Atomic Bomb Survivor Studies: Overview and Recent Findings

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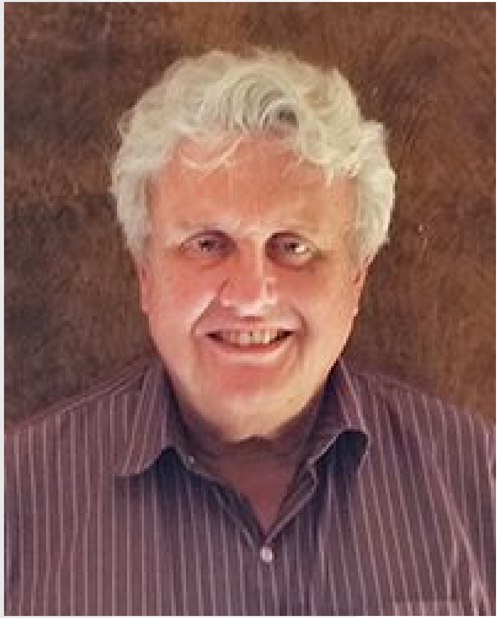


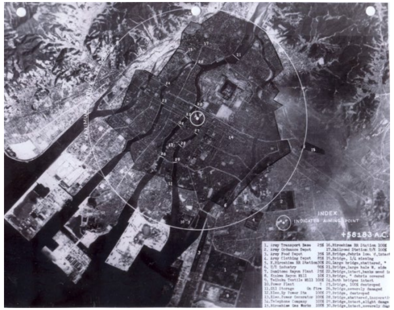
DCEG Radiation Epidemiology & Dosimetry Course 2019

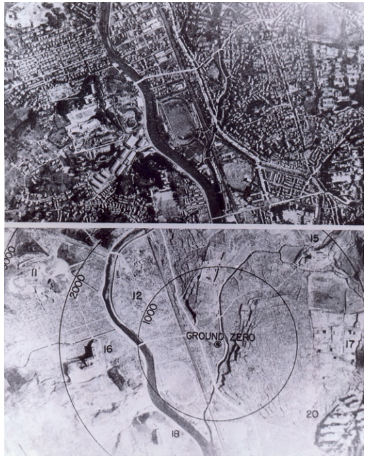
Outline

1. **ABCC/RERF background**
   - Immediate effects of the bombs
   - Early studies
   - Major cohorts
2. **Evolving studies**
   - Research programs
   - Dosimetry
3. **Some Current Findings**
   - Solid Cancer Incidence
   - Hematopoietic malignancies

Short-term effects

- **Result of**
  - Blast (50% of energy)
  - Heat (35% of energy)
    - Scorched wood up to 3.5km
  - Radiation (15% of energy)
    - Acute exposures (several seconds)
    - Virtually no residual radiation
- **Cities largely destroyed**
  - Wooden structures burned up to ~2.5km from hypocenter
  - Blast effects apparent over similar distance range



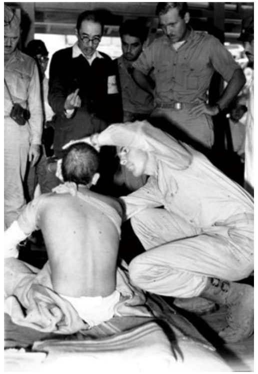


Short Term Effects (2)

- **Populations decimated**
  - Hiroshima 110,000 -140,000 deaths (30-40% of population)
  - Nagasaki 70,000 deaths (30% of population)
  - > 60% mortality within 1km of hypocenter

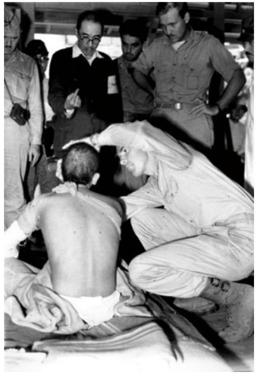
Health Effects Research 1945 - 1946

- **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



Health Effects Research 1945 - 1946

- **US – Japan Joint Commission**
  - Characterize extent of early mortality
  - Nature of acute effects
    - Nausea – Orapharyngeal lesions
    - Epilation – Leukopenia
    - Flash burns
    - Bleeding



