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Atomic Bomb Survivor Studies: Overview and Recent Findings

Radiation Epidemiology & Dosimetry Course

National Cancer Institute

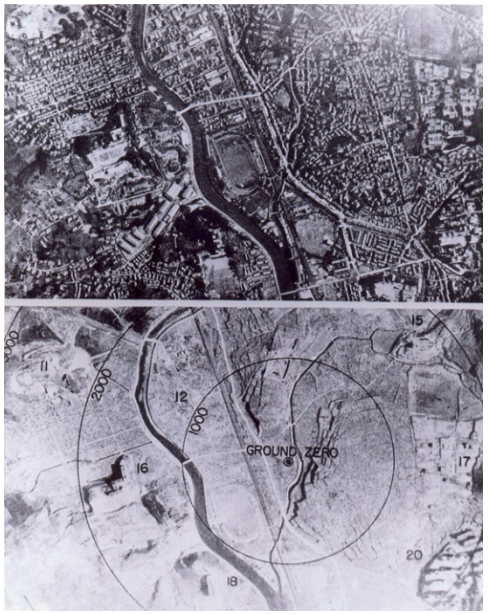
www.dceg.cancer.gov/RadEpiCourse

Outline

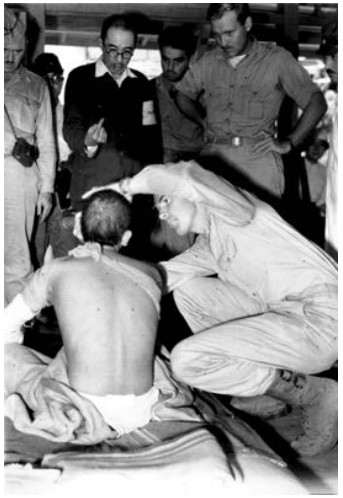
1. **ABCC/RERF background**
   - Immediate effects of the bombs
   - Early studies
   - Major cohorts
2. **Dosimetry**
   - Survivor shielding and location
   - Evolving dose estimates T57D → DS02
   - Dose uncertainties
3. **Risk Estimation**
   - Relative versus absolute risks
   - Describing risk patterns
     - Relative risks and excess rates
     - Dose response
     - Effect modification
   - Issues
     - Time-since-exposure vs attained age
     - Latent periods
     - Interactions
     - Interpreting site-specific risks

Short-term effects

- **Result of**
  - Blast (50% of energy)
  - Heat (35% of energy)
    - Scorched wood up to 3.5km
  - Radiation (15% of energy)
- **Cities largely destroyed**
  - Wooden structures burned up to ~2.5km from hypocenter
  - Blast effects apparent over similar distance range
- **Populations decimated**
  - Hiroshima 110,000 -140,000 deaths
  - Nagasaki 70,000 deaths
  - > 60% mortality within 1km of hypocenter



Health Effects Research 1945 - 1946



- **Japanese research groups**
  - Entered cities within days of bombings
  - Carried out surveys of injuries and deaths
- **US research groups**
  - Medical teams began arriving in September 1945
  - Efforts directed at cataloging acute radiation effects
- **US – Japan Joint Commission**
  - Characterize extent of early mortality
  - Nature of acute effects
    - Nausea
    - Epilation
    - Flash burns
    - Bleeding
    - – Orapharyngeal lesions
    - – Leukopenia

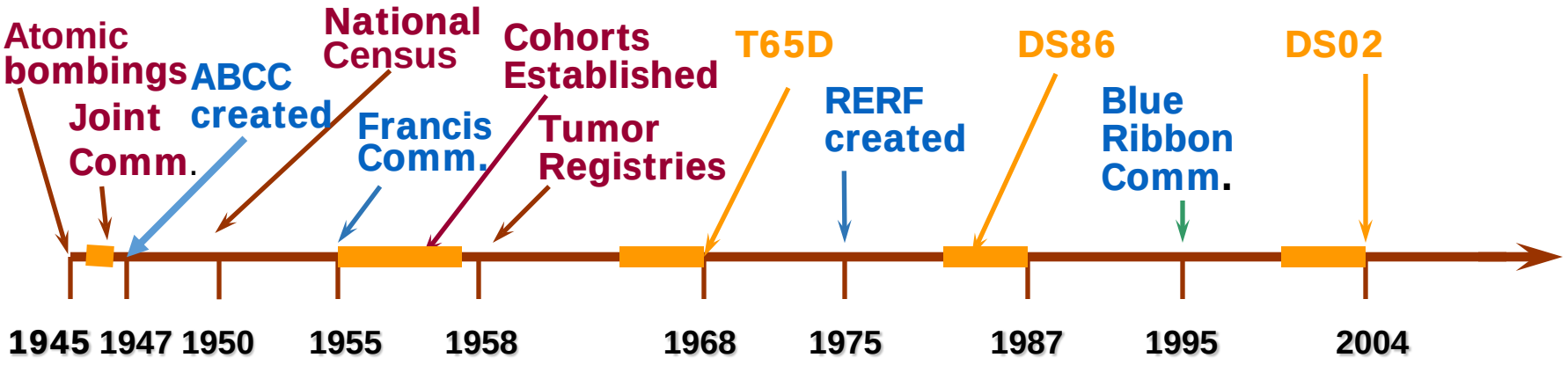
ABCC Activities (1)
1947-1955

- **Pregnancy outcomes**
  - 77,000 births 1947-1952
  - Malformations, premature births, birthweight, sex ratio
  - No significant effects
- **Leukemia**
  - Increase apparent by late 1940's
  - Established leukemia registry
  - Descriptive analyses in ill-defined population
    - No risk estimates

ABCC Activities (2)
1947-1955

- **1950 national census**
  - ABCC managed data processing
  - Special questionnaire for people who were in or near the cities at the time of the bombs used to define ABCC/RERF Master Sample
- **Long-term study plan (Gil Beebe, Seymour Jablon)**
  - Fixed cohorts of survivors, in-utero exposed, children
  - Clinical cohorts of survivors and in-utero-exposed
  - Mortality and cancer incidence follow-up
  - Autopsy program
  - Recognized need for individual dose estimates
    - Systematic program for collection of exposure data

A-bomb Survivor Studies



ABCC Studies

Mortality Study (LSS)

Cancer Incidence Study (LSS)

Clinical Study (AHS)

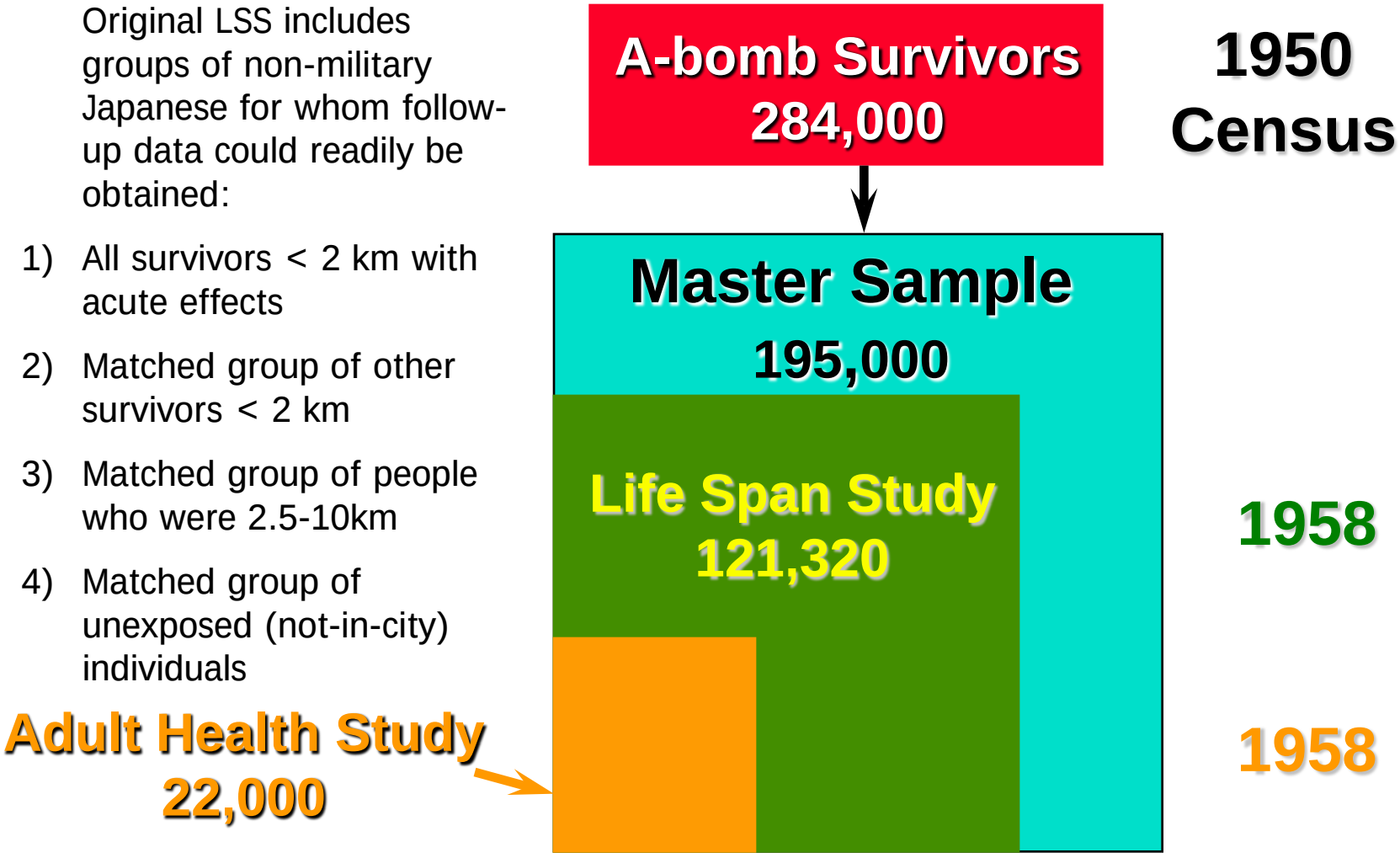
F1 Mortality Study

F1 Clinical Study (FOCS)

