The International Nuclear Worker Study (INWORKS)

Improving knowledge on cancer mortality risk from low-dose exposure to ionizing radiation

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The INWORKS study was approved by the IARC ethics committee

Disclaimer: The findings and conclusions in this study are those of the authors and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

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Protection standards for nuclear workers and public against risks associated with ionizing radiation (IR) exposure are primarily based on epidemiological studies of Japanese survivors of the atomic bombings of Hiroshima and Nagasaki in 1945.

These studies brought out an excess of leukaemia and later an excess of solid cancer due to IR.

However, the pattern of exposure in the cohort of the survivors, i.e. acute high dose rate exposure, is not typical of exposure received by workers and public, i.e. protracted low dose rate exposures.

There remains still today a lack of precision in the estimation of health risks associated with exposure to protracted low doses of IR accrued at low dose rates.
In the 2000s, an international study pooled data from nuclear workers of 15 countries (Cardis et al., BMJ, 2005)

- this study showed an excess of solid cancer associated to the dose of IR
- the power of this study was hampered by the short length of follow-up

A new large International Nuclear WORKer Study, INWORKS, was set out in 2011

- large number of subjects
- long length of time for follow-up (observation)
INWORKS Approach

- Cohort study of nuclear workers

- INWORKS consortium
  - Coordination: IARC
  - Cohort provision: IRSN (France), PHE (UK), NIOSH (US)
  - Expertise: UNC (US), CREAL (Spain)

- Protocol approved in 2011

- Data (and analyses) housed at IARC

- Analytical contributions by all partners
INWORKS Objectives

To quantify the risk of cancer and non-cancer mortality associated with low protracted IR dose

What is the dose-risk relationship between external doses cumulated by nuclear workers and mortality from solid cancer and leukemia?

Are the dose-risk relationships observed among nuclear workers similar to those derived from the follow-up of the A-Bomb survivors?

What do the results bring regarding the current radiation protection system?
General methods applied in INWORKS
Methods

Pooled analysis of mortality in nuclear worker cohorts assembled from three countries

National cohort
n = 59,003

UK NRRW
n = 147,866

US combined cohort
n = 101,428

Workers employed at least 1 year and monitored for external exposure to ionizing radiation (individual dosimeters)

- CEA civil
- AREVA NC
- EDF
- UK Atomic Energy Authority
- British Nuclear Fuels plc
- British Energy Generation and Magnox Electric Ltd
- Atomic Weapons Establishment
- Ministry of Defence
- Hanford Site
- Idaho National Laboratory
- Oak Ridge National Laboratory
- Portsmouth Naval Shipyard
- Savannah River Site

308,297 workers
Methods

Mortality follow up

- Until 2001 (UK), 2004 (Fr), and 2005 (US)
- Vital status and underlying cause of death obtained from national registries

Dosimetry

- Dose calculation methods identical in the three cohorts
- Recorded gamma doses converted into estimates of individual equivalent $H_p(10)$ doses
- Estimated organ doses (colon, lung, red bone marrow, female breast)
- Characterized uncertainty (by types of dosimeter, monitoring period...)
- Flagging of workers exposed to neutrons and internal contamination
Methods

- **Statistical analysis**
  - Regression modeling controlling for key confounders (age, sex, country...)

- **Estimation of mortality rate associated with cumulative dose**
  
  \[ RR(dose) = 1 + \beta \times dose \]

  where \( \beta \) is an estimate of the **excess relative rate** (ERR)

- **Cumulative doses were lagged to allow for an induction and latency period between exposure to IR and death: 2 or 10 years**

- **Sensitivity analyses**
  - Dose-response shape, restricted dose range, country effects...
Results
Results – Characteristics of INWORKS cohort, 1943-2005