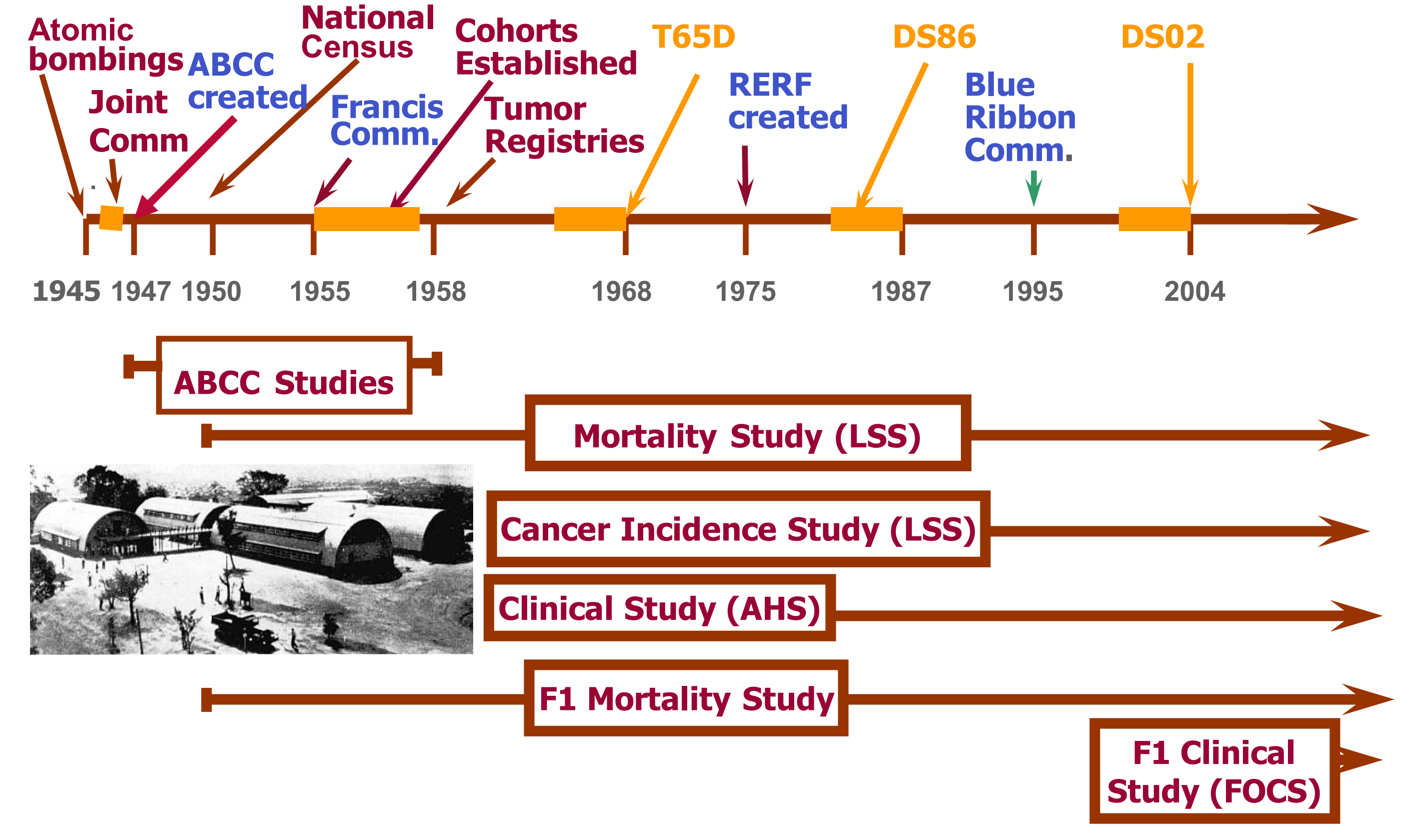
ABCC Activities (1)
1947-1955

- **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
  - Need for individual dose estimates
    - Systematic program for collection of exposure data

