Epidemiological Studies on the Atomic-bomb Survivors (Handout)

Kotaro OZASA

Department of Epidemiology

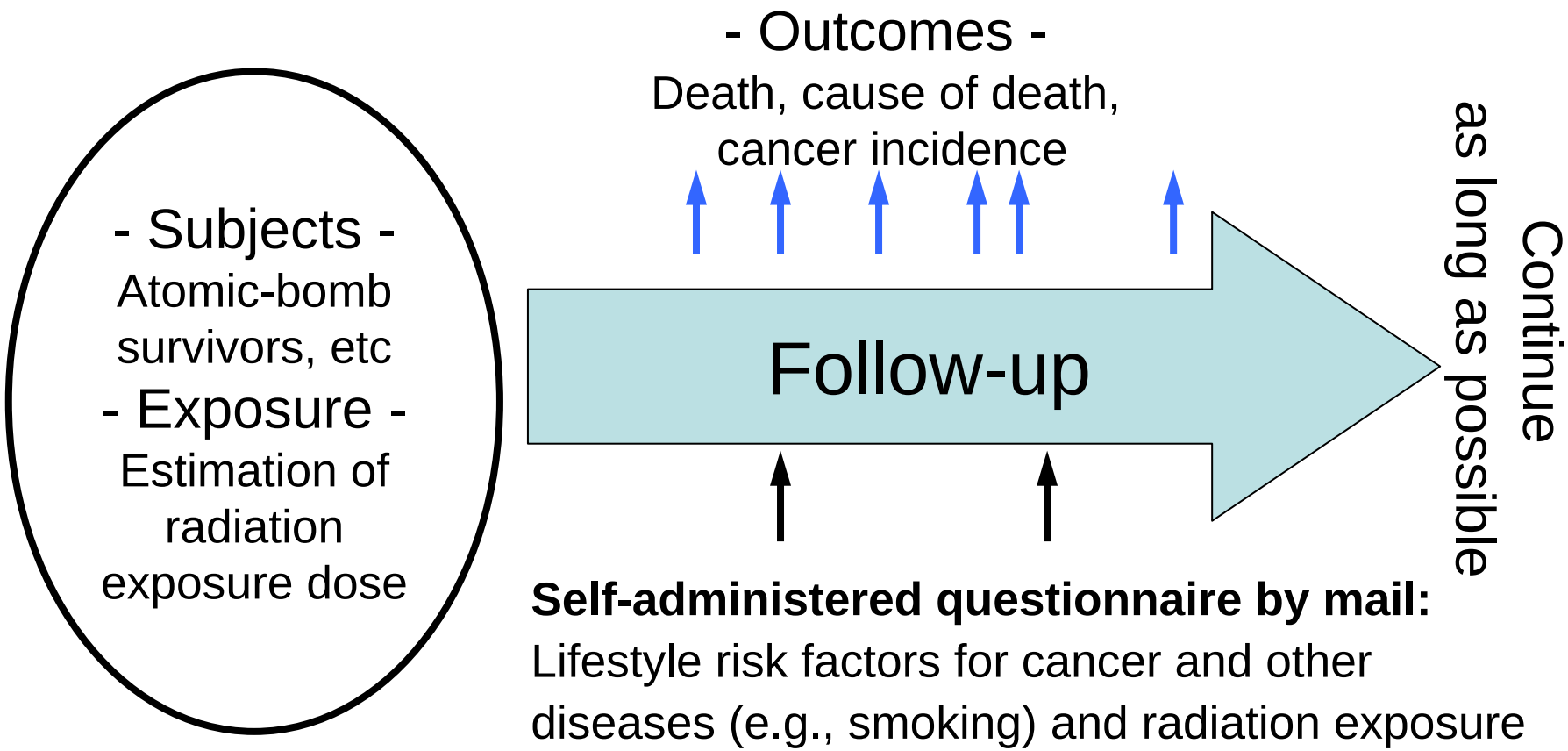
Radiation Effects Research Foundation

Hiroshima, JAPAN

Atomic-bombings in Hiroshima and Nagasaki in August 1945

- *Energy*
  - 16kt in Hiroshima, 21kt in Nagasaki
  - Blast (50%)、Heat (35%)、Radiation (15%)
- *Estimated population before atomic bombing*
  - 360,000 in Hiroshima
  - 250,000 in Nagasaki
- *Deaths by December 31, 1945*
  - 140,000 (38%) in Hiroshima
  - 70,000 (28%) in Nagasaki
- *Injuries by blast and heat, and acute symptoms by radiation deterministic effects*