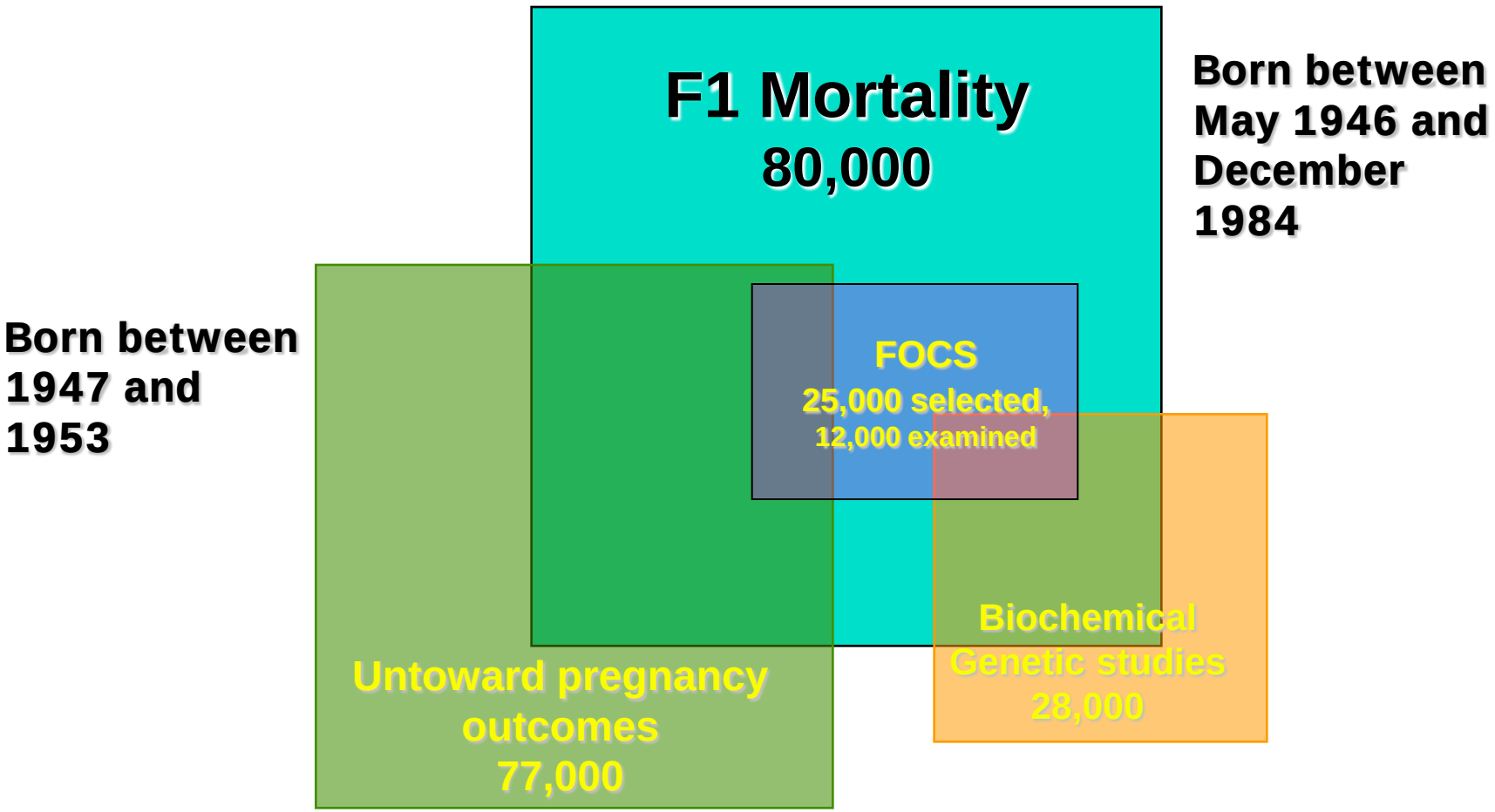
ABCC/RERF Cohorts
Life Span Study (LSS)

Original LSS includes groups of non-military Japanese for whom follow-up data could readily be obtained:

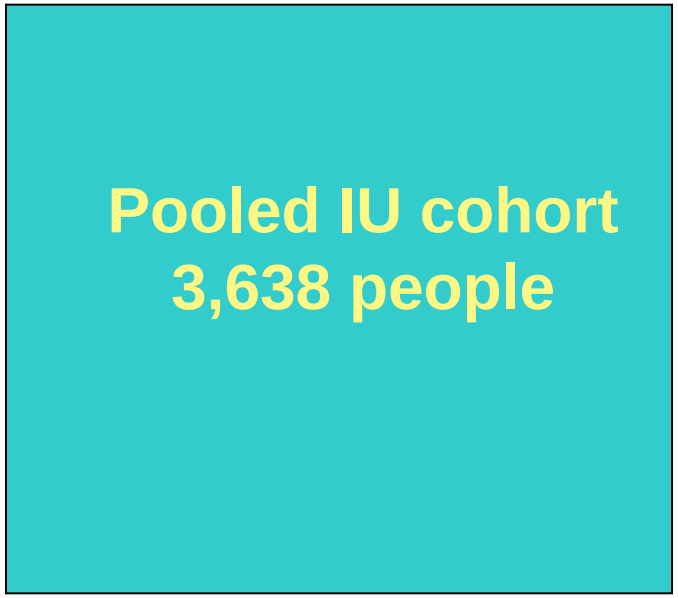
1) All survivors < 2 km with acute effects
2) Matched group of other survivors < 2 km
3) Matched group of people who were 2.5-10km
4) Matched group of unexposed (not-in-city) individuals



ABCC/RERF - F1 study cohorts



ABCC-RERF cohorts
In-utero cohort



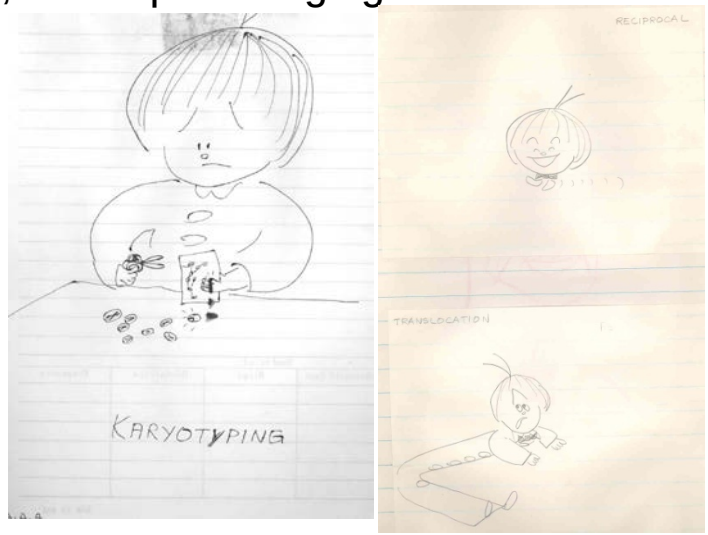
- Pooled cohort combines overlapping clinical (1,606 members) and mortality (2,802 members) cohorts.
- Mortality and cancer incidence data are available for all members of the cohort.

ABCC/RERF Follow-up Programs

- **Mortality**
  - Based on mandatory nation-wide family registration
  - Updated on a three-year cycle
- **Cancer incidence**
  - Hiroshima & Nagasaki tumor registries (1958 – present)
  - ABCC pathology program 1958 – 1972
  - Hiroshima & Nagasaki tissue registries 1973 - present
- **Leukemia and related disorders**
  - Leukemia registry 1950 – 1987
  - Hiroshima & Nagasaki Tumor Registries 1958 – present
- **Clinical Examinations**
  - Biennial exams
  - 70-80% participation through 25 AHS exam cycles
  - Adapted for use in F1 clinical study (FOCS)
- **Mail Surveys**
  - 1965 (Ni-hon-san study men), 1968 (women), 1978, 1991, 2008

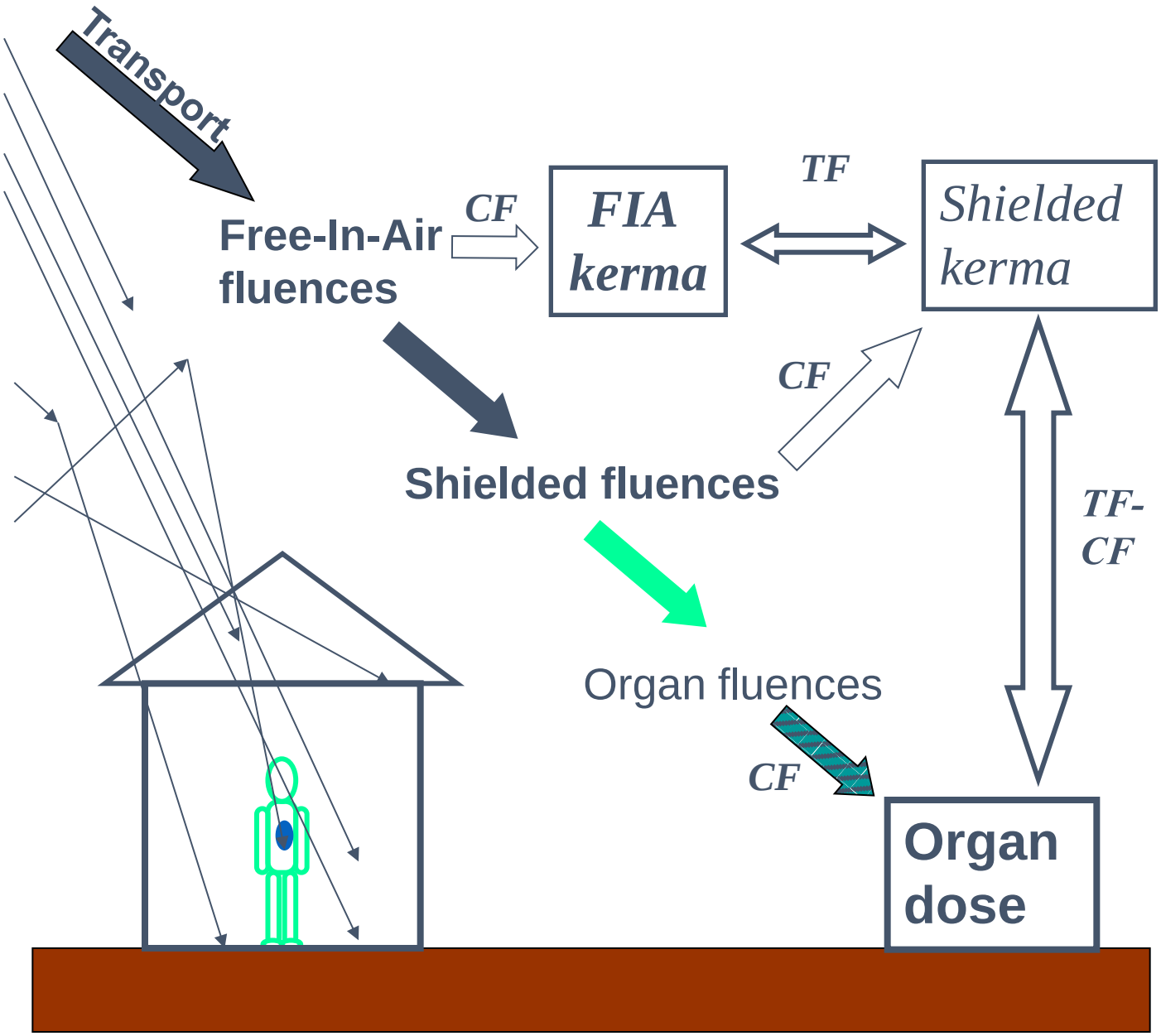
ABCC Research 1958 - 1975

- **Dosimetry** **(Auxier, Kerr, Fujita, Kaul, Egbert, Cullings)**
  - Development of location and shielding information
  - Introduction of first broadly accepted dosimetry system (T65D)
- **Periodic LSS cancer mortality reports** **(Land, Beebe, Jablon, Kato)**
  - Methodological developments & risk estimation
- **Clinical studies**
  - Cardiovascular disease (Ni-Hon-San), Non-specific aging
  - Thyroid and skin diseases
  - Radiation cataract
- **Cytogenetics studies** **(Awa)**
- **In-utero**
  - Physical growth and development
  - IQ
  - Mortality
- **F1**
  - Leukemia incidence
  - General mortality