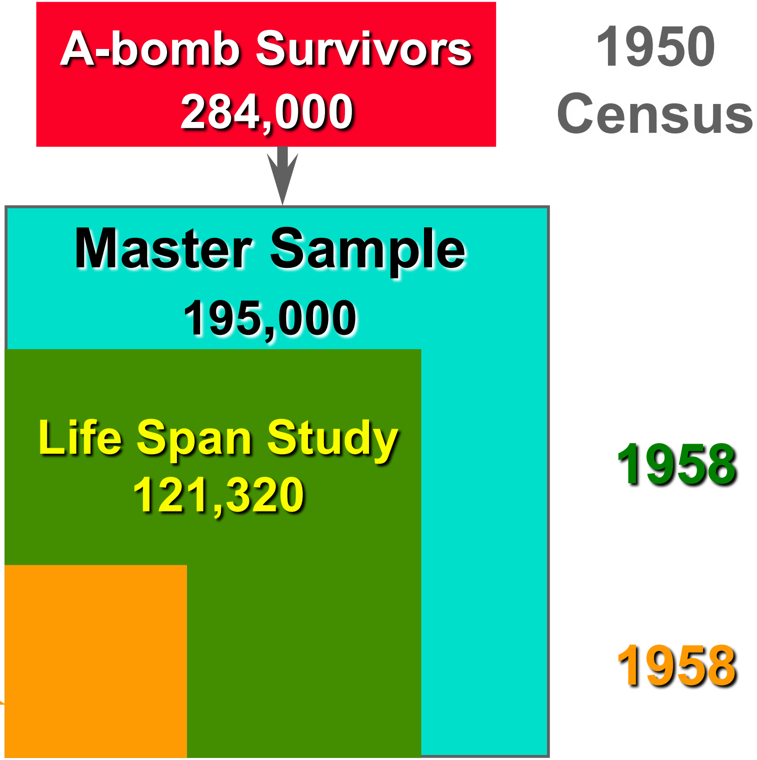
A-bomb Survivor Studies



ABCC/RERF Cohorts
Life Span Study (LSS)

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

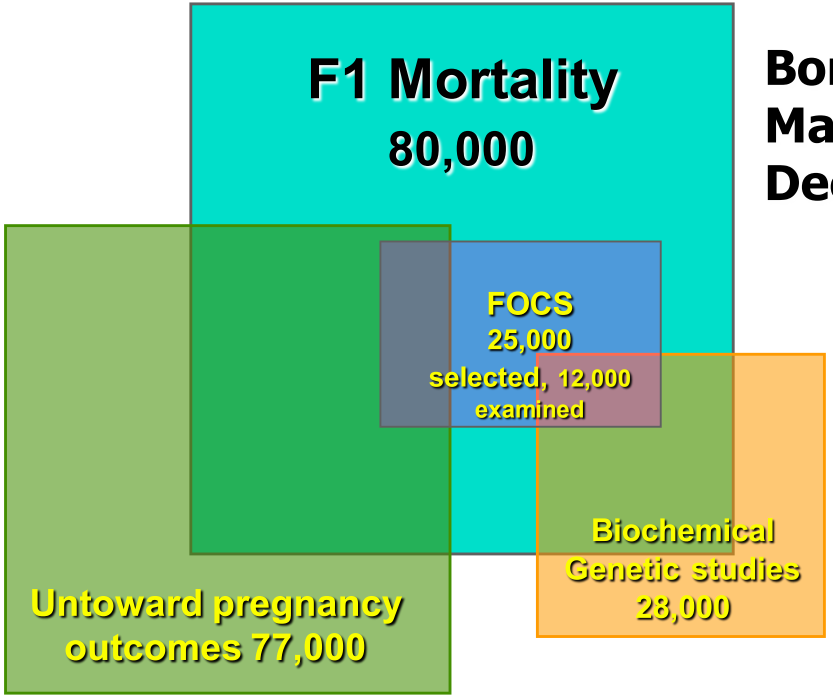
1) All survivors < 2 km with acute effects
2) Matched group of other survivors < 2 km
3) Matched group of people who were 2.5-10km
4) Matched group of unexposed (not-in-city) individuals



ABCC/RERF - F1 study cohorts

Born between May 1946 and December 1984

Born between 1947 and 1953



ABCC-RERF cohorts
In-utero cohort

Pooled IU cohort
3,638 people

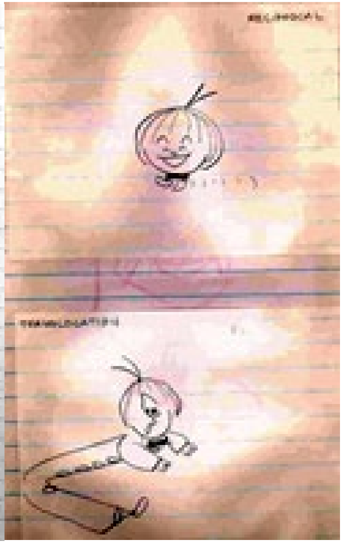
- Pooled cohort combines overlapping clinical (1,606 members) and mortality (2,802 members) cohorts.
- Mortality and cancer incidence data are available for all members of the cohort.

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, 2008

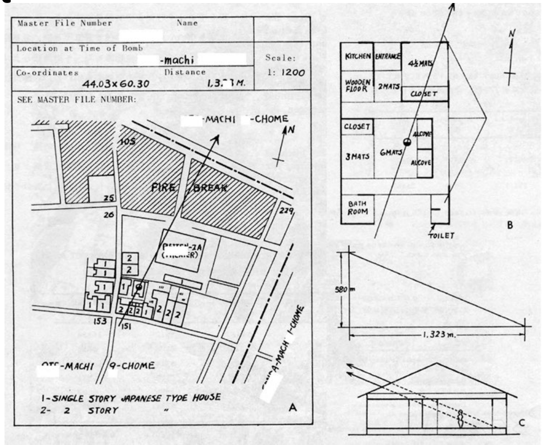
ABCC Research 1958 - 1975

- **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)**
  - Giemsa-staining and karyotyping
- **In-utero**
  - Physical growth and development
  - IQ
  - Mortality
- **F1**
  - Leukemia incidence and general mortality
  - Biochemical and molecular genetics



