Atomic Bomb Survivor Studies
History, Dosimetry, Risk Estimation

Radiation Epidemiology Course 2007

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Radiation Epidemiology Branch

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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 (smoothing) risk patterns
     - Relative risk and excess rate models
     - Dose response
     - Effect modification
   - Issues
     - Time-since-exposure vs attained age
     - Latent periods
     - Interpreting effect modifiers

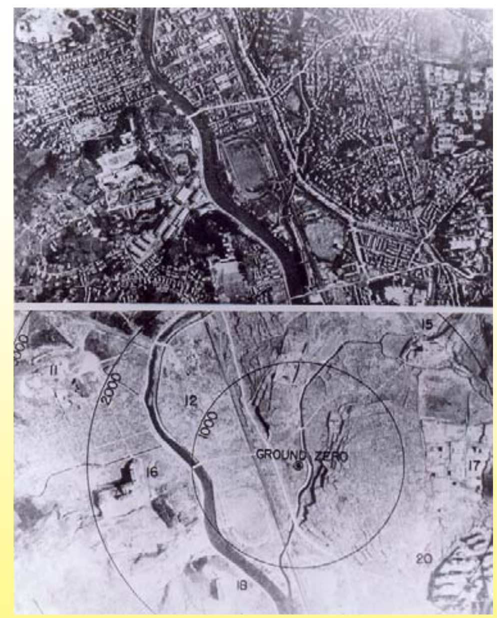
Nature of the bombs


- Hiroshima (Little boy)
  - Unique U^{235} gun-type device
  - 16kt yield
  - Height of burst 600m
  - Hypocenter near city center

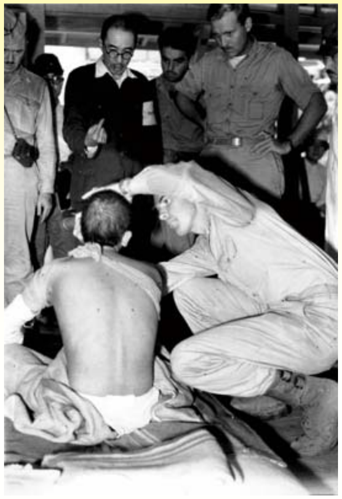

- Nagasaki (Fat man)
  - Plutonium implosion device
  - 21 kt yield
  - Height of burst 503m
  - Hypocenter in Urakami valley a residential / industrial area near Nagasaki University about 1.5km north of city center

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 in areas near hypocenter decimated
  - Hiroshima 110,000 -140,000 deaths
  - Nagasaki 70,000 deaths
  - > 60% mortality within 1km of hypocenter

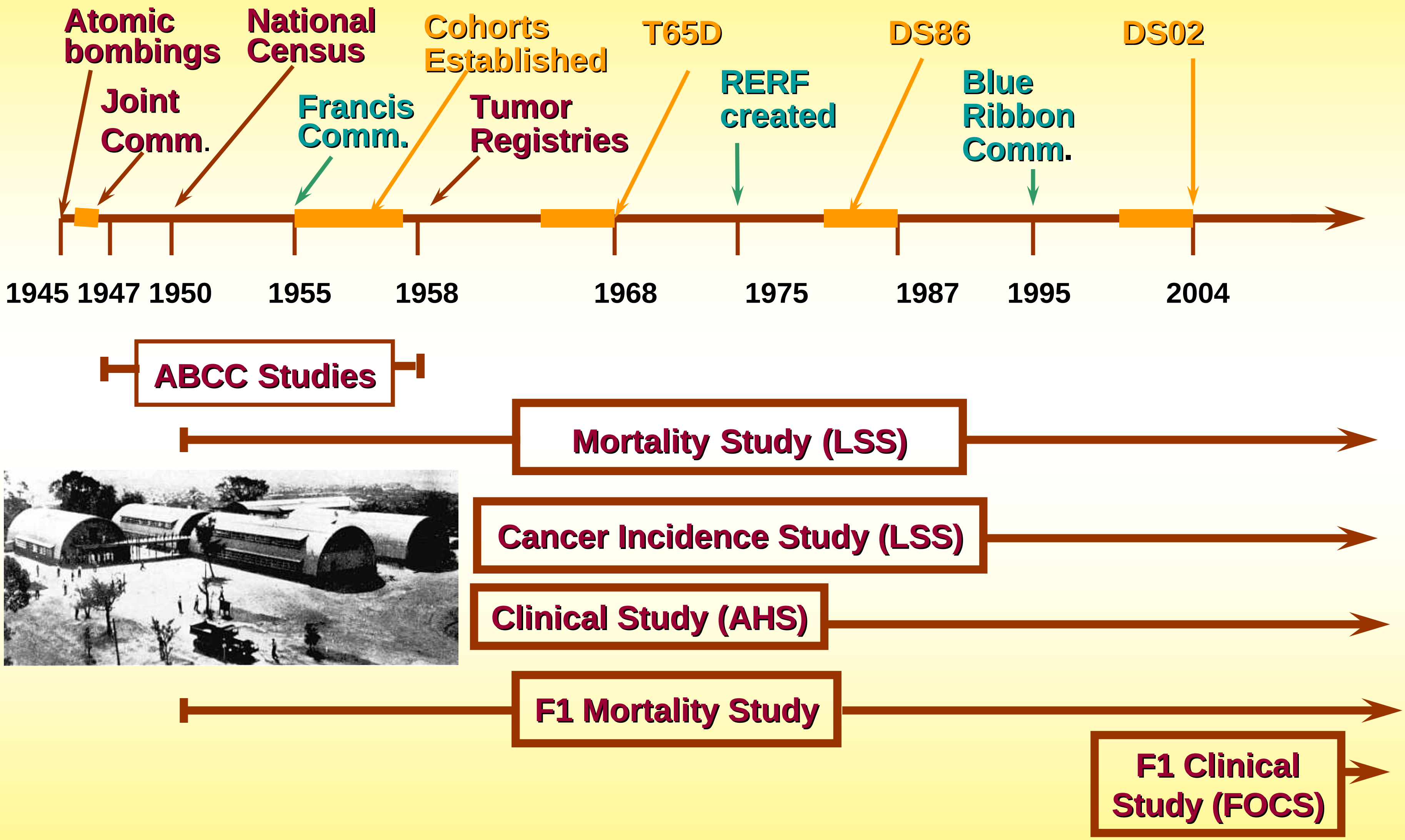


Health Effects Research 1945 - 1946



- Japanese research groups
  – Entered cities within days of bombings
  – Carried out various 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

A-bomb Survivor Studies



Health Effects Research 1947-1955
The Atomic Bomb Casualty Commission (ABCC)

