Current Research on Non-cancer Diseases in Atomic Bomb Survivors

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Life Span Study (LSS) and Adult Health Study (AHS)

**Epidemiological studies**
- **Life Span Study** (120,000), *in utero* exposed (3,600), F₁ (76,000)

**Clinical studies**
- **Adult Health Study** (24,000), *in utero* (1,000), F₁ (12,000)

**Follow-up**
- Vital statistics and population-based cancer registries
  - Death and cause of death (All Japan since 1950)
  - Cancer incidence (Hiroshima and Nagasaki since 1957/58)
- Health examinations at ABCC-RERF
  - Questionnaire surveys, physical exam, blood exam, X-ray/echogram, etc. since 1958
  - Donation of research biosamples

Death and cause of death (All Japan since 1950)
Cancer incidence (Hiroshima and Nagasaki since 1957/58)
Death and cause of death (All Japan since 1950)
Cancer incidence (Hiroshima and Nagasaki since 1957/58)
Radiation-associated Non-cancer Diseases among LSS, 1950-2003

<table>
<thead>
<tr>
<th>Non-cancer outcomes</th>
<th>ERR/Gy (95% CI)</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circulatory disease</td>
<td>0.11 (0.05, 0.17)</td>
<td>19,054</td>
</tr>
<tr>
<td>Respiratory disease</td>
<td>0.21 (0.10, 0.33)</td>
<td>5,119</td>
</tr>
<tr>
<td>Digestive disease</td>
<td>0.11 (-0.01, 0.24)</td>
<td>3,394</td>
</tr>
<tr>
<td>Genitourinary disease</td>
<td>0.14 (-0.06, 0.38)</td>
<td>1,309</td>
</tr>
<tr>
<td>Infectious disease</td>
<td>-0.02 (-0.15, 0.13)</td>
<td>1,962</td>
</tr>
<tr>
<td>Other disease</td>
<td>0.01 (-0.1, 0.12)</td>
<td>4,847</td>
</tr>
<tr>
<td>External cause</td>
<td>-0.11 (-0.21, 0.02)</td>
<td>2,432</td>
</tr>
</tbody>
</table>

Cardiovascular Disease (CVD) among Atomic Bomb Survivors

• Radiation-associated CVD among atomic bomb survivors
  – Current knowledge/findings
  – Potential mechanisms of association with radiation exposure
    • Hypertension may be the intermediate pathogenesis
      – Exposure to atomic bomb radiation was systemic irradiation
    • It seems different from the perceived mechanisms
      – i.e., atherosclerotic changes due to endothelial cell injuries or inflammation
    • Another aspect is uncertainty of diagnosis at death in the LSS

• Pathogenesis of CVD in general population of Japan
  – in order to understand the association
Radiation-associated CVD among Atomic Bomb Survivors (1)

  - Stroke showed a possible upward curvature in dose-response
  - Heart disease showed a linear dose-response
  - Much heterogeneous radiation risks among subtypes of HD and stroke

<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>

Bar shows 95% confidence intervals

Data from Shimizu, et al. *BMJ*, 2010
Radiation-associated CVD among Atomic Bomb Survivors (2)

  - Quadratic dose-response models were significant for hypertension and myocardial infarction (age at the bombing <40 years).
  - However, radiation-related risk was not increased in a linear dose-response model for any CVD subtype
  - Increased risk was shown in hemorrhagic stroke in both sexes (with threshold in females), but not shown in ischemic stroke

Potential Mechanism- Intermediate Pathogenesis (1)

  - A significant quadratic model for chronic kidney disease
  - Moderate + severe chronic kidney diseases were associated with radiation exposure
Potential Mechanism- Intermediate Pathogenesis (2)

• **Increase of blood pressure in AHS** (Sasaki, et al. *J Clin Epidemiol* 2002)
  
  - Systolic and diastolic blood pressure levels were higher in exposed subjects than in unexposed subjects among younger birth cohorts, but lower among older birth cohorts
  
  - The difference was significant, but small, about 1 mmHg/Gy.

• **Increase of total serum cholesterol in AHS** (Wong, et al. *Radiat Res* 1999)
  
  - About 2.4 mg/dl at 1 Gy in women and about 1.5 mg/dl in men at most

• **Increase of CRP and IL-6** (Hayashi, et al. *Hum Immunol* 2003)
  
  - Inflammatory markers associated with endothelial cell injuries or inflammation, which induce atherosclerosis
  
  - Increase by 28% and 9.8% per gray, respectively

➢ It remains unclear how strong these changes influenced clinically manifested radiation-associated CVD
Summary of Radiation-associated CVD in the LSS and AHS of Atomic Bomb Survivors

- Increased at relatively high-dose levels (>2 Gy) with non-linear dose-response, especially when including non-fatal incidence outcomes.
- Rather apparent in those exposed at younger ages.
- Intermediate pathogenesis may be hypertension rather than atherosclerosis.
- But, there are some exceptional/remaining issues.
- Uncertainty of diagnosis in death certificates (association in LSS):
  - Heart failure and others/unspecified stroke (i.e., ill-defined disease categories) as the underlying cause of death might include undiagnosed malignancies.
Pathogenesis of CVD in Japan

- Difference of CVD profile between Japan and Western countries
- Nutritional and metabolic background of CVD in Japan
Mortality of heart disease has been much lower in Japan than in US/UK.
Proportion of arteriosclerotic/ischemic heart disease has been smaller in Japan than in US/UK.
Hypertension is the most potent risk factor in Japan for stroke and heart disease including cerebral infarction and ischemic heart disease.