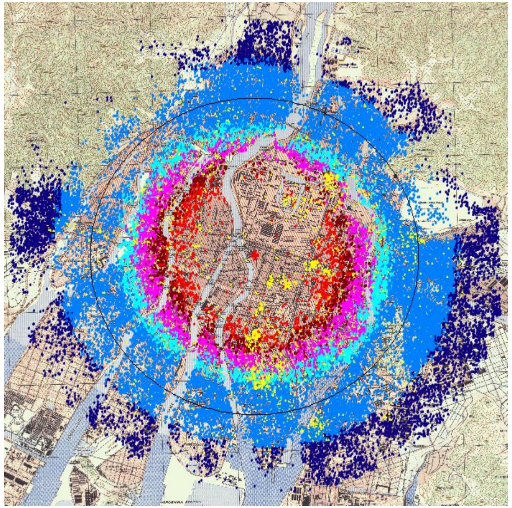
Dosimetry

- **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

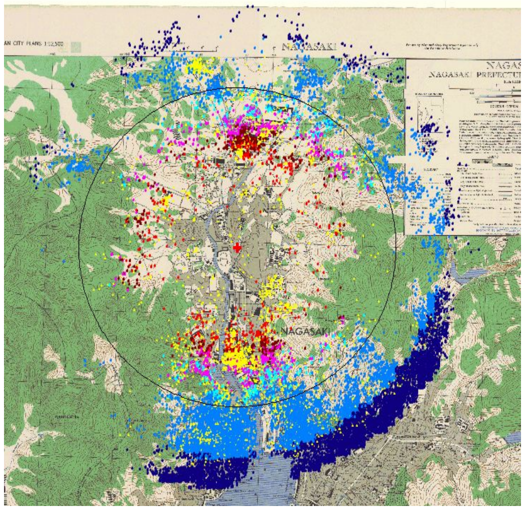


LSS Survivors within 3 Km

Hiroshima



Nagasaki



✚ Hypocenter

Dose (mSv)

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

* LSS: Life Span Study Cohort

Dosimetry History

- **Distance and acute effects**
- **Tentative 1957 Dosimetry (T57D)**
  - Declassified gamma and neutron "air dose" curves by city with 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 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
- **Recently updated with improved location and shielding data**

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
- **Doses corrected for 35% random errors using regression calibration: D_{est} replaced by $E(D_{true} \mid D_{est})$**

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

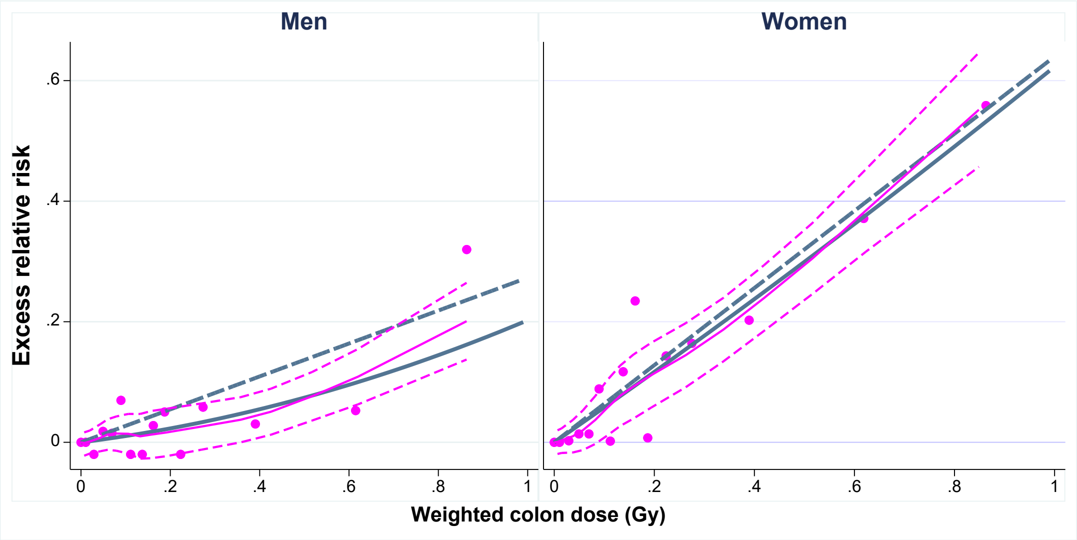
LSS Solid Cancer Incidence 1958-2009

(Grant et al, *Rad Res* 2017)

