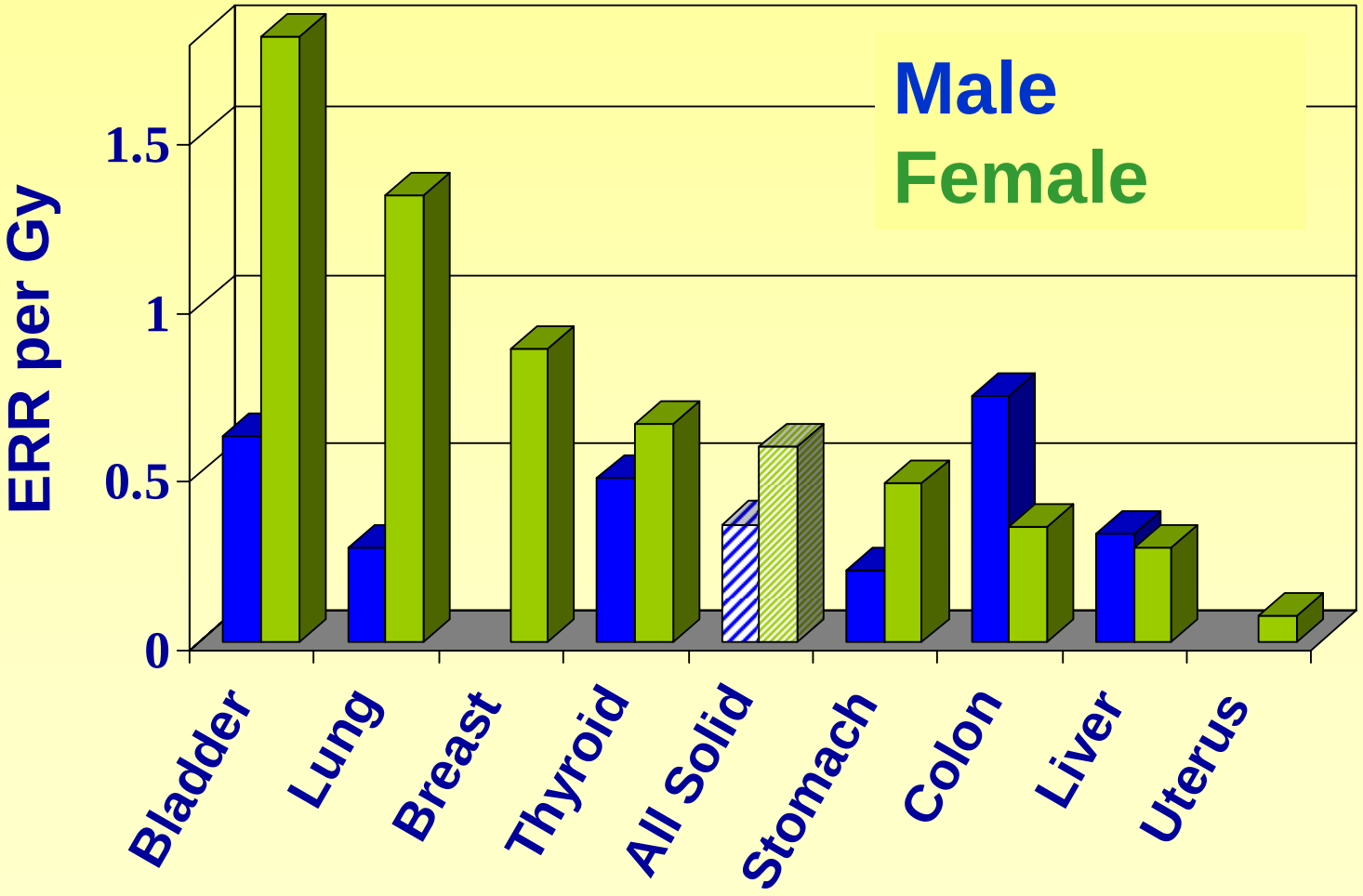
For person age 70 exposed at age 30

Site-Specific Risk Estimates

Site	AF* %	EAR per 10^4 PY Gy	Excess Cases
All Solid	**10.7**	**50.1**	**853**
Breast	27.1	9.2	147
Thyroid	24.5	1.2	63
Bladder	16.4	3.2	35
Lung	14.7	7.5	117
Colon	11.4	8.0	78
Liver	8.1	4.3	54
Stomach	7.2	9.5	151

