Radiation Effects on Circulatory Diseases
Scientific Understandings and Uncertainties

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Hirosoft International

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Topics

• Epidemiological evidence
  – Radiotherapy patients (High dose 5+ Gy)
  – Atomic bomb survivors
  – Other low dose populations

• Mechanisms

• Implications for radiation protection
Circulatory disease

- Cardiovascular disease (heart disease)
  - Ischaemic (coronary) heart disease (mainly MI)
  - Hypertensive heart disease
  - Valvular heart disease
- Cerebrovascular disease (stroke)
- Peripheral vascular disease
High-Dose Cancer Radiotherapy Patients

• Radiation-induced heart disease (primarily MI)
  – Hodgkin’s lymphoma patients
  – Childhood cancer survivors
  – Breast cancer patients
  – Testicular cancer patients

• Thought to be high dose tissue reaction (deterministic) effect
A-Bomb Survivor Studies

• Mounting evidence of increased risks for non-cancer diseases at lower doses (< 2 Gy)
• Prompting increased interest in possibility of effects at doses relevant for radiation protection
  – UNSCEAR 2006
  – McGale & Darby 2005
  – Little et al 2008
A-Bomb Survivor Studies

History

• Suggestions of elevated circulatory disease risks
  – Life Span Study (LSS) mortality 1950-70
    (Jablons et al, 1971)
    • Only in women
  – Adult Health Study (AHS) morbidity 1958-78
    (Robertson et al, 1974, Kodama et al 1984)
    • Stroke and heart disease Hiroshima females only
    • Heart disease in men and women
A-Bomb Survivor Studies
Initial Concerns

• Effects initially limited to specific subgroups
  – Over time effect has become apparent in men and women in both cities

• Death certificate misclassification

• Confounding by non-radiation factors
  – Are radiation risk estimates affected by smoking, economic status, or other factors

• Selection effects
  – Does the fact of survival affect inference about dose response
A-bomb Survivors
Death Certificate Misclassification

• 22% cancer-to-noncancer misclassification in autopsy data

• Statistical adjustment
  – Reduced non-cancer disease excess relative risk (ERR) by 20% (ERR per Gy 0.06 → 0.05)
  – Increased solid cancer ERR estimate by 13% (ERR per Gy 0.85 → 0.96)
  – Non-cancer risk remains highly significant (P = 0.006)

Spoto et al 1992
Atomic Bomb Survivors
Effect of Confounding

<table>
<thead>
<tr>
<th></th>
<th>People</th>
<th>Deaths</th>
<th>Non-cancer ERR/Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Undajusted</td>
</tr>
<tr>
<td>Men</td>
<td>10,308</td>
<td>1,163</td>
<td>0.07</td>
</tr>
<tr>
<td>Women</td>
<td>13,154</td>
<td>1,121</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Adjustment based on mail survey responses did not appreciably change non-cancer risk estimates.

Potential Confounders
- Smoking
- Education
- Occupation
- Marital status
- House size
- Japanese diet
- Physical activity

LSS Report 12 Shimizu et al 1999
LSS Noncancer Mortality 1950-90
Unmeasurable Confounders

• Confounding less likely when analyses limited to survivors in smaller areas

• Significant dose response seen for
  – 60,000 survivors within 3 km of hypocenter
  – 2,900 survivors between 0.9 and 1.2 km from hypocenter
A-Bomb Survivors
Noncancer Mortality 1968-1997

<table>
<thead>
<tr>
<th>Dose (Gy)</th>
<th>Noncancer disease deaths</th>
<th>Excess</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed</td>
<td>Expected</td>
</tr>
<tr>
<td>&lt;0.005</td>
<td>13,832</td>
<td>13,954</td>
</tr>
<tr>
<td>0.005-0.1</td>
<td>11,633</td>
<td>11,442</td>
</tr>
<tr>
<td>0.1-0.2</td>
<td>2,163</td>
<td>2,235</td>
</tr>
<tr>
<td>0.2-0.5</td>
<td>2,423</td>
<td>2,347</td>
</tr>
<tr>
<td>0.5-1</td>
<td>1,161</td>
<td>1,075</td>
</tr>
<tr>
<td>1-2</td>
<td>506</td>
<td>467</td>
</tr>
<tr>
<td>2+</td>
<td>163</td>
<td>111</td>
</tr>
<tr>
<td>Total</td>
<td>31,881</td>
<td>31,631</td>
</tr>
</tbody>
</table>

