Recent Studies at RERF

Robert Ullrich, PhD
Chief of Research
Vice-Chairman
Long-term Epidemiological Studies of Atomic Bomb Survivors and Their Offspring

- A-bomb survivors (120,000)
  - Mortality
  - Cancer incidence
  - Morbidity (24,000)

- In-utero exposed (3,600)
  - Mortality
  - Cancer incidence
  - Morbidity (1,000)

- Offspring (F1) (77,000)
  - Mortality
  - Cancer incidence
  - Morbidity (13,000)

Launch of Program: 1945
Unified Study Program: 1947
Atomic Bomb National Census: 1950
Life Span Study (LSS): 1955
Adult Health Study (AHS): 1958
Morbidity (1,000)
Conclusive Results at Higher Doses

- Non-selectively exposed population with rapidly decreasing doses by distance
- Little chance for bias or confounding by major cancer risk factors
- Highly significant risks by dose for all solid cancers in aggregate

# Dose by Sex, City, and Age at Exposure

**TABLE 2**

Distribution of Weighted Absorbed Colon Dose by Sex, City and Age at Exposure: LSS Solid Cancer Incidence Cohort, 1958–2009

<table>
<thead>
<tr>
<th>Age at exposure (years)</th>
<th>Eligible LSS members&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Subjects with known dose (%)</th>
<th>No. of subjects (%) per DS02R1 colon dose indicated</th>
<th>Dose unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>NIC</td>
<td>0–0.005 Gy</td>
<td>0.005–0.5 Gy</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>45,864</td>
<td>10,488 (24)</td>
<td>14,574 (34)</td>
<td>15,608 (36)</td>
</tr>
<tr>
<td>Female</td>
<td>66,053</td>
<td>14,751 (24)</td>
<td>21,404 (34)</td>
<td>23,423 (37)</td>
</tr>
<tr>
<td>City</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hiroshima</td>
<td>76,549</td>
<td>19,249 (26)</td>
<td>20,087 (27)</td>
<td>30,556 (42)</td>
</tr>
<tr>
<td>Nagasaki</td>
<td>35,368</td>
<td>5,990 (19)</td>
<td>15,891 (50)</td>
<td>8,475 (26)</td>
</tr>
<tr>
<td>Age at exposure (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>23,562</td>
<td>4,995 (22)</td>
<td>7,928 (35)</td>
<td>8,909 (39)</td>
</tr>
<tr>
<td>10–19</td>
<td>25,442</td>
<td>5,878 (25)</td>
<td>7,973 (35)</td>
<td>7,750 (34)</td>
</tr>
<tr>
<td>20–29</td>
<td>15,352</td>
<td>3,675 (26)</td>
<td>4,718 (33)</td>
<td>5,070 (36)</td>
</tr>
<tr>
<td>30–39</td>
<td>16,642</td>
<td>4,034 (25)</td>
<td>5,127 (32)</td>
<td>5,953 (38)</td>
</tr>
<tr>
<td>40–49</td>
<td>16,877</td>
<td>3,727 (23)</td>
<td>5,472 (34)</td>
<td>6,067 (38)</td>
</tr>
<tr>
<td>≥50</td>
<td>14,042</td>
<td>2,930 (22)</td>
<td>4,760 (35)</td>
<td>5,282 (39)</td>
</tr>
<tr>
<td>Total</td>
<td>111,917</td>
<td>25,239 (24)</td>
<td>35,978 (34)</td>
<td>39,031 (37)</td>
</tr>
</tbody>
</table>

*Note.* NIC = not in either city.

<sup>a</sup> Alive and not known to have cancer as of the start of follow-up.
Adjusted for smoking, At age 70, Exposed at age 30

Sex-averaged ERR/Gy=0.47 (95% CI: 0.39, 0.55), f/m=1.81
No. of cases= 10,473 (m), 12,065 (f)
No threshold dose observed
Lowest range of a significant dose response was 0-100 mGy
Radiation risk was not confounded by smoking habits in general

Grant, et at. Radiat Res, 2017

• Since the last report (through 1998), the surviving population has decreased from 52% to 37%;
  – 5,090 new solid cancer cases were observed
  – 22,538 total solid cancer cases observed (1958-2009)
  – 992 cancers associated with radiation exposure
  – Among those with more than 5mGy of exposure, 10% of all cancers were associated with radiation exposure