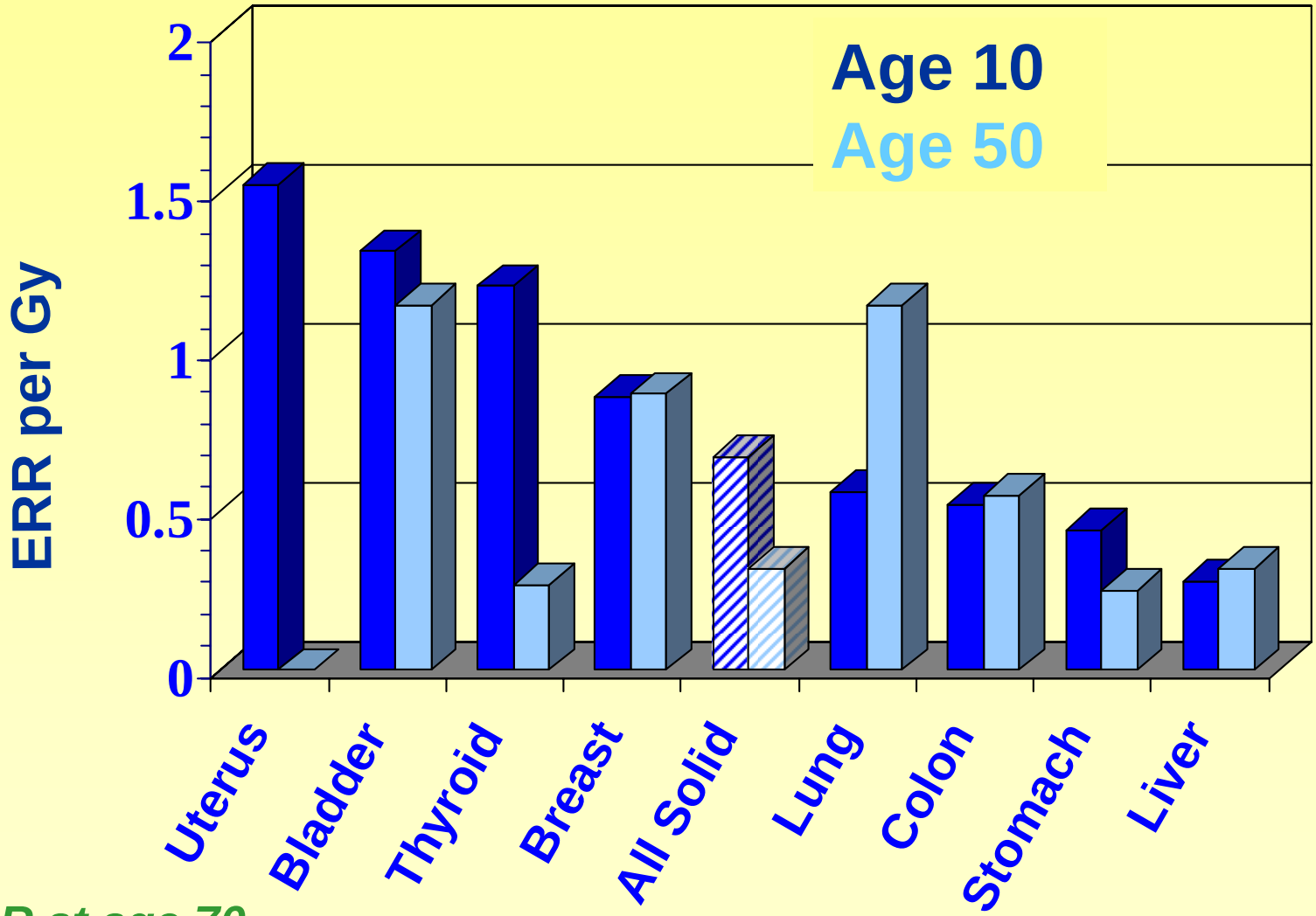
***AF% among survivors exposed to >0.005 Gy**