- 11 years of additional follow-up since last reports (Preston et al 2001)
- DS02R1 dose estimates
- Exclusion of autopsy-only cases
  - Limited in time 1958 - ~1962
  - Higher doses and older ages at exposure
- Adjustment for smoking and, for some sites, other risk factors
  - Little indication of confounding

- 22,538 solid cancer cases among 105,444 people with over 3 million years of follow-up
- 56% of cohort members are female
- 40% exposed before age 20
- 38% alive at the end of follow-up
  - 34% of males and 41% of females

LSS Solid Cancer Incidence: Dose Response



- Dose response differs by sex
  - Upward curving for men
  - Linear for women
- Not due to sex-specific or smoking related cases
- Sites with most impact on male curvature are :
  - Esophagus, non-melanoma skin, brain, bone/connective tissue, and thyroid (Cologne et al 2019)

LSS Solid Cancer: Excess Cases - Males

Colon Dose (Gy)	People	Person years	Cases	Excess cases		AF %	
				Radiation	Smoking	Radiation*	Smoking
Male							
< 0.005	25,062	666,525	6,012	0.5	1,710.3	--	40%
- 0.1	11,175	302,141	2,635	14.2	782.4	1%	42%
- 0.2	2,132	57,898	497	13.3	157.9	2%	43%
- 0.5	2,301	59,840	599	36.3	173.7	6%	44%
- 1	1,282	32,202	382	58.4	102.0	16%	48%
- 2	716	17,816	254	86.2	71.7	35%	64%
2+	242	5,778	94	57.6	29.8	55%	92%
Male Total	**42,910**	**1,142,200**	**10,473**	**266.4**	**3,027.8**	**6%**	**42%**
M+F Total	***105,444***	***3,079,484***	***22,538***	***991.9***	***3,359.5***	***10%***	***15%***

- **6% of solid cancers in women associated with radiation exposure and 42% with smoking**

* **Radiation Attributable fraction based on people with dose > 0.005 Gy**

LSS Solid Cancer: Excess Cases - Females

Colon Dose (Gy)	People	Person years	Cases	Excess cases		AF %	
				Radiation	Smoking	Radiation*	Smoking
Female							
< 0.005	36,155	1,127,605	6,580	3.0	147.0	--	2%
- 0.1	16,336	505,744	3,039	73.6	91.0	2%	3%
- 0.2	3,462	106,213	720	72.6	27.5	10%	4%
- 0.5	3,625	109,337	815	167.2	32.6	20%	5%
- 1	1,854	56,790	507	191.6	18.9	37%	6%
- 2	849	24,420	306	154.2	11.7	54%	9%
2+	253	7,175	98	63.2	2.9	64%	9%
Female Total	**62,534**	**1,937,284**	**12,065**	**725.5**	**331.7**	**13%**	**3%**
M+ F Total	***105,444***	***3,079,484***	***22,538***	***991.9***	***3,359.5***	***10%***	***15%***

- **13% of solid cancers in women associated with radiation exposure and 3% with smoking**

* Radiation Attributable fraction based on people with dose > 0.005 Gy

LSS Solid Cancer: Excess Cases by Exposure Age

Age at Exposure	People	Person years	Cases	Excess cases		AF %	
				Radiation	Smoking	Radiation*	Smoking
Male							
0 - 19	21,588	727,781	4,845	185.3	1,324.7	9%	28%
20 - 39	8,525	238,547	2,909	55.0	953.1	5%	32%
40+	12,797	175,872	2,719	26.2	750.0	2%	28%
Male Total	**42,910**	**1,142,200**	**10,473**	**266.4**	**3,027.8**	**6%**	**29%**

