Issues in Radiation-related Breast Cancer Risk

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Overview of Radiation-Related Breast Cancer Risk

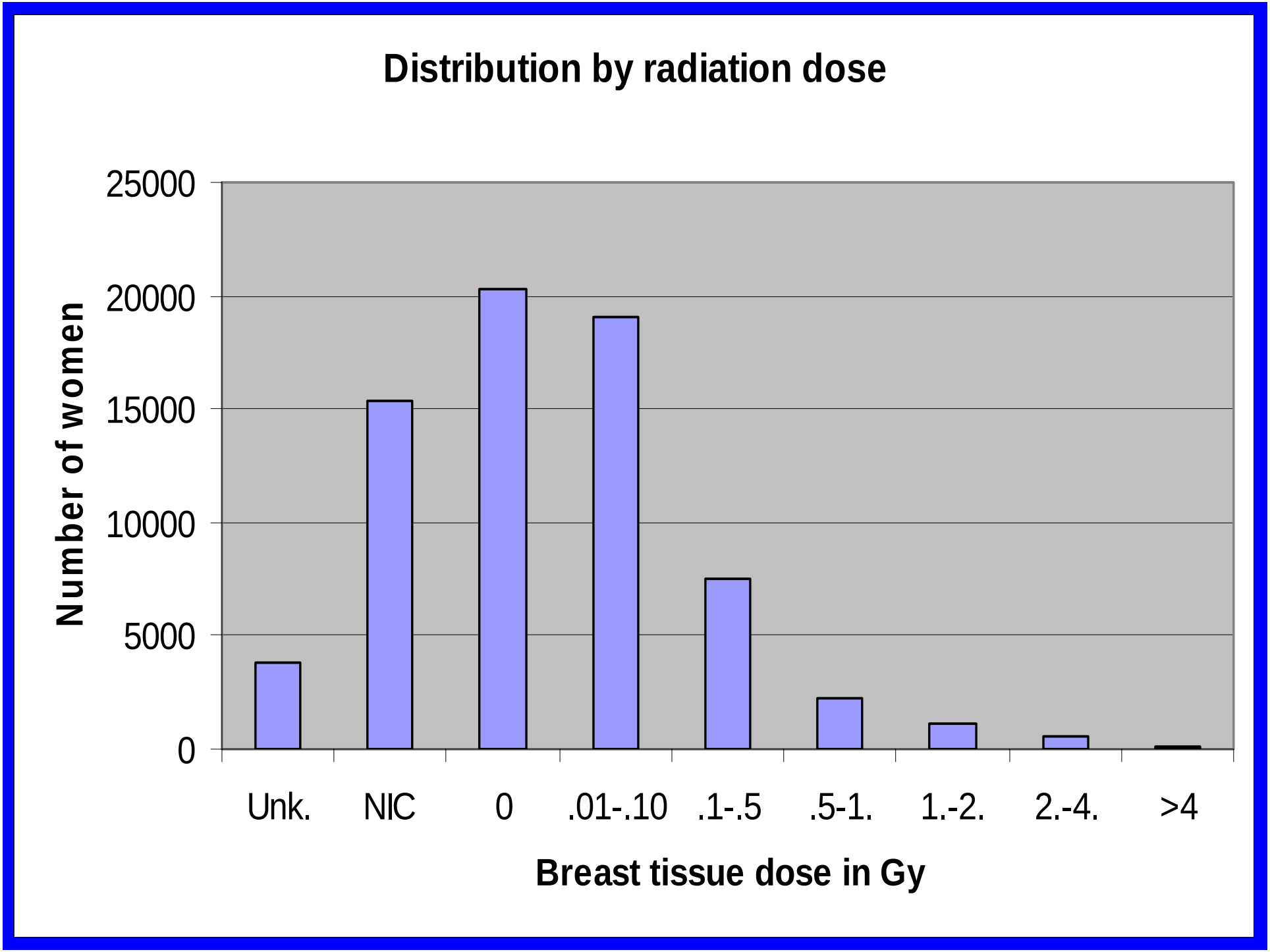
- Demonstrated in different irradiated populations
  - TB fluoroscopy patients
  - A-bomb survivors
  - Benign breast disease
  - Infants with “enlarged thymus”
  - Scoliosis patients
  - Radium dial painters
  - Hemangioma patients
  - Hodgkin disease patients
  - Mayak plutonium workers

Issues

- Dose response – risk per unit dose
  - Extrapolation of risk to low doses & dose rates
  - Radiation quality (gamma ray cf. medical x ray)
- Dose-response modifiers
  - Age at exposure
  - Age at diagnosis (attained age)
  - Reproductive history
  - Secular changes in baseline risk within populations
  - Population baseline risk: how do we transfer risk estimates to other populations?

The RERF Life Span Study

- Cohort of 94,000 A-bomb survivors and 26,000 non-exposed comparison subjects
- Initial selection based on addendum to 1950 Japanese national census
  - Survivors resident in Hiroshima or Nagasaki on October 1, 1950, 5 years after the bombings
- Individual dose estimates (92% of survivors)
  - Interviews, location ATB, detailed shielding histories
  - Neutron-weighted dose, in Sv (neutron wt. = 10)


Distribution by radiation dose
Number of women
25000
20000
15000
10000
5000
0
Unk.
NIC
0
.01-.10
.1-.5
.5-1.
1.-2.
2.-4.
>4
Breast tissue dose in Gy

