Epidemiological evidence for circulatory diseases – Occupational exposure

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Health Protection Agency, UK

EU Scientific Seminar
Emerging evidence for radiation induced circulatory diseases
Luxembourg, 25 November 2008
Topics to be covered

• Summary of findings from occupational studies
• Limitations of these studies
• Background to the Mayak worker cohort and attributes of this study
• Main findings from Mayak workers on circulatory disease and radiation
• Comparison of the Mayak worker results with those from other occupational studies
• Future research needs
Studies of circulatory disease among radiologists and radiologic technologists

- Higher mortality among US radiologic technologists who started work early in the 20th century compared with those who started work later
  - but less evidence of such a trend among UK and US radiologists (McGale & Darby, Radiat Res, 2005)

- Mortality often less than expected from national rates

- Interpretation restricted by the lack of information on individual doses
  - doses are now being reconstructed for US technologists
Radon-exposed miners

- Studies of circulatory disease mortality have given mixed results (UNSCEAR, 2006)

- By far the largest study was of 59,000 German uranium miners (Kreuzer et al, Radiat Environ Biophys, 2006)
  - This showed no association with cumulative exposure to radon, external gamma radiation or long-lived radionuclides
  - Doses to the heart and arteries are likely to have been low (roughly <100 mSv on average)
  - No information on potential confounders
Nuclear industry workers: international

- Vrijheid et al (Int J Epidemiol, 2007) examined non-cancer mortality among 275,000 workers from 14 countries.
- Findings were consistent both with no raised risk and with a risk of the size seen in the LSS.
- The low statistical power of this analysis reflected:
  - The relatively short follow-up (average age at end of follow-up was 46 years).
  - Relatively low mean dose (20.7 mSv).
- Study excluded workers with potential internal exposures.
Nuclear industry workers: BNFL (UK)

• McGeoghegan *et al* (*Int J Epidemiol*, 2008) examined non-cancer mortality among about 42 000 radiation workers

• Longer follow-up and higher mean external dose (53.0 mSv) than in the international study

• Included workers with internal exposures, but analysis focussed on external doses

• Mortality from circulatory disease and from non-cancer causes combined was less than expected from rates for north-west England
Trend with external dose in circulatory disease mortality among BNFL workers

Excess relative risk, ERR per Sv (90% CI)

All radiation workers 0.65 (0.31, 1.05)

Sub-groups of workers:

- Industrial, external 1.25 (0.44, 2.25)
- Non-industrial, external 1.38 (-0.28, 3.70)
- Industrial, internal* 0.76 (0.30, 1.32)
- Non-industrial, internal -0.29 (-0.73, 0.33)

*Ever monitored for internal exposure
Problems with interpretation of occupational studies of circulatory disease

Potential for bias or confounding

- “Healthy worker effect” complicates comparisons with national mortality rates
- Usually based on mortality data
  - potential for misclassification of specific disease types
- Generally lack information on known risk factors for circulatory disease
  - eg. smoking, alcohol consumption
Problems with interpretation of occupational studies of circulatory disease (continued)

Low statistical power

- Many studies restricted in terms of cohort size, length of follow-up and/or range of doses
- LSS suggests that raised risk of circulatory disease is lower – in relative terms – than that for cancer
  - less than 10% increase for doses below 0.5 Sv
- However, important to recognise that, because circulatory disease is so common, a small relative risk may represent an absolute excess risk similar to that for cancer
The first Russian nuclear facility – Mayak Production Association – started operation in June 1948. Mayak PA is located 10 km from Ozyorsk city in the Southern Urals.