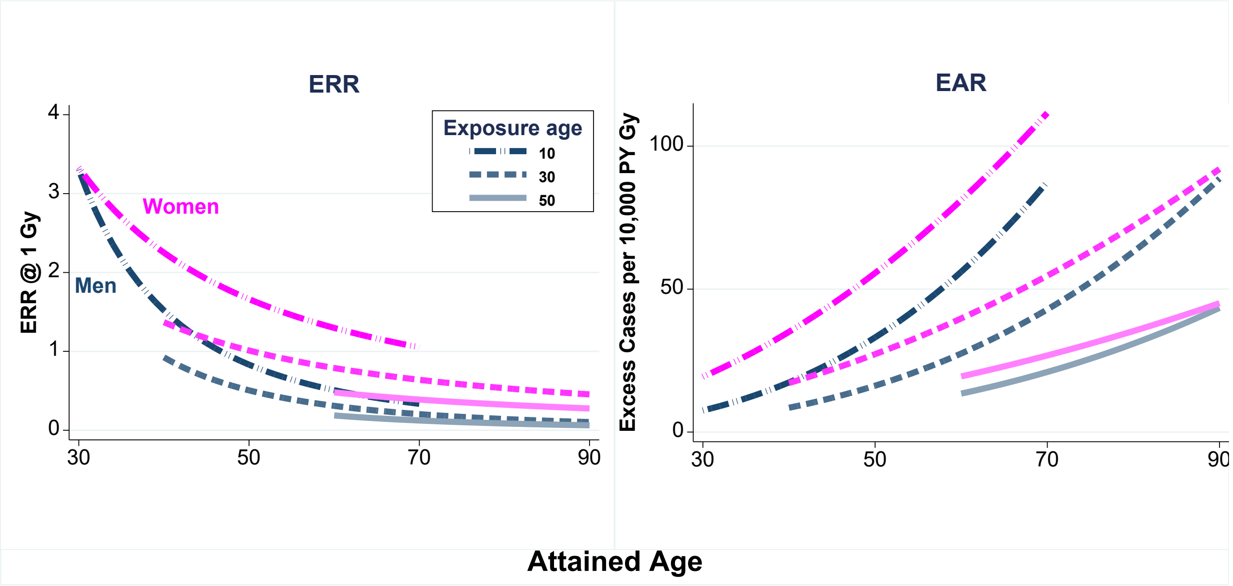
Age at Exposure	People	Person years	Cases	Excess cases		AF %	
				Radiation	Smoking	Radiation*	Smoking
Female							
0 - 19	24,199	901,249	3,845	372.4	105.3	21%	3%
20 - 39	21,564	749,970	5,554	278.9	180.4	11%	3%
40+	16,771	286,066	2,666	74.2	46.0	6%	2%
Female Total	**62,534**	**1,937,284**	**12,065**	**725.5**	**331.7**	**13%**	**3%**
Total	***105,444***	***3,079,484***	***22,538***	***992***	***3,359***	***10%***	***15%***

* Radiation Attributable fraction based on people with dose > 0.005 Gy

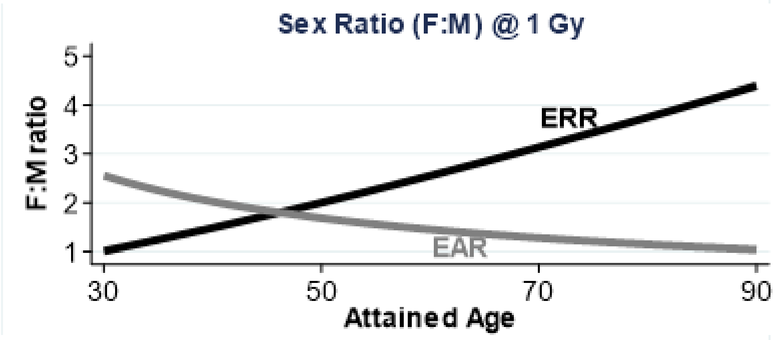
- **Largest radiation attributable fractions for those exposed as children**
-

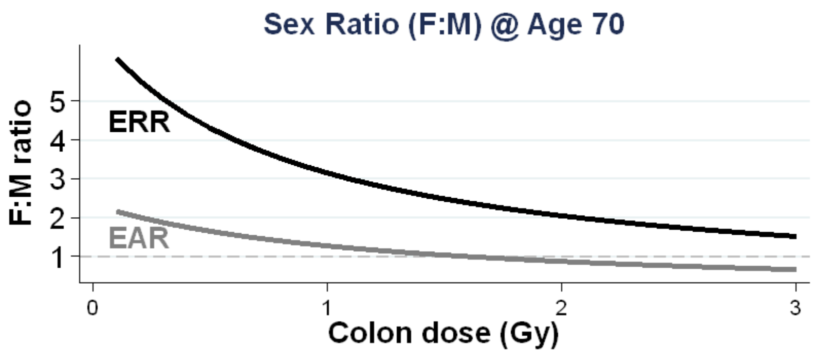
LSS Solid Cancer: Temporal Variation

- **Excess risk depends on attained age, sex and age at exposure**
  - ERR and EAR patterns differ
  - Temporal variation is sex dependent



LSS Solid Cancer: Sex differences





- Sex ratio varies with attained age and dose
- At older ages EAR ratio smaller than ERR ratio and approaches 1
- At all doses EAR ratio less than half ERR ratio

LSS Solid Cancer Incidence: Site Specific ERRs

- **Lung cancer (Cahoon et al 2017):**
  - Linear dose response with larger ERRs for women and complex dependence on smoking intensity
- **Breast cancer (Brenner et al 2018):**
  - Linear dose response decreasing with attained age with higher risks for earlier menarche ages and for exposures around the age at menarche
- **Uterine cancer (Utada et al 2019):**
  - Linear dose response for corpus cancers limited to peri-menarchal exposures
  - No dose response for cervical cancer
- **Colorectal cancer (Sugiyama et al 2019):**
  - Linear dose response for colon cancer with attained age dependence
  - No indication of effect for rectal cancer