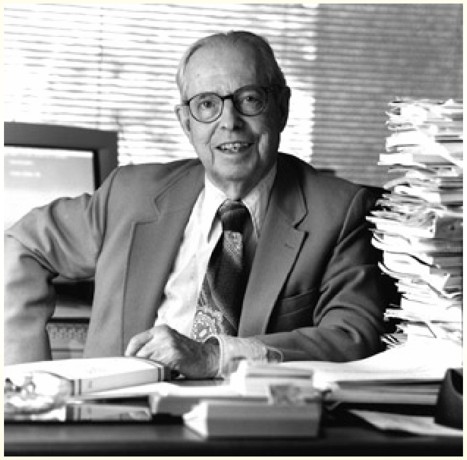
- President Truman authorizes NAS to create and manage ABCC
  - "…undertake a long range, continuing study of the biological and medical effects of the atomic bomb on man."
- Jim Neel, Jack Schull and others develop and implement genetic-effects studies
  - Multiple outcomes
    - Major malformations, premature birth, low birth weight, sex-ratio
  - 72,000 registered pregnancies 1948 -1953
  - Midwife reports, at-birth exams, nine-month exams
  - Results appeared in 1956
    - No apparent effects of radiation exposure (defined by distance and acute effects) on any outcome considered

Health Effects Research 1947-1955
The Atomic Bomb Casualty Commission (ABCC)

- Leukemia
  - Japanese physicians noticed increase in childhood leukemia cases in late 1940's
  - First published report in 1952
    - Descriptive analyses
    - Ill-defined population
    - No real risk estimates
- 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

Health Effects Research 1947-1955
The Atomic Bomb Casualty Commission (ABCC)

- Gil Beebe and NAS
  - Developed ideas for cohort-based studies of cancer and other outcomes
    - Paralleled ideas on development do WWII vets follow-up study (Medical Follow-up Agency)
  - Developed ties to Yale and UCLA for recruitment of scientific staff



- Calls for end to ABCC studies
  - Major genetic studies were completed with no compelling evidence of hereditary effects
  - Leukemia excess risk appeared to be declining
  - Studies being carried out in ad-hoc manner
  - Costs for program rising
  - Staff morale low

Francis Committee

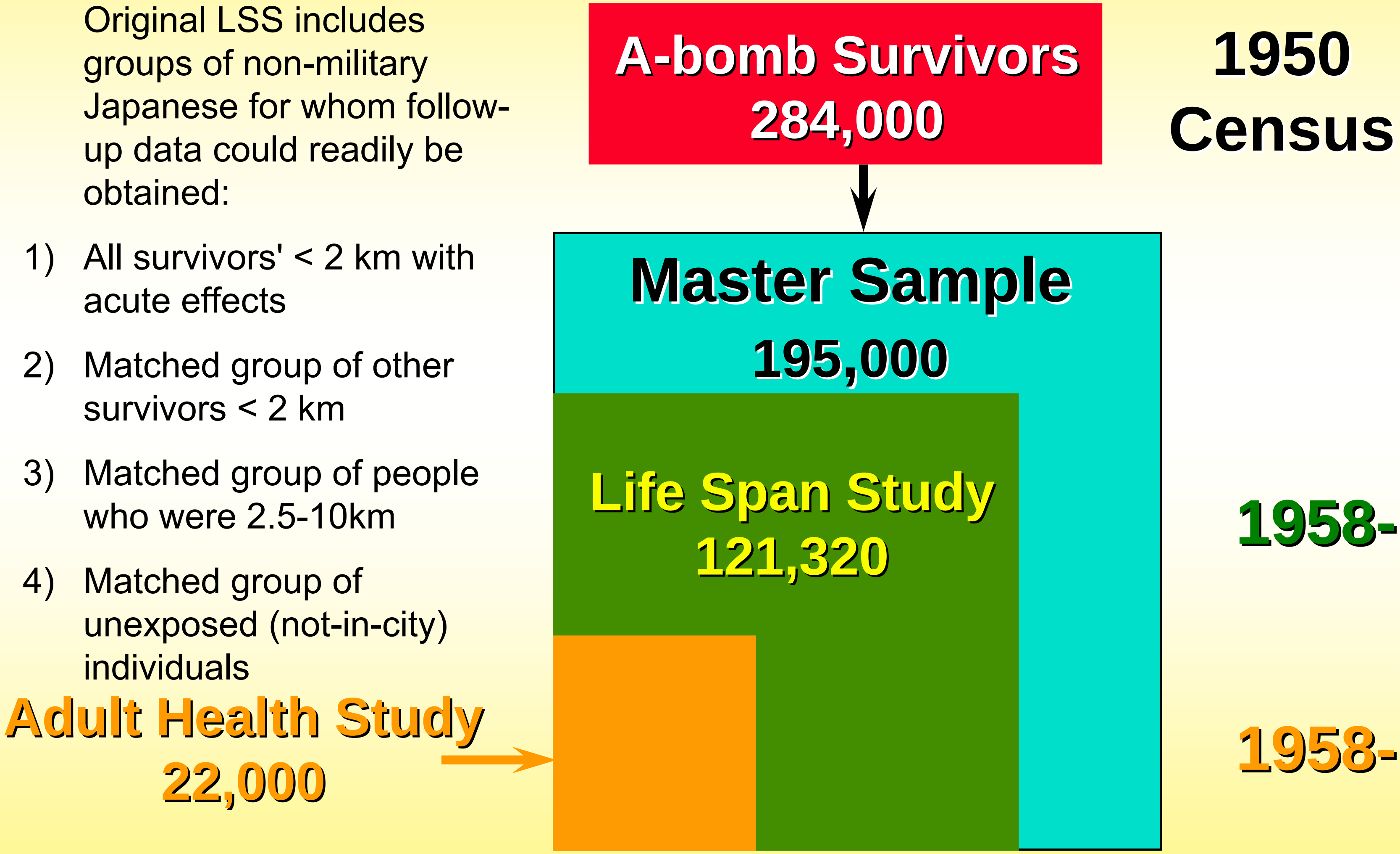
(Thomas Francis, Felix Moore, Seymour Jablon)

- NAS-organized committee to assess what should be done about ABCC research
- Recommendations
  - Reorganized program should continue
  - Unified study plan
    - Focus on fixed cohorts of survivors and their children with internal comparison groups
    - Mortality follow-up
    - Pathology (autopsy) program
    - Clinical studies
    - Highlighted need for dose estimates