Methodology of Epidemiological Research



Self-administered questionnaire by mail:
Lifestyle risk factors for cancer and other diseases (e.g., smoking) and radiation exposure other than atomic-bomb (e.g., medical exposure) to evaluate confounding and interaction (effect modification)

Definition of the Population

Subjects of Follow-up

- Atomic-bomb survivors
  - Living in Hiroshima or Nagasaki at the National Census in 1950
  - In the city of 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
    - Life Span Study: 120,000 （1950-）
    - Adult Health Study: 22,000 （1958-）
- In-utero survivors
  - Fetus (in-utero) at the time of bombing
    - LSS about 3,600 （1945-）
    - AHS about 1,000 （1976-）
- Children of the survivors (F1)
  - People who were born in Hiroshima or Nagasaki from 1946-05-01 to 1984-12-31 from the selected survivors with known situation at the time of bombing
    - Epidemiological follow-up: about77,000 （1946-）
    - Clinical Study: about 12,000（2002-）

Estimation of Individual Radiation Dose (Evaluation of Exposure)

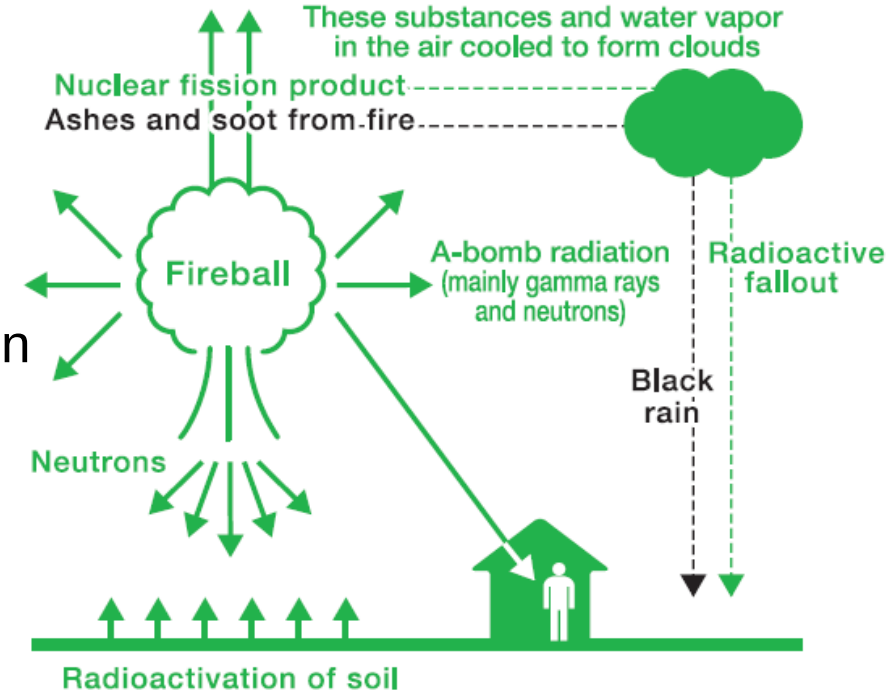
Radiation from Atomic Bomb

Radiation from A-bomb

- **Initial Radiation**
  - At explosion (<1min)
- **Residual Radiation**
  - Induced radiation
    - Radioactivation by neutron
  - Radioactive Fallout
    - Nuclear fission products

Estimation of individual dose

- **Distance from the hypocenter**
- **Shielding condition**
- **Personal condition**
  - Body size, Posture, Direction
- **Individual dose for 15 organs**
  - Weighted absorbed dose (Gy)
    - Neutron x 10 + gamma-ray



People were exposed to not only radiation released directly from the bombs but also radiation from radioactive fallout contained in black rain and from neutron activation in soils. Estimation of radiation doses from such sources requires each individual's actual record of activities, such as his or her location and time spent in that location after the bombing.

