

Atomic Bomb Survivor Studies History, Dosimetry, Risk Estimation

Radiation Epidemiology Course 2007
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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

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Nature of the bombs

- **Hiroshima (Little boy)**
 - Unique U²³⁵ 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

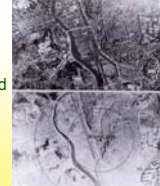


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Short-term effects

- **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



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Health Effects Research 1945 - 1946

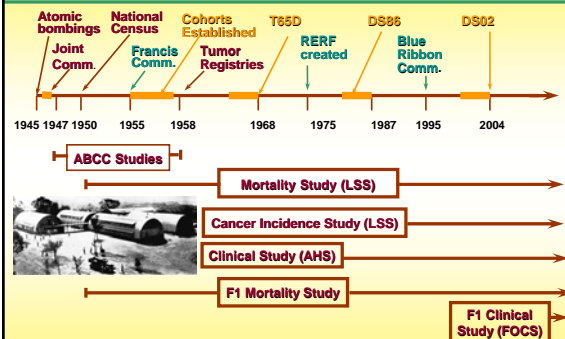
- **Japanese research groups**
 - Entered cities within days of bombings
 - Carried out various surveys of injuries and deaths
- **US research groups**
 - Medical teams began arriving in September 1945
 - Efforts directed at cataloging acute radiation effects
- **US - Japan Joint Commission**
 - Characterize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



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A-bomb Survivor Studies



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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



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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

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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



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Francis Committee (Thomas Francis, Felix Moore, Seymour Jablon)

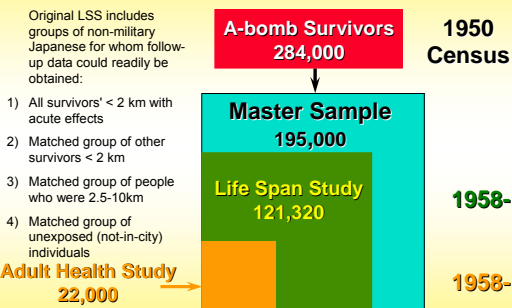
- NAS-organized committee to assess what should be done about ABCC research
- Recommendations
 - Reorganized program should continue
 - Unified study plan
 - Focus on fixed cohorts of survivors and their children with internal comparison groups
 - Mortality follow-up
 - Pathology (autopsy) program
 -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



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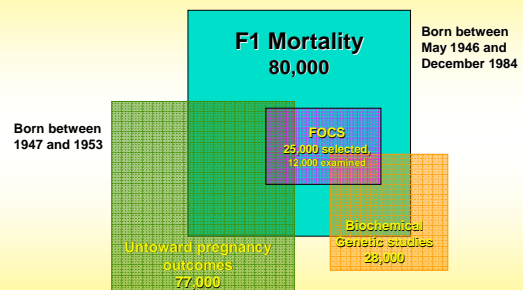
ABCC/RERF Cohorts Life Span Study (LSS)



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ABCC/RERF - F1 study cohorts



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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.

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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, 2007

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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)
 - Chromosomes
- In-utero
 - Physical growth and development
 - IQ
 - Mortality
- F1
 - Leukemia incidence
 - General mortality



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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

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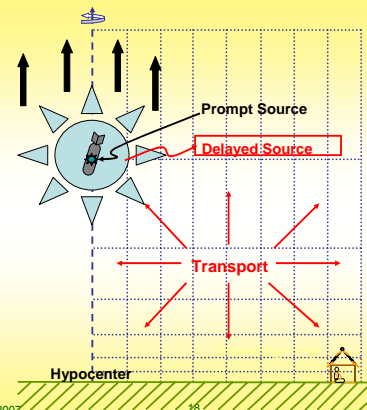
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RERF Research 1995 - present

- 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

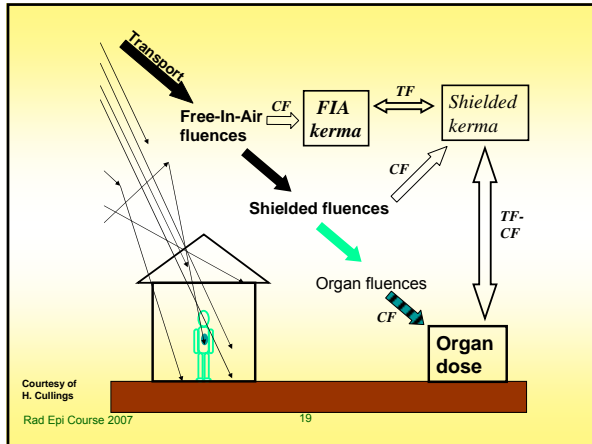
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Dosimetry



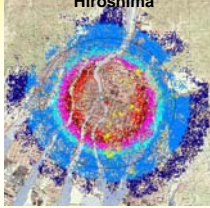
- **Location**
 - Specified as coordinates on fairly crude US army maps
 - Sought corroboration of location
 - Recorded to nearest 10m in each coordinate if detailed shielding history obtained and nearest 100m for others
- **External Shielding**
 - Crude shielding category information available on virtually 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