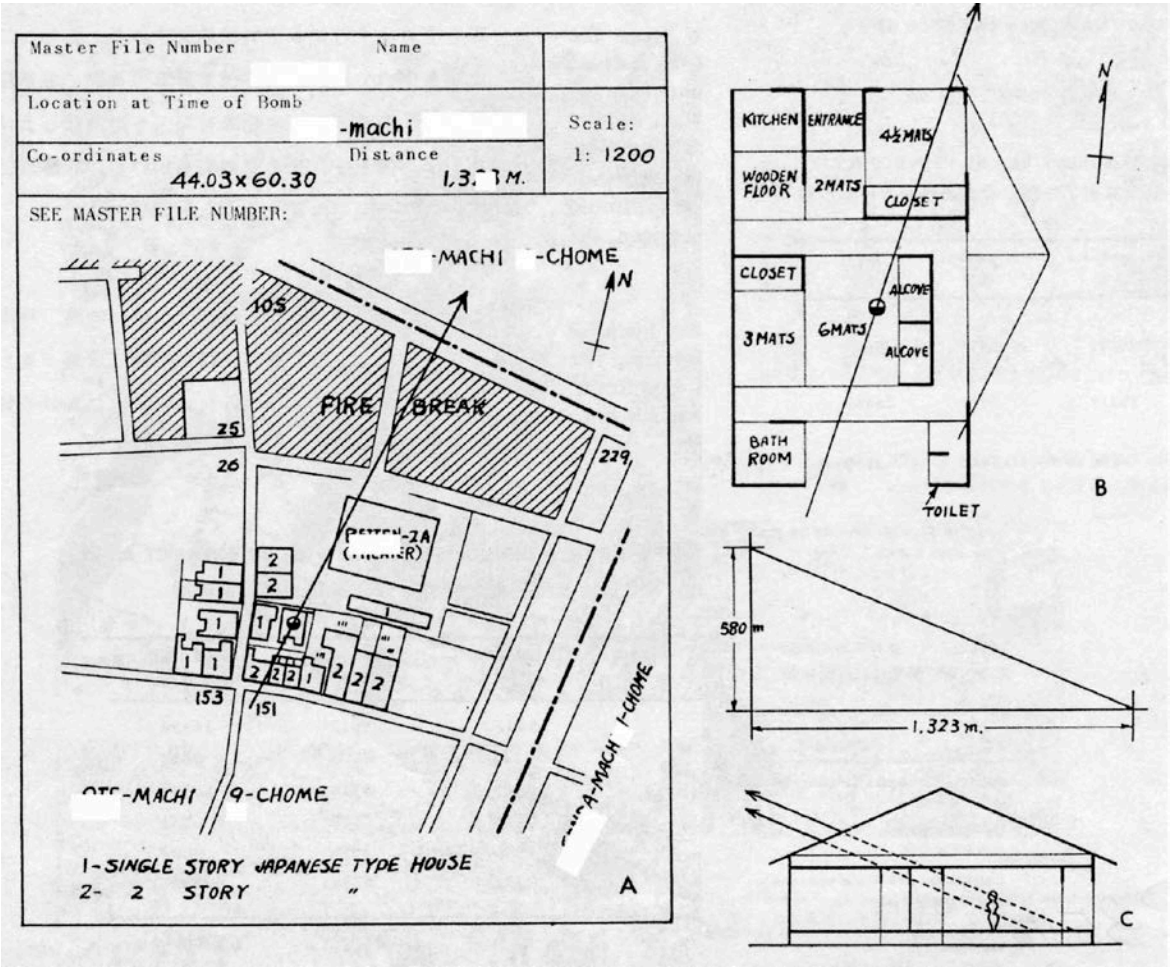
Dosimetry

- **Location**
  - Specified as coordinates on fairly crude US army maps
    - Sought corroboration of location
    - Recorded to nearest 10m in each coordinate if detailed shielding history obtained and nearest 100m for others
  - Recently refined coordinates based on additional archival informaiton and GIS methods
- **External Shielding**
  - Crude shielding categories available for virtually all people of interest
  - Detailed shielding histories for most survivors within 1.6km in Hiroshima and 2 km in Nagasaki
- **Self shielding (organ dose)**
  - Shielding histories contain information on orientation and position



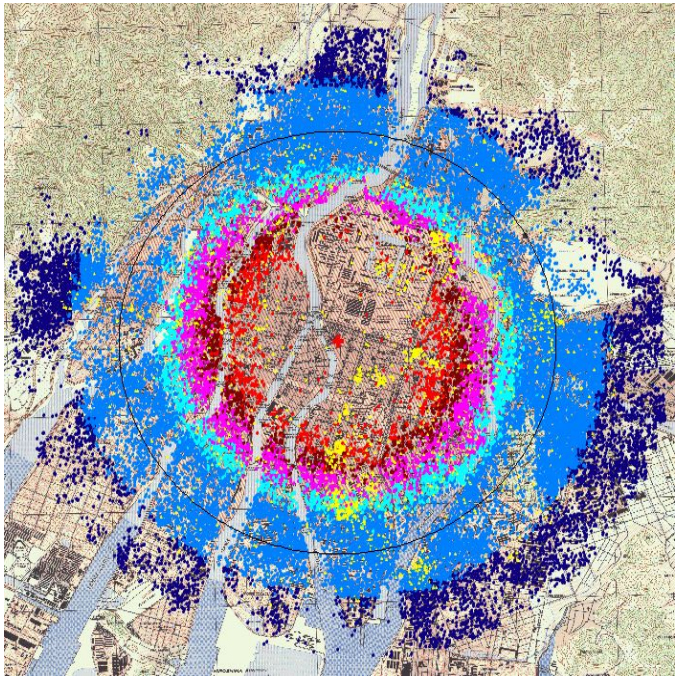
Courtesy of H. Cullings

Sample Shielding History

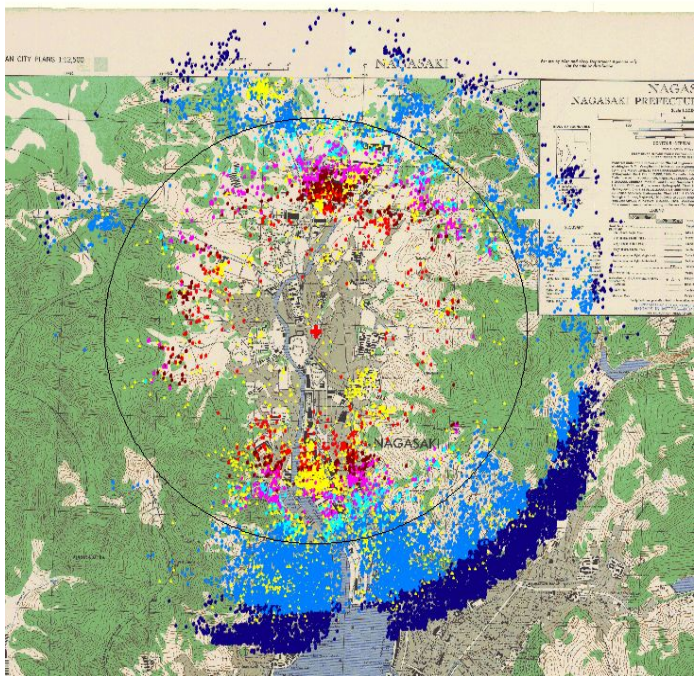


LSS Survivors within 3 Km

Hiroshima



Nagasaki



Dose (mSv)

- < 5
- 5 – 100
- 100 – 200
- 200 - 500
- 500 – 1000
- 1000 +
- unknown

✚ Hypocenter

* LSS: Life Span Study Cohort

Dosimetry History

- **Distance and acute effects**
- **Tentative 1957 Dosimetry (T57D)**
  - Declassified gamma and neutron “air dose” curves by city
  - Crude allowance for shielding
  - Never used for routine analyses
- **T65D**
  - City-specific gamma and neutron equations for free-in-air kerma versus distance
  - Limited validation from physical measurements (TLD and Co^{60} activation)
  - External shielding effects described as transmission factors
    - House shielding based on nine-parameter model or average values
    - Globe method (look at shadows in model conditions)
    - Nagasaki factory model

Dosimetry History
DS86 (Fujita, Kerr, Egbert)

- **Motivated by concerns about T65D neutrons**
- **Involved review of all aspects of bombs, transport, and shielding**
- **Used (then-)modern monte-carlo transport codes**
- **Provided shielded kerma and dose estimates for 15 tissues with up to six components**
- **Reduced neutron doses (especially for Hiroshima) and transmission factors for houses**
- **Some validation by measurements, but some questions about neutron doses lingered**

Dosimetry History
DS02 (Fujita, Kerr, Egbert, Cullings)

- **Possibility of increased Hiroshima neutrons at distance received much attention**
- **Extensive program of validation measurements and inter-laboratory comparisons**
- **Additional review of bomb parameters**
  - Hiroshima yield increased from 15 to 16kt
  - Hiroshima height of burst 580 → 600
  - Nagasaki prompt gamma per kt increased by 9%
- **Further review of shielding effects**
  - New models for large wooden buildings and Nagasaki factories
  - Allowance for distal terrain shielding

Dose Uncertainty
(Jablon, Gilbert, Pierce, Stram Vaeth, Cullings)

- **Uncertainty recognized from the beginning, but**
- **Until recently little effort to allow for or assess impact of uncertainty on risk estimates**
- **Types of uncertainty**
  - Grouping (Berkson) errors
  - Error in individual location / shielding information (classical error)
  - Shared errors – yield, shielding parameters etc
- **Current doses corrected for 35% random errors using a regression calibration method in which D_{est} is replaced by $E(D_{true} | D_{est})$**

Dosimetry Current and Future Developments

- **Refinement of survivor locations**
  - Shielding history reassessment
  - GIS-based locations
- **Improved dose uncertainty adjustments**
  - New adjustment methods
  - Allowance for both grouping and measurement
  - Consideration of shared uncertainties