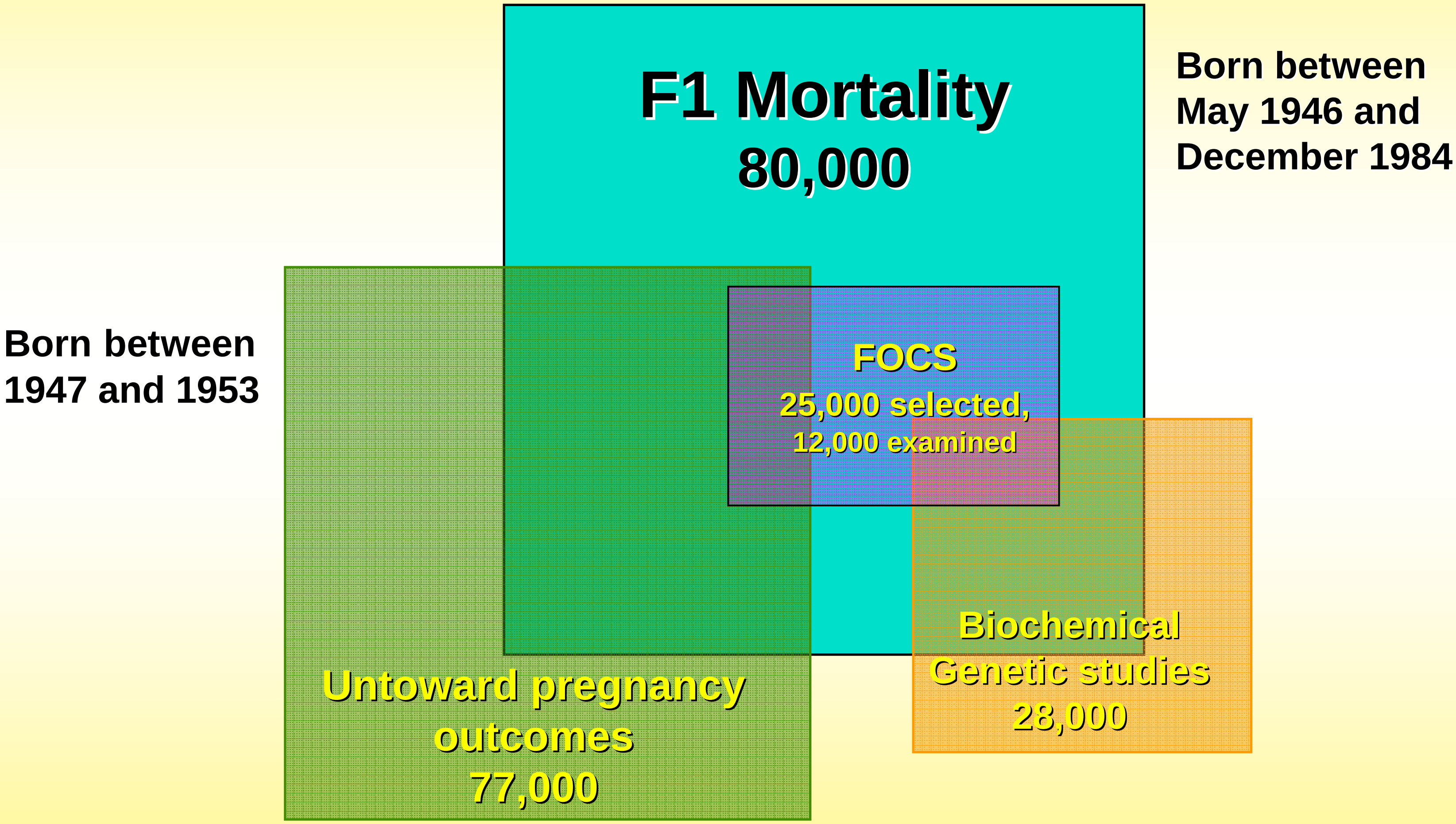
ABCC/RERF Cohorts
Life Span Study (LSS)

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 IU cohort
3,638 people

- 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, 200?

ABCC Research 1958 - 1975

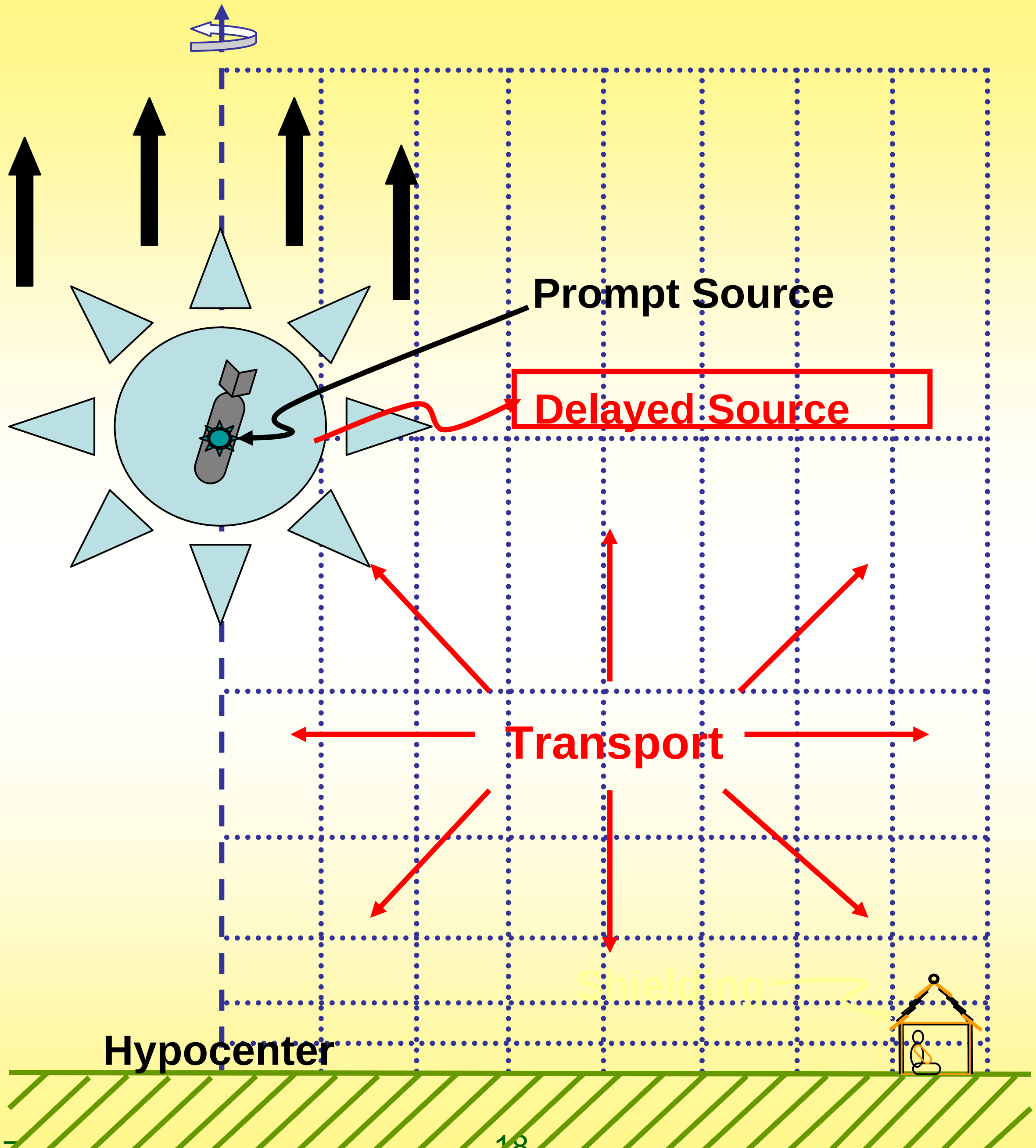
- Dosimetry (Auxier, Kerr, Fujita)
  - Development of location and shielding information
  - Introduction of first broadly accepted dosimetry system (T65D)
- Periodic LSS cancer mortality reports (Land, Beebe, Jablon, Kato)
  - Methodological developments & risk estimation
- Clinical studies
  - Cardiovascular 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