RERF. Basic Guide to Radiation and Health Science

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. Kerr GD. Dosimetry System 2002, RERF, 2005

Estimated Individual Dose (DS02)

- Around 20,000 subjects (<2km)
  - Interviewed for detailed shielding histories to estimate precise individual dose
- Others
  - Approximation, average transparency of Japanese wooden house, etc
- Individual dose was estimated for around 95% of the subjects →

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**

Cullings HM, et al. Radiat Res 2004

Residual Radiation at Hiroshima/Nagasaki

Induced radiation by neutron

Radiation dose by staying at the location from the hypocenter for 12hr daytime

Distance	200m	500m	1000m
Hiroshima, 7th Aug	82	15	<0.5
Hiroshima, 8th Aug	40	8	<0.5
Nagasaki, 10th Aug	18	3	<0.5
Nagasaki, 11th Aug	9	1	<0.5

Radioactive fallout

- Maximum expected external exposure
  - Hiroshima: 0.01-0.03Gy
  - Nagasaki: 0.2-0.4Gy
- Maximum expected internal exposure
  - Nagasaki: Cumulated dose 1945-85: 8-10mrem (0.08-0.1mSv)*
  - Hiroshima: Less than 1/10 of Nagasaki *

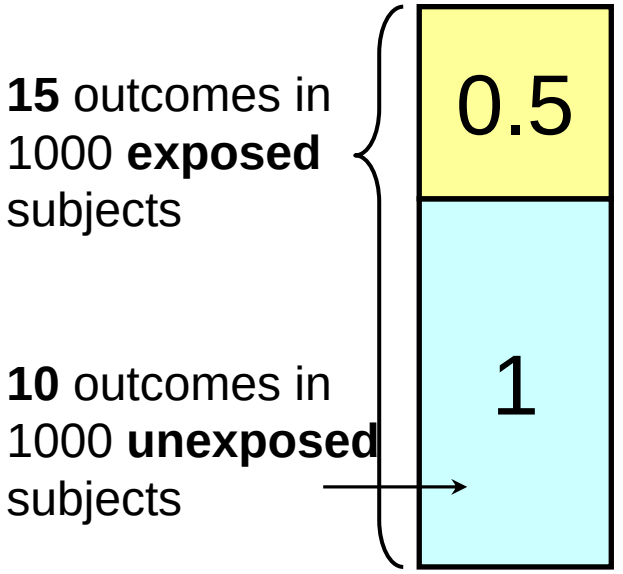
*DS86 Report (A-Bomb Radiation Effects 1992, Bunko-do)
A Brief Description (http://www.rerf.jp/shared/briefdescript/briefdescript.pdf)、TR 2-62, 7-67
http://www.rerf.or.jp/news/pdf/residualrad_ps_e.pdf

Collection of Outcome Information

- Death and cause of death
  - All subjects (all Japan)
- Cancer (malignant tumor) incidence
  - Population-based cancer registry
  - Residents in Hiroshima or Nagasaki