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of workers</td>
<td>308,297</td>
</tr>
<tr>
<td>Male workers</td>
<td>87%</td>
</tr>
<tr>
<td>Range of year of birth</td>
<td>1873-1983</td>
</tr>
<tr>
<td>Mean duration of employment (SD) in years</td>
<td>15 (11)</td>
</tr>
<tr>
<td>Mean age at last observation (SD) in years</td>
<td>58 (15)</td>
</tr>
<tr>
<td>Mean duration of follow-up (SD) in years</td>
<td>27 (12)</td>
</tr>
<tr>
<td>Total person years (million)</td>
<td>8.2</td>
</tr>
<tr>
<td>Vital status</td>
<td></td>
</tr>
<tr>
<td>Alive</td>
<td>236,913 (76.9%)</td>
</tr>
<tr>
<td>Deceased</td>
<td>66,632 (21.6%)</td>
</tr>
<tr>
<td>solid cancer</td>
<td>17,957</td>
</tr>
<tr>
<td>leukemia (excluding chronic lymphocytic leukemia)</td>
<td>531</td>
</tr>
<tr>
<td>circulatory diseases</td>
<td>27,848</td>
</tr>
<tr>
<td>Emigrated or lost to follow-up</td>
<td>4,752 (1.5%)</td>
</tr>
</tbody>
</table>
## Results – Characteristics of INWORKS cohort, 1943-2005

Distribution of individual doses among cohort participants

<table>
<thead>
<tr>
<th></th>
<th>$H_p(10)$ dose (mSv)</th>
<th>Colon dose (mGy)</th>
<th>RBM dose (mGy)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Annual doses</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>1.73</td>
<td>1.20</td>
<td>1.09</td>
</tr>
<tr>
<td><strong>Cumulative doses</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (range)</td>
<td><strong>25.2</strong> (0.0, 1932.5)</td>
<td><strong>17.4</strong> (0.0, 1331.7)</td>
<td><strong>15.9</strong> (0.0, 1217.5)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td><strong>3.4</strong> (0.4, 18.4)</td>
<td><strong>2.3</strong> (0.3, 12.8)</td>
<td><strong>2.1</strong> (0.3, 11.7)</td>
</tr>
</tbody>
</table>

Values include doses recorded as zero. RBM = red bone marrow. IQR = interquartile range (25th percentile, 75th percentile)
Results – Characteristics of INWORKS cohort, 1943-2005

Distribution of cumulative red bone marrow doses among workers
Results for lymphatic & hematopoietic cancers
## Results – Lymphatic & hematopoietic cancers

### ERR per Gy of cumulative red bone marrow dose

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>No of deaths</th>
<th>ERR per Gy</th>
<th>(90%-CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia excluding CLL*</td>
<td>531</td>
<td>2.96</td>
<td>(1.17–5.21)</td>
</tr>
<tr>
<td>Chronic myeloid leukemia*</td>
<td>100</td>
<td>10.45</td>
<td>(4.48–19.65)</td>
</tr>
<tr>
<td>Acute myeloid leukemia*</td>
<td>254</td>
<td>1.29</td>
<td>(-0.82–4.28)</td>
</tr>
<tr>
<td>Acute lymphoblastic leukemia*</td>
<td>30</td>
<td>5.80</td>
<td>(ne–31.57)</td>
</tr>
<tr>
<td>CLL*</td>
<td>138</td>
<td>-1.06</td>
<td>(ne–1.81)</td>
</tr>
<tr>
<td>Multiple myeloma**</td>
<td>293</td>
<td>0.84</td>
<td>(-0.96–3.33)</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma**</td>
<td>710</td>
<td>0.47</td>
<td>(-0.76–2.03)</td>
</tr>
<tr>
<td>Hodgkin’s lymphoma**</td>
<td>104</td>
<td>2.94</td>
<td>(ne–11.49)</td>
</tr>
</tbody>
</table>

CLL=chronic lymphocytic leukemia. ne=not estimated. * 2-y lag assumption. ** 10-y lag assumption
Results – Risk of non-CLL leukemia and RBM dose

ERR per Gy = 2.96; 90%–CI [1.17–5.21]
Results – Risk of non-CLL leukemia and RBM dose