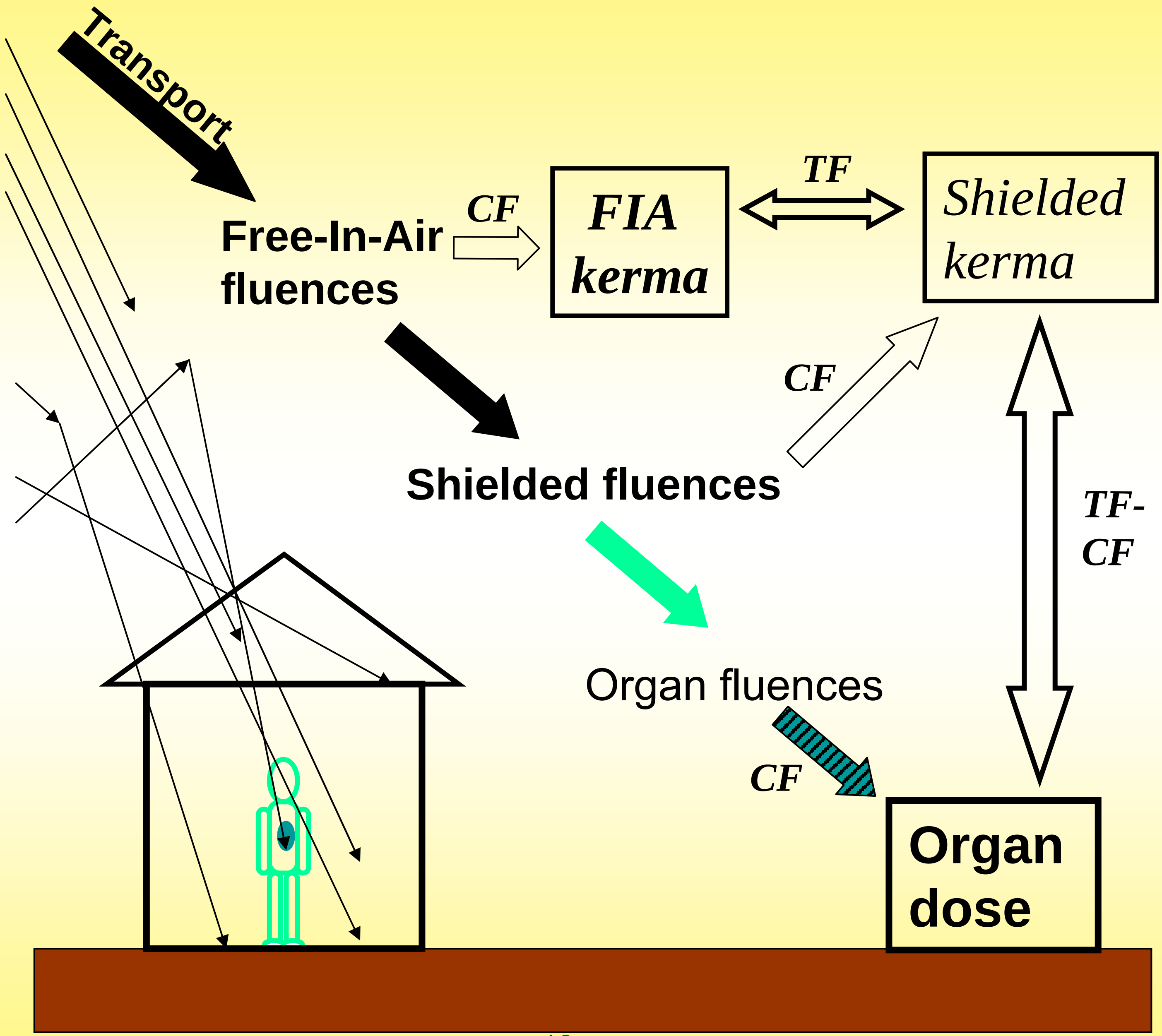
RERF Research 1975-1995

- 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
- Emerging evidence of non-cancer mortality risks
- Analyses of clinical data
  - Noncancer disease morbidity
  - Longitudinal laboratory measurements (blood pressure, cholesterol, inflammatory markers)
  - Cataracts