RERF Research 1975-1995

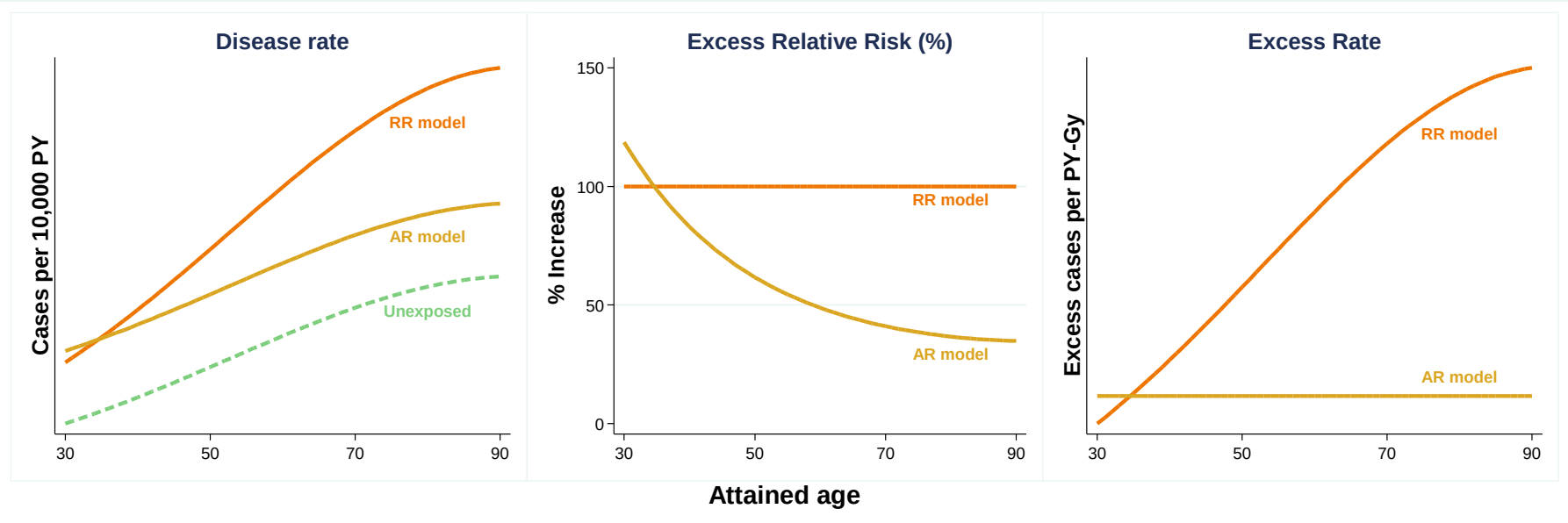
- **Improved LSS cancer mortality reports**
  - Dose–response shape & effect modification
- **Solid cancer and leukemia incidence reports**
- **Breast cancer incidence studies (Land, Tokunaga)**
  - Precursor to more recent site-specific incidence papers
- **F1 studies**
  - Biochemical and cytogenetics studies
- **In-utero**
  - Mental retardation, School performance
  - Cancer mortality, leukemia incidence

RERF Research 1995 - present

- **Increasing emphasis on site-specific cancer incidence**
- **Examination of joint effects of radiation and other risk factors**
- **Emerging evidence of non-cancer mortality risks**
- **Analyses of clinical data**
  - Noncancer disease morbidity
  - Longitudinal laboratory measurements (blood pressure, cholesterol, inflammatory markers)
  - Cataracts

The Old Debate
Relative versus Absolute Risks

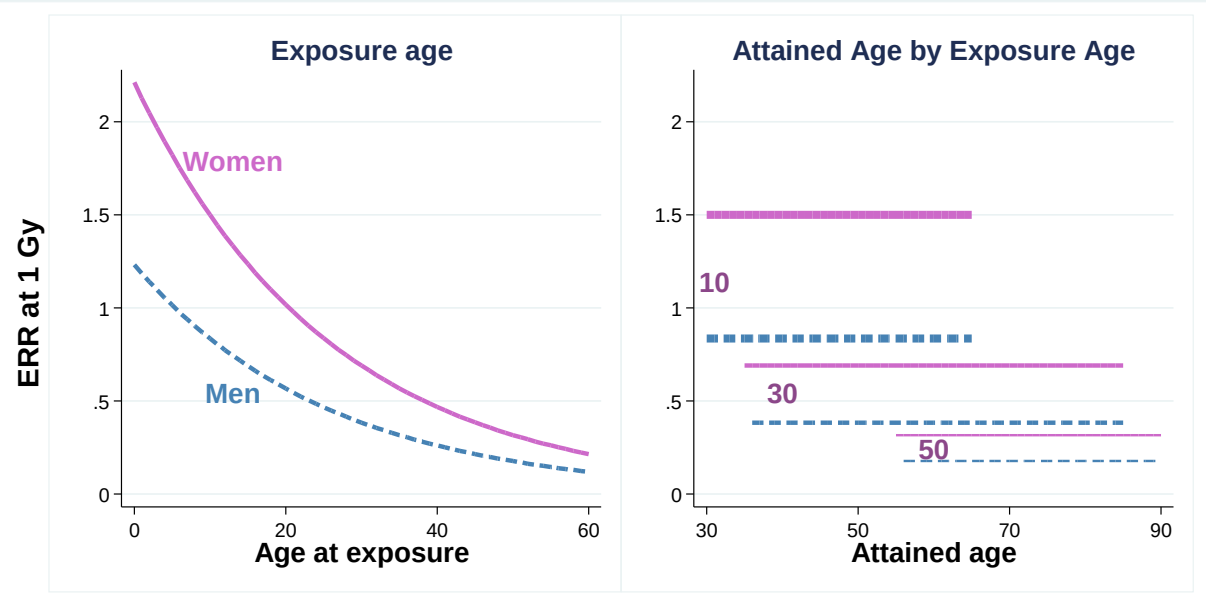
- **Do excess rates increase or become relatively less important as time goes by?**



- **By early 1980's it was agreed that constant relative risk provided a better description solid cancer risks**
- **Leukemia excess risk decreased over time and neither simple description was adequate**

Evolving Understandings
Excess Risk is Not a Number

- **(Relative) risk depends on sex and age at exposure**



- **Are excess relative risks constant in attained age (time) given age at exposure and sex?**
- **How should we interpret sex differences in the ERR?**

Evolving Understandings Describing Excess Risks

Excess relative risk (ERR) model

$$\lambda_o(a,s,b)[1+\rho(d)\varepsilon_R(s,e,a)]$$

Excess absolute rate (EAR) model

$$\lambda_o(a,s,b)+\rho(d)\varepsilon_A(s,e,a)$$

$\lambda_o(a,s,b)$	Baseline (zero dose) risk function (*a* age at risk; *s* sex; and *b* birth cohort)
$\rho(d)$	Dose-response shape , e.g. linear, linear-quadratic, threshold, …
$\varepsilon(s,e,a)$	Effect modification function (*e* age at exposure)

Evolving Understandings
ERR versus EAR description

- **ERR and EAR are (in principle) equivalent descriptions of the excess risk**

$$\varepsilon_R(s,e,a) = \frac{\varepsilon_A(s,e,a)}{\lambda_0(a,s,b)}$$

- **Both ERR and EAR descriptions are important**
- **ERR and EAR provide complimentary information**
  - Patterns in ERR effect modifiers may reflect factors such as sex and birth cohort effects in baseline rates
- **Description may be simpler or more informative on one scale than the other**

Describing Sex and Age-Time Effects

- **Smoothing the excess is essential to understanding**
  - Subset analyses have little power
  - Uncertainty can make it difficult to see patterns
- **Requires choice of variables and model form**
  - RERF analyses generally based on log-linear descriptions
  - Level of detail depends on amount of data

$$\varepsilon(s,e,a)=\exp(\beta_s+\theta e+\gamma\log(a))$$

$\exp(\beta_f)$ / $\exp(\beta_m)$	female:male excess (relative) risk ratio
$\exp(10\ \theta)-1$	% change per decade increase in age at exposure
γ	power of age at risk

Describing Sex and Age-Time Effects

- **LSS data suggest that ERR varies with attained age (time since exposure)**
  - Difficult to conceive of a radiation carcinogenesis mechanism leading to time-constant ERR
- **Extensions of basic model possible**
  - Sex-dependent age and age at exposure effects
  - Other functions of age and age at exposure
- **However, available data usually too limited to support such detailed descriptions**

Solid Cancer Incidence 1958-98

By age at exposure					
Age at exposure	**People**	**Person years**	**Cases**	**Estimated Excess**	**AR%***
Male					
0-19	21,571	632,341	2,409	150	13%
20-39	8,522	229,518	2,569	86	8%
40+	12,809	178,419	2,991	61	5%
Total	*42,902*	*1,040,278*	*7,969*	*297*	9%
Female					
0-19	24,169	755,387	2,186	240	24%
20-39	21,561	679,452	4,423	233	11%
40+	16,795	289,614	2,870	83	6%
Total	*62,525*	*1,724,453*	*9,479*	*556*	13%
Total	***105,427***	***2,764,731***	***17,448***	***853***	***11%***

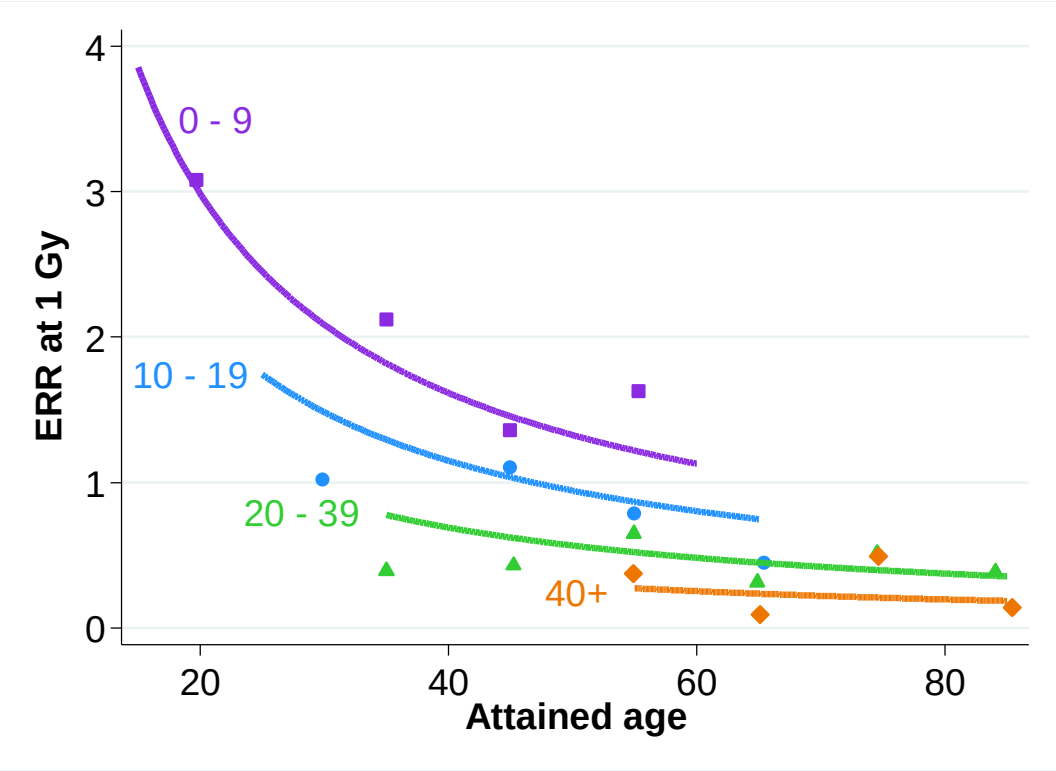
By colon dose					
Colon Dose	**People**	**Person years**	**Cases**	**Estimated Excess**	**AR%**
< 0.005	60,792	1,598,944	9,597	3	0%
- 0.1	27,789	729,603	4,406	81	2%
- 0.2	5,527	145,925	968	75	8%
- 0.5	5,935	153,886	1,144	179	16%
- 1	3,173	81,251	688	206	30%
- 2	1,647	41,412	460	196	43%
2+	564	13,711	185	111	60%
Total	***105,427***	***2,764,732***	***17,448***	***853***	***11%****