Solid Cancer ERR Gender Effects



ERR at age 70 for exposure at age 30

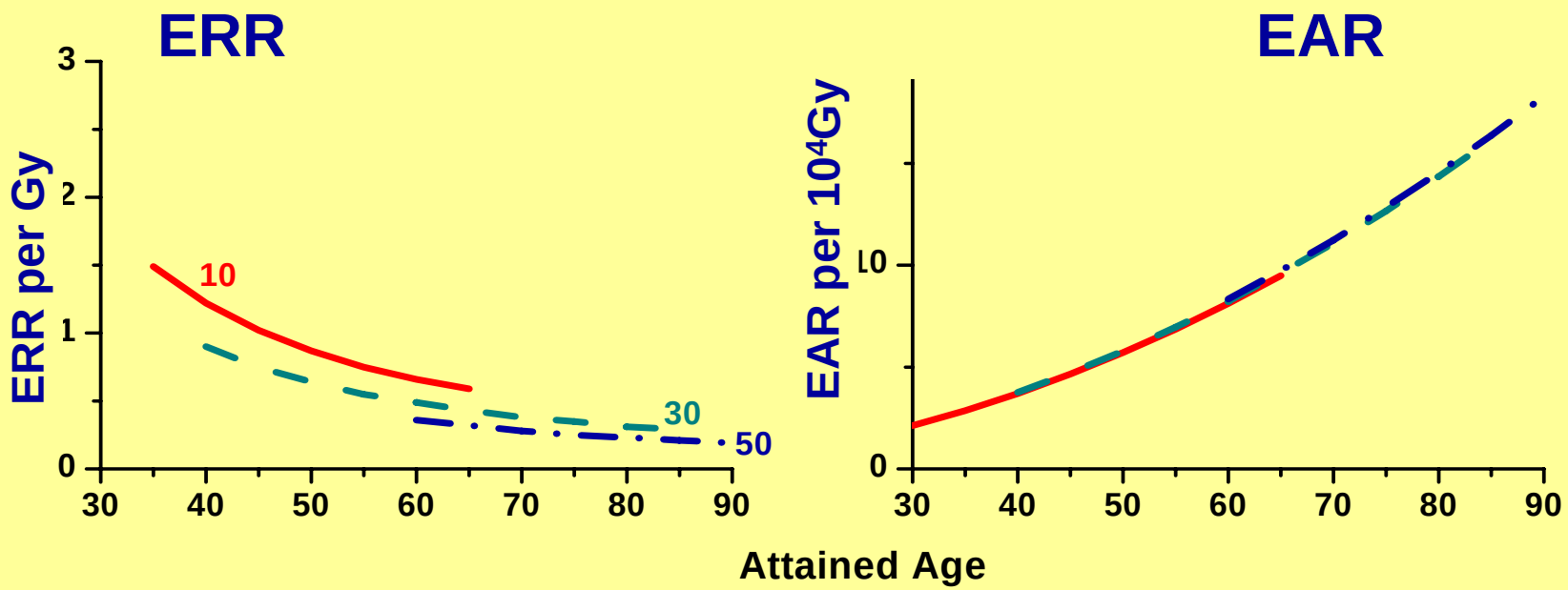
Age at Exposure Effects



ERR at age 70

Stomach Cancer

151 excess cases among 4,730

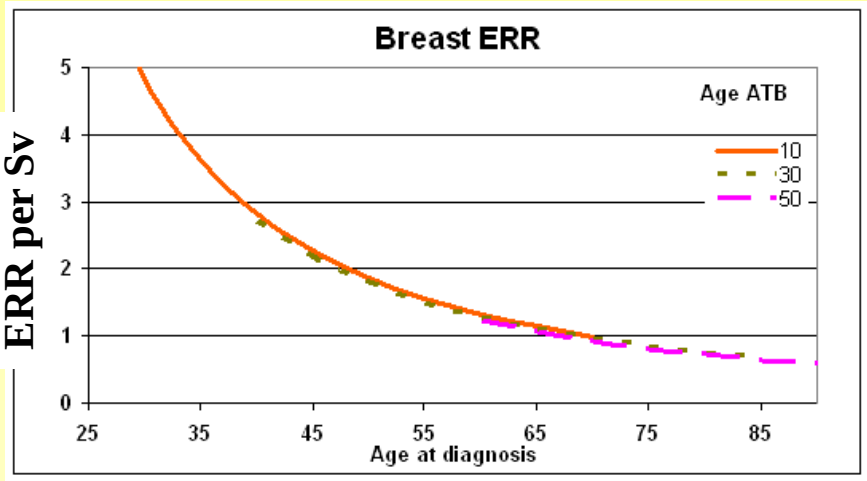


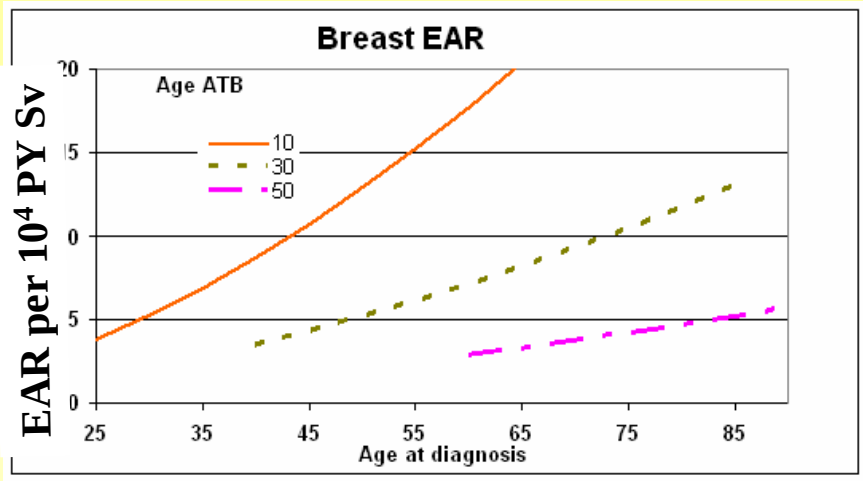
ERR/Gy = 0.34* **EAR/10^4 PYGy = 9.5***

***for person age 70 exposed at age 30**

Breast Cancer

148 excess cases among 1,073