Prompt Source
Delayed Source
Transport
Hypocenter

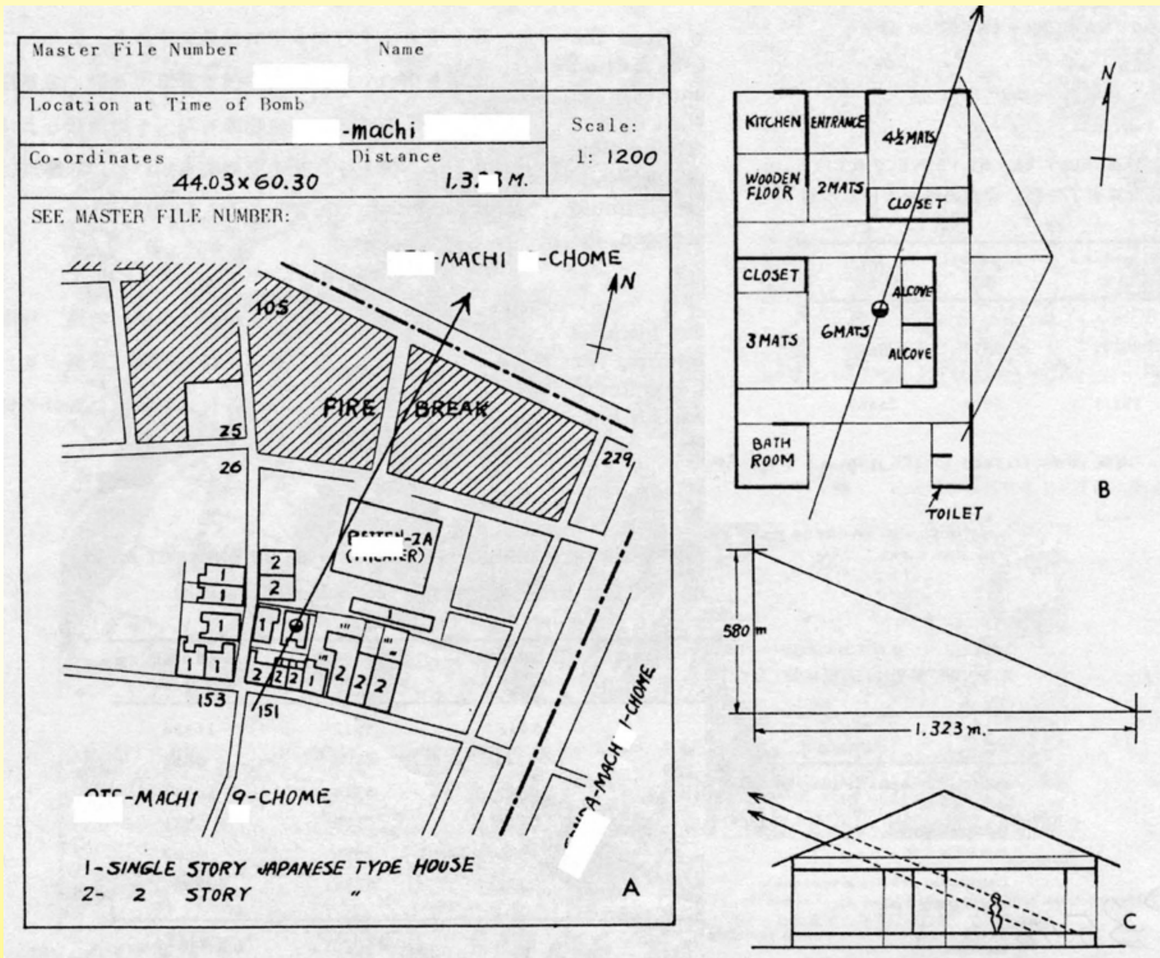


Courtesy of
H. Cullings

Dosimetry

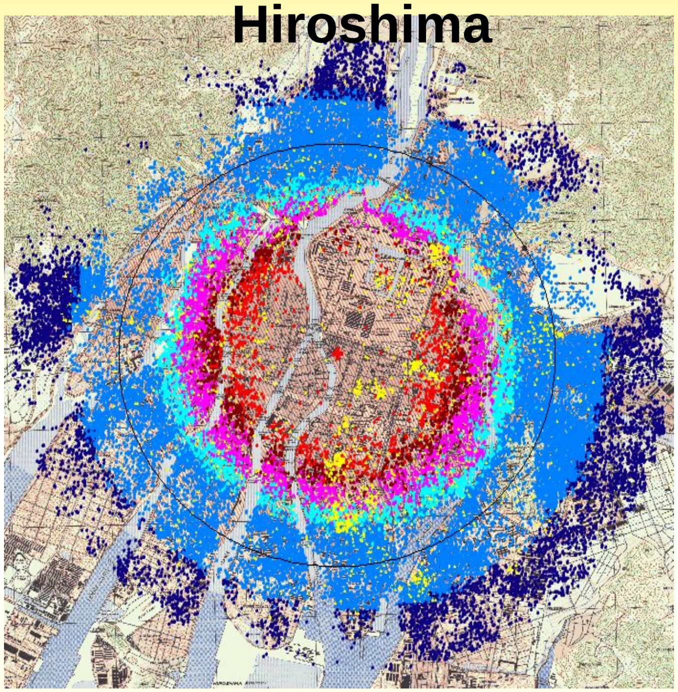
- Location
  - Specified as coordinates on fairly crude US army maps
    - Sought corroboration of location
    - Recorded to nearest 10m in each coordinate if detailed shielding history obtained and nearest 100m for others
- External Shielding
  - Crude shielding category information available on virtually all people of interest
  - Detailed shielding histories for most survivors within 1.6km in Hiroshima and 2 km in Nagasaki
- Self shielding (organ dose)
  - Available for survivors with detailed shielding histories

Sample Shielding History

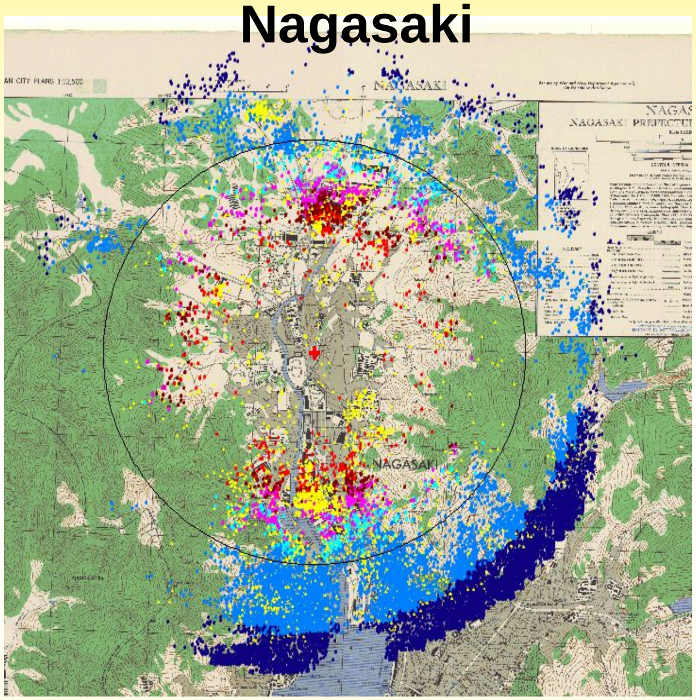


LSS Survivors within 3 Km

Hiroshima



Nagasaki



✚ **Hypocenter**

Dose (mSv)

• **< 5**	• **5 – 100**	• **100 – 200**	• **200 - 500**
• **500 – 1000**	• **1000 +**	▲ **unknown**	

*** LSS: Life Span Study Cohort**

Dosimetry History

- Early analyses based on categories defined by 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