“Mayak” PA:
- Production reactors
- Radiochemical plant
- Plutonium plant
- Auxiliary plants
Collection of primary data

- **SUBI Biophysical Laboratory database**
  - Doses of internal exposure from Pu, Pu body and organ burdens
  - Quality control

- **SUBI Epidemiological department database**
  - Identification data, vital status
  - Quality control

- **Mayak PA database**
  - Dose of external exposure, work history
  - Quality control

**“Clinic” medical-dosimetric database of the SUBI Clinical department**

- **Passport Department**
  - Residence status, address

- **SUBI archive**
  - Archival medical cards, archival case histories

- **City hospital archive**
  - Archival medical cards, archival case histories, autopsy protocols

- **City hospital and polyclinics**
  - Current medical cards, logs of admission to a hospital, registry logs of the emergency

Search, collection and extraction of medical and other information by physician and/or medical nurse; coding of diseases and causes of death (ICD-9) by physician

- **Coding cards**
  - Entry into database
  - Correction of errors
  - Entry into database

**“Clinic” medical-dosimetric database of SUBI Clinical Department**

**Civilian Registry Office**

**SUBI Cause of Death Registry**

**Date and cause of death**

Structure of the “Clinic” medical dosimetric database

Mayak worker cohort

Identification number

Passport data
• Surname, name, patronymic name
• Gender
• Date of birth
• Nationality
• Education

Medical history and vital status
• Date of pre-employment examination
• Date of “last medical information”
• Vital status
• Residence status (Ozyorsk resident or migrant)
• Date of death
• Cause of death
• Autopsy data

Initial state of health

Smoking history

Alcohol consumption history

Clinical data
• Morbidity data
• Peripheral blood
• Blood pressure
• Body mass

Selected workers
• Bone marrow
• Cytogenetic analysis
• Biochemical analysis of blood
• Respiratory function
• Roentgenography of lungs

Patients with Acute Radiation Syndrome (ARS)
• Symptoms and signs
• Treatment

Patients with Chronic Radiation Sickness (CRS)
• Symptoms and signs
• Treatment

Patients with plutonium pneumosclerosis (PuPn)
• Symptoms and signs
• Treatment

Workers with Local Radiation Injuries (LRI)
• Localization
• Severity degree
• Symptoms and signs
• Treatment

Expert review and verification of diseases and deterministic effects

Reproduction

Females
• Characteristics of reproductive cycle
• Pregnancies and their outcomes

Families
• Wife
• Husband
• Children

Work history
• Date of starting work
• Date of stopping work
• Place of employment
• Occupation

Dosimetry data
• Shift doses
• Monthly doses
• Annual doses
• Absorbed doses to organs

Internal exposure from incorporated plutonium-239
• Body burden
• Monthly and annual absorbed doses to organs

ARS patients
• Accident doses (gamma and neutron exposure)
• Duration of acute exposure

Preconception doses

Doses during pregnancy

Southern Urals Radiation Risk Research (SOUL)

- supported by the European Commission’s 6th Framework Programme (Euratom) and the Federal Medical Biological Agency (Russian Federation)

Work Package 2.4: Research objective

- To estimate risks of morbidity and mortality from circulatory diseases up to the end of 2000 in the cohort of workers first employed at the main facilities of Mayak PA in 1948-1958 in relation to external and internal radiation, whilst allowing for age, gender and non-radiation risk factors
## Characteristics of the cohort of Mayak workers first employed in 1948-1958

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Workers included in the cohort</strong></td>
<td>12210</td>
<td>100.0</td>
</tr>
<tr>
<td><strong>Females</strong></td>
<td>3552</td>
<td>29.1</td>
</tr>
<tr>
<td><strong>Migrants from Ozyorsk</strong></td>
<td>6557</td>
<td>53.7</td>
</tr>
<tr>
<td><strong>Vital status known</strong></td>
<td>10789</td>
<td>88.4</td>
</tr>
<tr>
<td><strong>Died</strong></td>
<td>5685</td>
<td>52.7</td>
</tr>
<tr>
<td><strong>Died in Ozyorsk</strong></td>
<td>3009</td>
<td>52.9</td>
</tr>
<tr>
<td><strong>Autopsy performed</strong></td>
<td>1948</td>
<td>34.3</td>
</tr>
<tr>
<td><strong>Autopsy performed in Ozyorsk</strong></td>
<td>1868</td>
<td>95.9</td>
</tr>
<tr>
<td><strong>Cause of death known</strong></td>
<td>5317</td>
<td>93.5</td>
</tr>
<tr>
<td><strong>Alive as of 31 December 2000</strong></td>
<td>5104</td>
<td>47.3</td>
</tr>
<tr>
<td><strong>Alive and lived in Ozyorsk as of 31 December 2000</strong></td>
<td>2548</td>
<td>49.9</td>
</tr>
<tr>
<td><strong>Medical documentation (morbidity data) available</strong></td>
<td>11597</td>
<td>95.0</td>
</tr>
</tbody>
</table>
Radiation monitoring