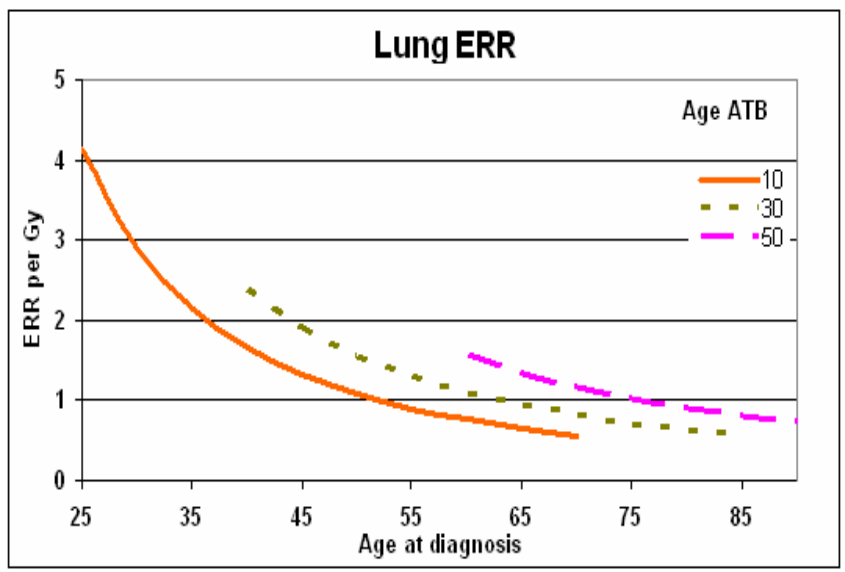
ERR/Gy = 0.87*

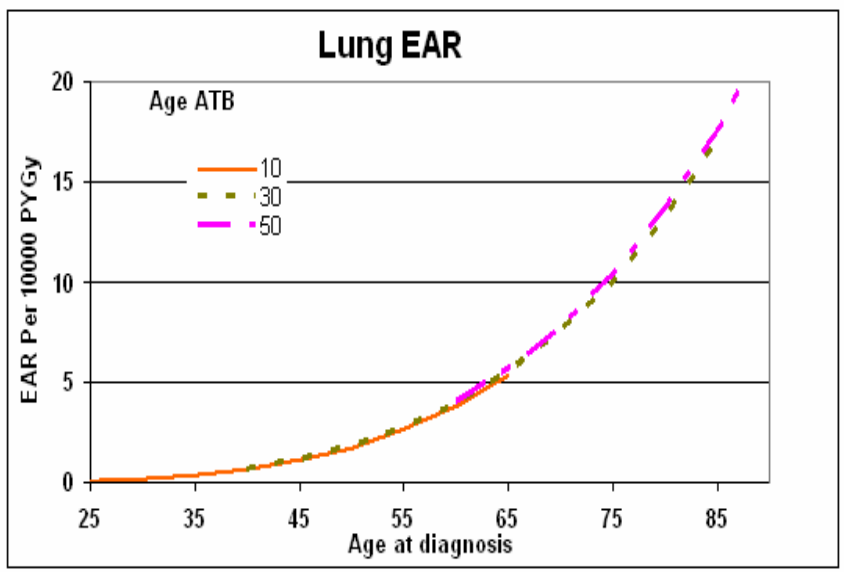
EAR/10^4 PYGy = 9.2*

***for person age 70 exposed at age 30**

Lung Cancer

117 excess cases among 1,759





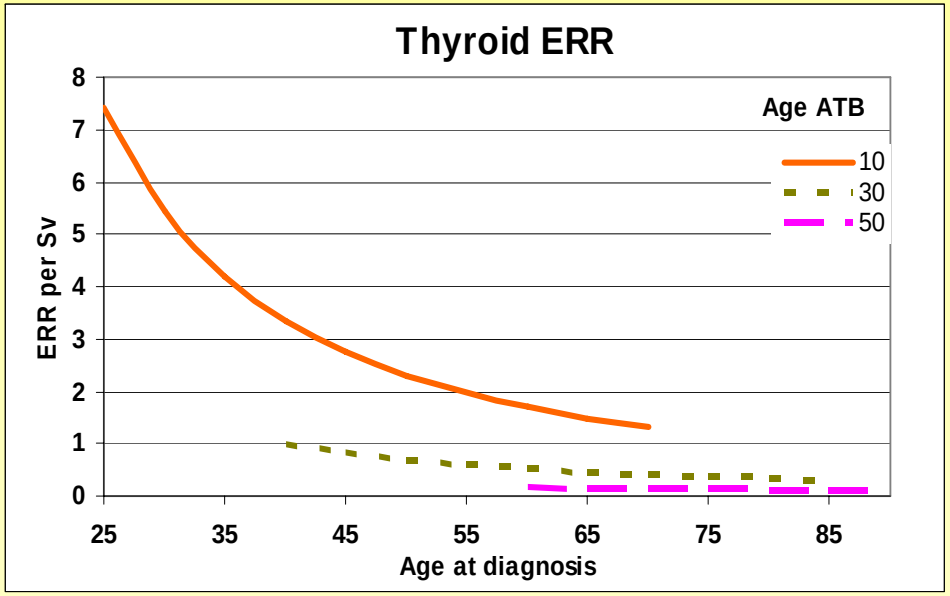
ERR/Gy = 0.81*

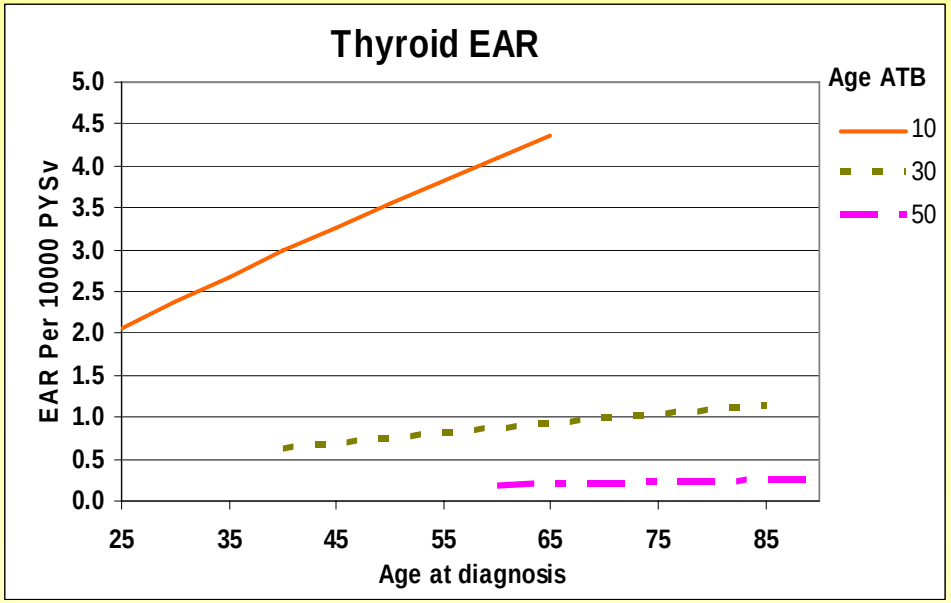
EAR/10^4 PYGy = 7.5*

***for person age 70 exposed at age 30**

Thyroid Cancer Incidence

63 excess cases of 471





ERR/Gy = 5.7* **EAR/10^4 PYGy = 1.2***

***for person age 70 exposed at age 30**

Interpreting Site-Specific Risks

- Data are limited even in the largest cohort
- Difficult to interpret and generalize effect modification
  - Age at exposure effects in the ERR may depend on birth cohort or period effects on baseline rates
  - ERR gender effects mirror baseline effects
  - Can also be problems in generalizing EAR patterns
- Useful to identify sites, e.g. breast, lung, thyroid with unusual patterns

Site-Specific Incidence: Special Pathology Studies

- Additional case-finding
- Benign tumors
- Review of pathology slides and records
- Detailed histologic diagnosis
- Allow for additional analyses

Salivary Gland Tumors, 1950-87

	Malignant	Benign
No.	41	94
ERR_{1Sv}	3.5	0.7
	(1.5-7.5)	(0.1-1.7)
$EAR/10^4$ PY	3.7	1.9
	(2.0-6.0)	(0.27-4.2)