* Attributable risk % for people with doses > 0.005 Gy

Preston et al 2007 LSS Solid cancer *Radiat. Res.*

- Information on sex and age-time patterns depends (only) on radiation-associated ("excess") cases
- Excess cases not explicitly identified
- Number of relevant cases is relatively small, especially for specific sites
- No evidence against linear dose response

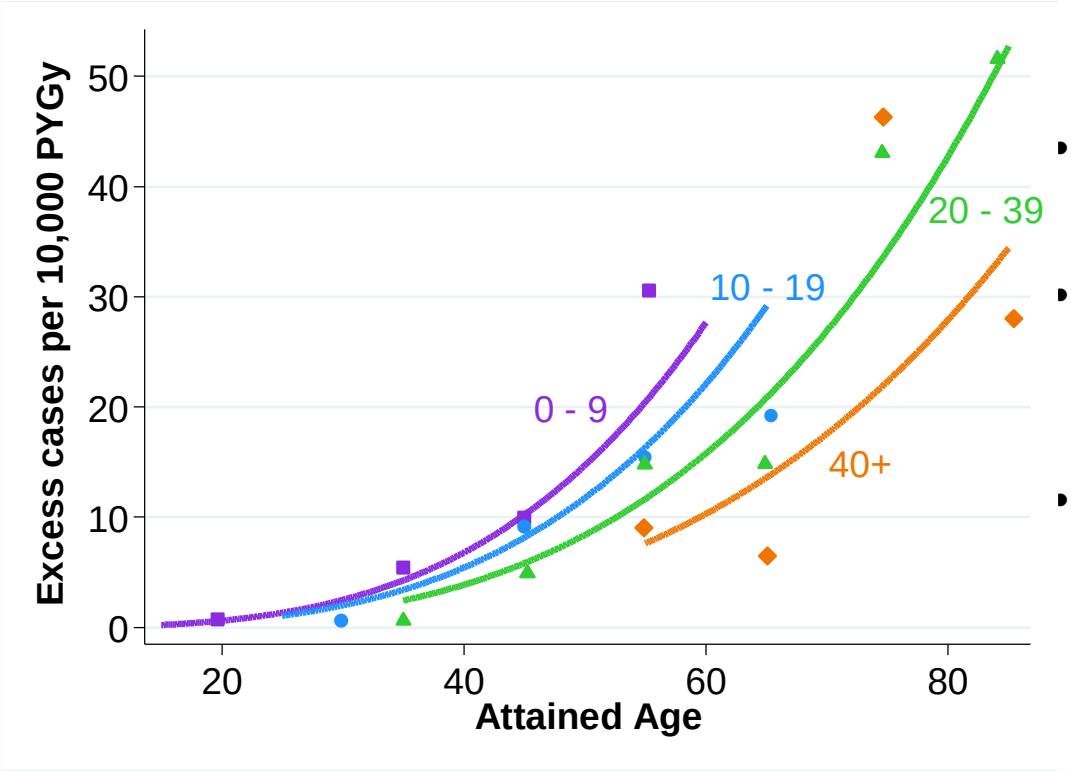
Solid Cancer Mortality 1950 – 2000
Excess Relative Risk Temporal Patterns



- Decrease proportional to *age* $^{-0.9}$
- ERR decreases by 29% per decade increase in age at exposure
- F:M ratio 1.9

Ozasa et al 2012 LSS Report 14, *Radiat. Res.*

Solid Cancer Mortality 1950 – 2000
Excess Rate Temporal Patterns



- Increase proportional to *age* $^{3.5}$
- EAR decreases by 20% per decade increase in exposure age
- F:M sex ratio 1.1

Ozasa et al 2012 LSS Report 14, *Radiat. Res.*

LSS Leukemia Mortality 1950-2000

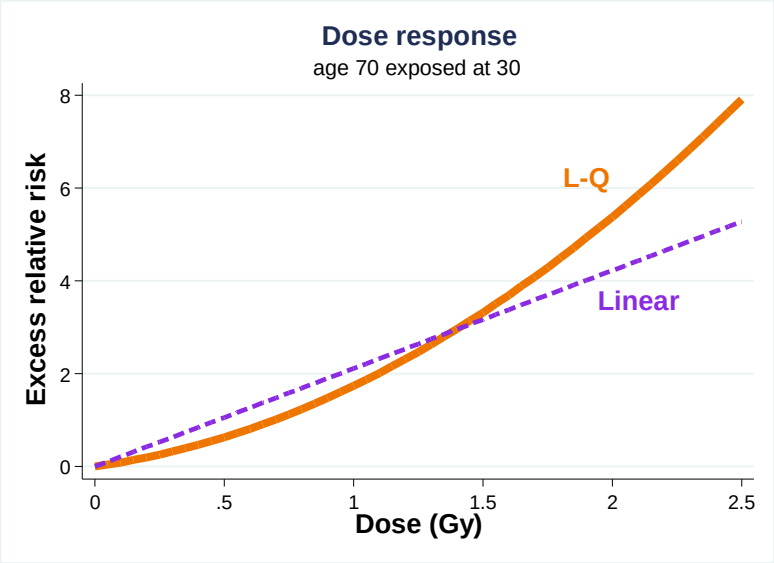
By age at exposure					
Age at exposure	**People**	**Person years**	**Cases**	**Estimated Excess**	**AR%***
Male					
0-19	16,827	783,098	60	26	58%
20-39	6,411	229,330	49	12	42%
40+	12,449	227,441	47	13	41%
Total	*35,687*	*1,239,869*	*156*	*52*	48%
Female					
0-19	18,569	891,288	42	16	51%
20-39	16,750	702,633	57	17	41%
40+	15,605	350,566	41	9	36%
Total	*50,924*	*1,944,487*	*140*	*43*	43%
Total	***86,611***	***3,184,355***	***296***	***94***	***46%***

By marrow dose					
Marrow Dose	**People**	**Person years**	**Cases**	**Estimated Excess**	**AR%**
< 0.005	36,502	1,342,168	89	0	0%
- 0.1	30,898	1,135,582	69	4	6%
- 0.2	6,006	223,701	17	4	25%
- 0.5	6,993	256,584	31	13	41%
- 1	3,512	129,053	27	18	68%
1+	2,700	97,267	63	55	87%
Total	***86,611***	***3,184,355***	***296***	***94***	***46%****

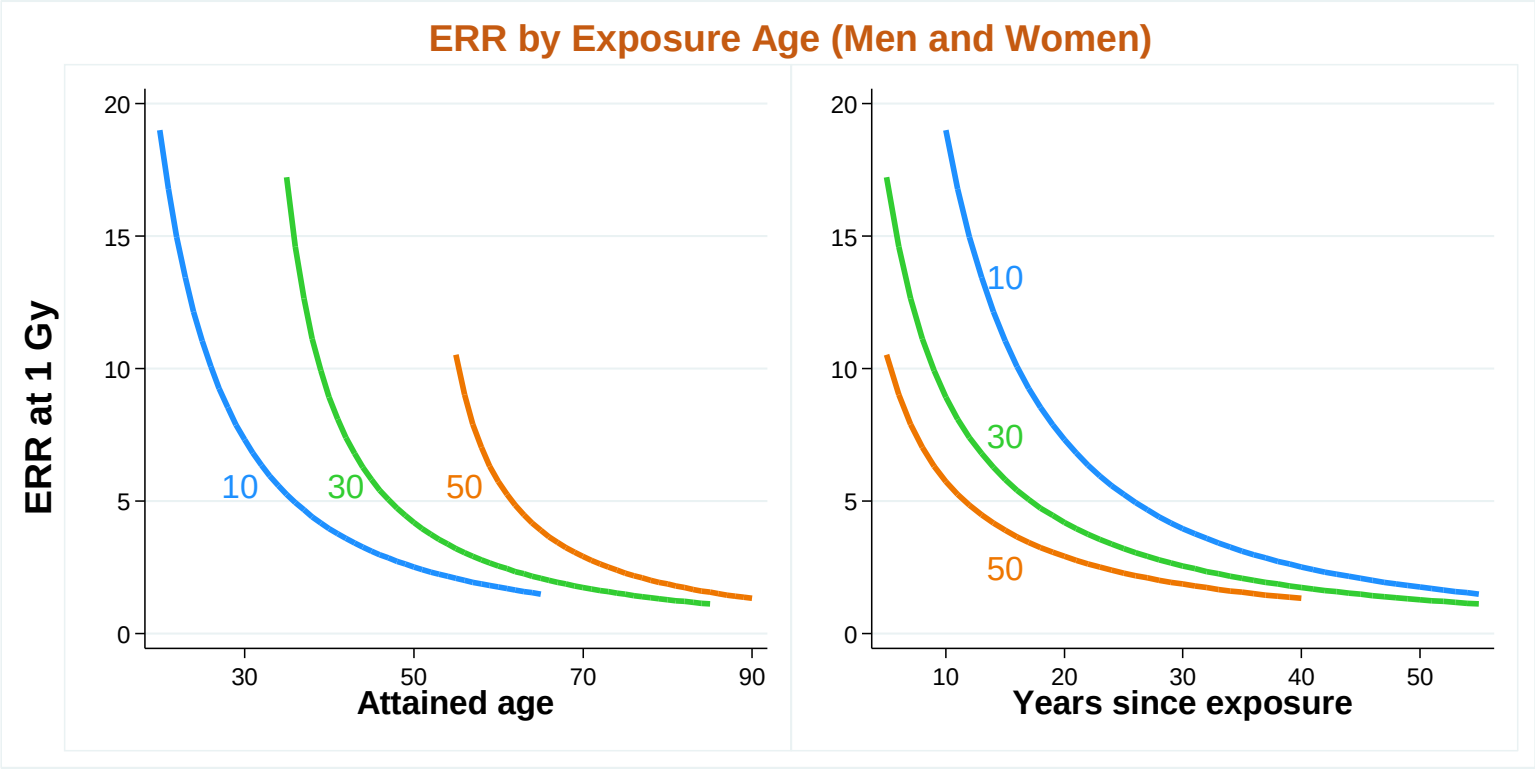
* Attributable risk % among survivors with marrow dose > 0.005 Gy

Ozasa et al 2012 LSS Report 14, *Radiat. Res.*

- Despite smaller number of excess cases, a considerably larger proportion of the cases are radiation-associated
- Non-linear dose response