- Individual monitoring of exposures to external gamma doses was conducted from the beginning of operations at Mayak
  - Annual external gamma doses are available for 99.9% of workers in the study cohort
- Regular monitoring of internal exposure among those who worked with transuranium radionuclides began later, during the 1960s
- Plutonium body burden was measured (and estimates of internal doses were subsequently derived) only for 30% of workers who were in contact with transuranium radionuclides
  - Analyses of internal exposures are restricted to monitored workers
## Dosimetry (Mayak Doses 2005)

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Average total dose ± SE (range), Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>External gamma</em></td>
<td></td>
</tr>
<tr>
<td>males</td>
<td>0.91±0.01 (0-5.92)</td>
</tr>
<tr>
<td>females</td>
<td>0.65±0.01 (0-5.70)</td>
</tr>
</tbody>
</table>
The distribution of workers in the study cohort by total external gamma dose is shown in the graph. The x-axis represents the total external gamma dose in Gy, while the y-axis indicates the percentage of total number of workers with measured dose. The graph is divided into categories: Males, Females, and Both. The distribution shows a higher percentage of males and females in the 0-1.00 Gy range, with a gradual decrease as the dose increases, indicating a lower percentage of workers with measured dose beyond 5.00 Gy.
## Dosimetry (Mayak Doses 2005)

### Exposure

<table>
<thead>
<tr>
<th>Internal alpha (Pu-239, liver)</th>
<th>Average total dose ± SE (range), Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>males</td>
<td>0.40±0.02 (0-17.90)</td>
</tr>
<tr>
<td>females</td>
<td>0.81±0.13 (0-127.82)</td>
</tr>
</tbody>
</table>

- Liver dose used as surrogate for dose to blood vessels/heart - *these doses would differ but they should be highly correlated*
Distribution of workers in the study cohort with measured plutonium body burden by total liver dose from internal alpha exposure to Pu-239

% of total number of workers with measured dose

Male
Female
Both

Total internal alpha dose to liver, Gy

0-0.025 0.025-0.05 0.05-0.10 0.10-0.25 0.25-0.50 0.50-1.00 >1.00

SUBI
SOUL
Quality control

• Conducted on a regular basis

• For this analysis, specific checks were conducted on:
  – *identification of the worker cohort*
  – *dosimetry*
  – *non-radiation risk factors*
  – *follow-up*

• These checks showed a high level of data accuracy and completeness
Examples of quality control findings

- Level of data loss was only about 2.5%
- Expert reviews of samples of circulatory diseases diagnosis showed high levels of diagnostic verification (98.8% for acute myocardial infarction and 94.9% for stroke)
- Estimated that only 1.7% of cases of circulatory diseases were missed in the database
- Comparison of smoking and alcohol consumption data from different sources showed good agreement (93 - 95%)
- Errors identified were corrected
Period of follow-up

Start of follow-up
• Date of first employment at one of the main plants of Mayak PA

End of follow-up  The earliest of:
• Date of first diagnosis of circulatory disease (*for morbidity analysis*);
• Date of death;
• 31 December 2000;
• Date of migration from Ozyorsk (*for morbidity analysis*);
• Date of last known vital status.
Effects studied

- Ischemic heart disease (IHD; ICD9: 410-414)

- Cerebrovascular disease (CVD; ICD9: 430-438)
### Numbers of deaths or cases and corresponding numbers of person-years for analyses of risks of circulatory disease morbidity and mortality