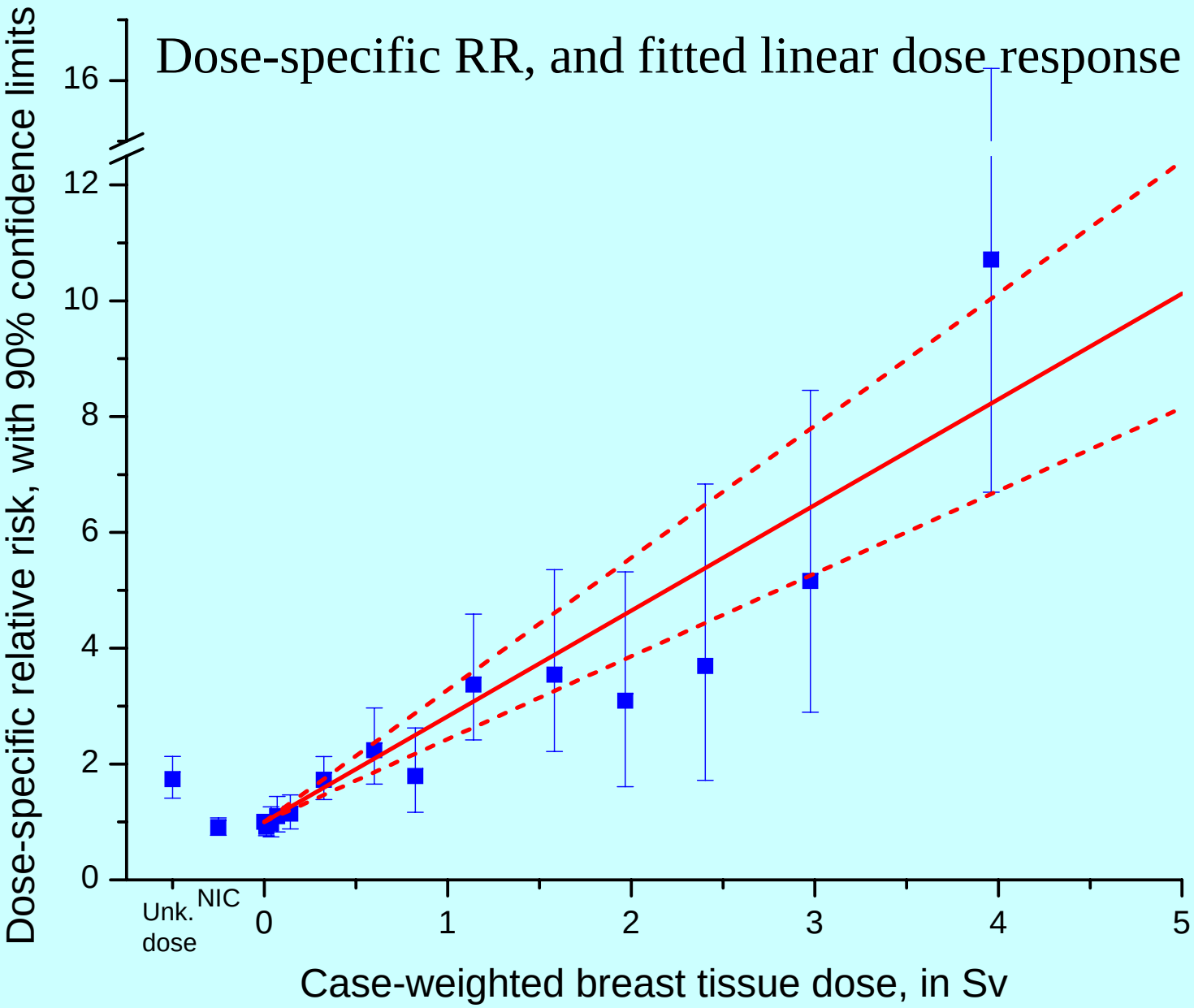
LSS Study: Resources

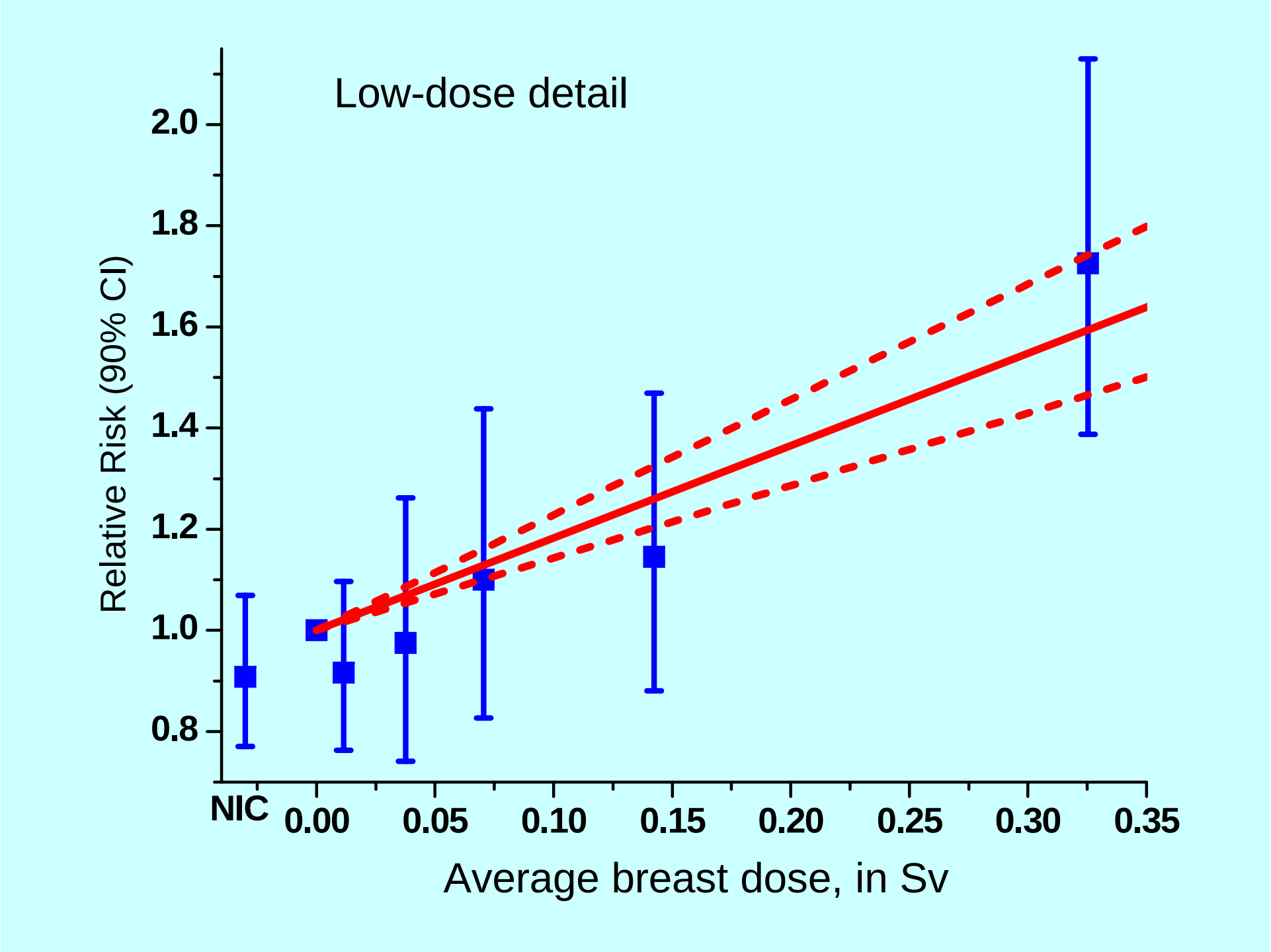
- Complete mortality follow-up at level of death certificate dx
- Tumor registry, based on local Hiroshima and Nagasaki registries, established 1958
- Tissue registry
- Clinical subsample
  - Examined on 2-year cycle
  - Stored serum, lymphocytes, clinical records

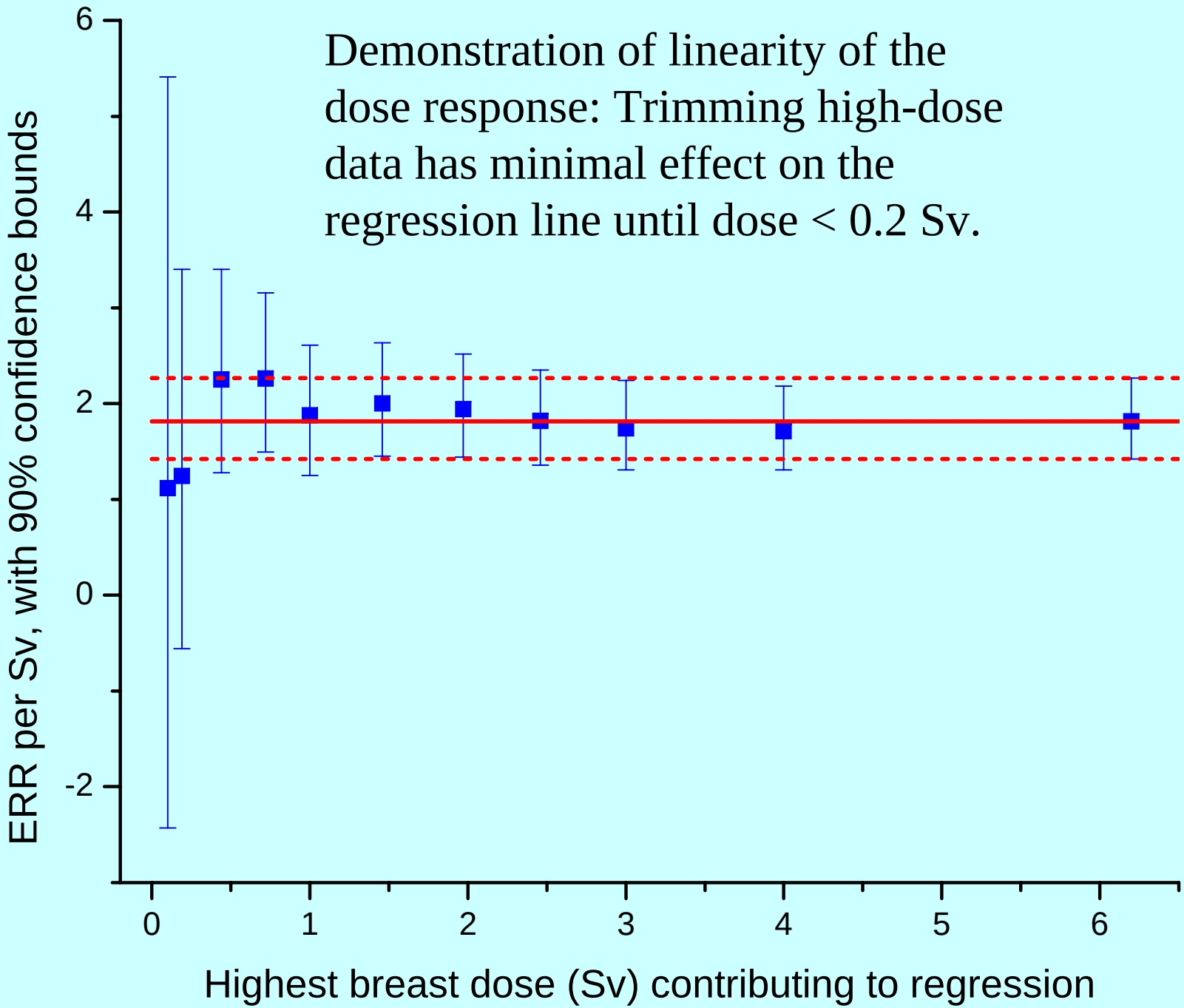
Breast Cancer Cases, 1950-1990

Radiation Research 2003; 160:707-17

- 1059 total cases among 70,000 women
  - 190 among non-exposed comparison subjects
  - 93 among exposed, with unknown dose
  - 876 among exposed with radiation dose estimates
  - 34 cases developed 2nd breast cancer


Dose-specific RR, and fitted linear dose response
Dose-specific relative risk, with 90% confidence limits
16
12
10
8
6
4
2
0
Unk. dose
NIC
0
1
2
3
4
5
Case-weighted breast tissue dose, in Sv


Low-dose detail
Relative Risk (90% CI)
2.0
1.8
1.6
1.4
1.2
1.0
0.8
NIC
0.00
0.05
0.10
0.15
0.20
0.25
0.30
0.35
Average breast dose, in Sv

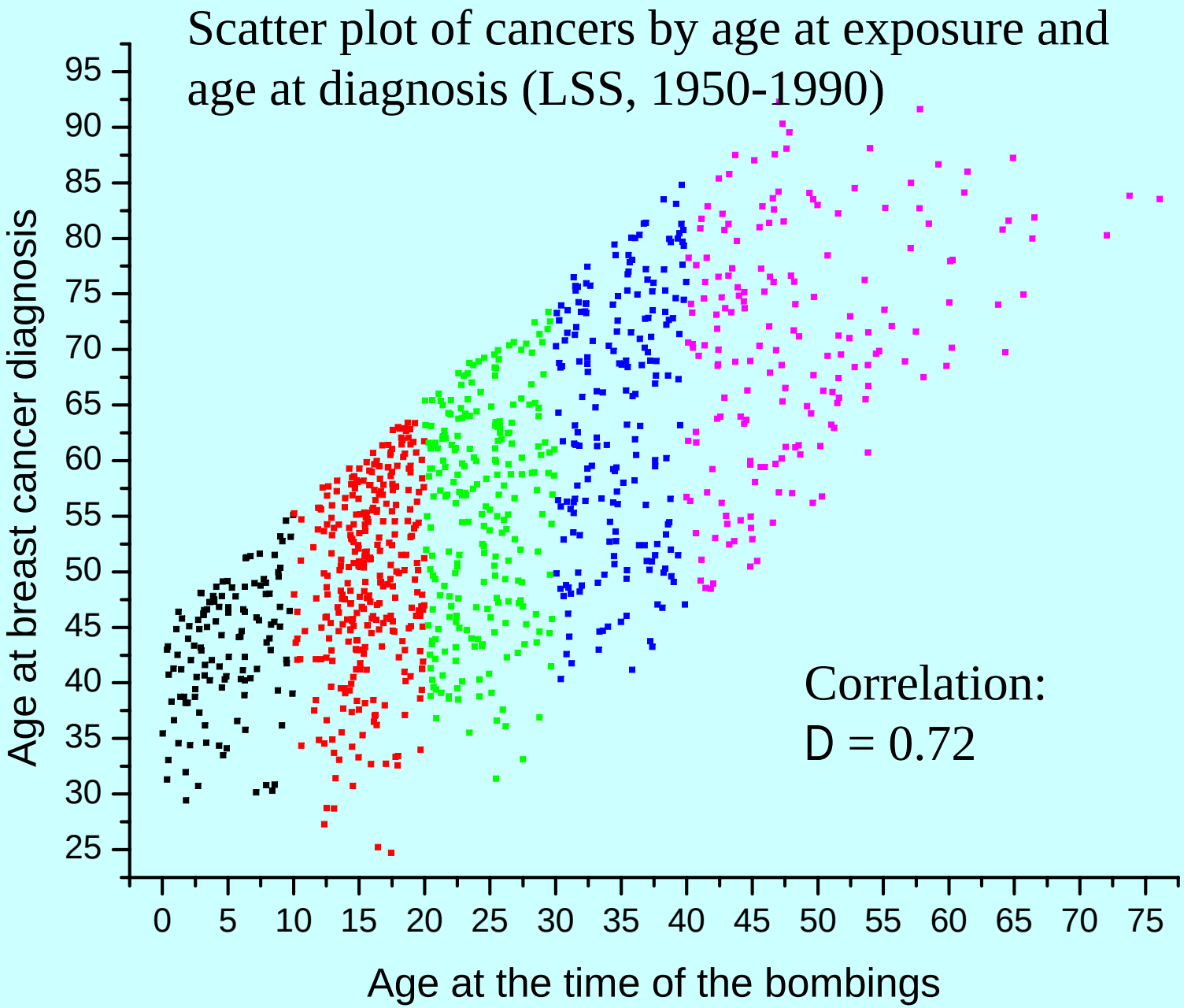

Demonstration of linearity of the dose response: Trimming high-dose data has minimal effect on the regression line until dose < 0.2 Sv.
ERR per Sv, with 90% confidence bounds
6
4
2
0
-2
0
1
2
3
4
5
6
Highest breast dose (Sv) contributing to regression

