Long-term Epidemiological Studies on Radiation Effects in A-bomb Survivors

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Outline of Presentation

1. Epidemiological studies on health effects of atomic bomb radiation

2. Study results
   1) Atomic bomb survivors
      • Cancers
      • Diseases other than cancers
   2) F1 offspring

3. Future perspectives
Studies on Health Effects of A-bomb Radiation

- History -

1945 '47 '48 1975 2000

Atomic Bomb Casualty Commission (ABCC)

Japanese National Institute of Health

Radiation Effects Research Foundation (RERF)

Hiroshima 6 August

Nagasaki 9 August

28 years

42 years
Long-term Epidemiological Studies of Atomic Bomb Survivors and Their Offspring

A-bomb survivors (120,000)
Life Span Study (LSS)
Adult Health Study (AHS)
In-utero exposed (3,600)
Offspring (F1) (77,000)

Mortality
Cancer incidence
Morbidity (24,000)
Morbidity (12,000)
Morbidity (1,000)

Atomic Bomb National Census Unified Study Program Launch of Program
Long-term Epidemiological Studies of Atomic Bomb Survivors

- The cohort study of the Japanese survivors of the atomic-bombings of Hiroshima and Nagasaki is broadly considered one of the most reliable sources of information on radiation health effects because of the size and nature of the population investigated and the scale of the data available.

- For this reason, the study has become fundamental to the risk assessment of radiation exposure and study results have been utilized by the international organizations, such as UNSCEAR, ICRP, IAEA and other authorities.
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(Grant EJ et al: Radiat Res 2017; 187: DOI: 10.1667/RR14492.1)
Radiation Risks of All Solid Cancers

<table>
<thead>
<tr>
<th></th>
<th>ERR per Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sex-averaged (95% CI)</td>
</tr>
<tr>
<td></td>
<td>Unadjusted for smoking</td>
</tr>
<tr>
<td></td>
<td>0.50 (0.42 to 0.59)</td>
</tr>
<tr>
<td></td>
<td>Adjusted for smoking, additive joint effect</td>
</tr>
<tr>
<td></td>
<td>0.56 (0.46 to 0.66)</td>
</tr>
<tr>
<td></td>
<td>Adjusted for smoking, multiplicative joint effect</td>
</tr>
<tr>
<td></td>
<td>0.47 (0.39 to 0.55)</td>
</tr>
</tbody>
</table>

(Grant EJ et al: Radiat Res 2017; 187: DOI: 10.1667/RR14492.1)
Solid Cancer Incidence - Dose Response -

Sex-averaged at age 70 for exposure at age 30

(Grant EJ et al: Radiat Res 2017; 187: DOI: 10.1667/RR14492.1)
Lowest Significant Dose Range (LSS, Cancer Incidence, 1958-2009)

The lowest dose range for which there are statistically significant risks:
- 0-100 mGy
- Sex-averaged linear ERR model
- No adjustment for smoking
- $\text{ERR} = 0.49/\text{Gy} \ (95\% \text{CI}: 0.026-1.01)$

(Grant EJ et al: Radiat Res 2017; 187: DOI: 10.1667/RR14492.1)

Gender-averaged for 1 Gy at age 70 after exposure at age 30

(Preston DL et al. RERF UPDATE 2007; 18: 9-13)
Cancer and leukemia

Other findings:

• Cancer risk elevation associated with A-bomb radiation exposure seems to continue for the lifetime.
• Leukemia risk elevation also persists.
• Myelodysplastic Syndrome (MDS) risk appears to be increased.
• The increases in the risk of first primary and second primary cancers seem comparable.
• Radiation effects on lung cancer risk seem to be stronger among smokers.
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Heart Disease Mortality in the Life Span Study, 1950–2008

Ikuno Takahashi, a,b,1 Yukiko Shimizu, b Eric J. Grant, b John Cologne, c Kotaro Ozasa b and Kazunori Kodama a,d

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Heart Disease Subtype-Specific Risk (LSS, Mortality, 1950-2008)

<table>
<thead>
<tr>
<th>Disease category</th>
<th>No. of deaths</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart disease overall*</td>
<td>9,303</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ischemic heart disease (IHD)</td>
<td>3,556</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1,883</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>Other IHD</td>
<td>1,673</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>Valvular disease</td>
<td>744</td>
<td>0.004</td>
</tr>
<tr>
<td>Rheumatic</td>
<td>223</td>
<td>0.002</td>
</tr>
<tr>
<td>Non-rheumatic</td>
<td>521</td>
<td>0.16</td>
</tr>
<tr>
<td>Hypertensive organ damage†</td>
<td>1,122</td>
<td>0.004</td>
</tr>
<tr>
<td>Heart failure</td>
<td>3,334</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Heart Disease Subtype-Specific Dose Response (LSS, Mortality, 1950-2008)

Mortality study indicated an elevated risk of heart disease at doses above 0.5 Gy.

Among heart diseases, hypertensive heart disease and rheumatic heart disease are showing elevated risk in mortality.

There are additional findings indicating elevated risk of stroke mortality, myocardial infarction incidence, CKD mortality, and elevation of risk factor levels, presence of inflammation, and alteration of immune function associated with radiation dose.
Dose-response relationship appeared to be linear for HD mortality. However, there are indications that dose-response could be linear-quadratic or quadratic for other CVD endpoints, such as stroke mortality, incidence of myocardial infarction, incidence of hypertension and mortality of renal failure.

However, it is still unclear that the observed association has causal link or not.

It is also unclear whether the biological mechanisms operating at high doses of radiation apply to lower doses.
CONTROVERSIAL ISSUE

Cardiovascular effects after low-dose exposure and radiotherapy: what research is needed?

Jan Wondergem · Marjan Boerma · Kazunori Kodama · Fiona A. Stewart · Klaus R. Trott

Cardiovascular effects after low-dose exposure and radiotherapy: what research is needed?

- Recommendation for Epidemiological Studies-

1. Subtype specific risk estimations
   - Epidemiological studies, evaluating all heart diseases together, are not expected to solve the important questions.
   - Each disease may have a different pathogenesis, a different clinical manifestation and a different prognosis.
   - Once specific radiation-induced heart diseases are identified and risk estimation has been made, measures for primary and secondary prevention can be implemented.

Cardiovascular effects after low-dose exposure and radiotherapy: what research is needed? - Recommendation for Epidemiological Studies-

2. Dose response analysis

• With regard to the risk estimation in prospective cohort studies, attention should be placed on dose-response analysis based on individual dose to identify whether dose responses are linear or nonlinear.

• In the A-bomb survivor’s data, the dose response of some specific heart diseases may well be nonlinear such as the linear-quadratic or quadratic dose dependence of the incidence of myocardial infarction.

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Health Effects among F1 Offspring of A-bomb Survivors

- Past studies (e.g., studies of birth defects, sex ratio, and chromosome aberrations, and biochemical studies) reported no genetic effects.
- Ongoing studies (mortality, cancer incidence, and health examination studies) have yet to show evidence that parental radiation exposure increases disease risks among F1 offspring.
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• Radiation-associated cancer and noncancer diseases will likely increase in the next 10-15 years.
• Accumulated epidemiological data will continue to lead to important findings on radiation-associated cancer and noncancer disease risks.
• Continued epidemiological studies are essential for risk assessment among A-bomb survivors exposed at age 20 or under.
• For elucidation of mechanisms of radiation-associated diseases, research based on stored biosamples and animal experiment will become increasingly important.
Peace Memorial Park, Hiroshima

Thank you for listening!