• Most important finding: single acute exposure increases solid cancer risks for life

• Shape of dose response more curvilinear since the last report but significant elevated risks still evident in low dose range (0-100 mGy)
Less Certainty at Lower Doses

- Despite large size of LSS, statistical power is limited at lower doses
- Less accuracy of dose parameters at longer distances
  - Proximal survivors had detailed shielding histories; distal survivors had fewer interviews
- Medical exposures and/or residual radiation exposures become larger compared to direct exposure from bombs
- Higher probability of bias/confounding factors associated with survivors’ geospatial distribution (affects background rates)
  - Socio-economic factors
  - Urban/rural differences
Lung Cancer Incidence
LSS, 1958-2009

Cases: 1,445 (male); 1,002 (female)

Sex-averaged, attained age 70, age-at-exposure=30, adjusted for smoking

Cahoon et al., Rad. Res. 2017; 187:513-537
Colon Cancer Incidence
LSS, 1958-2009

Cases: 782 (male); 1,132 (female)

Excess Relative Risk

Weighted Absorbed Colon Dose (Gy)

Sex-averaged, attained age 70, age-at-exposure=30, adjusted for smoking, alcohol, meat, BMI

Liver Cancer Incidence
LSS, 1958-2009

Cases: 1,445 (male); 1,002 (female)

Sex-averaged, attained age 70, age-at-exposure=30, adjusted for smoking, alcohol, BMI

8% of all solid cases

Sadakane et al., submitted
Study Participants in LSS and F1
Breast Cancer
LSS, 1958-2009

Brenner et al., Rad Res, 2018
Uterine Cancer
LSS, 1958-2009

Utada et al., JNCI-CS, 2019
**Effect of Age At Exposure**

**Breast cancer**
Around menarche
(Brenner et al., Rad Res, 2018)

MEDIAN AGE AT MENARCHE (15 yr)

**Uterine corpus cancer**
Before menarche
(Utada et al., JNCI-CS, 2019)

**Median age at menarche (15 yr)**

ERR/Gy by age at exposure for several ages at menarche at attained age 50.
Linear spline model with a knot age at menarche.

ERR/Gy by age at exposure without effect modification by attained age or age at menarche.
Quadratic spline model with a knot at age 15.
Accumulation of large epi/clinical data and biosamples
RERF Cohorts with Biosamples

A-bomb Survivors

Life Span Study (LSS)
120,000 [1950– ]

Adult Health Study (AHS)
25,000 [1958– ]

Offspring of A-bomb Survivors

F₁ Study
77,000 [1946– ]

F₁ Clinical Study (FOCS)
13,000 [2002– ]

In Utero Study
3,600 [1945– ]
(1,000) [1978– ]

Trios
1,000 Families

Blood or Urine
## Current Holdings of Biosamples – AHS and FOCS –

<table>
<thead>
<tr>
<th>Type</th>
<th>Start Year</th>
<th>Subjects</th>
<th>Tubes</th>
<th>Storage Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum</td>
<td>1969</td>
<td>31,000</td>
<td>746,000</td>
<td>–80°C, 4°C</td>
</tr>
<tr>
<td>Plasma</td>
<td>1990</td>
<td>22,000</td>
<td>364,000</td>
<td>–80°C</td>
</tr>
<tr>
<td>Blood Cells</td>
<td>1990</td>
<td>21,000</td>
<td>266,000</td>
<td>–80°C</td>
</tr>
<tr>
<td>Urine</td>
<td>1999</td>
<td>20,000</td>
<td>212,000</td>
<td>–80°C</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>1999</strong></td>
<td><strong>20,000</strong></td>
<td><strong>212,000</strong></td>
<td><strong>–80°C</strong></td>
</tr>
</tbody>
</table>
Summary

Studies to date suggest a linear response at low doses (0-1 mGy) but statistical power is limited in spite of large sample size.

Current studies allow the study of the effect of age on sensitivity to carcinogenic effects.

In breast and uterine cancer sensitivity is associated with age at menarche.

Longitudinally collected biosamples allow the study of early events and underlying mechanisms.