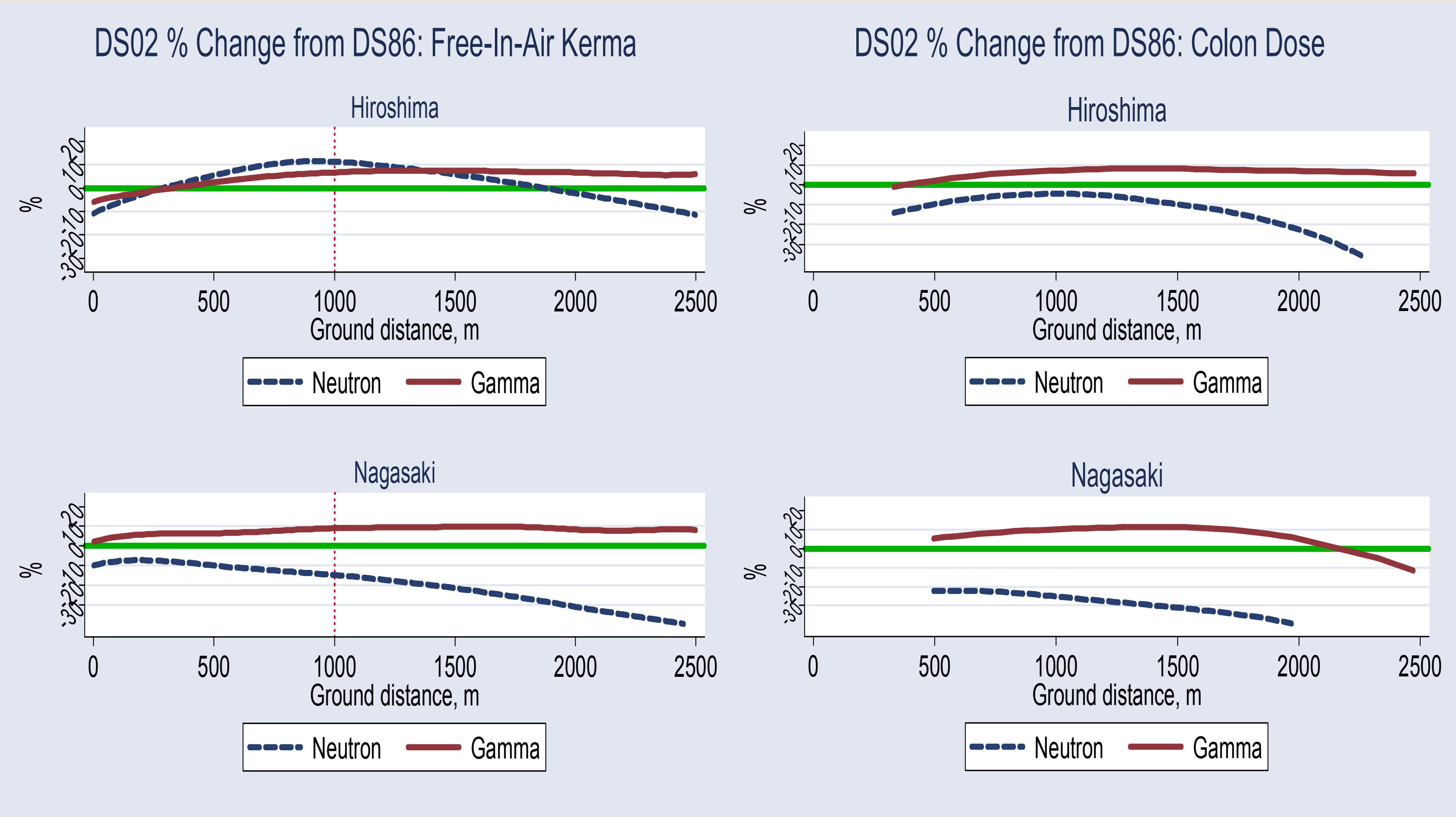
Dosimetry History

- DS86
  - 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
  - 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

DS02 – DS86 Comparison

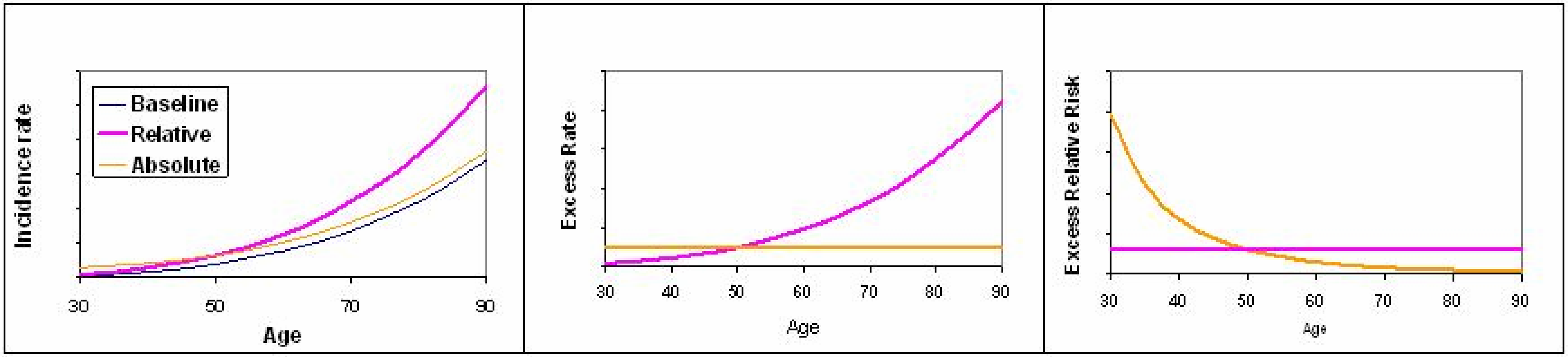


Dose Uncertainty

- Uncertainty in survivor dose estimates recognized from the beginning, but
- Until recently little effort to allow for or assess impact of uncertainty on risk estimates
- Types of uncertainty
  - Shared errors – yield, shielding parameters etc.
  - Grouping (Berkson) errors
  - Error in individual location / shielding information (classical error)
- Currently doses are corrected for 35% random errors using a regression calibration method in which D_{est} is replaced by $E(D_{true}| D_{est})$
- Can expect further advances in next few years
  - More use of biodosimetry data
  - Explicit consideration of Berkson, classical, and shared error effects

The Old Debate
Relative versus Absolute Risks

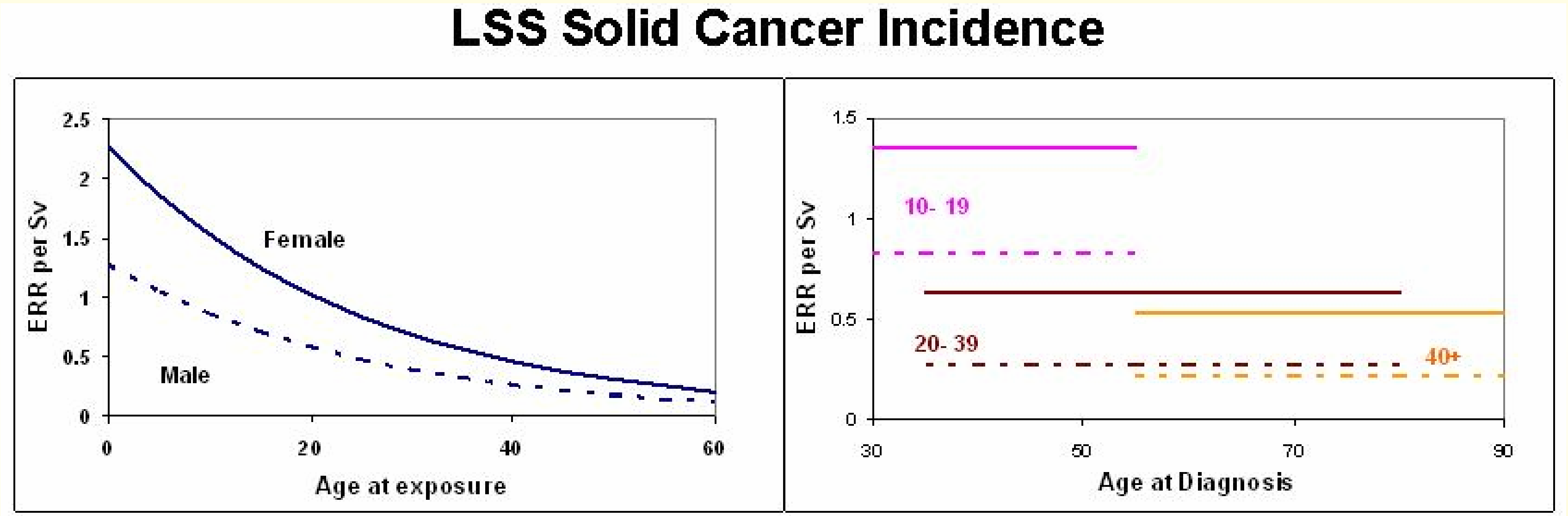
- Do excess risks increase or become relatively less important as time goes by?