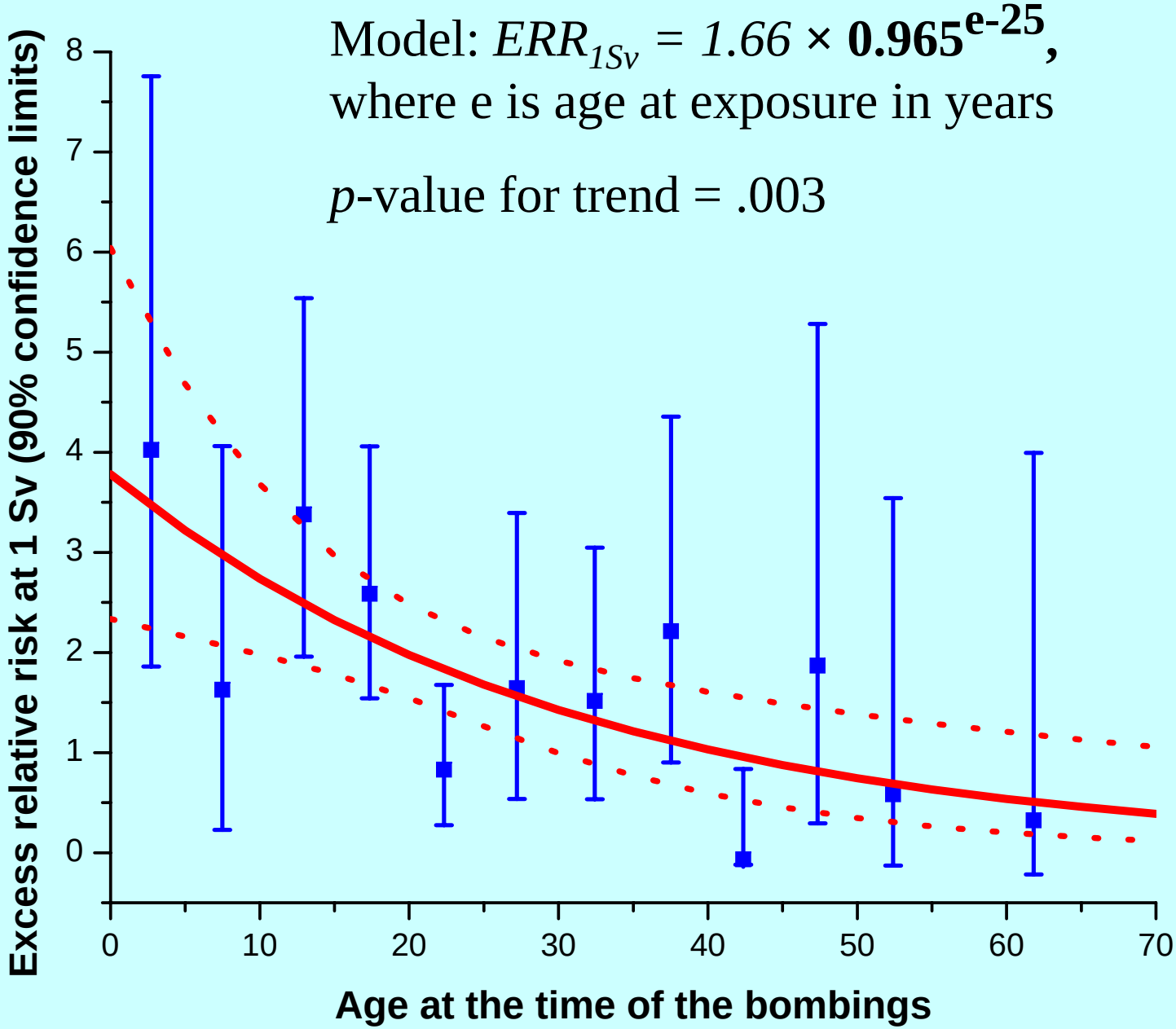
Age modification of dose-response

- Although not uniform, ERR in different populations tends to decline with increasing exposure age, and with age at observation for risk (attained age)
- In most studies, exposure age and attained age are correlated
  - Modifying effects are difficult to separate
- Interpretation has implications for lifetime risk and risk management

A-bomb survivors, 1950-90

- Age at diagnosis ranges from 24 to 98
- Following slide shows distribution of cases by age at exposure and age at diagnosis
  - Correlation is 72%

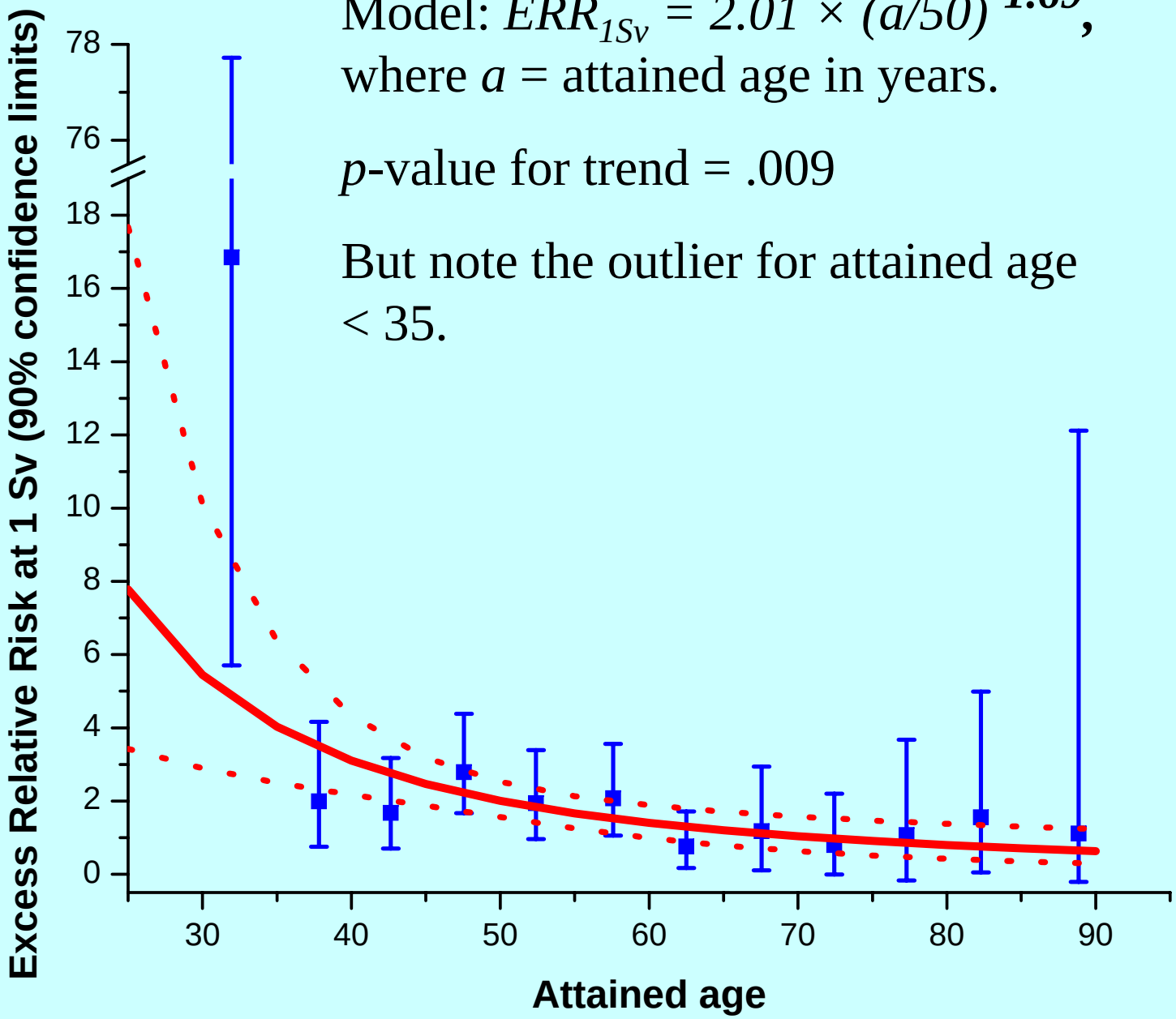

Scatter plot of cancers by age at exposure and age at diagnosis (LSS, 1950-1990)
Age at breast cancer diagnosis
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
0
5
10
15
20
25
30
35
40
45
50
55
60
65
70
75
Age at the time of the bombings
Correlation:
D = 0.72


Model: $ERR_{1Sv} = 1.66 \times \mathbf{0.965^{e-25}}$,
where e is age at exposure in years
p-value for trend = .003
Excess relative risk at 1 Sv (90% confidence limits)
Age at the time of the bombings
0
1
2
3
4
5
6
7
8
0
10
20
30
40
50
60
70

Model: $ERR_{1Sv} = 2.01 \times (a/50)^{-1.69}$,
where a = attained age in years.

p-value for trend = .009

But note the outlier for attained age < 35.



Analysis modified by exposure age *e* and attained age *a*

- Model:

ERR/Sv = " H exp{$ H(*e*-*25*) + (H (*a/50*)}

Where $ = 0.97 (p = .11)

(= 0.78 (p = .38)

But p = .009 for the two parameters combined.

Modification of Radiation Dose Response by Age Factors

- The very high dose-related relative risk for early-onset breast cancer (at ages < 35) is clearly an anomaly.
  - Possible existence of a sensitive population subset?
  - To what extent does it drive the attained age curve?