(from Leuraud et al., Lancet Haematol 2015)

No improvement compared to the linear model
Results – Risk of leukemia over restricted RBM dose ranges

Not significant when restricted to less than 300 mGy but similar slopes

ERR per Gy=2.68; 90%CI[-1.45–7.78]
Results – Sensitivity analyses for non CLL-leukemia risk

- Dose-response did not substantially improve with addition of nonlinear (quadratic) term in model
- Little between-country heterogeneity
- Alternative lag assumptions changed results little
- The ERR persisted when excluding neutron-exposed workers
  - ERR per Gy=4.19; 90%-CI [1.42–7.80]
- The ERR persisted when adjusting for internal contamination:
  - ERR per Gy=3.39; 90%-CI [1.39–5.93]
Results – Risk of leukemia, interpretation and excess deaths

- Note that the ERR is expressed per Gy
  - Similarly, the estimated ERR from non CLL-leukemia can be expressed per 10 mGy, a scale more representative of the average mean of the workers
  - ERR per 10 mGy=0.03; 90%-CI [0.01-0.05]
  - An exposure at 10 mGy multiplies the baseline cancer risk by 1.03

- Estimated number of excess deaths due to non-CLL leukemia under the hypothesis of a linear ERR model
  - 31 excess deaths among 531 observed deaths

- Additional probability of death by leukemia attributable to exposure to IR in the studied population
  - ≈ 1 death per 10 000 persons
Risk of cancer other than leukemia
## Results – Risk of cancer and colon dose

ERR per Gy for death due to specific cancer categories under a 10-y lag assumption

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>No of deaths</th>
<th>ERR per Gy (90%-CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cancer</td>
<td>19 748</td>
<td>0.51 (0.23–0.82)</td>
</tr>
<tr>
<td>All cancer other than leukemia</td>
<td>19 064</td>
<td>0.48 (0.20–0.79)</td>
</tr>
<tr>
<td>Solid cancer</td>
<td>17 957</td>
<td>0.47 (0.18–0.79)</td>
</tr>
<tr>
<td>Solid cancer other than lung cancer</td>
<td>12 155</td>
<td>0.46 (0.11–0.85)</td>
</tr>
</tbody>
</table>
Results – Risk of cancer excluding leukemia and colon dose

ERR per Gy = 0.48; 90%-CI [0.20–0.79]
## Results – Risk of cancer excluding leukemia, excess deaths

<table>
<thead>
<tr>
<th>10-y lagged cumulative colon dose (in mGy)</th>
<th>Mean dose</th>
<th>Person-years (thousands)</th>
<th>Observed</th>
<th>Fitted Excess</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5</td>
<td>0.6</td>
<td>6089</td>
<td>10 433</td>
<td>5.4</td>
</tr>
<tr>
<td>5-&lt;10</td>
<td>7.2</td>
<td>595</td>
<td>2 065</td>
<td>7.1</td>
</tr>
<tr>
<td>10-&lt;20</td>
<td>14.3</td>
<td>545</td>
<td>2 026</td>
<td>14.3</td>
</tr>
<tr>
<td>20-&lt;50</td>
<td>31.7</td>
<td>533</td>
<td>2 126</td>
<td>32.2</td>
</tr>
<tr>
<td>50-&lt;100</td>
<td>70.1</td>
<td>257</td>
<td>1 167</td>
<td>37.9</td>
</tr>
<tr>
<td>100-&lt;150</td>
<td>121.7</td>
<td>95</td>
<td>489</td>
<td>27.0</td>
</tr>
<tr>
<td>150-&lt;200</td>
<td>172.1</td>
<td>46</td>
<td>306</td>
<td>20.3</td>
</tr>
<tr>
<td>200-&lt;300</td>
<td>240.6</td>
<td>39</td>
<td>241</td>
<td>29.2</td>
</tr>
<tr>
<td>300-&lt;400</td>
<td>341.4</td>
<td>14</td>
<td>122</td>
<td>16.9</td>
</tr>
<tr>
<td>400-&lt;500</td>
<td>442.3</td>
<td>5</td>
<td>49</td>
<td>9.1</td>
</tr>
<tr>
<td>500-</td>
<td>630.8</td>
<td>4</td>
<td>40</td>
<td>9.8</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>--</strong></td>
<td><strong>8 222</strong></td>
<td><strong>19 064</strong></td>
<td><strong>209.2</strong></td>
</tr>
</tbody>
</table>