- > 50% of the noncancer disease deaths are circulatory disease deaths
- Solid cancer 7,578 deaths 334 excess
- Leukemia: 249 deaths 87 excess

Preston et al 2003
A-Bomb Survivors
Circulatory Disease Mortality 1968-1997

- Significant effect for both heart disease and stroke
- No indication of non-linearity in dose response
- Narrowest dose range with significant effect is 0 to 0.5/1 Gy
A-Bomb Survivors
Other Noncancer diseases 1968-1997

- Significant effects seen for digestive and respiratory disease but not for the infectious or other disease groups
A-bomb Survivors
Healthy Survivor Selection Effects

- Baseline rates ~15% lower for proximal (< 3 km) survivors in 1950
- Difference decline over time and is less than 2% by late 1960’s
- Early period curvature likely to reflect selection effects
AHS Heart Disease Incidence
1958-1998

- 5,035 cases among 10,339 participants
- Significant quadratic dose response

- 117 cases
- Significant quadratic dose response
AHS Clinical Studies
Subclinical changes

Radiation effects on various circulatory disease risk factors

• Changes in age trends for serum cholesterol and blood pressure
• Increased prevalence of isolated systolic hypertension, aortic arch calcification, pulse wave velocity
• Increased inflammatory response markers elevated C-reactive protein levels
LSS Circulatory Disease Risks
Updated analyses

- Follow-up 1950-2003 (6 additional years)
- 19,000 circulatory disease deaths
  - 51% stroke, 45% heart disease
- Significant dose response for heart disease and stroke
- ERR estimates similar to earlier analyses
- Suggestion risk heterogeneity for heart disease subtypes
  - Possibly lower for ischemic heart disease than other types

Shimizu, Kodama et al in progress to appear 2008/9
LSS Circulatory Disease Risks

• Radiation doses below 2 Gy are associated with increased heart disease risks
  – Contribute a significant proportion of radiation-associated mortality

• Cannot rule out linearity, but

• No clear indication of risks below about 0.5 Gy
Other “Low” Dose Studies

- About 45 potentially useful cohorts (<4-5 Gy)
  - Cancer radiotherapy (4)
  - Non-cancer radiotherapy (14)
  - Diagnostic radiation (3)
  - Occupational exposure (24)
- 29 report circulatory disease results
Circulatory Disease Analyses

• **Some dose response analysis** (16 studies)
  • 8 with significant radiation effects (6 from occupational studies)
  • 8 with no significant effects (6 from occupational studies)

• **Internal comparisons** (6 studies)
  • 2 with significant effects
  • 4 with no significant effects

• **External comparison (SMRs, O/E ratios)** (5 studies)
  • One with significantly elevated SMR
  • 4 with no significant differences

• **Not presented** (18 studies)
Ankylosing Spondylitis Patients

- 1,400 with a single course of x-ray therapy
- 2.5 Gy mean cardiac dose; 0.04-4.75 (10-90% range)
- Cerebrovascular disease O/E = 1.14
- Other circulatory disease O/E = 1.25
- Relative risk (compared to a separate un-irradiated spondylitic cohort) = 0.66 for stroke, 0.97 for other circulatory disease

Darby, 1987; McGale 2005
Benign gynecological disease patients

1930-40s, uterus and ovaries irradiated for abnormal bleeding

<table>
<thead>
<tr>
<th>Bone marrow dose, Gy</th>
<th>Coronary heart O/E</th>
<th>Bone marrow dose, Gy</th>
<th>Circulatory O/E</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1.25</td>
<td>0.70</td>
<td>0.01-</td>
<td>0.8</td>
</tr>
<tr>
<td>1.25-1.49</td>
<td>1.27</td>
<td>0.26-</td>
<td>1.0</td>
</tr>
<tr>
<td>&gt;1.5</td>
<td>1.17</td>
<td>0.51-</td>
<td>1.0</td>
</tr>
<tr>
<td>Trend</td>
<td>Borderline significance</td>
<td>&gt;0.76</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unknown</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Cautions: underlying hyper-estrogenic status; cell-killing effects of RT on ovaries