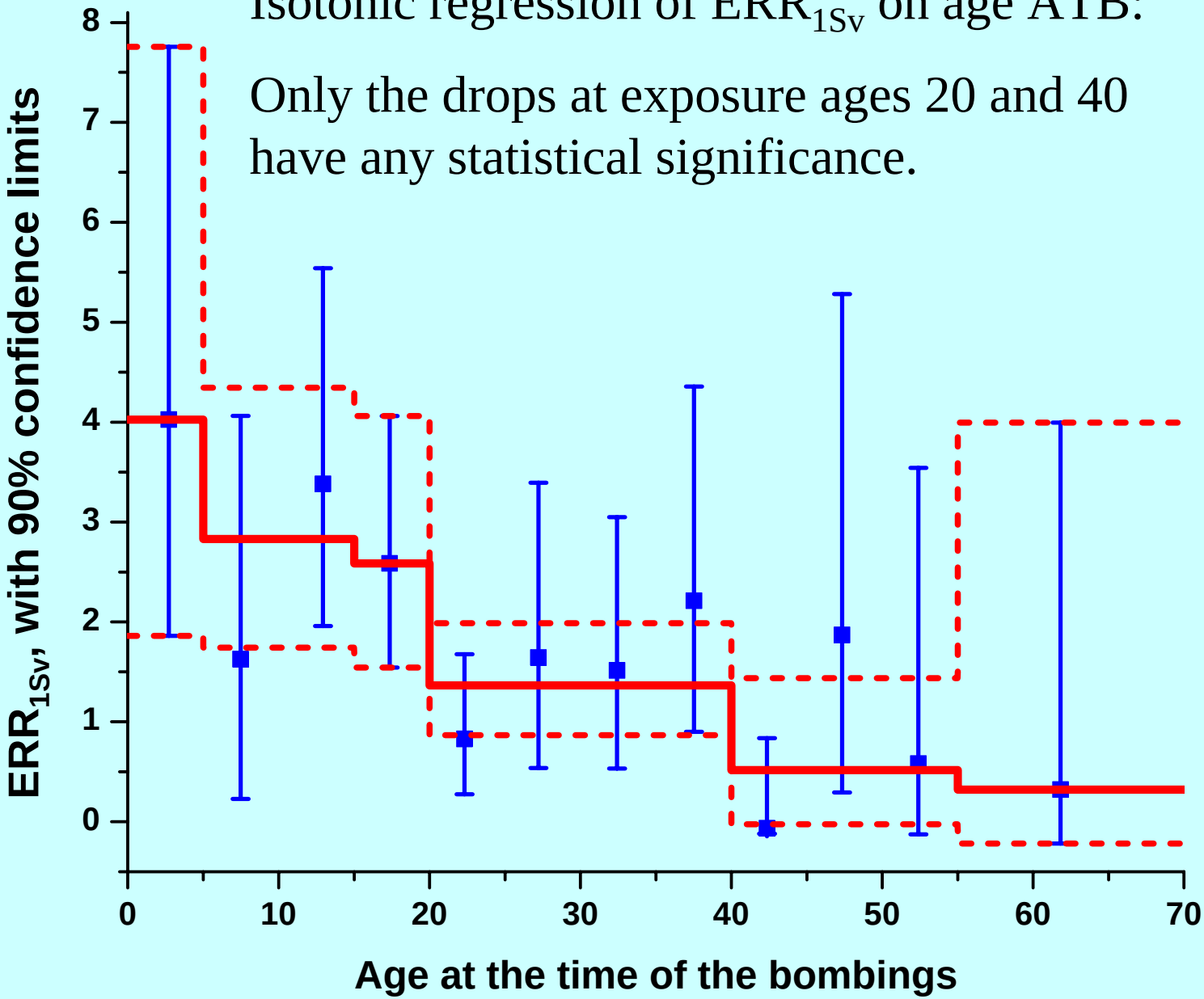
- The high correlation of the 2 age variables ($\rho = 0.72$) makes it difficult to separate their effects.
  - Neither variable is statistically significant when both are in the exponential modification model.
  - $p = .009$ for both age factors together (2 df)
  - $p = .11$ for exposure age given attained age,
  - $P = .38$ for attained age given exposure age

Isotonic Regression:
An Alternative Approach

- Unlike the exponential modeling of ERR_{1Sv} as a function of age ATB and attained age, isotonic regression requires only that the dependence be monotone increasing or decreasing.
- This relative lack of structure allows the data to “tell us what is going on”, at the cost of some decrease in statistical stability.

Isotonic regression of ERR_{1Sv} on age ATB:

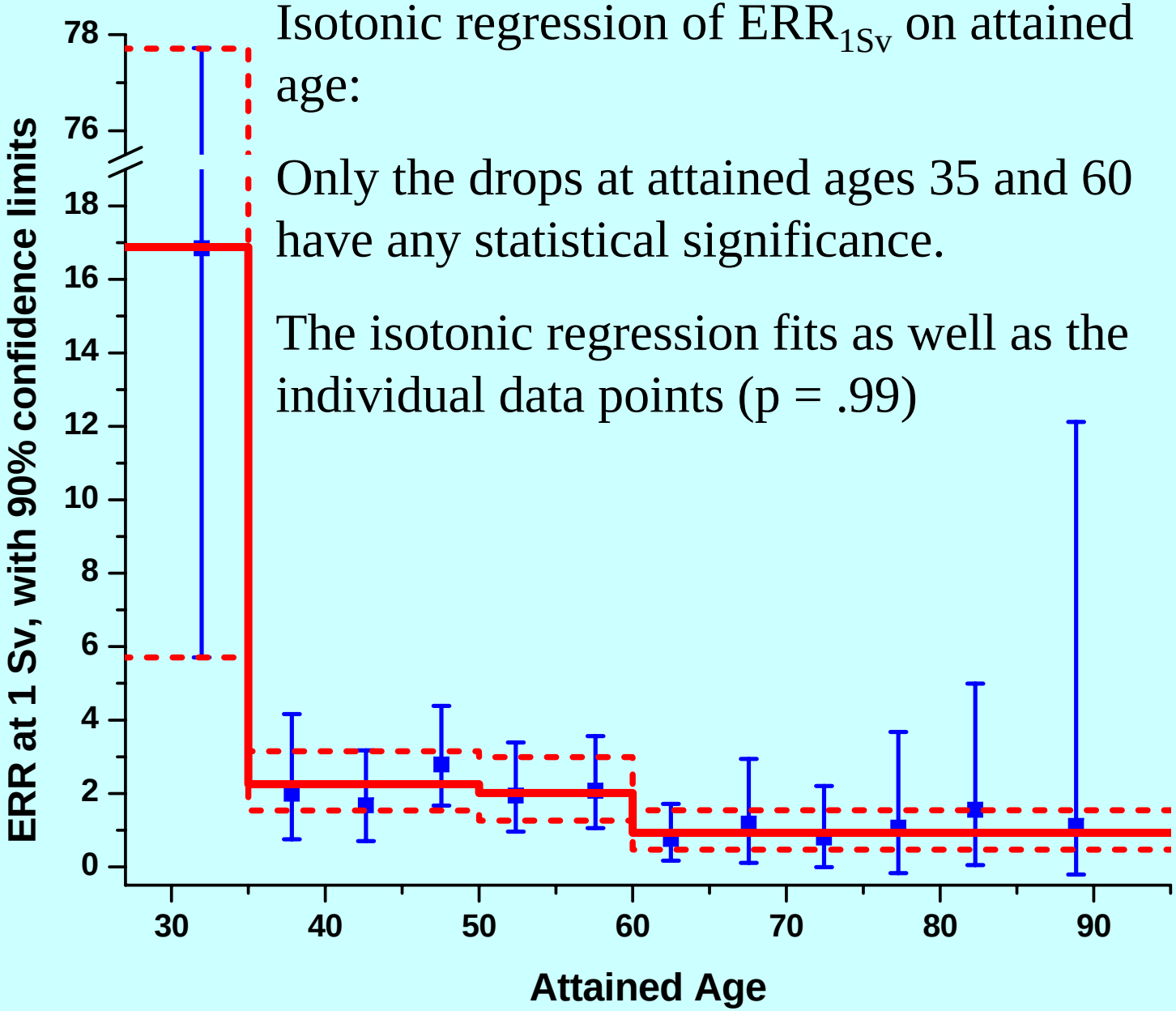
Only the drops at exposure ages 20 and 40 have any statistical significance.



Isotonic regression of ERR_{1Sv} on attained age:

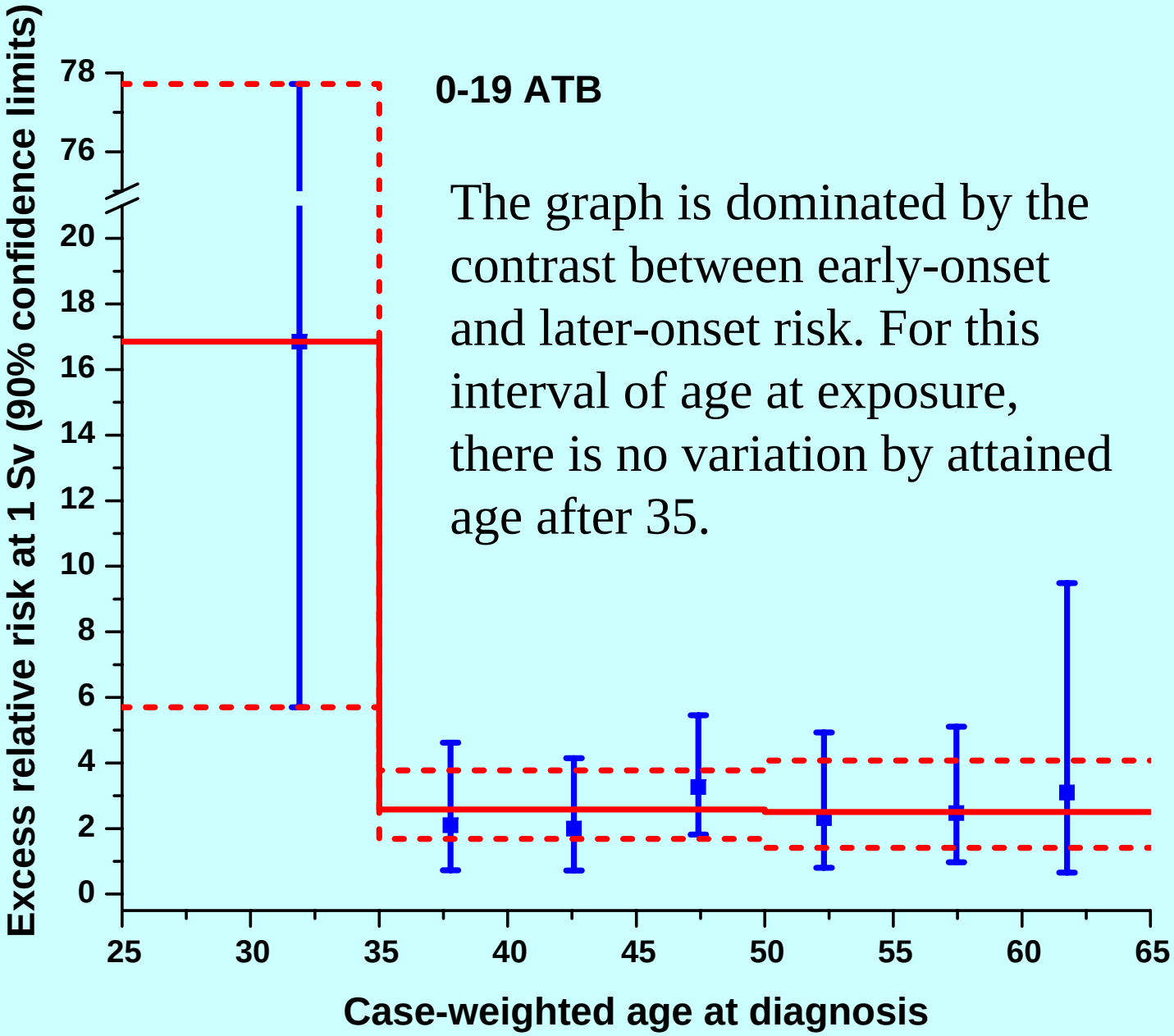
Only the drops at attained ages 35 and 60 have any statistical significance.