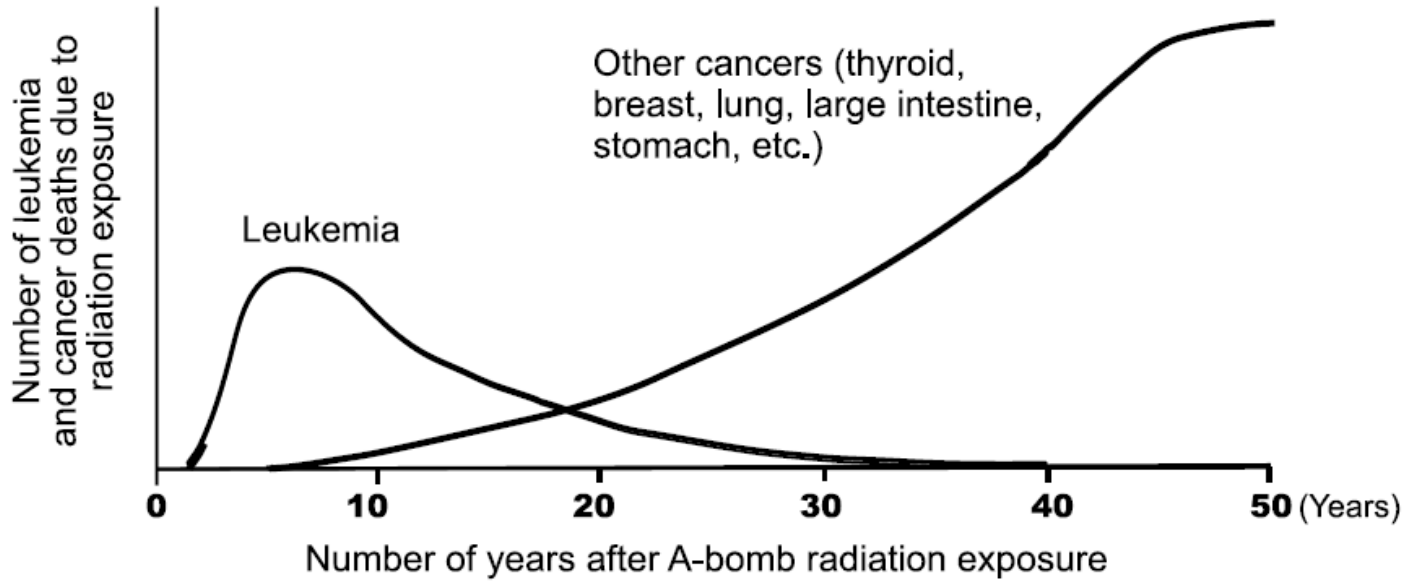
Measurement of Risk

- **Relative risk（RR）**
  - **Ratio** of rate in exposed subjects relative to rate in unexposed subjects (unexposed=1)
  - RR=1.5（1.5 time higher）
- **Excess absolute risk（EAR）**
  - **Difference** between the rates of exposed and unexposed subjects
    - EAR＝5 per 1000
- **Excess relative risk（ERR）**
  - **Proportional difference** (unexposed=1)
  - ERR=0.5 （50% increment）
    - ERR=EAR/Rate in unexposed
    - ERR=RR－1
- **Per unit dose of radiation exposure**
  - ERR/Gy（per 1Gy）
  - ERR_{1Gy}（at 1Gy）



Results

Excess of Leukemia and Cancer due to Radiation Exposure (Schema)



- Leukemia began to increase a few years after the exposure, then decreased
- Other cancers began to increase around ten years or later and the increased risks continue throughout the life

Trend of Leukemia Mortality Risk, LSS, 1950-2000

The risk of leukemia peaked within 10 years after the bombings, especially higher in people who were exposed at young age (e.g., around 70-times in those who were 10 years of age at exposure, but around 10 times in those 20 years of age and almost none in those 30 years or older at exposure)

The risk slightly increased again 40 to 50 years after the exposure

Richardson DB et al, Radiat Res, 2009

Dose Response in Leukemia, LSS, 1950-2001

Leukemia other than CLL or ATL showed some linear-quadratic dose-response curve

It mostly depended on the shape of AML (acute myeloid leukemia) whereas ALL (acute lymphocytic leukemia) and CML (chronic myeloid leukemia) showed linear dose-response