<table>
<thead>
<tr>
<th></th>
<th>Number of cases</th>
<th>Number of person-years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality - IHD</td>
<td>1495</td>
<td>443350</td>
</tr>
<tr>
<td>Mortality - CVD</td>
<td>753</td>
<td>443350</td>
</tr>
<tr>
<td>Morbidity - IHD</td>
<td>3751</td>
<td>205249</td>
</tr>
<tr>
<td>Morbidity - CVD</td>
<td>4418</td>
<td>197344</td>
</tr>
</tbody>
</table>
Analyses of non-radiation risk factors

Increased risks of morbidity and mortality from circulatory diseases were found in the study cohort in relation to:

- Gender
- Age
- Hypertension
- Increased body mass index
- Smoking
Methods for analysing radiation risks

• Relative risks were calculated for categories of external/internal dose, having adjusted for non-radiation factors via stratification

• Trends in relative risk with dose (excess relative risk per Gy, ERR/Gy) calculated using a similar approach

• Sensitivity analyses considered impact of adjusting for additional factors and using different lag periods

• Effect modification was considered by considering sub-groups of workers
Relative risk & 95% CI for analyses of external dose

<table>
<thead>
<tr>
<th></th>
<th>IHD (vs. &lt;0.5 Gy)</th>
<th>CVD (vs. &lt;0.5 Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5 - 1.0 Gy</td>
<td>0.5 - 1.0 Gy</td>
</tr>
<tr>
<td>Mortality</td>
<td>0.92 (0.78, 1.08)</td>
<td>1.15 (0.92, 1.43)</td>
</tr>
<tr>
<td>Morbidity</td>
<td>1.02 (0.92, 1.13)</td>
<td>1.14 (1.04, 1.25)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.20 (1.09, 1.32)</td>
</tr>
</tbody>
</table>
ERR/Gy & 95% CI for analyses of external dose
IHD (morbidity)
ERR/Gy = 0.109 (0.049-0.168)
ERR/Gy & 95% CI for analyses of external dose
CVD (morbidity)
ERR/Gy = 0.464 (0.360-0.567)
Sensitivity analyses and effect modification for external dose analyses

- Findings for IHD morbidity and CVD morbidity did not vary greatly when:
  - adjusting for extra non-radiation factors;
  - adjusting for internal dose;
  - using different lag periods

- Raised risk of IHD morbidity seen mainly in males, but findings were consistent across genders

- Raised risk of CVD morbidity seen in both genders:
  \[ \text{ERR/Gy} = 0.39 \, (0.28-0.52), \text{ males} \]
  \[ = 0.71 \, (0.44-0.97), \text{ females} \]
**Relative risk & 95% CI for analyses of internal liver dose**

<table>
<thead>
<tr>
<th></th>
<th>IHD (vs. &lt;0.1 Gy)</th>
<th>CVD (vs. &lt;0.1 Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.1- 0.5 Gy</td>
<td>&gt; 0.5 Gy</td>
</tr>
<tr>
<td>Mortality</td>
<td>1.33 (1.08, 1.64)</td>
<td>1.59 (1.16, 2.19)</td>
</tr>
<tr>
<td>Morbidity</td>
<td>1.17 (1.06, 1.30)</td>
<td>1.23 (1.04, 1.45)</td>
</tr>
<tr>
<td>Mortality</td>
<td>1.40 (1.02, 1.92)</td>
<td>1.05 (0.61, 1.80)</td>
</tr>
<tr>
<td>Morbidity</td>
<td>1.23 (1.13, 1.35)</td>
<td>1.58 (1.35, 1.85)</td>
</tr>
</tbody>
</table>
ERR/Gy & 95% CI for analyses of internal liver dose
IHD (mortality)
ERR/Gy = 0.275 (0.050-0.501)
ERR/Gy & 95% CI for analyses of internal liver dose
CVD (morbidity)
ERR/Gy = 0.155 (0.075-0.235)
Sensitivity analyses and effect modification for internal dose analyses

IHD mortality

- Little change in results when adjusting for extra non-radiation factors or using different lag periods
- However, ERR/Gy is lower and not statistically significant after adjusting for external dose