### Crude attributable rate

\[
209.2 / 308 297 \approx 7 \text{ per } 10 000 \text{ persons}
\]
**Results – Risk of cancer excluding leukemia over restricted colon dose ranges**

<table>
<thead>
<tr>
<th>10-y lagged cumulative dose range (mGy)</th>
<th>ERR per Gy</th>
<th>90%-CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entire dose range</td>
<td>0.48</td>
<td>0.20–0.79</td>
</tr>
<tr>
<td>0–200</td>
<td>1.04</td>
<td>0.55–1.56</td>
</tr>
<tr>
<td>0–150</td>
<td>0.69</td>
<td>0.10–1.30</td>
</tr>
<tr>
<td>0–100</td>
<td>0.81</td>
<td>0.01–1.64</td>
</tr>
</tbody>
</table>
Results – Sensitivity analyses for cancer other than leukemia

- Dose-response did not substantially improve with addition of nonlinear (quadratic) term in model
- No evidence of between-country heterogeneity
- Alternative lag assumptions changed results little
- Excluding neutron-exposed workers: ERR per Gy=0.55; 90%-CI [0.17–0.95]
- Adjusting for internal contamination: ERR per Gy=0.46; 90%-CI [0.17–0.78]
Comparison with other studies
Consistency of dose-risk relationships

- **15-Country study** [Cardis 2005]
  - **INWORKS** [Richardson 2015, Leuraud 2015]
  - **Life Span Study** [Ozasa 2012]
    (restricted to men aged between 20-60 at time of exposure)

**Solid cancers**
- 0.47 (17,957)
- 0.25 (3,475)
- 0.87 (4,770)

**Non-CLL leukemia**
- 1.93 (196)
- 2.96 (531)
- 2.63 (94)

Estimated ERR per Gy in INWORKS close to estimates derived in the LSS
Strengths and limitations of INWORKS

Limitations

- Mortality study, not ideal for highly survivable cancers
- Poor precision of flags (neutron, contamination)
- Uncertainties in dose (reporting limits, measurement errors)
- No non-occupational dose information
- No information on other risk factors (e.g., benzene, smoking)
- Age at end of follow-up still limited (mean 58 years)

Strengths

- High-quality occupational dose
- Predominantly gamma dose (good confidence in organ dosimetry)
- Large pooled cohort with lengthy follow-up: ↑ power (8.2 millions person-years vs 3.3 for the total LSS)
- Standardized protocol across three countries
- Elaborated statistical analyses (recognized methodology, different partners, use of different modelling approaches, sensitivity analyses)
INWORKS has a large capacity to demonstrate dose-risk relationships associated with exposure to protracted low doses of external radiation

- Significant, robust dose-responses observed for cancers (solid, leukemia)
- Analyses on temporal factors effects (age at exposure, time since exposure): manuscript submitted to journal
- Analyses of non-cancer diseases: manuscript submitted to journal

Dose-risk relationships are no more significant below several tens of mGy but the risk coefficients remain similar

Derived attributable risks are small
Conclusion

- Risk coefficients in INWORKS are similar to those derived from the A-bomb survivors study

- The results are compatible with one of the main underlying hypothesis of the current radiation protection system
  - extrapolation of relationships obtained from acute high doses settings to low protracted doses settings

- These results support the rationale for radiation protection of populations exposed to low protracted doses of IR

- Results are complementary to radiobiological research
Publications


INWORKS collaborators

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