LSS Solid Cancer Incidence: Site Specific ERRs

- **Upper GI cancers (Sakata et al 2019):**
  - Dose response for salivary gland tumors decreasing with attained age with no evidence of effects for other cancers of the oral cavity
  - Quadratic dose response for esophageal cancers decreasing with attained age with less nonlinearity and larger ERRs for women
  - Linear dose response for stomach cancer decreasing with attained age
- **Liver and pancreatic cancers (Sadakane et al 2019):**
  - Linear dose response for liver cancer for those exposed before age 30
  - Significant linear trend for pancreatic cancer among women but not men
- **Papers will soon be published on cancers of the prostate, ovary, brain/cns and other sites as well as a summary paper on the site-specific risks**

LSS Solid Cancer Incidence: Summary

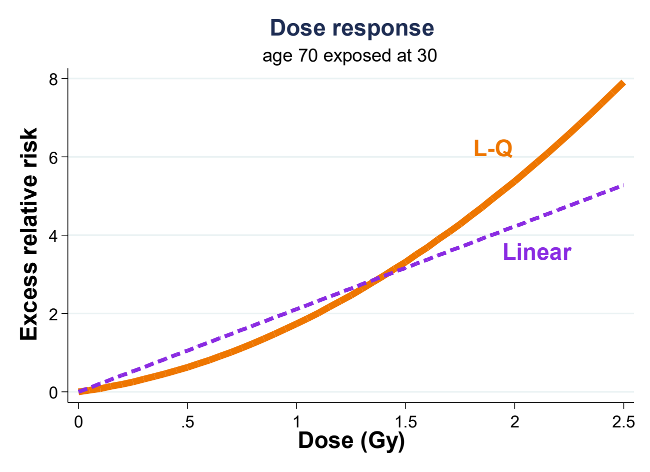
- **Emerging indications of non-linearity in male dose response**
  - Reasons and implications are unclear
  - Issue is being examined in mortality data
- **More detailed examination of site-specific risks and confounding/effect modification**
  - Smoking is not an important confounder of the radiation effects but is an effect modifier for lung cancer risk
  - Suggestions of menarche age effects in radiation risks for breast and uterine corpus cancer

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%****

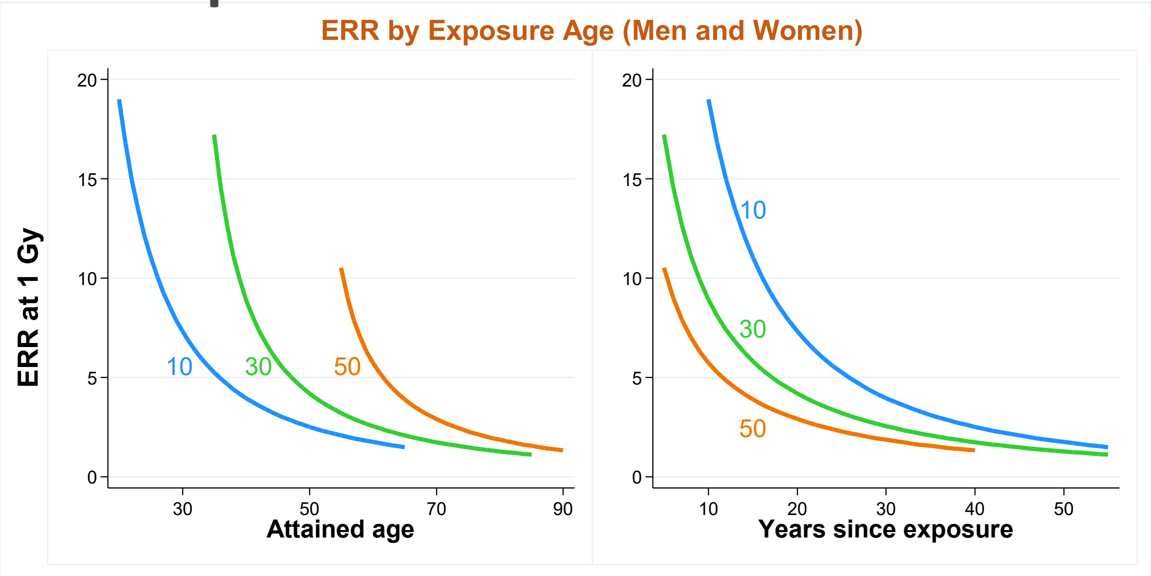
- Despite smaller number of excess cases, a considerably larger proportion of the cases are radiation-associated
- Non-linear dose response