The isotonic regression fits as well as the individual data points (p = .99)

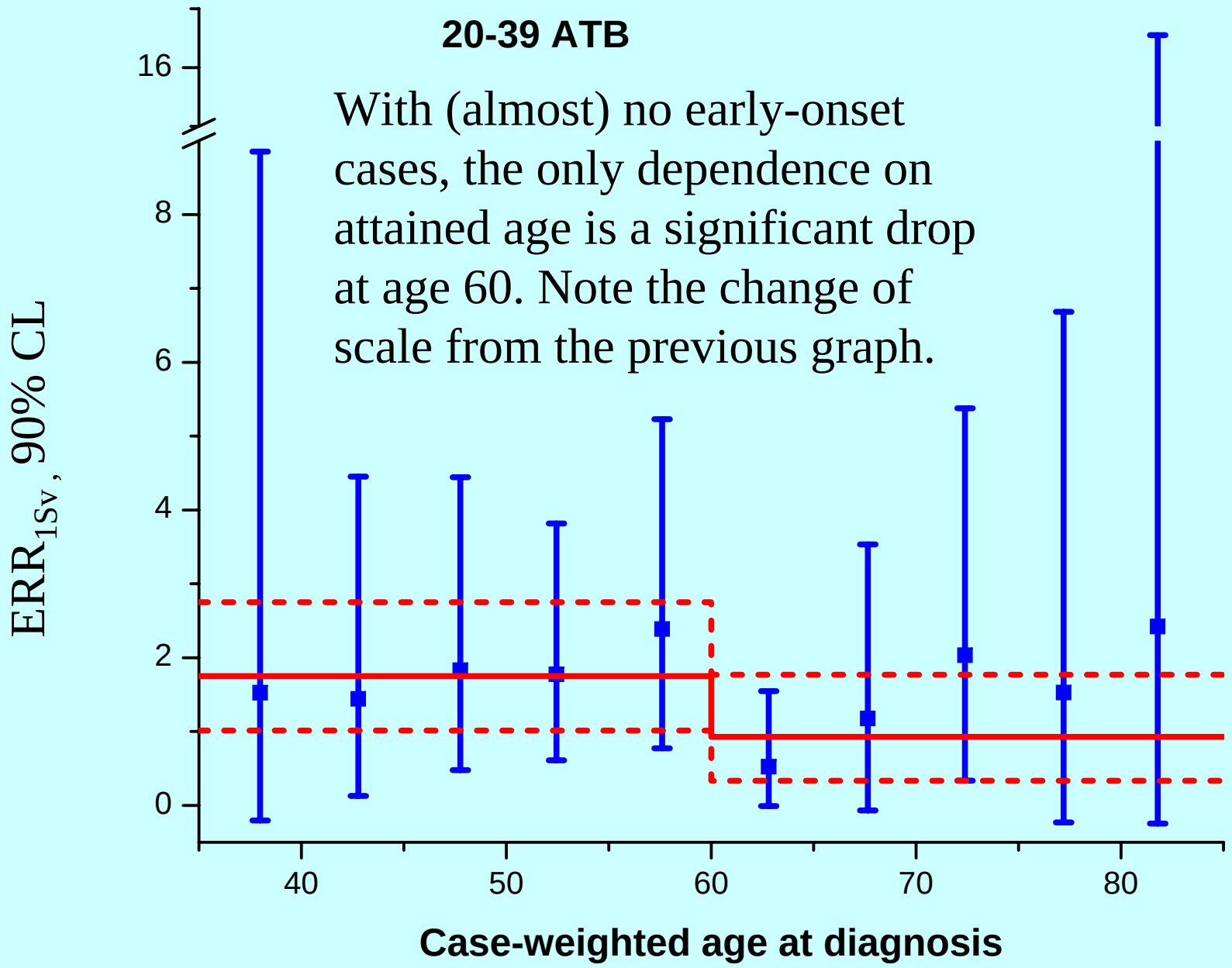


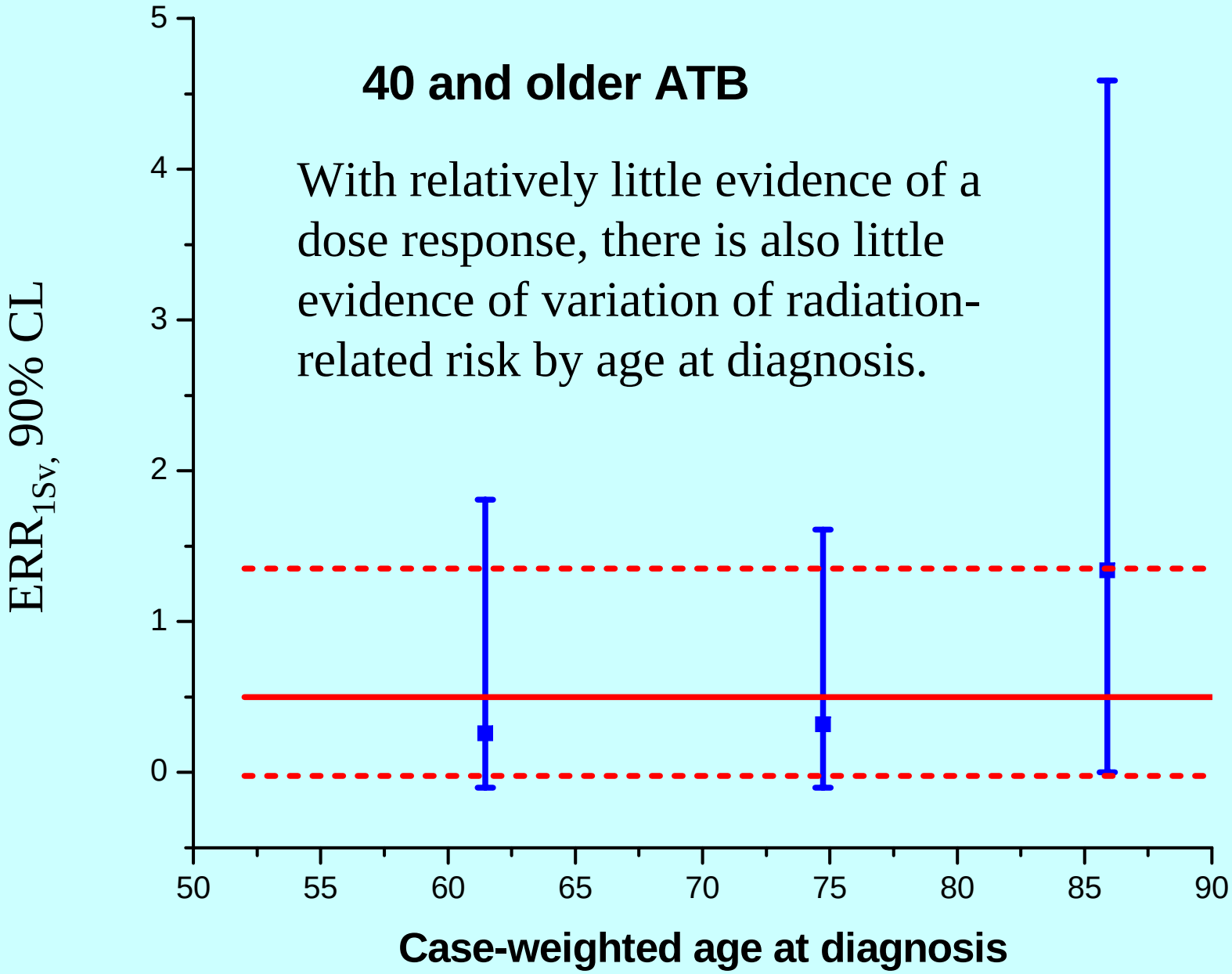
Implications of Isotonic Regression Analysis

- By age at exposure, age-specific estimates of ERR_{1Sv} are similar within 3 age intervals:
  - 0-19 ATB, 20-39 ATB, and 40+ ATB
- By attained age, there are also 3 intervals of similarity:
  - <35 (early-onset), 35-60, and 60+
- The following 3 graphs show regressions on attained age within intervals of age ATB