Hsu WL, et al, Radiat Res, 2013

Solid Cancer

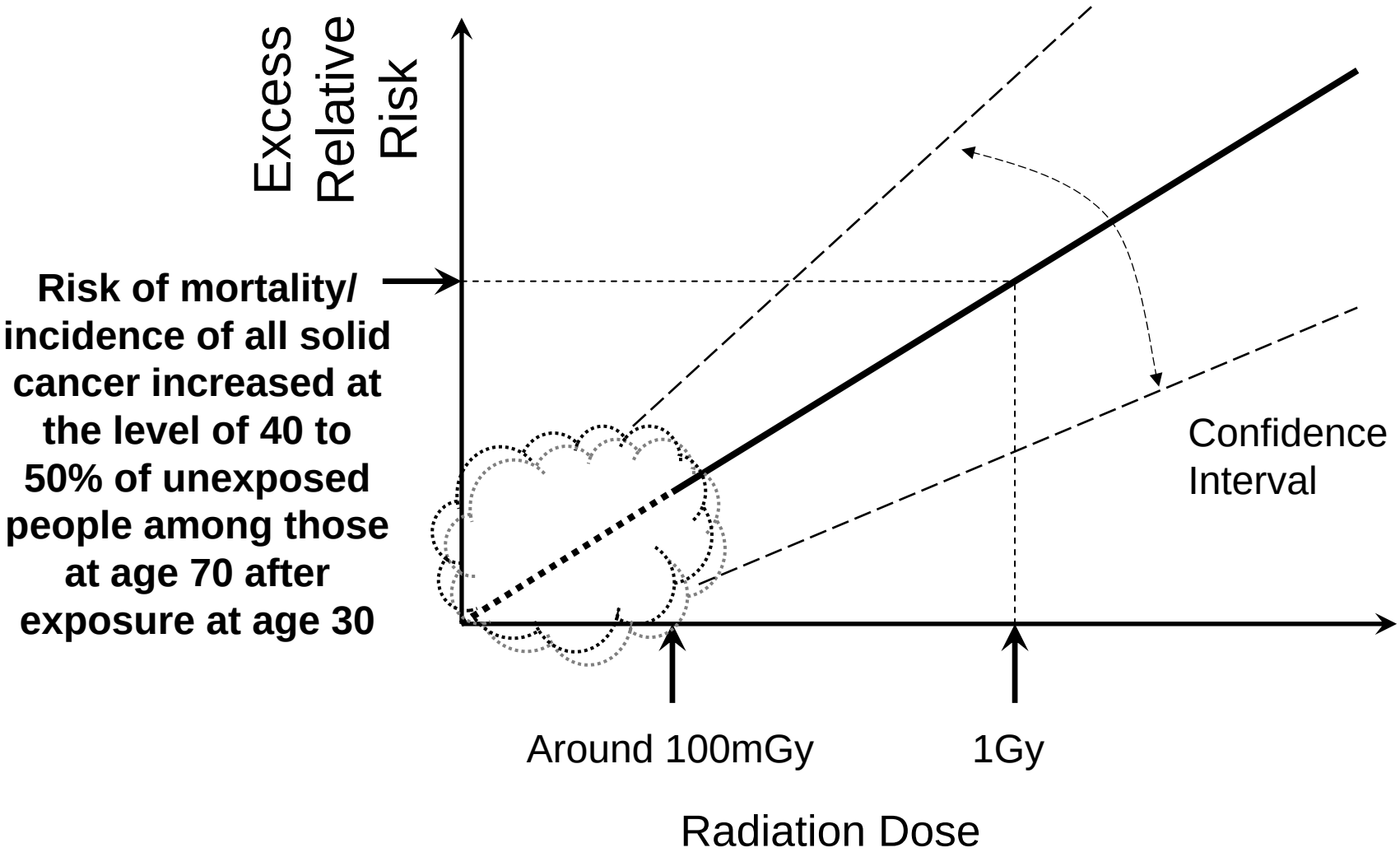
Follow-up, 1950-2003

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

Summarized Schema of Dose-response of All Solid Cancer



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 risk was statistically significant at the level of **0.20Gy** or higher
- 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
  - –Radiosensitivity/vulnerability in the young ages
- ERR decreased along with attained age while EAR increased
  - –Effects seem to be weakening after the exposure.
  - –Increase in background mortality of cancer along with ageing may make EAR increase and ERR decease.

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

Estimated Lifetime Risk of Mortality of Radiation-associated Solid Cancer in the LSS after Exposure to 0.1 Gy, Based on the Data of 1950-1997

Age at Exposure	Sex	Lifetime risk	Background risk
10 years	Male	2.1 %	30 %
	Female	2.2 %	20 %
30 years	Male	0.9 %	25 %
	Female	1.1 %	19 %
50 years	Male	0.3 %	20 %
	Female	0.4 %	16 %

Preston DL, et al Radiat Res, 2003

Associations with Site-specific Cancers

- **Observed association with radiation exposure**
  - Stomach, Lung, Liver, Colon, Breast, Gallbladder, Esophagus, Bladder (pelvis, ureter), Ovary, Thyroid, Skin, ...
- **No observation of association with radiation exposure**
  - Pancreas, Rectum, Uterus, Prostate, Renal parenchyma

Preston DL, et al Radiat Res, 2007

Risk of Thyroid Cancer Incidence, 1958-2005

Risk of thyroid cancer was high (ERR/Gy= 1.28, 95%CI: 0.59, 2.70), especially in a young age at exposure

Furukawa K, et al. Int J Cancer, 2012

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

ERR at 1 Gy was 0.7 in non-smokers (cigarettes/day=0)

ERR at 1 Gy showed a remarkable **positive interaction** with smoking in light smokers

Almost no additional increase in risk by radiation in heavy smokers

Furukawa K, et al. Radiat Res, 2010

Risk of Second Primary Cancer

Radiation risk of second primary cancer (SPC) was similar to that of first primary cancer (FPC) although the background rate of SPC among the carrier of FPC was higher than the rate of FPC in all subjects