Includes NIC, 90% CI; Land et al, 1996

Salivary Gland Tumors, 1950-87

Level of risk differs by cell type

Mucoepidermoid carcinoma ERR_{Sv}=8.3
Other malignant ERR_{Sv}= 1.4

Warthin's tumor ERR_{Sv}= 3.1
Other benign ERR_{Sv}=0.3

Includes NIC, 90% CI; Land et al, 1996

Skin Tumors, 1958-89

Histology	ERR_{Sv}	90% CI
Melanoma	**2.1**	**<0.1; 12**
Nonmelanoma	**0.6**	**0.23; 1.3**
Basal cell	***1.8***	***0.83; 3.3***
Squamous cell	***<-0.1***	***<-0.1; 0.1***
Other epithelial	***1.4***	***0.02; 5.8***
Non-epithelial & NOS	***0.5***	***<-0.1; 6.7***
Bowen's tumor	**0.9**	**-0.4; 3.1**

Ron et al, 1998

Basal Cell Carcinoma, 1958-89

Age at Exposure	No. Cancers	ERR_{Sv} (90%CI)
0-9	3	21 (4.1 ; 73)
10-19	8	6.7 (2.1 ; 17)
20-39	28	1.7 (0.5 ; 3.8)
40+	41	0.7 (-0.05 ; 2.2)

Heterogeneity P=0.03; Trend P < 0.001

Ron et al, 1998

Basal Cell Carcinoma, 1958-89

UV exposure*	Cancers	ERR_{Sv} (90%CI)
High	37	0.4 (< -0.1 ; 2.1)
Low	43	4.7 (1.2 ; 13)

Heterogeneity P < 0.02

*Estimates for a person exposed to the bombings at age 30
High = face and hands; Low = rest of body

Skin Tumors

- Possible non-linear dose response
- Risk only for basal cell carcinoma
- Increased risk during childhood
- No interaction with UV
- Almost no melanomas

Nervous System Tumors, 1958-95

Histology	Cases	ERR_{Sv}	90% CI
All CNS	**228**	**1.2**	**0.7; 1.9**
Glioma	*43*	*0.56*	*-0.1; 1.8*
Meningioma	*88*	*0.64*	*0.03; 1.6*
Schwannoma	*55*	*4.5*	*2.0; 7.3*
Other	*42*	*0.51*	*-0.2-1.9*
Benign Pituitary	**35**	**0.98**	**-0.1; 3.1**

