The Latest Update on Atomic-Bomb Survivor Studies

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Subjects of Life Span Study

- **Atomic-bomb survivors**
  - National Census in 1950: **284,000** people answered that they met A-bomb in Hiroshima/Nagasaki
  - **Master Sample:** those who lived in Hiroshima/Nagasaki in 1950 (195,000)
  - A total of **120,000** were collected by stratified sampling for exposure status
    - Lived in Hiroshima or Nagasaki at the time of bombing
      - <2.5 km from the hypocenters: about **54,000**
      - 2.5 to 10 km: about **40,000**
    - Not in either city at the time of bombing : about **27,000**
  - They have been followed-up since 1950

Estimation of Individual Radiation Dose (Evaluation of Exposure)

Radiation from Atomic Bomb

- **Initial Radiation**
  - At explosion (<1min)
- **Residual Radiation**
  - Induced radiation
  - Radioactive Fallout

➢ **Factors Influencing Individual Dose from initial radiation**

- Non-shielded dose
  - Distance from the explosion center
- Shielding condition
  - Building, Terrain
- Personal condition
  - Body size, posture, direction
- Individual dose for 15 organs
  - Weighted absorbed dose (neutron x10+gamma dose)

Non-Shielded Dose (Free-in-Air Tissue Kerma) by Distance from the Hypocenter by DS02(Gy)

Distance (m)	Hiroshima			Nagasaki		
	Neutron	Gamma-ray	Total (X10 for neutron)	Neutron	Gamma-ray	Total (X10 for neutron)
1000	0.260	4.22	6.82	0.125	8.62	9.87
1200	0.067	1.81	2.48	0.034	3.49	3.83
1500	0.0090	0.527	0.617	0.0051	0.983	1.03
1800	0.0013	0.165	0.178	0.0008	0.299	0.307
2000	0.0004	0.076	0.080	0.0002	0.138	0.140
2500	0.0000	0.013	0.013	0.0000	0.023	0.023

Young RW, et al. DS02, RERF, 2005

Estimated Individual Doses

DS02 dose	Hiroshima	Nagasaki	Total
Not-in-City	20,230	6,350	26,529
<5 mGy	21,713	16,812	38,509
5-99	22,744	7,232	29,976
100-499	10,115	2,226	12,341
500-999	2,376	1,052	3,428
1000-1999	1,151	614	1,765
2000+	436	189	625
Unknown	3,449	3,621	7,070
Total	82,214	38,107	120,321

Other Risk Factors (Confounding and Interaction)

- **Mail surveys**
  - Self-administered questionnaire
  - Lifestyle, etc
  - Conducted in 1965, 69, 79, 91, and 2008-11
  - Response rate; around 60% of whole LSS subjects

Results based on 1950-2003 (LSS 14)

Follow-up, 1950-2003

Age at bombing	No. of subjects	Observed person-years	No. of death*	Alive (%)
0-9	17,833	910,347	2,200	88%
10-19	17,563	848,826	4,887	72%
20-29	10,891	494,021	5,178	52%
30-39	12,270	462,694	10,410	15%
40-49	13,504	365,240	13,397	1%
50+	14,550	213,079	14,548	0%
Total	86,611[+]	3,294,210	50,620	42%

*Excluding the deletion by the authority office

[+] Excluding NIC

Ozasa K, Shimizu Y, et al, Radiat Res, 2012

Analytical Models

- **Excess relative risk (ERR) model**

$$\lambda_{exposed} = \lambda_0 (c,s,a,b)[1+ERR(d,s,e,a)]$$

- **Excess absolute risk (EAR) model**

$$\lambda_{exposed} = \lambda_0 (c,s,a,b) + EAR(d,s,e,a)$$

  - c: city, s: sex, a: attained age (follow-up period), b/e: birth year/ age at exposure
  - $\lambda_0(c,s,a,b)$: rate at non-exposure defined by c,s,a,b

- **Main effects of radiation (ρ) and effect modification (ε)**

$$ERR, EAR = \rho(d)\ \varepsilon(e,s,a)$$

  - $\rho(d) = \beta d$ (linear), γd^2 (quadratic), $\beta+\gamma d^2$ (linear-quadratic)
  - $\varepsilon(e,s,a) = \exp(\tau e) \bullet a^{\upsilon} \bullet \sigma s$

ERR by Dose for All Solid Cancer, LSS, 1950-2003

- The **linear (L) model** provides the best fit over the full-dose range
- **ERR/Gy=0.42** (95%CI: 0.32, 0.53) for the gender-averaged risk estimates **at age 70 after radiation exposure at age 30**, based on the model with effect modification by sex, age at exposure and attained age
- **The lowest dose range** with a statistically significant trend is **0-0.20Gy** with ERR/Gy of 0.56
- Estimated **threshold** dose is **0.0Gy** and upper 95% confidence limit is 0.15Gy

Ozasa K, Shimizu Y, et al, Radiat Res, 2012

Modification of ERR and EAR of All Solid Cancer by Age at Exposure and Attained Age

- Both ERR and EAR were higher in the young at the time of the bombings
- ERR decreased along with attained age while EAR increased

Ozasa K, Shimizu Y, et al, Radiat Res, 2012

Confounding and Interaction of Radiation Effects with Life Style and Other Factors

Interaction of Radiation and Smoking on Lung Cancer Risk, Incidence, 1958-99

Risk of radiation for lung cancer:

- ERR at 1 Gy was around 0.7 in non-smokers
- ERR at 1 Gy was around 2.0 in light smokers who consumed 7-8 cigarettes per day (positive interaction)
- No additional increase in risk by radiation in heavy smokers (negative interaction, risk of lung cancer seemed to be saturated by smoking)

Furukawa K, et al. Radiat Res, 2010

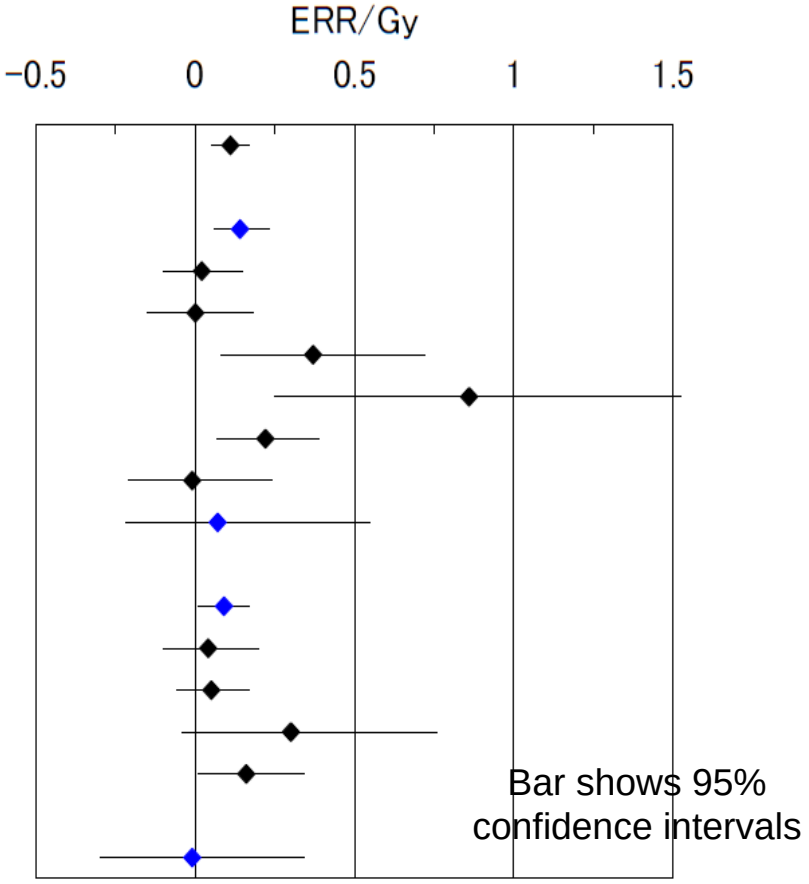
Issues on Risk Estimation at Low-dose Radiation Exposure

- **Small effects at low-dose levels**
  - Low power of detection needs a large number of subjects
- **Effects of non-radiation risk factors**
  - Lifestyle such as smoking, and geographical factors
    - Bias and confounding
      - Proximal/high dose survivors lived in urban area in Hiroshima and rather vise versa in Nagasaki
    - Non-differential effects (i.e., widen the confidence intervals)
    - Interaction (i.e., alter the risks of radiation between different strata of non-radiation risk factors)
- **Effects of residual radiation and medical radiation exposure, revision of dose estimates, etc**

Non-cancer Diseases

Risk of Circulatory Diseases, 1950-2003

Disease category (ICD-9 code)	No of deaths
Circulatory disease (390-459)	19,054
Heart disease (390-398, 402, 404, 410-429)	8,463
Ischemic heart disease (410-414)	3,252
Myocardial infarction (410)	1,735
Hypertensive heart disease (402, 404)	922
Rheumatic heart disease (393-398)	242
Heart failure (428)	2,983
Other heart diseases	1,064
Hypertensive disease without heart diseases (401, 403, 405)	411
Stroke (430-438)	9,622
Cerebral infarction (433, 434)	2,659
Cerebral hemorrhage (431)	4,060
Subarachnoid hemorrhage (430)	461
Others or unspecified	2,442
Other circulatory disease	558



- Heart disease and stroke as a whole had significantly increased risks
- Specific disease types except for hypertensive and rheumatic heart diseases had no increased risks, but rather ill-defined diseases had them

Shimizu Y, et al, BMJ, 2010

(this figure was made by the presenter using the numbers in e-table)

Risk of Possible Chronic Renal Failure Death, 1950-2003

- Several diagnostic criteria of chronic kidney disease were applied and the broadest chronic renal failure had a significant risk of radiation in a quadratic model (ERR/Gy^2=0.091, 95%CI: 0.05, 0.198)
- Renal dysfunction could be part of the mechanism causing increased risk after whole-body irradiation, which hypothesis deserves further study

Adams MJ Y, et al, Radiat Res, 2012

Issues on Circulatory Diseases

- **Risk of radiation exposure increased for rather ill-defined diseases**
- **Additional analyses on dose-response is being investigated by disease type, study period, age at exposure, attained age, etc**
  - Prolonged effects of deterministic effects at high dose level?
  - Confounding by socioeconomic status and other factors related to spatial distribution of survivors?
  - Influence of changes of dominant non-cancer diseases in Japan during these decades?
  - Suspicious underlying malignancies?
  - Diagnostic preciseness of death certificates?
- **These effects would be prominent especially at low-dose levels**

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RERF. Basic Guide to Radiation and Health Sciences, http://www.rerf.jp/shared/basicg/basicg_e.pdf

RERF. Brief Description, http://www.rerf.jp/shared/briefdescript/briefdescript.pdf