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

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

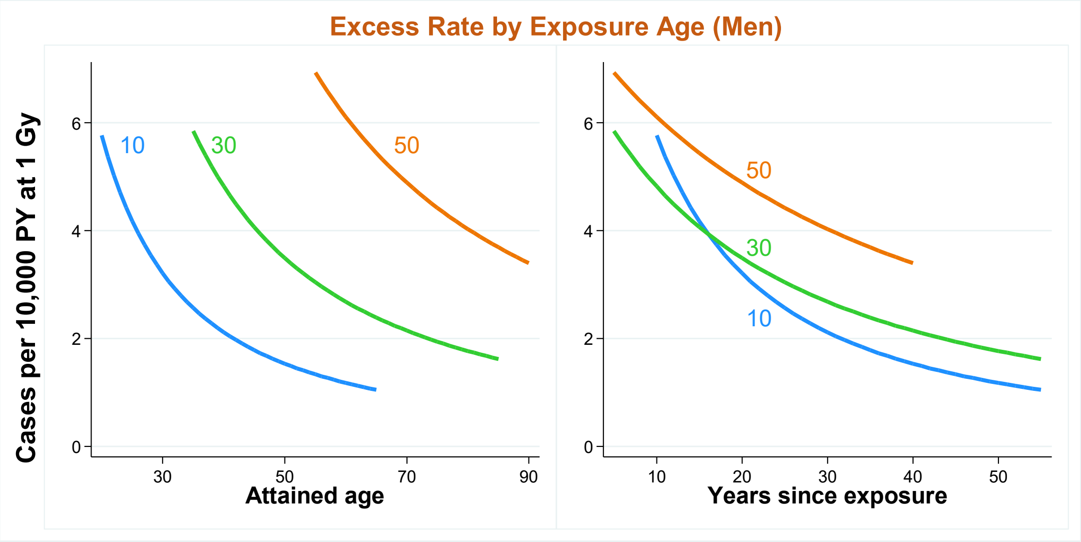
Leukemia incidence 1950 – 2001
ERR Temporal Patterns



- 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 Temporal Patterns



- 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.*

LSS Hematopoietic cancers: Summary

- **AML risks described by an ERR with age and age at exposure dependence**
  - ERRs have tended to decreas with attained age especially for those exposed early in life
- **ALL ERR largest for those exposure as children declines with age**
- **CML radiation effect appears to depend on time-since exposure and excess largely disappeared in a few decades**
- **No useful information on CLL risks (CLL extremely rare in Japan)**
- **Suggestion of a radiation effect on NHL in men but not in women**
- **No compelling evidence of radiation effects on Hodgkins disease or multiple myeloma rates**

Final Remarks (1)

- **The ABCC/RERF studies of the atomic bomb survivors is one of the largest and most comprehensive longitudinal studies ever conducted**
  - Even after 70 years the study continues to provide important new insights in the \ nature of acute radiation exposure effects
- **Can expect important new insights in the coming years**
  - Updated analyses of cancer and non-cancer disease rates people who were exposed in-utero
  - Studies of the children of the survivors, including genetic sequencing of mother-father-child trios, will provide new insights into hereditary effects

Final Remarks (2)

- **The LSS is the most powerful study of radiation health effects, but it is not the only important study**
  - Will retain a central role in the formulation of radiation protection guidelines, but other studies will/should take a larger role
  - Cannot answer questions about how risk estimates apply to non-Japanese populations
  - Cannot address questions of low-dose rate chronic exposures

Acknowledgments

- **Early visionaries**
  - Gilbert Beebe, Seymour Jablon, James Neel, Jack Schull, Masao Tsuksui
- **Leaders**
  - George Darling, Itsuzo Shigematsu, Ohtsura Niwa and others
- **Leading scientists**
  - Akio Awa, John Cologne, Harry Cullings, Shoichiro Fujita, Hiroo Kato, Kazunori Kodama, George Kerr, Charles Land, Kiyohiko Mabuchi, Donald Pierce, Elaine Ron, Yukiko Shimizu, Michiko Yamada, James Yamasaki and many more
- **1,000’s of people who supported the research over the decades**

Q1: What is the most surprising new finding form the recent LSS solid cancer incidence analyses?

A. Excess solid cancer rates continue to increase throughout life after exposure
B. Suggestion of curvature in the dose response for men
C. Adjustment for smoking markedly changed radiation risk estimates
D. Little apparent change from earlier results

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Q2: Which of the following statements about the description of radiation effects on disease risks is not true?

A. Excess rates are the most useful summaries for public health And radiation protection purposes
B. (Excess) relative risks and excess rates provide complementary descriptions of the excess risk
C. The (excess) relative risk is primary summary of radiation effects on disease risks
D. One can estimate excess rates from (excess) relative risks and vice-versa

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