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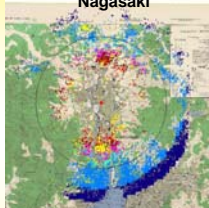
Sample Shielding History

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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

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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

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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

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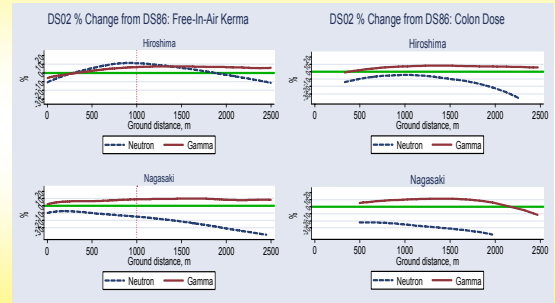
Dosimetry History

- 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

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DS02 – DS86 Comparison



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Dose Uncertainty

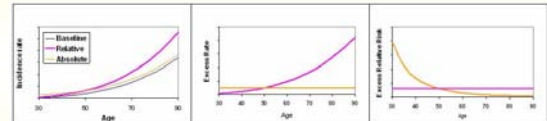
- Uncertainty in survivor dose estimates recognized from the beginning, but
- Until recently little effort to allow for or assess impact of uncertainty on risk estimates
- Types of uncertainty
 - Shared errors – yield, shielding parameters etc.
 - Grouping (Berkson) errors
 - Error in individual location / 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

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The Old Debate Relative versus Absolute Risks

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



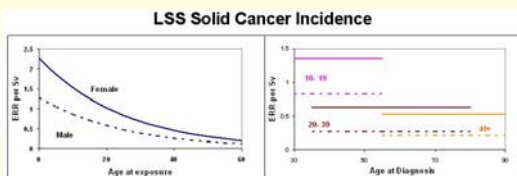
- By early 1980's it was agreed that relative risk provided a better description
- Time-constant (excess) relative risk became standard risk summary

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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?

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Evolving Understandings Describing Excess Risks

Excess relative risk (ERR) model

$$\lambda_0(a, s, b) [1 + \rho(d) \varepsilon_R(s, e, a)]$$

Excess absolute rate (EAR) model

$$\lambda_0(a, s, b) + \rho(d) \varepsilon_A(s, e, a)$$

$\lambda_0(a, s, b)$ 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

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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

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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
 - REF analyses generally based on log-linear descriptions (when there is enough data)

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

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

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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

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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	652,341	2,458	150	13%
20-39	8,522	229,518	2,569	86	8%
40+	12,839	178,419	2,991	81	5%
Total	42,932	1,060,278	7,959	237	5%
Female					
0-19	24,169	755,387	2,198	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	2,784,731	17,448	853	11%
By colon dose					
Colon Dose	People	Person years	Cases	Estimated Excess	AR%
< 0.005	60,792	1,588,944	9,597	3	0%
-0.1	27,789	729,603	4,406	81	2%
-0.2	5,527	145,905	968	79	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+	584	13,711	185	111	80%
Total	105,427	2,784,732	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

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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	38,502	1,342,168	89	0	0%
-0.1	30,898	1,135,582	69	4	6%
-0.2	6,006	223,701	17	4	24%
-0.5	6,953	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%*

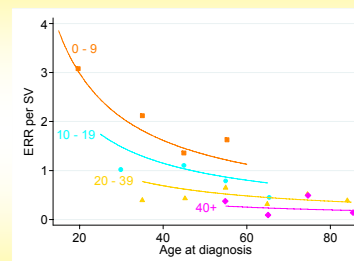
* Attributable risk % among survivors with marrow dose > 0.005 Gy

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- 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)

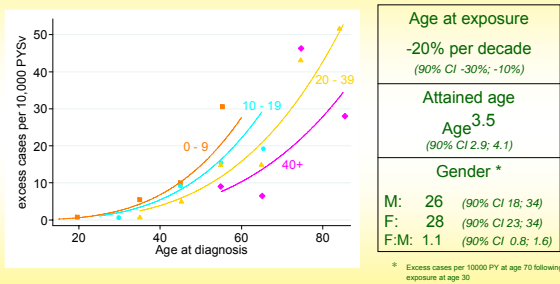
Gender*
M: 0.29 (90% CI 0.21; 0.39)
F: 0.58 (90% CI 0.42; 0.68)
F:M: 1.9 (90% CI 1.4; 2.7)

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

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LSS Solid Cancer Mortality 1950 – 2000 Excess Rate Temporal Patterns



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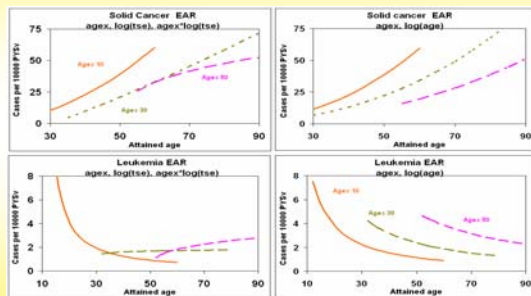
Related Issues Time-Since-Exposure

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

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



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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

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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

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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

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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

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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

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