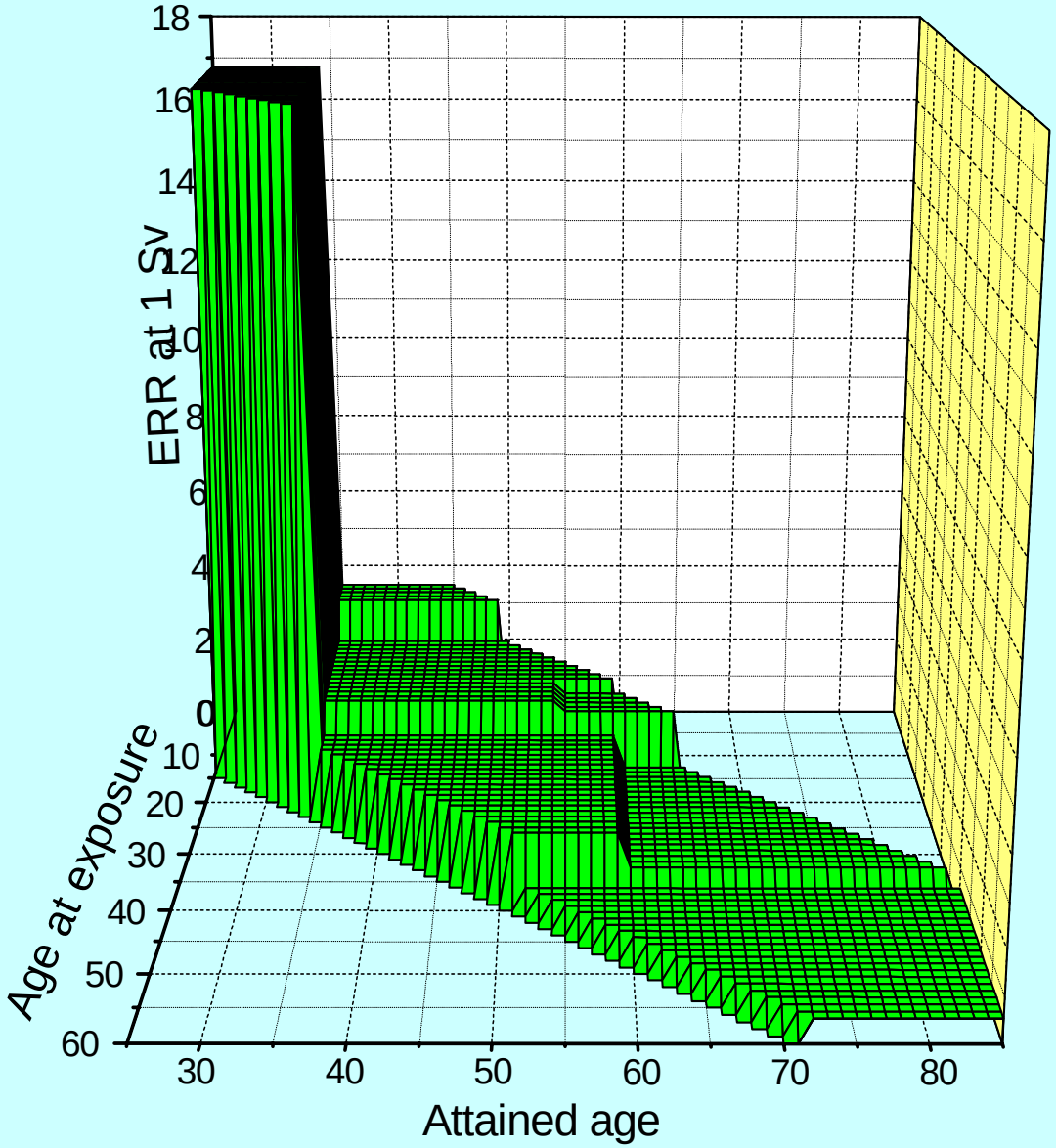


The graph is dominated by the contrast between early-onset and later-onset risk. For this interval of age at exposure, there is no variation by attained age after 35.


20-39 ATB
With (almost) no early-onset cases, the only dependence on attained age is a significant drop at age 60. Note the change of scale from the previous graph.
ERR1Sv , 90% CL
16
8
6
4
2
0
40
50
60
70
80
Case-weighted age at diagnosis


40 and older ATB
With relatively little evidence of a dose response, there is also little evidence of variation of radiation-related risk by age at diagnosis.
ERR1Sv, 90% CL
5
4
3
2
1
0
50
55
60
65
70
75
80
85
90
Case-weighted age at diagnosis

3-D plot: isotonic regression of ERR_{1Sv} on both age factors



Some Conclusions

- The “early-onset” phenomenon may be real
- Similar finding in female Hodgkin’s disease patients treated by radiation at ages <20 (van Leeuwen et al, J Clin Oncol 2000; 18:487-97)
  - ERR = 61.5 (25-127) for diagnosis under 40
  - ERR = 5.4 (0.7-20) for diagnosis age 40-49
- Genetic subgroup of high sensitivity?

Some Conclusions

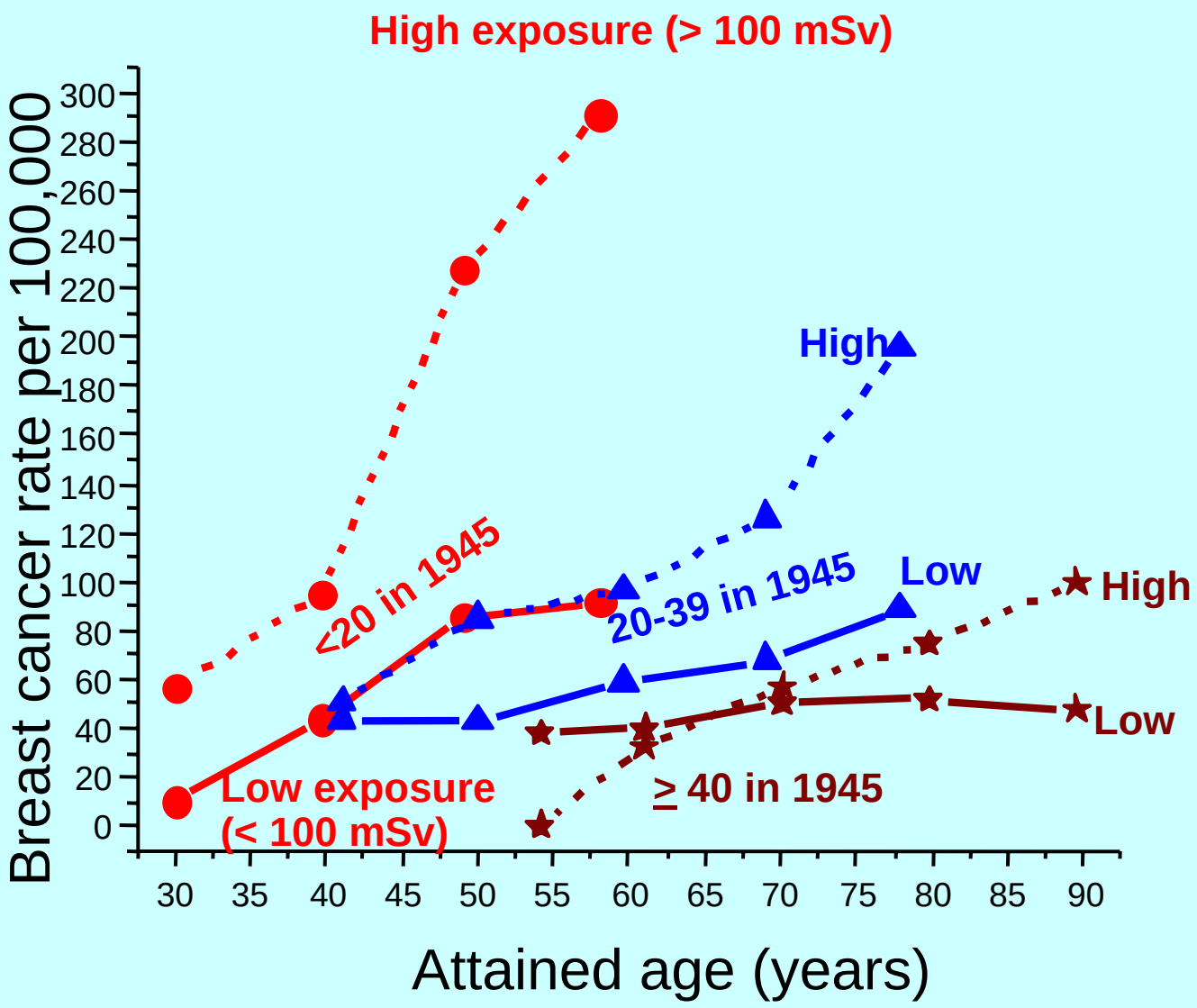
- Both exposure age and age at diagnosis are important modifiers of radiation-related breast cancer risk
  - Simpler models (i.e., with only one age modifier) tend to overestimate or underestimate lifetime risk
- Higher risk for exposure before age 20
- No evidence for a “window” of higher sensitivity within that age interval, related to menarche or breast budding
  - Precursor cells are at risk (see also patients exposed in infancy for “enlarged thymus”, hemangioma)

Modified exponential model:

ERR/Sv = " H exp{*HI_{35}(*a*) + $H(*e*-25) + (Hln(*a*/50)}

- ERR at 1 Sv proportional to dose
  - times an indicator for early-onset cancer (*p=.008 for *)*
  - times an exponential in exposure age *(p= .041 for $)*
  - exponential in attained age not significant *(p>.5 for ()*
- Exposure age and early-onset cancer more important than variation by attained age after 35
- *Note: different case-inclusion rules lead to somewhat weaker conclusions about the separate roles of exposure age and attained age.*

Both baseline breast cancer rates and radiation-related excess vary by birth cohort



Speculation

- Some of the variation in ERR_{1Sv} by exposure age may reflect normal life events
- Full-term pregnancies, ~ age 20?
  - Differentiated breast cells less sensitive to chemical carcinogenesis (Russo)
- Approach of menopause, ~ age 40 in 1945?
  - Possible interaction of radiation exposure with serum estrogen levels?

Explanations for age ATB effect?

- Case-control interview study of potential modifiers of radiation-related risk (Cancer Causes Control 1994;5:157-65, 167-76).
  - Cases and controls matched on radiation dose
- Major risk factors (all were protective):
  - Young age 1st full-term pregnancy
  - multiple births
  - lengthy cumulative lactation period

Explanations (continued)

- Interactions with radiation dose were
  - Consistent with multiplicative model
  - Inconsistent with additive model
- i.e., all were protective against radiation-related breast cancer risk
- Moreover, this was especially true for women exposed before age 16.
  - reproductive history after exposure, as well as before, modified radiation-related risk
  - Terminal end bud differentiation of breast cells is protective against effects of prior exposure to experimental carcinogens (Clifton & Crowley, Ca Res 1978; 38: 1507-13)