Data from WHO, World Health Statistics (cited from Kokumin-eisei-no-doko, HLW Statistics Association, Japan)
Cerebral hemorrhage had markedly decreased from 1960s to 80s whereas cerebral infarction and heart disease (especially heart failure) had increased.

‘Heart failure’ should be avoided for a underlying cause of death then cerebral infarction and ischemic heart disease (mostly myocardial infarction) increased.

Data from MHLW, Vital Statistics of Japan
# Blood Pressure Level of Japanese Population

<table>
<thead>
<tr>
<th>Year</th>
<th>Age class</th>
<th>Average blood pressure</th>
<th>Proportion of hypertensive people</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Systolic (mmHg)</td>
<td>Diastolic (mmHg)</td>
</tr>
<tr>
<td>1980</td>
<td>60-69</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1990</td>
<td>60-69</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2000</td>
<td>60-69</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

M: male, F: female

- Blood pressure level of Japanese population was high in the past then consistently decreased

Data from MHLW, National Nutrition Survey of Japan
## Nutrition Intake per Person in Japan

<table>
<thead>
<tr>
<th>Year</th>
<th>Energy (kcal)</th>
<th>Protein (g)</th>
<th>Fat (g)</th>
<th>Salt (g)</th>
<th>% energy from fat</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total</td>
<td>Animal</td>
<td>Total</td>
<td>Animal</td>
</tr>
<tr>
<td>1950 (urban)</td>
<td>1,972</td>
<td>70.1</td>
<td>21.3</td>
<td>21.2</td>
<td>-</td>
</tr>
<tr>
<td>1950 (rural)</td>
<td>2,163</td>
<td>66.1</td>
<td>13.8</td>
<td>15.4</td>
<td>-</td>
</tr>
<tr>
<td>1960</td>
<td>2,096</td>
<td>69.7</td>
<td>24.7</td>
<td>24.7</td>
<td>9.2</td>
</tr>
<tr>
<td>1970</td>
<td>2,210</td>
<td>77.6</td>
<td>34.2</td>
<td>46.5</td>
<td>20.9</td>
</tr>
<tr>
<td>1980</td>
<td>2,084</td>
<td>77.9</td>
<td>39.2</td>
<td>52.4</td>
<td>27.2</td>
</tr>
<tr>
<td>1990</td>
<td>2,026</td>
<td>78.7</td>
<td>41.4</td>
<td>56.9</td>
<td>27.5</td>
</tr>
<tr>
<td>2000 (male)</td>
<td>2,152</td>
<td>84.9</td>
<td>45.9</td>
<td>61.7</td>
<td>31.6</td>
</tr>
<tr>
<td>2000 (female)</td>
<td>1,764</td>
<td>71.1</td>
<td>37.8</td>
<td>53.5</td>
<td>26.4</td>
</tr>
<tr>
<td>2010</td>
<td>1,849</td>
<td>67.3</td>
<td>36.0</td>
<td>53.7</td>
<td>27.1</td>
</tr>
</tbody>
</table>

- Animal protein intake and fat intake, especially animal fat, were low in the past in Japan.
- Salt intake was high in the past.

Data from MHLW, National Nutrition Survey of Japan.
Summary of Pathogenesis of CVD in Japan

• Hypertension was the basic pathogenesis of CVD in Japan
  – Lack of animal protein and fat raised cerebral hemorrhage in the early period
  – A large fraction of cerebral infarction was lacunar type (arteriosclerosis of the cerebral parenchymatous small arteries induced by hypertension)
  – Ischemic heart disease was more attributed to hypertension

• Westernization of lifestyle has increased atherosclerotic change
  – Likely affected younger generations
  – Still at lower level than Western countries

➢ These background may influence the profile of radiation-associated CVD in atomic bomb survivors
Non-cancer Respiratory Disease (NCRD) in the Atomic Bomb Survivors
Radiation Dose-response of ERR for All NCRD in LSS, 1950-2005

1950-1964
ERR/Gy=0.11
(95%CI: -0.08, 0.36)
N=849
Increased at the highest dose level

1965-79
ERR/Gy=0.08
(95%CI: -0.09, 0.29)
N=1149
Almost no increase over the whole dose range

1980-2005
ERR/Gy=0.21
(95%CI: 0.10, 0.34)
N=3,517
Linear function was the best fit

For 1950-2005, ERR/Gy=0.17 (95%CI: 0.08, 0.27), N=5,515
Adjustment for cancer incidence reduced the ERR/Gy to 0.12

• Radiation-associated risk of NCRD was also associated with ill-defined death at old ages, which could in part be attributed to coincident malignancies

The End