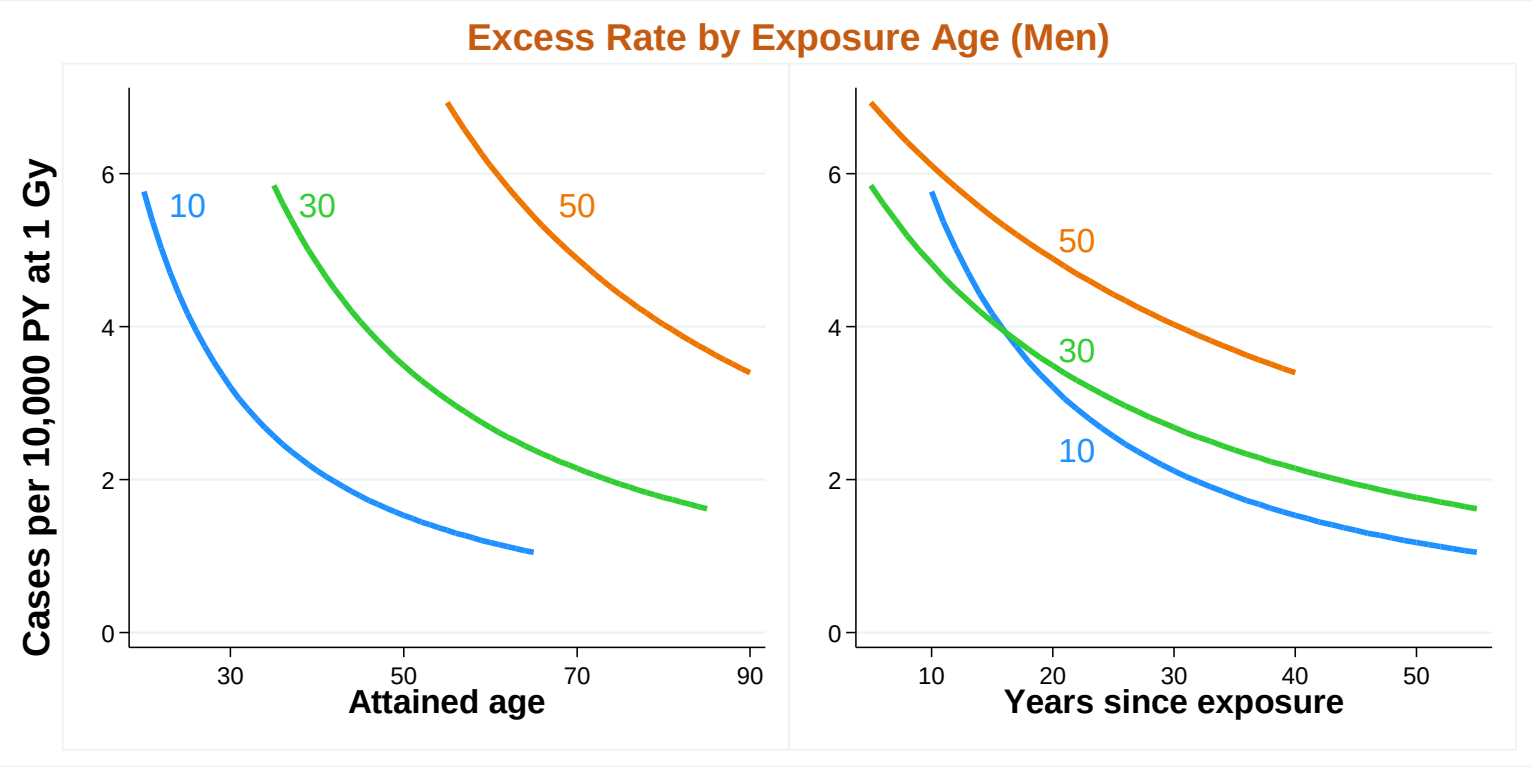
Leukemia incidence 1950 – 2001
Excess Absolute Rate



- Decrease proportional to *age* $^{-1.1}$ and *tsx* $^{-0.8}$
- No additional age-at-exposure effect
- No sex difference

Hsu et all 2013 LSS Leukemia risks, *Radiat. Res.*

Leukemia incidence 1950 – 2001
Excess Rate



- Decrease proportional to *age* $^{-1.4}$
- Increases by 50% per decade increase in exposure age
- F:M ratio 0.66
- Naga:Hiro ratio 0.52

Hsu et all 2013 LSS Leukemia risks, *Radiat. Res.*

Related Issues
Time-Since-Exposure

- **Solid cancer**
  - LSS data suggest that largest risks occur late in life regardless of age at exposure
  - EAR TSE model fits worse than attained-age model without an agex-by-TSE interaction
- **Leukemia**
  - TSE models motivated by EAR decrease and the belief that the excess disappeared after 15 to 20 years
    - Incorrect for ALL and AML
    - Possibly true for CML
  - TSE models involve significant agex-by-TSE interaction
  - Attained age models provide comparable fit without need for interaction

Radiation and Other Risk Factors Interaction and Effect Modification

- **Interaction**
  - Joint effect is not simply the sum of the radiation effect (R) and the other effect (E).

    $$\mathbf{f}(R,E) \neq R + E$$

  - Joint effect model needs to include interaction term, e.g. $R + E + R\,E$
- **Effect Modification**
  - Radiation effect differs for different levels of the other risk factor

    $$\mathbf{f}(R \mid E = e_0) \neq \mathbf{f}(R \mid E = e_1)$$

  - Radiation effect model should depend on E
  - E need to have an effect when R=0
  - Radiation effect model should depend on E

Radiation and Other Risk Factors
Confounding

- **Occurs when**
  - Risk depends on both *R* and *E*
    - *E* may or may not be an effect modifier
    - May be no interaction between *R* and *E*
  - Radiation exposure/dose is correlated with level of *E*
  - Effect of *E* is not included in risk model
- **Results in biased estimates of radiation effect**
- **Model joint effect of R and E**

Joint Effect Models

- **Focus on relative risk models**
  - ERR models are the most natural way to describe interactions
  - Use smoking and radiation as illustration
- **Simple models**
  - Additive: **Rate = BKG_{ns} (1 + ERR_{smk} + ERR_{rad})**
    - No interaction or effect modification
    - ERR_{smk} and ERR_{rad} are relative to rates for unexposed non-smokers
  - Multiplicative: **Rate = BKG_{ns}(1 + ERR_{smk}) (1 + ERR_{rad})**
    = BKG_{ns}(1 + ERR_{smk} + ERR_{rad} + $ERR_{smk}ERR_{rad}$)
    - ERR_{rad} the same for all levels of smoking
    - ERR_{rad} relative to rates that include smoking effect

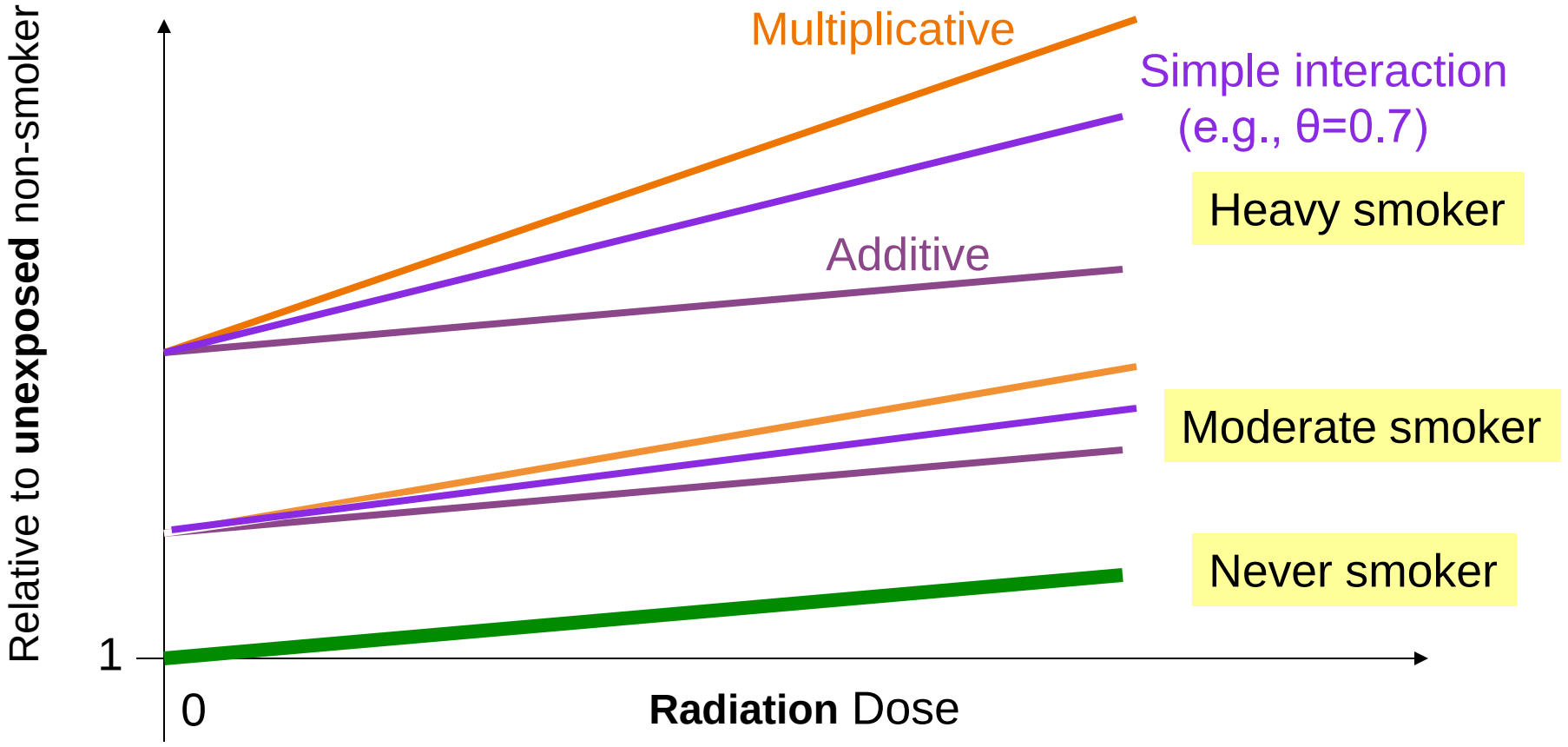
Radiation and Other Risk Factors Interaction Models

- **Simple generalized interaction model**
  - Rate = BKG (1 + ERR_{smk} + ERR_{rad} + θ ERR_{smk} ERR_{rad})