Scottish metropathia hemorrhagica (Smith, 1976) (n= 2,068)

New England BGD patients (Inskip, 1989) (n = 4,483)
Other Medically Irradiated Cohorts

• Massachusetts TB fluoroscopy (repeated exams)
  – 3,351 patients; mean lung dose = 0.91 Gy
  – Circulatory disease SMR
    • 1.0 (exposed women), 1.0 (exposed men)
    • 1.1 (unexposed women), 1.1 (unexposed men)
  – No dose response analysis

• Scoliosis patients (repeated radiographic exams)
  – 5,573 women; mean lung dose = 0.41 Gy
  – Significant dose response
Peptic Ulcer Disease

- 1,859 patients irradiated between 1940 and 1960’s
- Significant trend with dose

<table>
<thead>
<tr>
<th>Weighted cardiac dose, Gy</th>
<th>In-field* dose, Gy</th>
<th>Coronary heart disease RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>1.00</td>
</tr>
<tr>
<td>0.1 – 1.9</td>
<td>0.86 – 9.1</td>
<td>1.00</td>
</tr>
<tr>
<td>2.0 – 2.5</td>
<td>9.2 – 11.7</td>
<td>1.23</td>
</tr>
<tr>
<td>2.6 – 3.0</td>
<td>12.0 – 13.9</td>
<td>1.54</td>
</tr>
<tr>
<td>3.1 – 7.6</td>
<td>14.4 – 35.6</td>
<td>1.51</td>
</tr>
</tbody>
</table>

* 5% of heart in the radiation field

Carr, 2005
Nuclear Worker Studies

• IARC 15-country study  (Vrijheid 2007)
  – 275,000 workers, ~8 years follow-up per person
  average dose 21mSv
  – No significant effects but risk estimates consistent with LSS

• UK NRRW (Muirhead, 1999)
  – 125,000 workers
  – No significant trend

• Chernobyl liquidators (Ivanov, 2006)
  – 61,000 workers
  – Large ERR estimates, but concerns about biases

• No consistent patterns across numerous studies
Radiologists and X-Ray Techs

- **UK radiologists** (Berrington, 2001)
  - SMR comparisons to general population or other type of practitioners provide no indication of increased risk
  - No dose information

- **US radiologists** (Matanoski, 1984)
  - SMR comparisons to other physician specialists suggest higher cardiovascular disease rates especially later in life
  - No dose information

- **US X-ray Techs** (Hauptman, 2003)
  - Higher SMR’s for earlier (higher dose) subcohort
  - No dose estimates (yet)
Current State of Knowledge

• A-bomb survivor evidence compelling for moderate doses (e.g. 0.5 – 2 Gy), unclear at lower doses
• No consistent indications from other studies
• Unconsidered in many populations
• Follow-up often limited
• Power often low
• Mechanisms uncertain
  – A-bomb survivor results increased interest
Mechanisms?

• Inflammation/Microvasculature theory
  – Possible signature changes in microvasculature, e.g., fibrosis
  – Endothelial injury / dysfunction and inflammatory response
    • Possible long-term radiation effects on immune system

• Mutation theory
  – Monoclonal origin of atherosclerotic plaques (G6PD)
    • Transformation of smooth muscle cells in atherogenesis pathway?
  – Oncogene activation, LOH, and microsatellite instability
What Next?
Epidemiology

• Can expect updated / new results
  – A-bomb survivors
    • More information on younger survivors, temporal patterns etc.
    • Type-specific risk estimates
  – New and updated worker studies
    (Sellafield, Mayak., …)
  – Dose response analyses in US XRT cohort

• None of these are likely to provide definitive answers, but should help to reduce uncertainties
What Next? Radiation Protection

• Increasing attention to potential risks (e.g. UNSCEAR, 2008, Little 2008, Schultz-Hector, 2007)

• Uncertainty inhibits direct impact on guidelines now

• Increased pressure for consideration is likely
  – Difficult to incorporate in current framework
  – Need better ways to allow for uncertainties about risk and incorporate them into risk assessment
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