Speculation

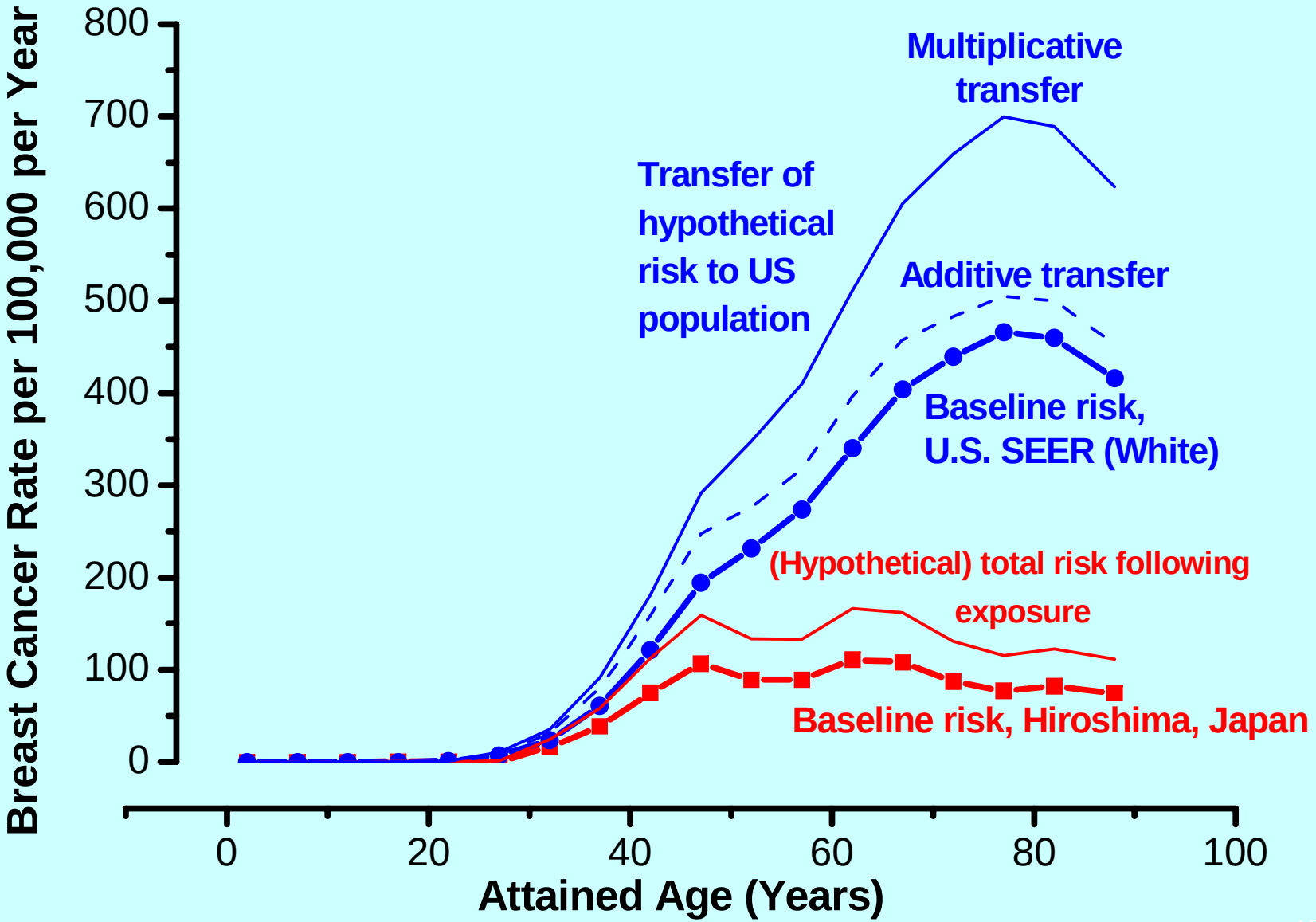
- Secular changes (increases) in Japanese breast cancer rates -- and radiation-related risks -- may (in part) reflect post-WWII changes in Japanese reproductive patterns
- Case-control interview study:

	<20 ATB	20+ ATB
Av. age 1st full-term preg	24.8	23.8
Av. number of deliveries	2.0	3.1
Av. cum. lactation (yrs)	1.3	2.5

An unavoidable problem

- Breast cancer rates are ~ 4 times higher in the US than in Japan
- Rates among granddaughters of Japanese immigrants to the US are typical of the US population
- Presumably, life-style factors are involved
- How do they interact with radiation dose?
- How do we apply the LSS information to a US population?

Comparison of U.S. and Japanese Breast Cancer Rates



Epidemiological comparisons

- Dose-response estimates can be compared among irradiated populations with varying baseline breast cancer rates
  - Best effort to date is pooled analysis of 8 cohorts (Preston et al, Rad. Res. 2002)
- Uncertain RBE of medical x ray cf. gamma ray is a confounding factor
  - RBE > 1 would increase dose-specific RR for medical cf. A-bomb survivors
  - Conventional wisdom: RBE ~ 2
- Fractionation effect is another confounding factor
  - ICRP: DDREF = 2 (but generally agreed to be uncertain)

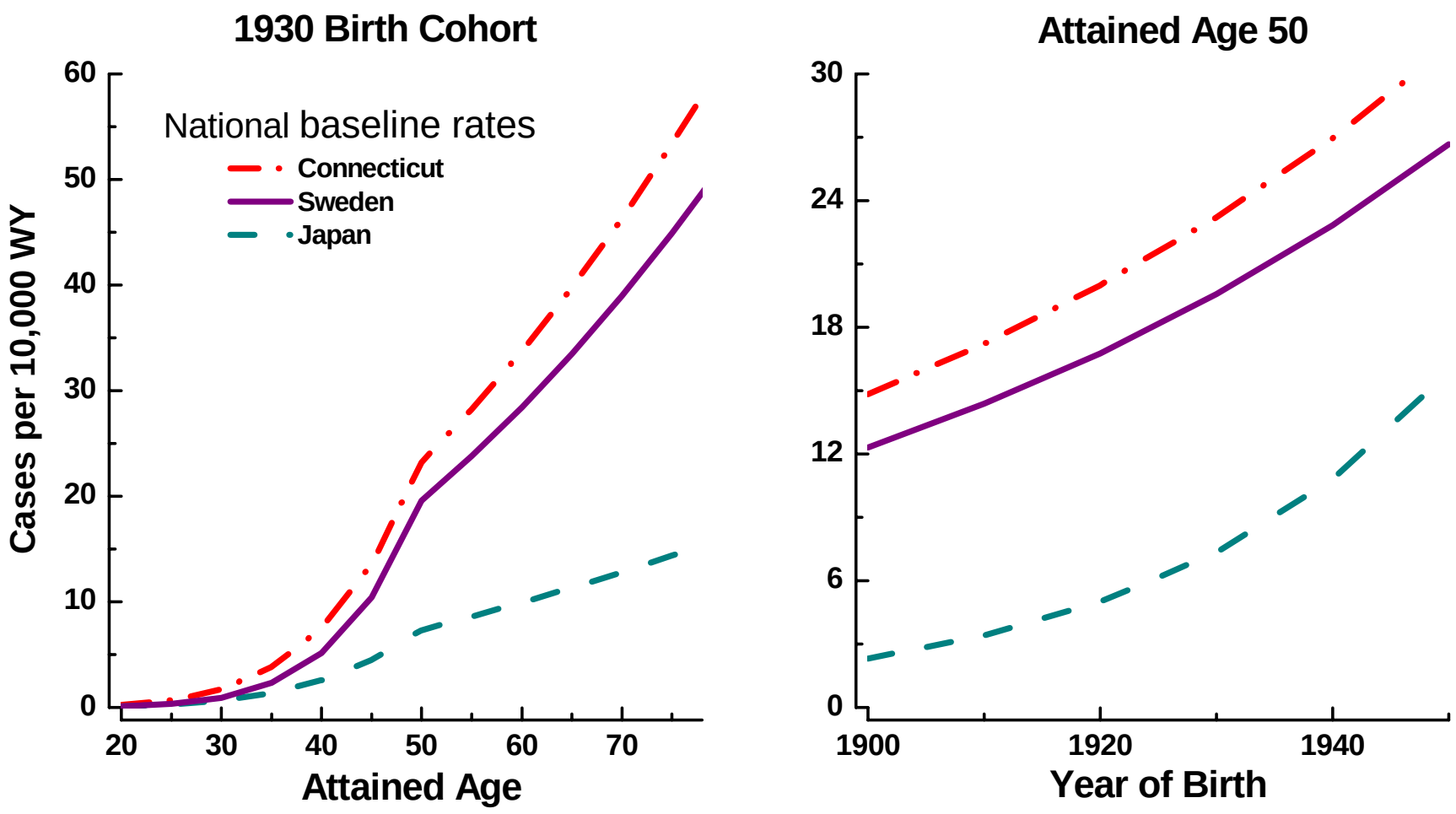
Populations studied by Preston

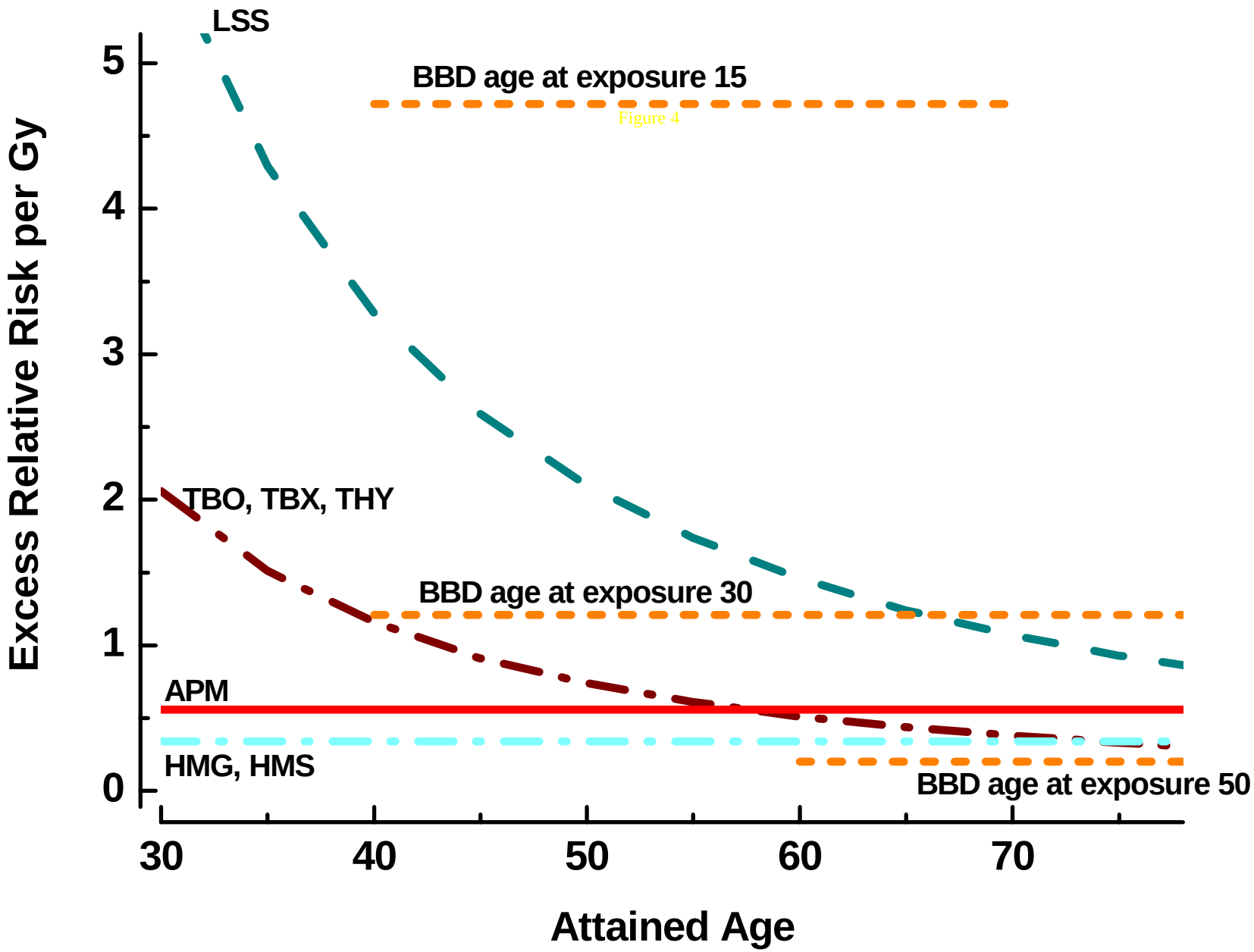
- A-bomb survivors , Tumor Reg. 1958-87 (LSS)
- Massachusetts TB fluoroscopy patients
  - Original (TBO)
  - Extension (TBX)
- New York mastitis patients (APM)
- Rochester infants with “enlarged thymus” (THY)
- Sweden benign breast disease patients (BBD)
- Sweden hemangioma patients
  - Gothenburg (HMG)
  - Stockholm (HMS)