Li CI, et al. Cancer Res, 2010

Risk of Noncancer Diseases

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

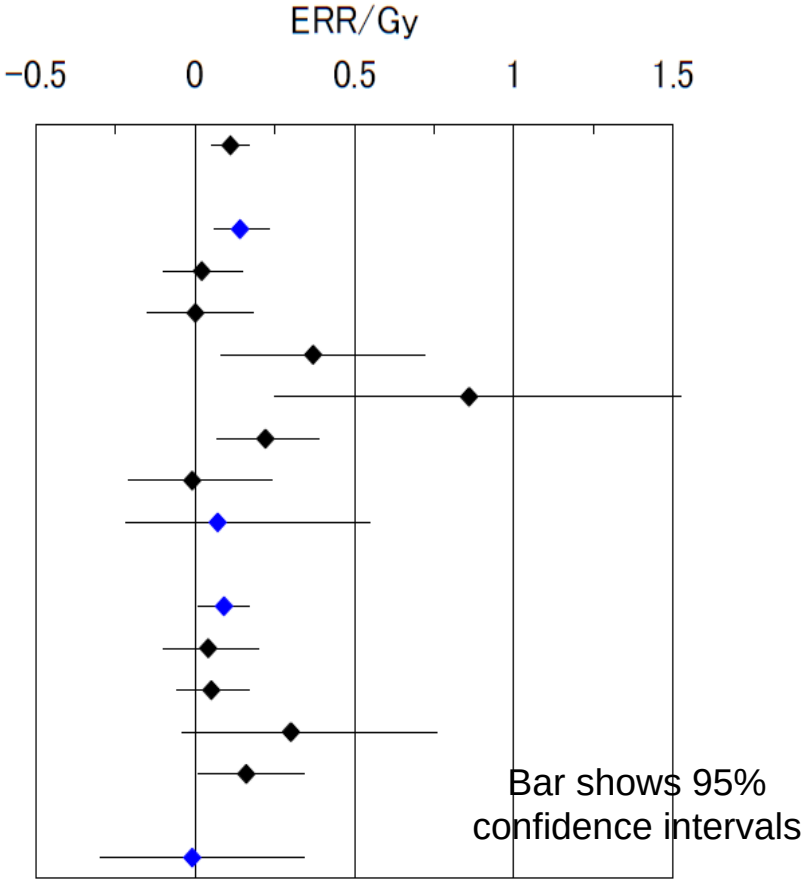
Dose Response of Heart Disease and Stroke Mortality, LSS, 1950-2003

- ✓ Heart disease showed the linear dose-response and suggested no threshold (95% CI; <0, 0.5 Gy)
- ✓ Stroke showed non-linear dose-response and the point estimate of threshold= 0.5 Gy (95% CI; <0, 2.0)

Shimizu Y, et al, BMJ, 2010;340

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 had various risks as well as various shapes of dose response

Shimizu Y, et al, BMJ, 2010

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

Effects on In-utero Survivors

Risk of Solid Cancer in In-utero and Young-at-bombing Survivors (1958-1998)

Subjects: 2,452 **In-utero** survivors and 15,388 survivors **who were 6 years old or younger** at the time of bombing

Outcomes: **Solid cancer incidence** during 12 to 55 years of attained age （94 and 649 cases, respectively）.

	ERR/Gy at age of 50 years			Effect modification by attained age (power)
	Male	Female	Sex-averaged	
In-utero	0.31 (0.0, 2.0)	0.53 (0.0, 2.4)	0.42 (0.0, 2.0)	-2.8 (-9.3, 2.8)
Young-at-bombing	1.3 (0.6, 2.2)	2.2 (1.3, 3.4)	1.7 (1.1, 2.5)	-1.1 (-2.3, 0.2)

( ): 95%Confidence interval

Risk of cancer incidence in in-utero survivors did not reach the level in young-at-bombing survivors although the observed ages were young (till 55 years of age).