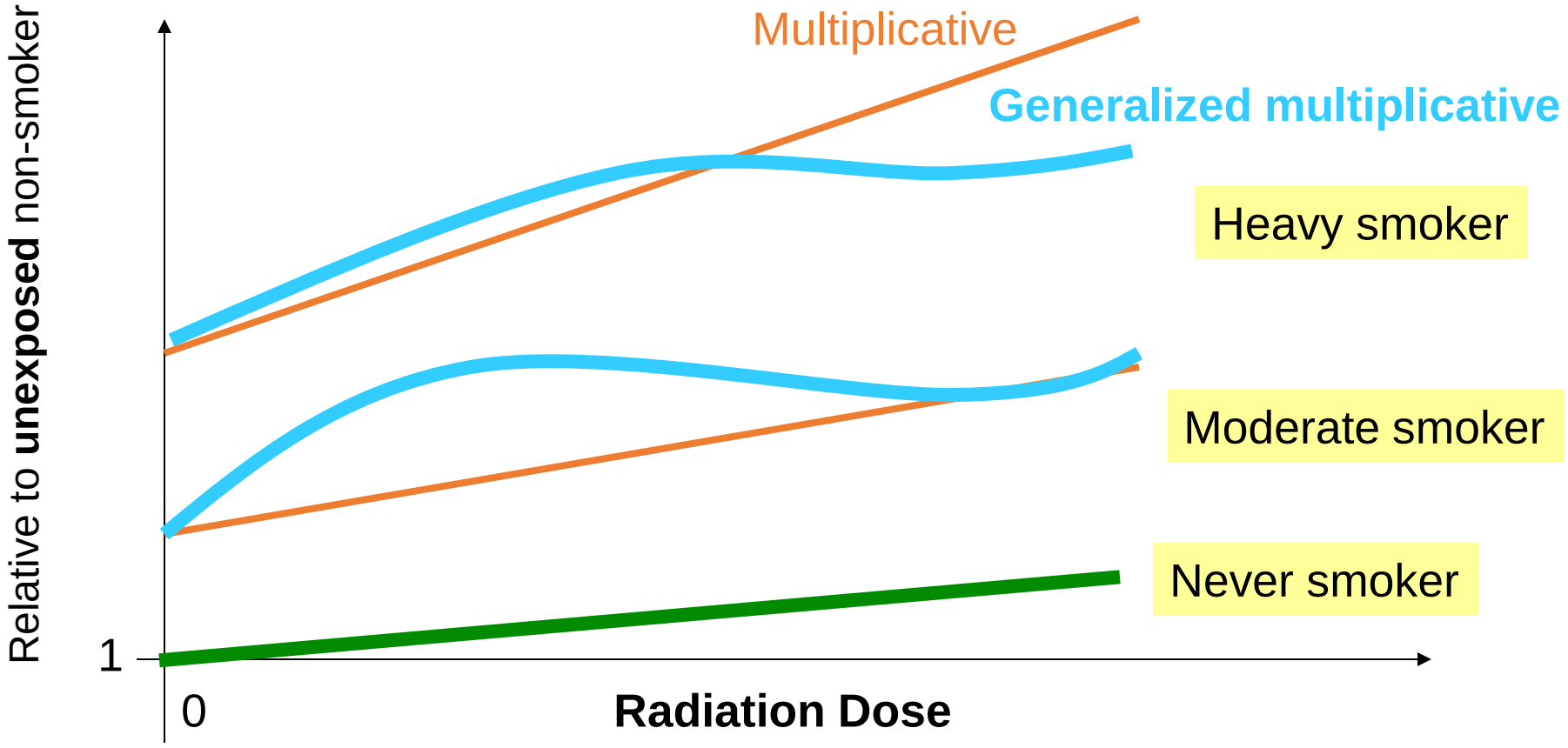
    simple additive (θ=0) and multiplicative (θ=1) models are special cases
- **Generalized additive model**
  - Rate = BKG (1 + ERR_{smk} + ERR_{rad} *f(smk))

    f(smk) is a function of smoking behavior such that f(smk)=1 for non-smokers
- **Generalized multiplicative model**
  - Rate = BKG (1 + ERR_{smk})(1+ ERR_{rad} *f(smk))

Models
Additive or Multiplicative ?



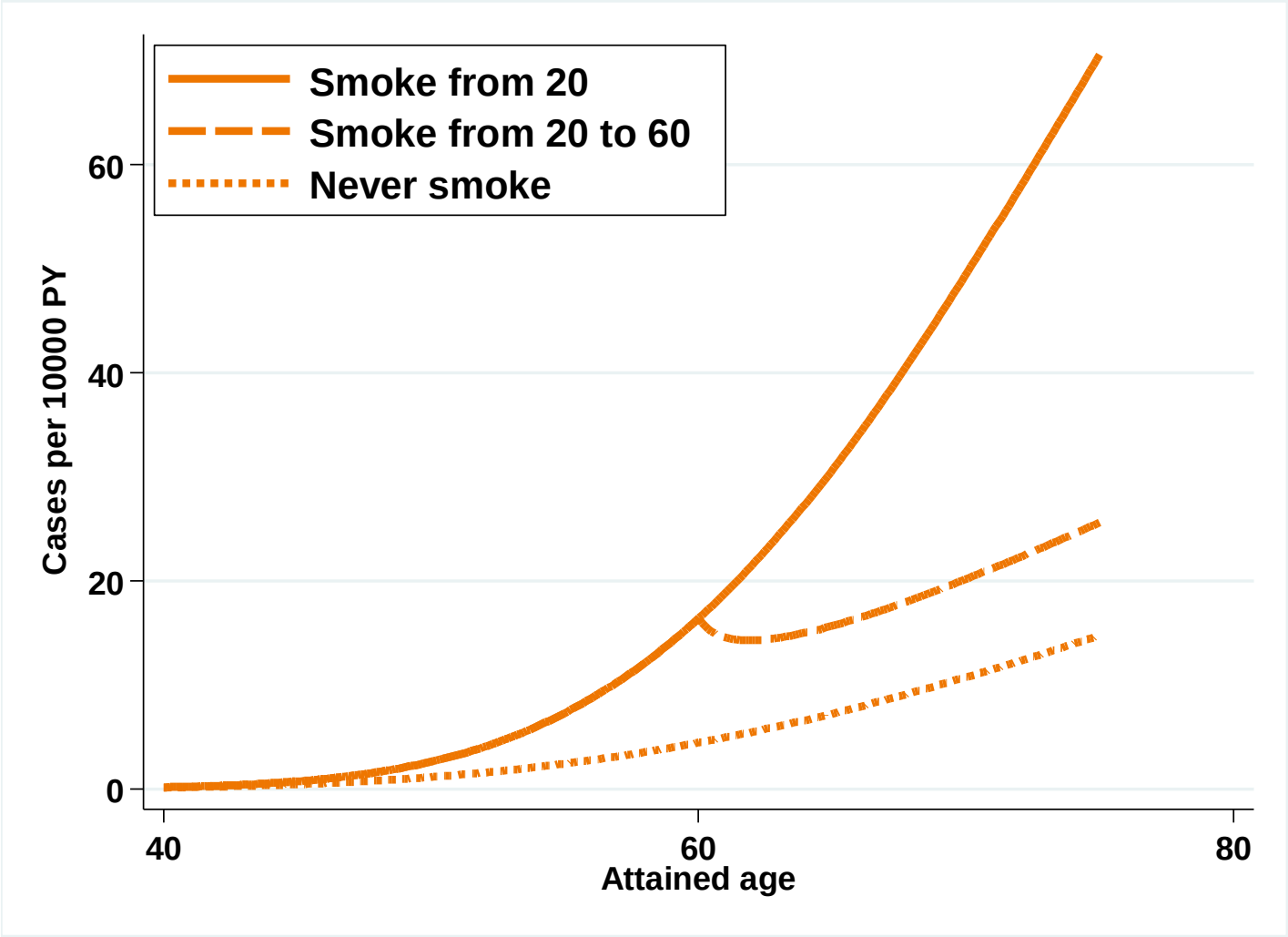
Models
Additive, Multiplicative or General?



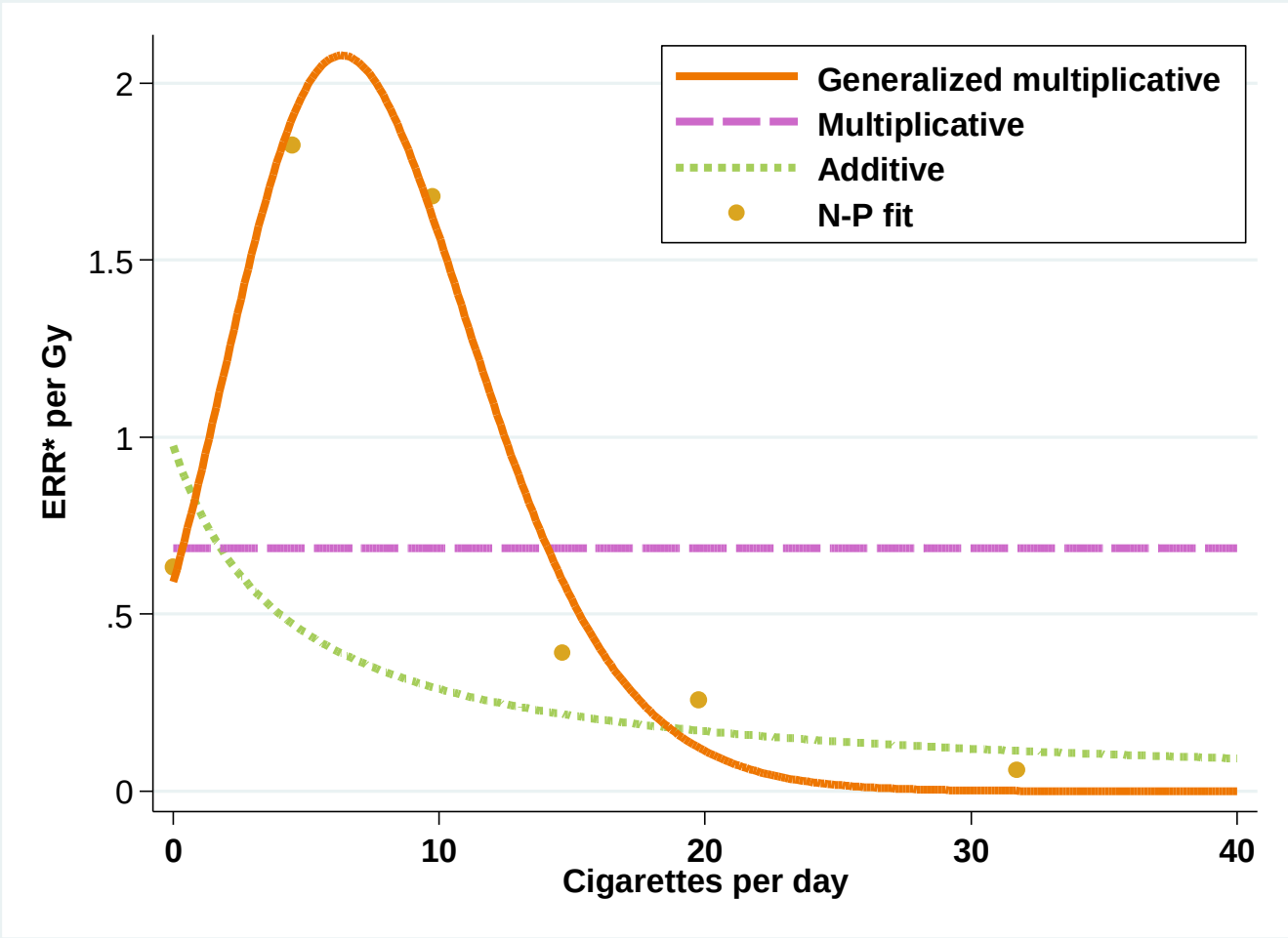
Lung Cancer Rate Model

- **Background rates (unexposed never smokers)**
  - Sex-specific log quadratic spline in log age
  - Additional effects for *year of birth*, *sex*, *city*, *location (in city or not)*
- **Radiation ERR**
  - $ERR_{rad} = \beta_{sex}\ dose \cdot age^{\gamma} \cdot \exp\{\alpha\ agex\}$
- **Smoking effect**
  - Dependent on smoking duration (*dur*), intensity(*pkday*), time since quitting (*tsq*) and pack-years (*pkyr* = *dura* · *pkday*)
  - $ERR_{smk} = \delta_{sex}\ pkyr\ \exp\{\zeta pkday + \eta \log(dur) + \varphi \log(1 + tsq)\}$
- **Generalized interaction**
  - $ERR_{rad(smk)} = ERR_{rad} \cdot \exp(\psi_1\ pkday + \psi_2\ pkday^2)$