Preston et al, 2002

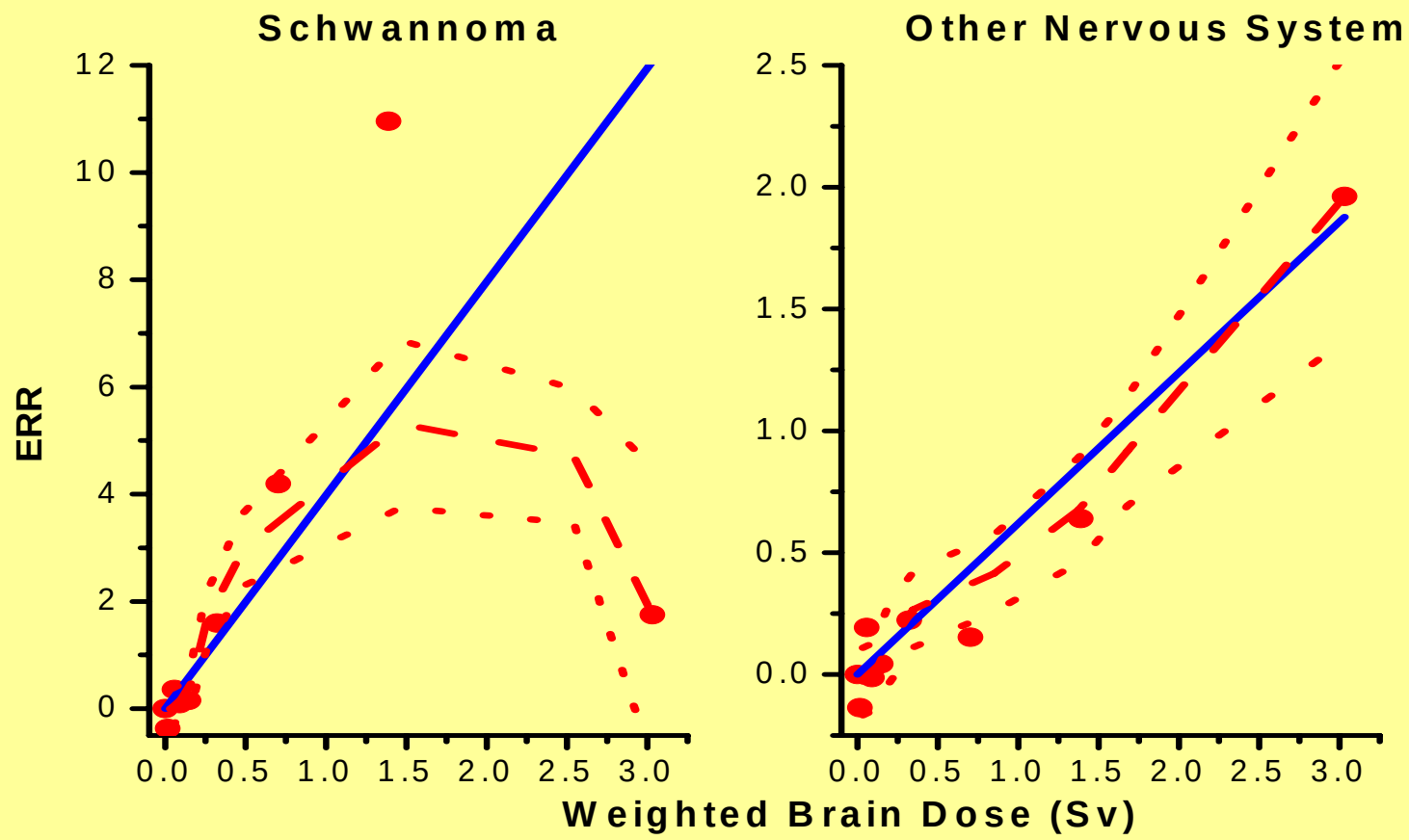
Nervous System Tumors, 1958-95

	Schwannoma	Other
Gender		
Male	8.0*	1.4
Female	2.4	0.11
	P= 0.12	*P=0.05*
Age at Exposure		
<20	6.0	1.2
20-40	2.7	0.3
40+	3.3	0.1
	P-trend >0.5	*P-trend=0.06*

$*ERR_{Sv}$

Preston et al, 2002

Nervous System Tumors, 1958-95 Dose Response



CNS Tumors

- First time excess risk of all neural tumors combined seen in A-bomb survivors
- Risk continued throughout follow-up
- Highest risk seen for Schwannomas
- Age at exposure effect mostly for meningiomas
- Patterns of risk similar to other studies

New Findings

- **Large excess relative risk for endometrial cancer among women exposed ATB <20 yr**
- **Radiation effect observed for male breast cancer**
- **Strong evidence that EAR increases with increasing age**
- **In contrast, ERR decreases with increasing age**

Summary and Conclusions

- **Solid cancer dose response still linear**
- **Solid cancer excess rates increase throughout life for all ages at exposure**
- **Excess risk for all solid cancers is higher for women than men**
- **Lifetime solid cancer excess estimated as about 20 times that for leukemia**

Summary and Conclusions

- Age-time patterns don't differ substantially for most individual sites
- With more detailed analyses, age at exposure and attained age differences difficult to distinguish
- Overall patterns similar to those seen in previous analyses
- Continue to find new results

Future

- **Most radiation-associated excess solid cancers are likely to occur in 15-20 yr**
- **The accumulating data will continue to offer important new insights into radiation effects on cancer risks**
- **Continued follow-up is necessary to understand risk patterns for persons less than age 20 years ATB**

Future

- **Additional site-specific incidence studies should provide additional information on the radiation-sensitivity of specific histologies**

- **More collaboration between statisticians, epidemiologists, and biologists will help in understanding these data and their implications for radiation protection**