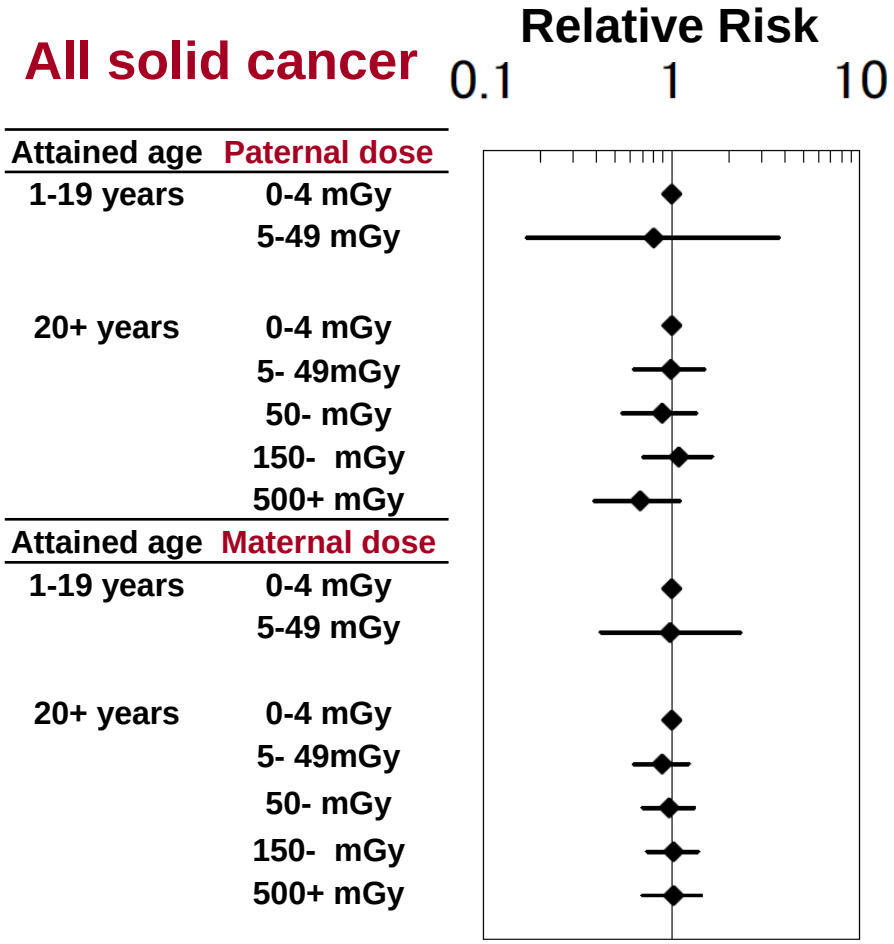
Preston DL, et al. JNCI, 2008

Effects on Children of Survivors

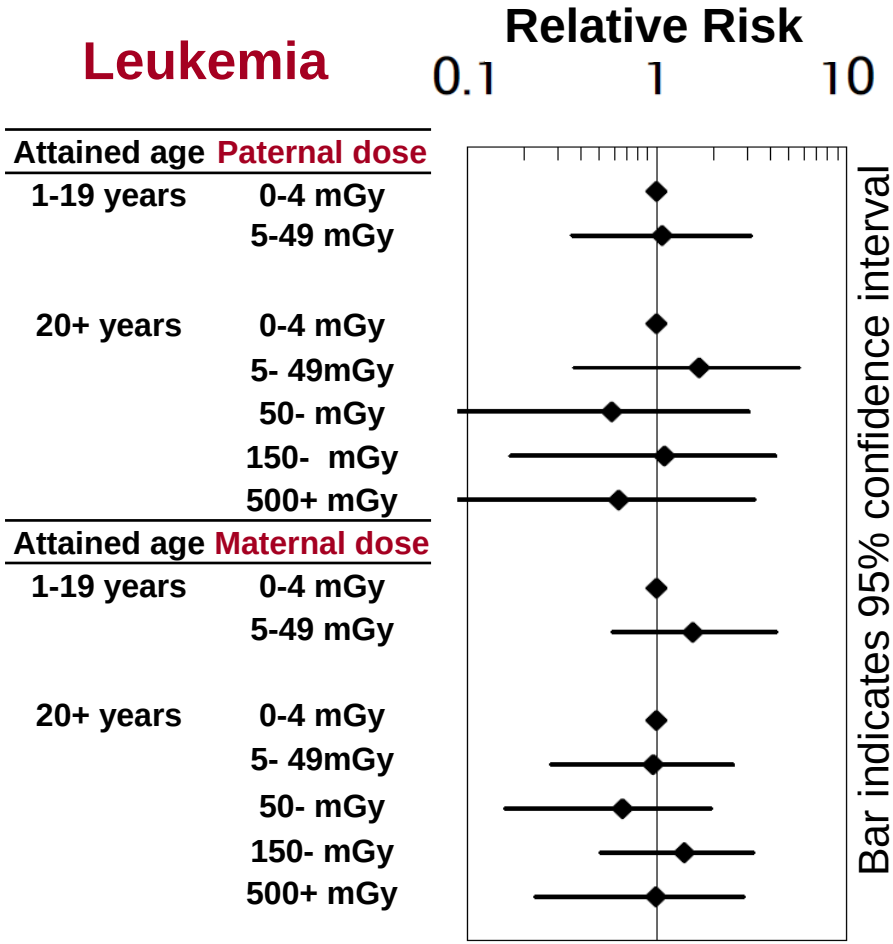
Association of Parental Radiation Dose and Risk of Cancer Incidence in Children of Survivors