- By early 1980’s it was agreed that relative risk provided a better description
- Time-constant (excess) relative risk became standard risk summary

Evolving Understandings
Excess Risk is Not a Number

- (Relative) risk depends on gender and age at exposure



- Are excess relative risks constant in attained age (time) given age at exposure and sex?
- How should we interpret gender 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* gender; 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 gender and birth cohort effects in baseline rates
- Description may be simpler or more informative on one scale than the other

Describing Gender 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 *(when there is enough 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 Gender and Age-Time Effects

- 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

LSS Solid Cancer Incidence 1958-94

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

- Information on gender 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

LSS Leukemia Mortality 1950-2000

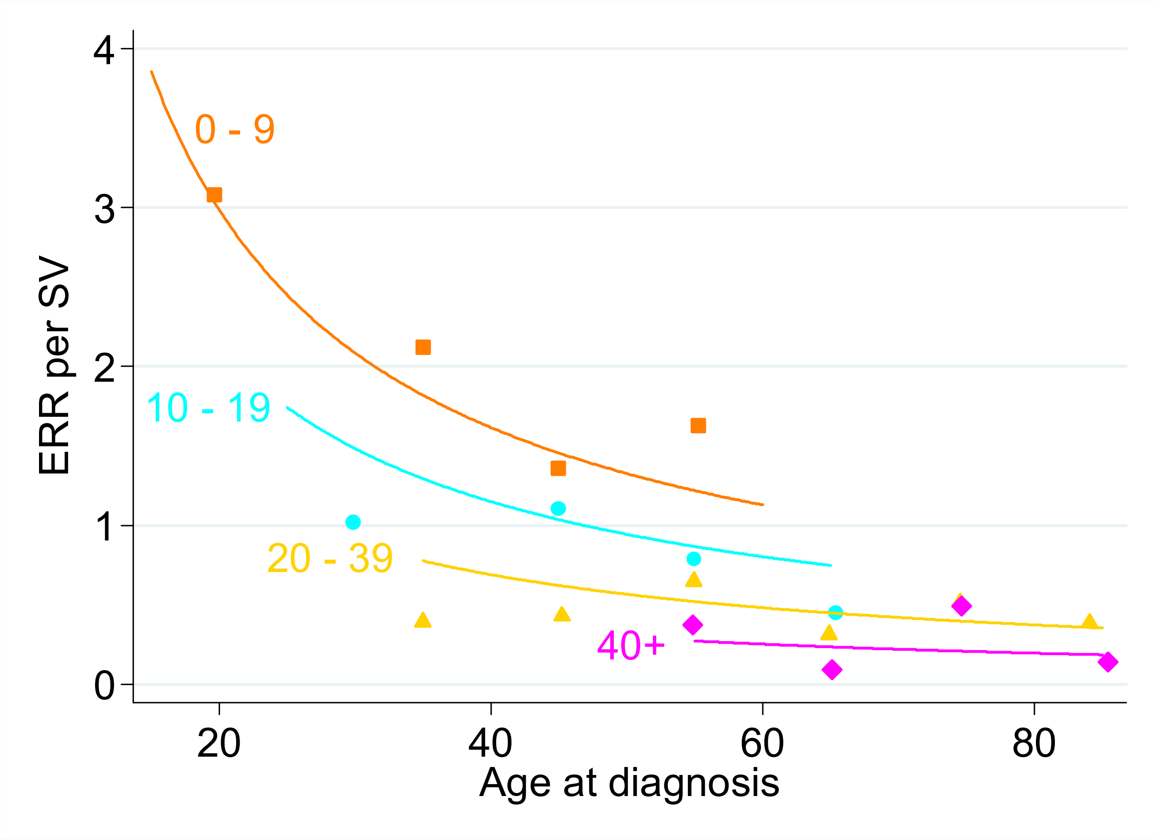
By age at exposure					
Age at exposure	People	Person years	Cases	Estimated Excess	AR%*
		Male			
0-19	16,827	783,098	60	26	58%
20-39	6,411	229,330	49	12	42%
40+	12,449	227,441	47	13	41%
Total	*35,687*	*1,239,869*	*156*	*52*	48%
		Female			
0-19	18,569	891,288	42	16	51%
20-39	16,750	702,633	57	17	41%
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

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

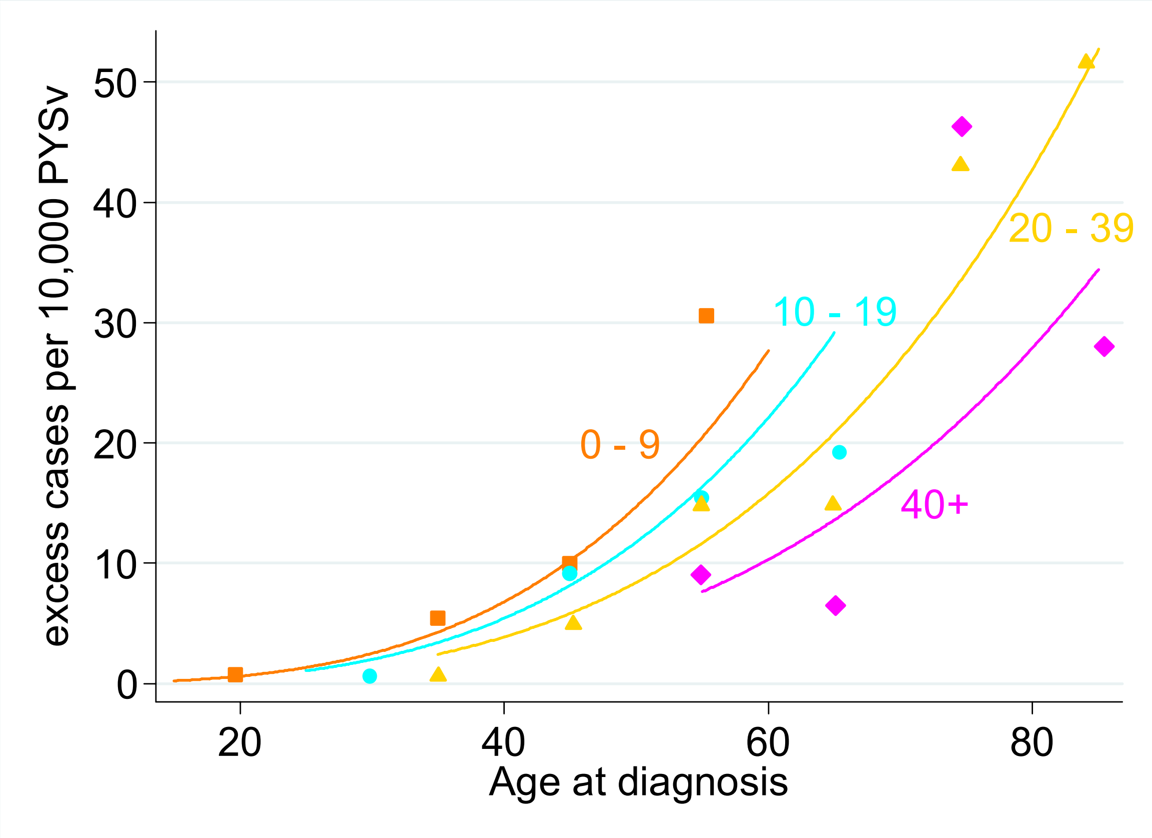
LSS Solid Cancer Mortality 1950 – 2000
Excess Relative Risk Temporal Patterns



