Epidemiological Studies on the Atomic-bomb Survivors (Handout)

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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

- Subjects - Atomic-bomb survivors, etc
- Exposure - Estimation of radiation exposure dose

Follow-up

- Outcomes - Death, cause of death, cancer incidence

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)

Continue as long as possible
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: about 77,000 (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)

<table>
<thead>
<tr>
<th>Distance (m)</th>
<th>Hiroshima</th>
<th>Nagasaki</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Neutron</td>
<td>Gamma-ray</td>
</tr>
<tr>
<td>1000</td>
<td>0.260</td>
<td>4.22</td>
</tr>
<tr>
<td>1200</td>
<td>0.067</td>
<td>1.81</td>
</tr>
<tr>
<td>1500</td>
<td>0.0090</td>
<td>0.527</td>
</tr>
<tr>
<td>1800</td>
<td>0.0013</td>
<td>0.165</td>
</tr>
<tr>
<td>2000</td>
<td>0.0004</td>
<td>0.076</td>
</tr>
<tr>
<td>2500</td>
<td>0.0000</td>
<td>0.013</td>
</tr>
</tbody>
</table>

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 →

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

Residual Radiation at Hiroshima/Nagasaki

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

<table>
<thead>
<tr>
<th>Distance</th>
<th>200m</th>
<th>500m</th>
<th>1000m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hiroshima, 7th Aug</td>
<td>82</td>
<td>15</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>Hiroshima, 8th Aug</td>
<td>40</td>
<td>8</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>Nagasaki, 10th Aug</td>
<td>18</td>
<td>3</td>
<td>&lt;0.5</td>
</tr>
<tr>
<td>Nagasaki, 11th Aug</td>
<td>9</td>
<td>1</td>
<td>&lt;0.5</td>
</tr>
</tbody>
</table>

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 *

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$_{1\text{Gy}}$ (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 (thyroid, breast, lung, large intestine, stomach, etc.) 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.

Solid Cancer
## Follow-up, 1950-2003

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

*Excluding the deletion by the authority office
+ Excluding NIC

Summarized Schema of Dose-response of All Solid Cancer

Risk of mortality/ incidence of all solid cancer increased at the level of 40 to 50% of unexposed people among those at age 70 after exposure at age 30.
ERR by Dose for All Solid Cancer, LSS, 1950-2003

- The linear (L) model provides the best fit over the full-dose range
- \( \text{ERR/Gy}=0.42 \) (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

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.
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

<table>
<thead>
<tr>
<th>Age at Exposure</th>
<th>Sex</th>
<th>Lifetime risk</th>
<th>Background risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 years</td>
<td>Male</td>
<td>2.1 %</td>
<td>30 %</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>2.2 %</td>
<td>20 %</td>
</tr>
<tr>
<td>30 years</td>
<td>Male</td>
<td>0.9 %</td>
<td>25 %</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>1.1 %</td>
<td>19 %</td>
</tr>
<tr>
<td>50 years</td>
<td>Male</td>
<td>0.3 %</td>
<td>20 %</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>0.4 %</td>
<td>16 %</td>
</tr>
</tbody>
</table>

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

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


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

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

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)

Risk of Circulatory Diseases, 1950-2003

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

- 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


(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).

<table>
<thead>
<tr>
<th></th>
<th>ERR/Gy at age of 50 years</th>
<th>Effect modification by attained age (power)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>In-utero</td>
<td>0.31 (0.0, 2.0)</td>
<td>0.53 (0.0, 2.4)</td>
</tr>
<tr>
<td>Young-at-bombing</td>
<td>1.3 (0.6, 2.2)</td>
<td>2.2 (1.3, 3.4)</td>
</tr>
</tbody>
</table>

( ): 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).
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)

<table>
<thead>
<tr>
<th>All solid cancer</th>
<th>Leukemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Relative Risk</strong></td>
<td><strong>Relative Risk</strong></td>
</tr>
<tr>
<td>0.1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Attained age</strong></td>
<td><strong>Paternal dose</strong></td>
</tr>
<tr>
<td>1-19 years</td>
<td>0-4 mGy</td>
</tr>
<tr>
<td>20+ years</td>
<td>0-4 mGy</td>
</tr>
<tr>
<td></td>
<td>5-49 mGy</td>
</tr>
<tr>
<td></td>
<td>50- mGy</td>
</tr>
<tr>
<td></td>
<td>150- mGy</td>
</tr>
<tr>
<td></td>
<td>500+ mGy</td>
</tr>
</tbody>
</table>

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


References (2)