Smoking Effect on Rates

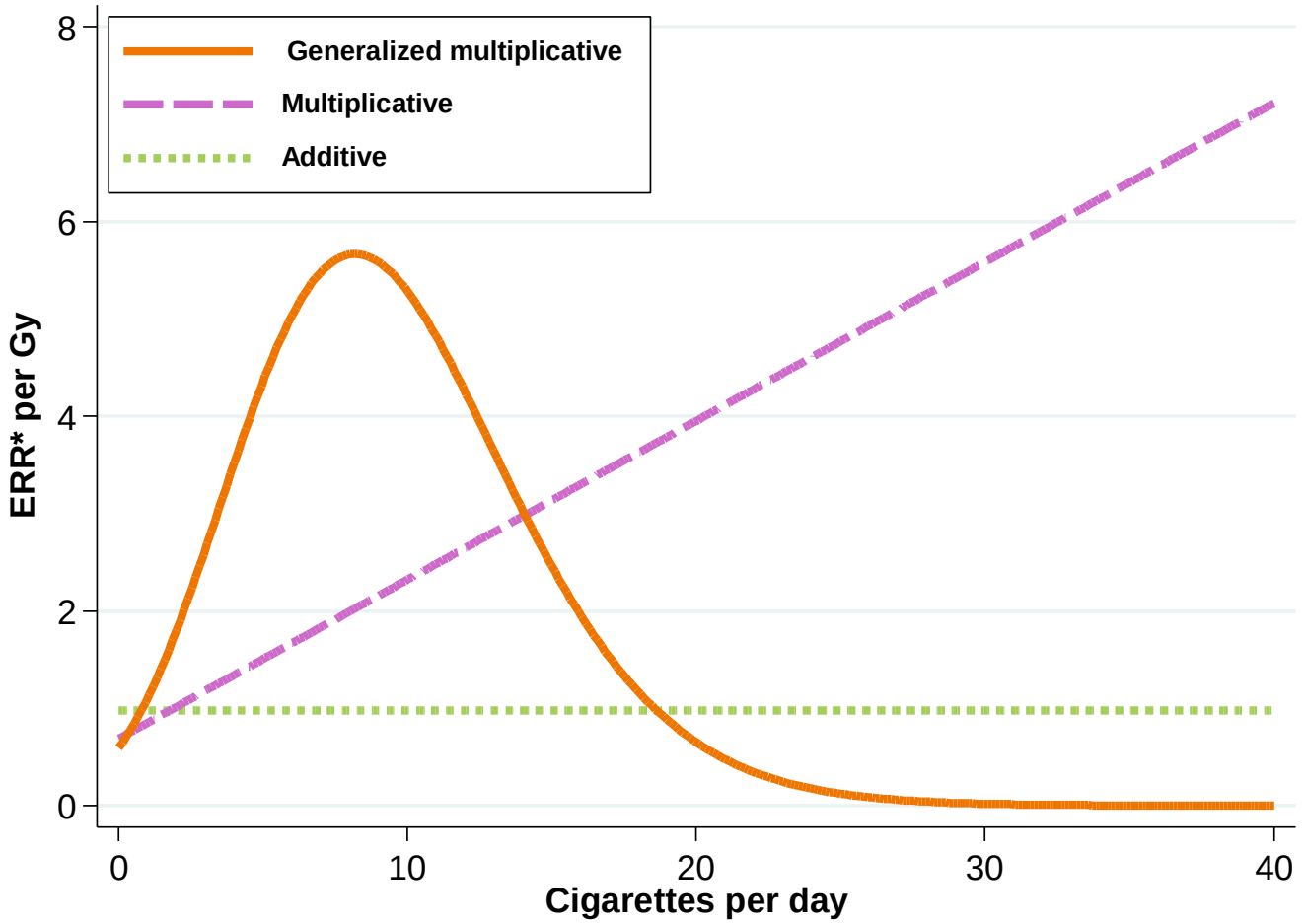


Smoking-Radiation Interaction (1)



*** Relative to unexposed with same smoking history**

Smoking-Radiation Interaction (2)



*** Relative to unexposed non-smoker**

LSS Radiation and Smoking in the LSS Summary

- **Smoking effects on lung cancer were modeled by intensity(rate) and duration.**
- **Neither simple additive nor multiplicative models are sufficient to model the joint effect of smoking and radiation.**
- **The interaction appears to be larger at lower smoking rates than higher rates.**

Interpreting Site-Specific Risks

- **Difficult to interpret and generalize effect modification**
  - ERR sex effects mirror baseline sex effects, but baseline effects may be similar across populations
  - Age at exposure effects in the ERR may depend on birth cohort or period effects on baseline rates
  - Can also be problems in generalizing EAR patterns
- **Site-specific differences in patterns are likely to exist**
  - However 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, sex effects and age-time patterns

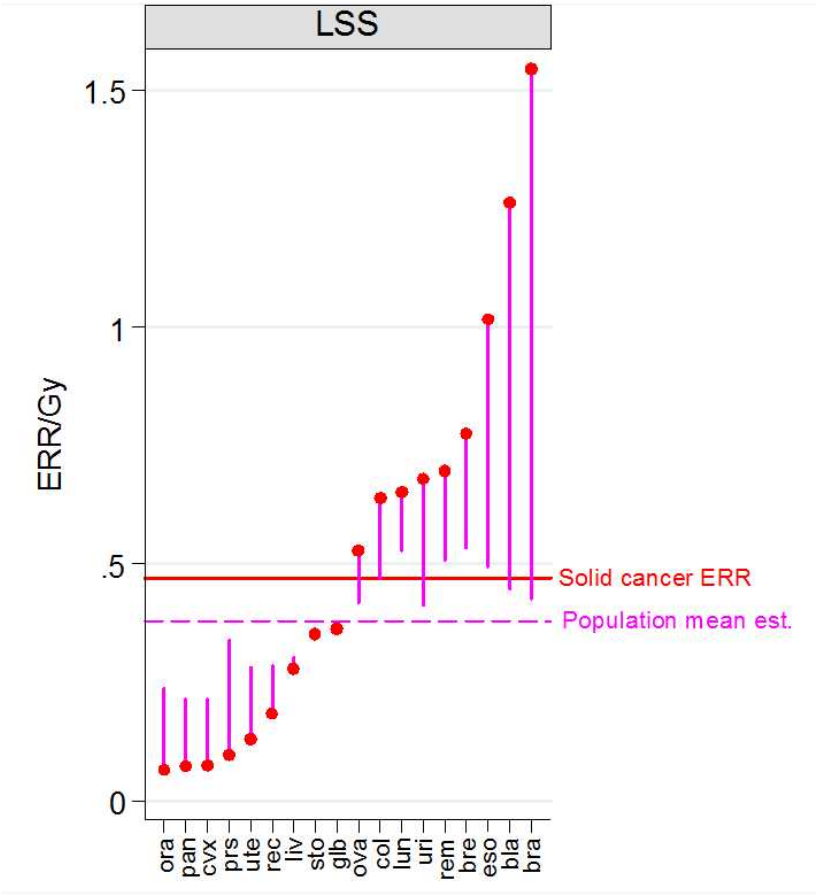
Adjusted Site-Specific Risk Estimates A Simple/Simplistic Example

- **LSS solid cancer mortality 1950 – 1997***
  - 86,572 in-city members of the LSS
  - 9,335 solid cancer deaths
    - ~440 associated with radiation exposure
- **ERR model for all solid cancers with sex, attained age, and age at exposure effects (similar to incidence model)**
- **ERR models also fit for 18 specific "sites"**
  - Site-specific ERR MLEs range from < 0.1 (oral cavity, pancreas, prostate) to 1 or more (breast, bladder, brain)
  - Estimated number of excess cases range from less than 3 (prostate oral cavity, cervix) to more than 80 (stomach, lung)

Adjusted Site-Specific Risk Estimates A Simple/Simplistic Example

- **Use Bayesian methods to describe population mean and variance and produce adjusted site-specific risk estimates**
  - "True" site-specific risk estimates taken as sample from a $N(\rho, \theta^2)$ distribution
  - Non-informative priors for ρ and θ^2
  - Posterior distributions for site specific risks and population parameters described using MCMC methods (WinBugs software) and summarized using the posterior mean values
  - Simplifying assumption: effect modifiers have same form for all sites
  - Implies that only level of the risk (ERR) varies by site

Adjusted Site-Specific Risk Estimates A Simple/Simplistic Example



MLE's shown as red dots
vertical lines extend to posterior mean estimate

- **Unadjusted estimates range from 0.06 to 1.6**
- **Adjusted estimates range from 0.2 to 0.5**
- **Considerable reductions for largest risk estimates**
- **Suggests that statistical uncertainties are relatively large**
- **More realistic approach would allow nature of effect modification to vary across sites**
  - Complicates calculations and summarization

Other major RERF findings

- **Cardiovascular disease**
  - Dose response seen for heart dose and stroke at doses less than 1 Gy
  - Excess cases much larger than for leukemia but somewhat less than solid cancers
- **In-utero exposure**
  - Radiation effects on school performance and on growth and development
  - Increased solid cancer risks after childhood – effect seems to be smaller than that seen in those exposed as children
  - Little indication of childhood cancer effects, but power is low
- **Children of survivors**
  - No evidence of radiation effects major malformations, birth weight, or sex ratio
  - No indication of effects on cancer or non-cancer disease risks

Summary and Conclusions

- **Accumulating data and modern analytical methods make it possible to investigate radiation effect modification in some detail**
- **Data are limited even in the largest cohort**
  - Especially true when modeling interactions
- **Both ERR and EAR descriptions provide equally important and complementary information**
  - Attained age is an important factor in both
  - Generalization of age at exposure and sex effects can be difficult
- **Pooled analyses may be useful in looking at effect modification**
- **More work is needed to address issues related to the interpretation of site-specific risks**

Acknowledgments

- **We stand on the shoulders of giants**

  Gil Beebe, Seymour Jablon, Jim Neel, Jack Schull

- **ABCC/RERF scientists and staff who made the ideas a reality**

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- **Collaborators**
  - Old

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  - New

    Kyoji Furukawa, Eric Grant, Hiromi Sugiyama, Ritsuko Sakata, Kotaro Ozasa

Questions and Answers

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