Age at exposure
-29% per decade *(90% CI -39%; -18%)*
Attained age
$Age^{-0.9}$ *(90% CI -1.5; -0.2)*
Gender *
M: 0.29 *(90% CI 0.21; 0.39)* F: 0.58 *(90% CI 0.42; 0.68)* F:M: 1.9 *(90% CI 1.4; 2.7)*

* ERR per Sv at age 70 following exposure at age 30

LSS Solid Cancer Mortality 1950 – 2000
Excess Rate Temporal Patterns



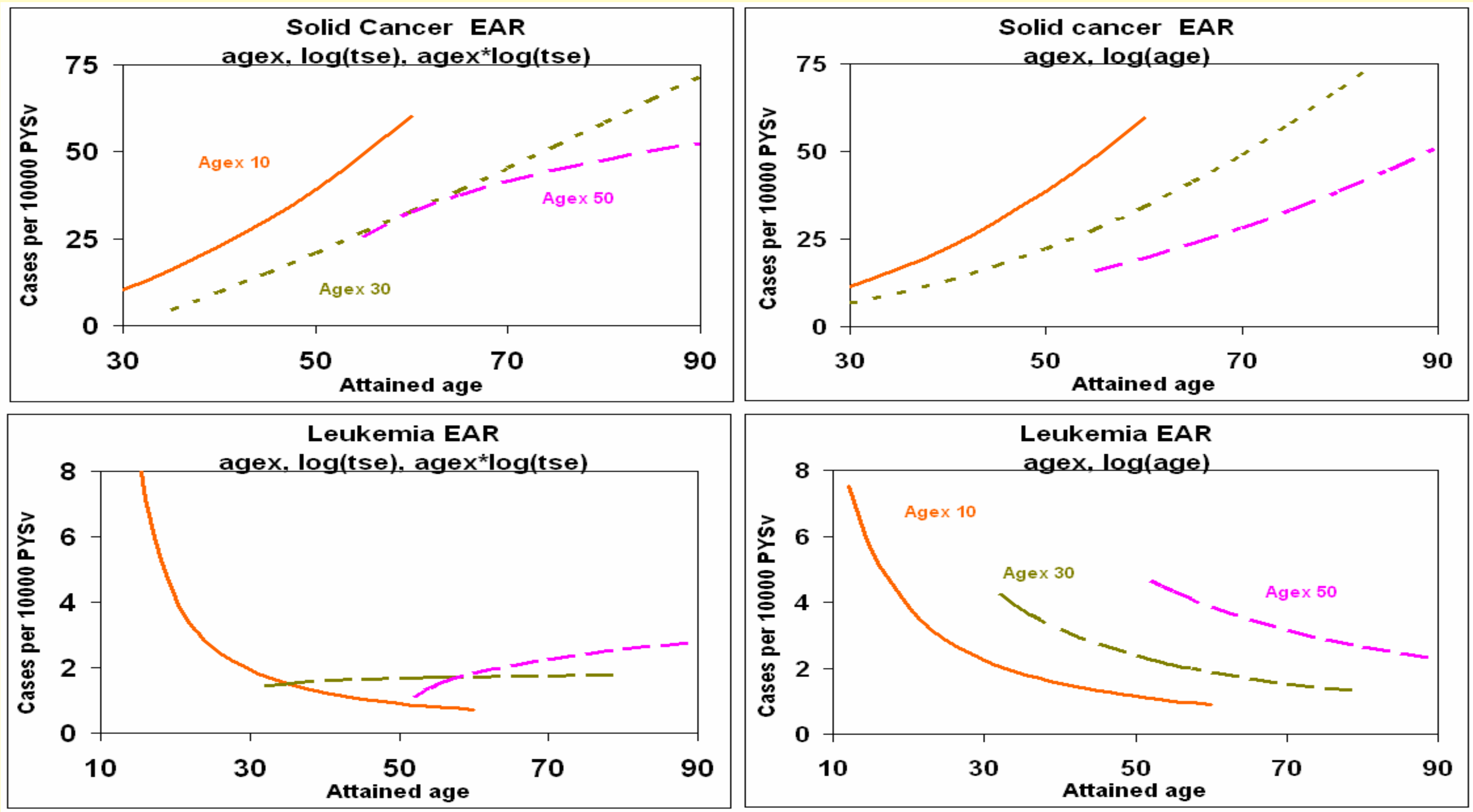
Age at exposure		
-20% per decade		
(90% CI -30%; -10%)		
Attained age		
$Age^{3.5}$		
(90% CI 2.9; 4.1)		
Gender *		
M:	26	*(90% CI 18; 34)*
F:	28	*(90% CI 23; 34)*
F:M:	1.1	*(90% CI 0.8; 1.6)*

* Excess cases per 10000 PY at age 70 following exposure at age 30

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
  - TSE models involve significant agex-by-TSE interaction
  - Attained age models provide comparable fit without need for interaction

Comparison of Time-Since-Exposure and Attained-Age Fits



Related Issues
Time-Constant ERR models

- LSS data clearly suggest that the ERR varies with attained age (time since exposure)
- It is difficult to conceive of a radiation carcinogenesis mechanism that would lead to time-constant increases in the ERR

Related Issues
Latency

- Concept of limited usefulness
  - Definition is vague
  - Dose response implies reductions in the expected time from exposure to tumor
  - Minimum latency period is at least time from the final conversion into a malignant cell until diagnosis or death but could be longer
    - Mayak and early a-bomb survivor data indicate that radiation-associated leukemia deaths can occur within two to three years of exposure
    - LSS solid mortality data provide some suggestion of elevated risk 5 to 10 years after exposure for older cohort members
- Better to simply describe age-time patterns

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
- 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 gender effects can be difficult
- Pooled analyses may be useful in looking at effect modification

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

  George Darling, Howard Hamilton, Tetsuo Imada, Hiroo Kato, M. Kanemitsu, Bob Miller, Kenji Omae, Itsuzo Shigematsu and hundreds more
- Collaborators

  Akio Awa, Harry Cullings, Saeko Fujiwara, Shochiro Fujita, Sachiyo Funamoto, Kazunori Kodama, Charles Land, Kiyo Mabuchi, Nori Nakamura, Don Pierce, Elaine Ron, Yukiko Shimizu, Michiko Yamada

Related Issues
Interpreting Site-Specific Risks

- Difficult to interpret and generalize effect modification
  - ERR gender effects mirror baseline gender 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, gender effects and age-time patterns