CVD morbidity

- Little change in results when adjusting for extra non-radiation factors or for external dose
- ERR/Gy increases with increasing lag period
- Raised risks seen separately among workers at the radiochemical plant and at the plutonium plant
Comparison of **IHD** findings from various studies of external exposure

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Mean cumulative dose (Gy)</th>
<th>Mortality or morbidity?</th>
<th>No. of deaths or cases</th>
<th>ERR/Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japanese A-bomb survivors:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LSS</td>
<td>0.20</td>
<td>Mortality</td>
<td>4,477</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(90% CI 0.08, 0.26)</td>
</tr>
<tr>
<td>Adult Health Study</td>
<td>0.57</td>
<td>Morbidity</td>
<td>1,546</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(95% CI -0.05, 0.16)</td>
</tr>
<tr>
<td>Mayak workers</td>
<td>0.84</td>
<td>Mortality</td>
<td>1,495</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(95% CI -0.02, 0.15)</td>
</tr>
<tr>
<td>Mayak workers</td>
<td>0.84</td>
<td>Morbidity</td>
<td>3,751</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(95% CI 0.05, 0.17)</td>
</tr>
<tr>
<td>Nuclear workers (international)</td>
<td>0.018</td>
<td>Mortality</td>
<td>5,821</td>
<td>-0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(95% CI -0.59, 0.69)</td>
</tr>
<tr>
<td>BNFL workers (UK)</td>
<td>0.053</td>
<td>Mortality</td>
<td>3,567</td>
<td>0.70</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(90% CI 0.33, 1.11)</td>
</tr>
<tr>
<td>Chernobyl recovery operations workers (Russia)</td>
<td>0.109</td>
<td>Morbidity</td>
<td>10,942</td>
<td>0.41</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(95% CI 0.05, 0.78)</td>
</tr>
</tbody>
</table>
## Comparison of CVD findings from various studies of external exposure

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Mean cumulative dose (Gy)</th>
<th>Mortality or morbidity?</th>
<th>No. of deaths or cases</th>
<th>ERR/Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japanese A-bomb survivors:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LSS</td>
<td>0.20</td>
<td>Mortality</td>
<td>3,954</td>
<td>0.12 (90% CI 0.02, 0.22)</td>
</tr>
<tr>
<td>Adult Health Study</td>
<td>0.57</td>
<td>Mortality</td>
<td>729</td>
<td>0.07 (95% CI -0.08, 0.24)</td>
</tr>
<tr>
<td>Mayak workers</td>
<td>0.84</td>
<td>Mortality</td>
<td>753</td>
<td>-0.02 (95% CI -0.12, 0.07)</td>
</tr>
<tr>
<td>Nuclear workers (international)</td>
<td>0.018</td>
<td>Mortality</td>
<td>1,224</td>
<td>0.88 (95% CI -0.67, 3.16)</td>
</tr>
<tr>
<td>BNFL workers (UK)</td>
<td>0.053</td>
<td>Mortality</td>
<td>1,018</td>
<td>0.43 (90% CI -0.10, 1.12)</td>
</tr>
<tr>
<td>Chernobyl recovery operations workers (Russia)</td>
<td>0.109</td>
<td>Mortality</td>
<td>12,832</td>
<td>0.45 (95% CI 0.11, 0.80)</td>
</tr>
</tbody>
</table>
Conclusions of Mayak analysis

- Raised risks of circulatory disease have been found in relation to:
  - external radiation dose, having adjusted for non-radiation factors and internal dose, and
  - internal radiation dose, having adjusted for non-radiation factors and (in the case of CVD morbidity) for external dose

- Risk estimates for external radiation are generally compatible with those from other large occupational studies and for the A-bomb survivors
Future research needs

• More powerful information on the effects of protracted exposures at lower doses, whilst allowing for non-radiation factors

• Among Mayak workers, this topic is currently being addressed by:
  - expanding the cohort to include workers employed after 1958, who tended to receive lower doses than earlier workers
  - extending the period of follow-up until 31 December 2005
  - considering diagnostic medical exposures
Acknowledgements

• European Commission

• Federal Medical Biological Agency of the Russian Federation