Population properties

- LSS: 707 cases, mean dose 0.3 Sv (0-5)
- TBO, TBX: 103 & 108 cases, many low-dose x-ray fractions, high dose rates, 0-5 Gy
- APM: 114 cases, few fractions, 3.8 (0.6-14)
- THY: 34 cases, few fractions, 0.7 (0.02-7.5)
- BBD: 210 cases, few fractions, 5.8 (0.02-50)
- HMG, HMS: 75 & 155 cases, protracted, low-dose fractions, 0.17 (0-22), 0.5 (0-35)

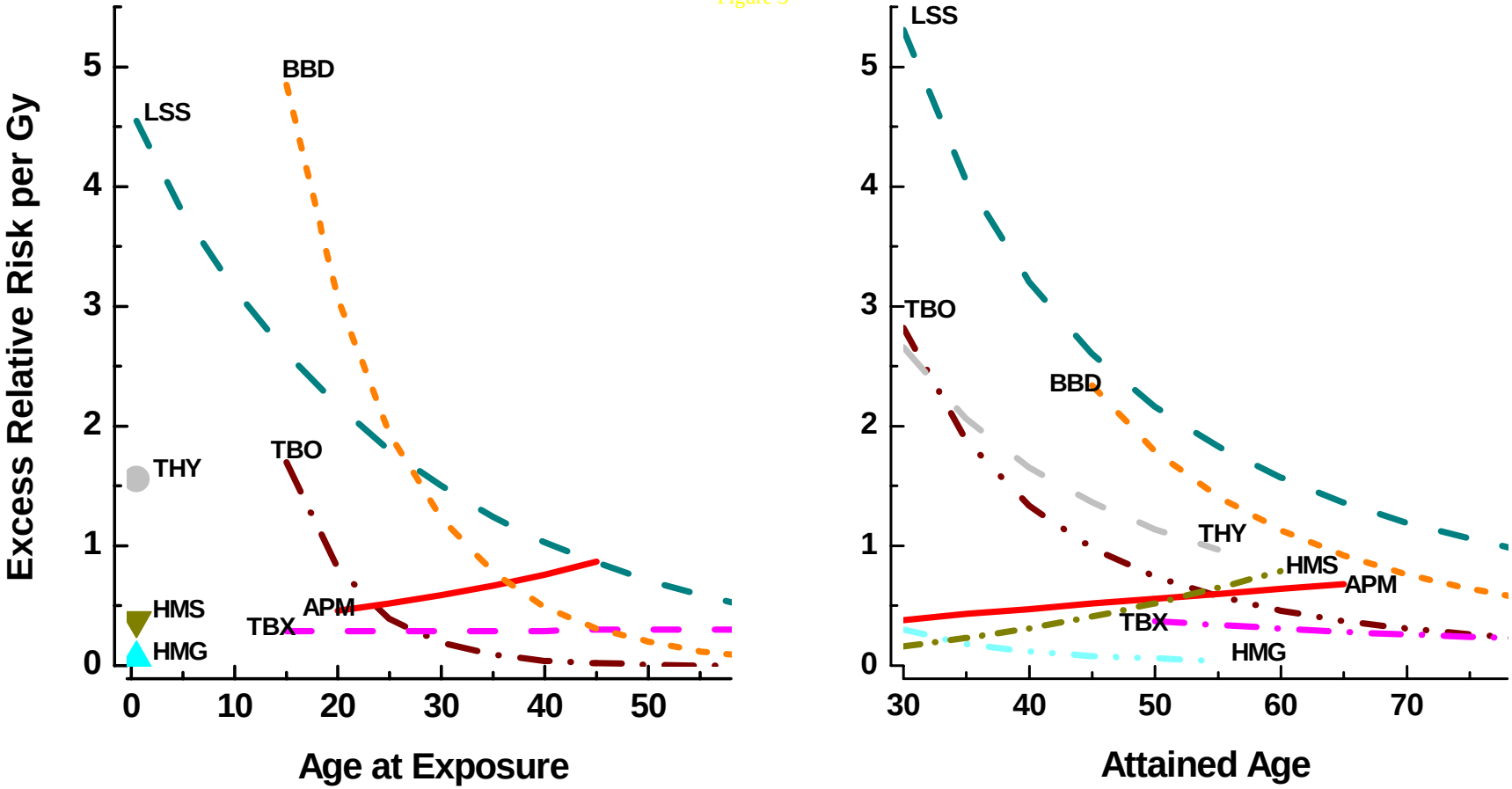
Figure 1


1930 Birth Cohort
National baseline rates
Connecticut
Sweden
Japan
Cases per 10,000 WY
0
10
20
30
40
50
60
20
30
40
50
60
70
Attained Age
Attained Age 50
0
6
12
18
24
30
1900
1920
1940
Year of Birth


LSS
BBD age at exposure 15
Figure 4
TBO, TBX, THY
BBD age at exposure 30
APM
HMG, HMS
BBD age at exposure 50
Excess Relative Risk per Gy
0
1
2
3
4
5
30
40
50
60
70
Attained Age

ERR per Gy, by age at exposure (left) and attained age (right) Preston et al, 2002

Figure 3



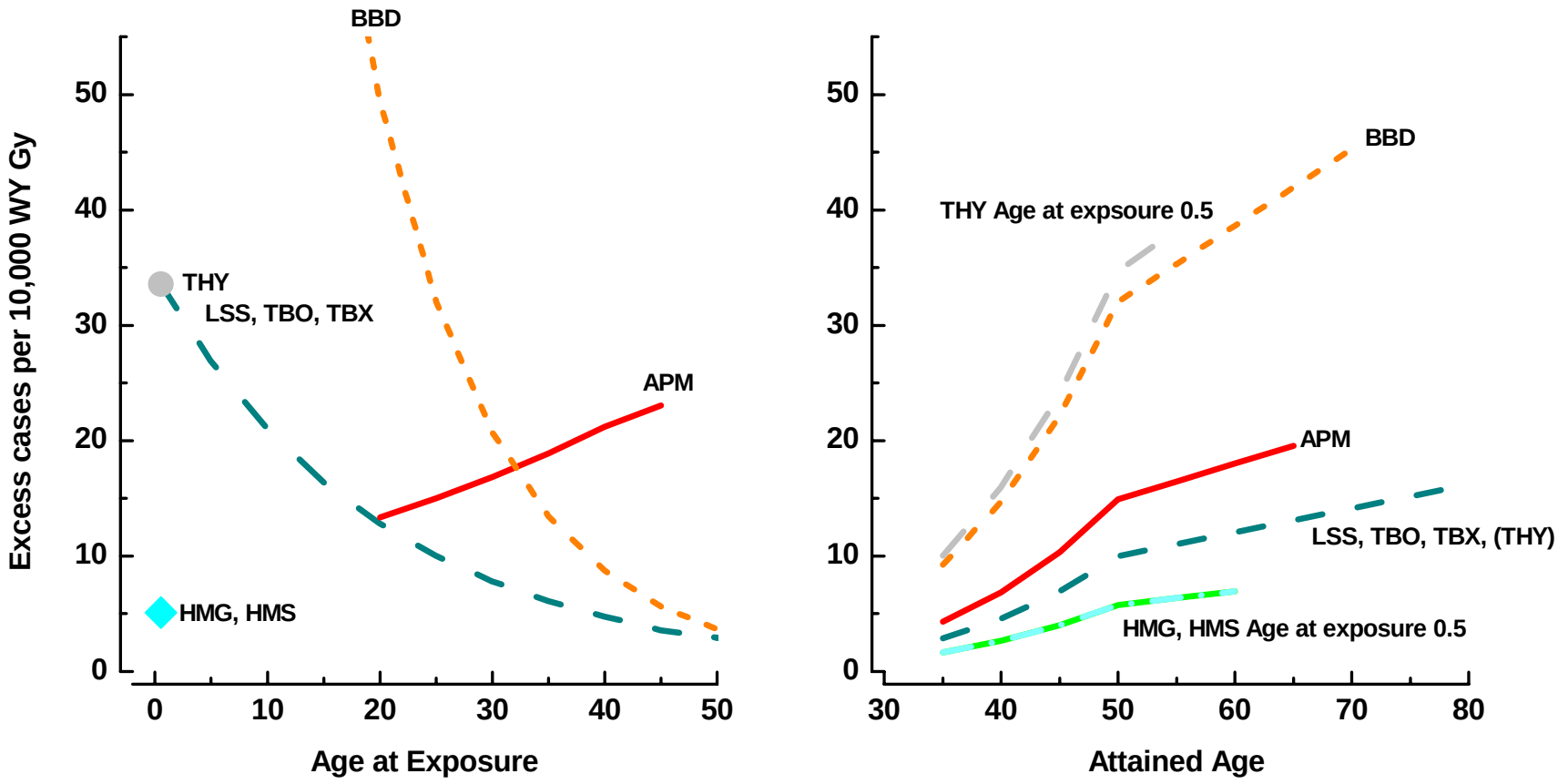

BBD
THY
LSS, TBO, TBX
APM
HMG, HMS
Excess cases per 10,000 WY Gy
Age at Exposure
0
10
20
30
40
50
THY Age at expsoure 0.5
BBD
APM
LSS, TBO, TBX, (THY)
HMG, HMS Age at exposure 0.5
Attained Age
30
40
50
60
70
80

Figure 6

Conclusions re transfer

- Dose-specific excess relative risk significantly greater in A-bomb survivor population than in western, medically-irradiated populations
- Dose-specific excess absolute risks similar among populations
- Not a uniform result, some uncertainty
- Preston et al, Radiation Research, 2002

Unresolved Issues

- Does the early-onset risk anomaly reflect presence of a sensitive genetic subpopulation, & if so, what are its characteristics?
- What is the projected lifetime risk of women exposed at young ages?
- Is breast cancer really different from other cancers re modification by age?

Acknowledgements

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- Collaborators:
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