（Born in 1946-84, Followed-up in 1958-97）

All solid cancer



Leukemia



No significant risks, but the age at end of follow-up was still young

(The figure was made by the presenter using the numbers in the table)

Izumi S, et al. Brit J Cancer, 2003

Summary of Late Radiation Effects in Atomic-bomb Survivors (1)

Cancer risks in survivors

- Radiation exposure is thought to increase the risk throughout life
- Dose-response relationship is thought to be linear, but still unclear at low-dose level
- Young people at the time of exposure had a higher risk than those exposed at old ages
- There were differences in risks between cancer sites, but the reasons are still unknown

Noncancer disease risks in survivors

- Increased mortality of cardiovascular disease and some other noncancer disease was associated with radiation exposure at high-dose level, but detailed association in subtypes and causal association is still controversial

Summary of Late Radiation Effects in Atomic-bomb Survivors (2)

Cancer risks in In-utero survivors

- Radiation risk of cancer in In-utero survivors increased with maternal dose, but might not be higher than the risk in the survivors exposed at young age (biological development could be related the difference)

Cancer risks in children of survivors

- Radiation risks of cancer in children of survivors were not associated with paternal or maternal dose based on current observations

➢**Further observations are required**

References (1)

RERF. http://www.rerf.jp/

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

RERF. RERF's Views on Residual Radiation, http://www.rerf.or.jp/news/pdf/residualrad_ps_e.pdf

RERF. Technical Report, 2-62, 7-67

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

Young RW, Kerr GD, eds. Reassessment of the atomic bomb radiation dosimetry for Hiroshima and Nagasaki—Dosimetry system 2002. Hiroshima, Japan: Radiation Effects Research Foundation; 2005

Cullings HM, et al. Dose estimation for atomic bomb survivor studies: Its evolution and present status. *Radiat Res* 166:219–54, 2006.

Ozasa K, et al. Studies of the mortality of atomic bomb survivors, Report 14, 1950-2003: An overview of cancer and noncancer diseases. *Radiat Res* 2012;177:229-243.

Preston DL, et al. Studies of mortality of atomic bomb survivors. Report 13: Solid cancer and noncancer disease mortality: 1950–1997. *Radiat Res* 2003;160: 381–407.

References (2)

Preston DL, et al. Solid cancer incidence in atomic bomb survivors: 1958–1998. *Radiat Res* 2007;168:1–64.

Richardson DB, et al. Ionizing radiation and leukemia mortality among Japanese atomic bomb survivors, 1950–2000. *Radiat Res* 2009;172:368–382.

Hsu WL, et al. The incidence of leukemia, lymphoma and multiple myeloma among atomic bomb survivors: 1950–2001. *Radiat Res* 2013;179:361–382

Furukawa K, et al. Long-term trend of thyroid cancer risk among Japanese atomic-bomb survivors: 60 years after exposure. *Int J Cancer*, 2013;132:1222–6.

Furukawa K, et al. Radiation and smoking effects on lung cancer incidence among atomic-bomb survivors. *Radiat Res* 2010; 74:72-82.

Li CI, et al. Relationship between radiation exposure and risk of second primary cancers among atomic bomb survivors. *Cancer Res*, 2010;70:7187-98.

Shimizu Y, et al. Radiation exposure and circulatory disease risk: Hiroshima and Nagasaki atomic bomb survivor data, 1950-2003. *Brit Med J* 2010;340:b5349, doi:10.1136/bmj.b5349

Preston DL, et al. Solid cancer incidence in atomic bomb survivors exposed in utero or as young children. *J Nat Cancer Inst*, 2008;100:428-36.

Izumi S, et al. Cancer incidence in children and young adults did not increase relative to parental exposure to atomic bombs. *Brit J Cancer*, 2003; 89:1709-1713.