Risk of leukaemia, lymphoma, and multiple myeloma in an international study of nuclear workers (INWORKS)

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Extrapolation from acute to protracted low doses

Transposition of risks from acute to chronic exposure is a major hypothesis of the radiation protection system.

Lack of information on health effects of low dose.
Advantages of nuclear worker studies

- Well defined populations, since mid 40s
- Large size
- Stable work history and good quality of follow-up
- Individual monitoring of external radiation exposure

Very good capacity to quantify the shape of the dose-risk relationship associated with low dose protracted exposure

Epidemiological cohorts first implemented in the 70s

Previous pooling studies (Cardis et al. Rad Res 1995; Cardis et al. BMJ 2005)
INWORKS population

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

International Agency for Research on Cancer
Centre International de Recherche sur le Cancer
308 297 workers
Objectives of INWORKS

To improve the characterization of the shape of the dose-risk relationship associated with low dose protracted external radiation exposure

- What is the gain in statistical power provided by the pooling of the 3 cohorts?

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

- What does it bring regarding the current radiation protection system?
Cohort Profile

Cohort Profile: The International Nuclear Workers Study (INWORKS)

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Comparison with the 15-country study

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>15-country study</th>
<th>INWORKS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of workers</td>
<td>407,391</td>
<td>308,297</td>
</tr>
<tr>
<td>Mean employment duration (years)</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>Mean age at end of follow-up (years)</td>
<td>46</td>
<td>58</td>
</tr>
<tr>
<td>Mean duration of follow-up (years)</td>
<td>13</td>
<td>27</td>
</tr>
<tr>
<td>Number of person-years (million)</td>
<td>5,2</td>
<td>8,2</td>
</tr>
<tr>
<td>Mean cumulative whole-body dose (mSv)</td>
<td>19</td>
<td>24</td>
</tr>
<tr>
<td>Number of deaths</td>
<td>24 158</td>
<td>66 632</td>
</tr>
<tr>
<td>solid cancer</td>
<td>4 770</td>
<td>17 957</td>
</tr>
<tr>
<td>leukemia excl LLC</td>
<td>196</td>
<td>531</td>
</tr>
<tr>
<td>circulatory disease</td>
<td>8 412</td>
<td>27 848</td>
</tr>
</tbody>
</table>

Better homogeneity of data quality
Increased statistical power
Longer duration of follow-up
Dose Estimation for a Study of Nuclear Workers in France, the United Kingdom and the United States of America: Methods for the International Nuclear Workers Study (INWORKS)

INWORKS: cumulative doses

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Total number of workers (percentage of exposed workers)</th>
<th>$H_{t}(10)$ (mSv) Mean (median; IQR)</th>
<th>Colon (mGy) Mean (median; IQR)</th>
<th>Lung (mGy) Mean (median; IQR)</th>
<th>RBM (mGy) Mean (median; IQR)</th>
<th>Breast (mGy) (women only) Mean (median; IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>France</td>
<td>59,003 (72%)</td>
<td>18.4 (2.1; 0.0,17.0)</td>
<td>12.6 (1.4; 0.0,11.6)</td>
<td>12.6 (1.4; 0.0,11.7)</td>
<td>11.6 (1.3; 0.0,10.7)</td>
<td>2.8 (0; 0.0,0.93)</td>
</tr>
<tr>
<td>UK</td>
<td>147,866 (88%)</td>
<td>28.7 (4.2; 0.6,2.4)</td>
<td>19.9 (2.9; 0.4,14.1)</td>
<td>19.8 (2.9; 0.4,14.1)</td>
<td>18.2 (2.6; 0.4,12.9)</td>
<td>5.1 (1.4; 0.4,4.3)</td>
</tr>
<tr>
<td>U.S.</td>
<td>101,428 (83%)</td>
<td>24.0 (2.9; 0.3,16.7)</td>
<td>16.7 (2.1; 0.2,11.6)</td>
<td>16.6 (2.0; 0.2,11.5)</td>
<td>15.2 (1.9; 0.2,10.6)</td>
<td>3.7 (0.4; 0.0,2.3)</td>
</tr>
<tr>
<td>Total</td>
<td>308,297 (83%)</td>
<td>25.2 (3.4; 0.4,18.4)</td>
<td>17.4 (2.3; 0.3,12.8)</td>
<td>17.4 (2.3; 0.3,12.7)</td>
<td>15.9 (2.1; 0.3,11.7)</td>
<td>4 (0.6; 0.0,2.8)</td>
</tr>
</tbody>
</table>

*Notes.* Values include doses recorded as zero. RBM = red bone marrow. IQR = interquartile range (25th percentile, 75th percentile).

*The cohort includes 268,262 men and 40,035 women.*

94% of workers cumulated less than 100 mSv

[Thierry-Chef et al, Rad Res 2015]
Ionising radiation and risk of death from leukaemia and lymphoma in radiation-monitored workers (INWORKS): an international cohort study


Lancet Haematol 2015; 2: e276–81
Published Online
June 22, 2015
http://dx.doi.org/10.1016/S2352-3026(15)00094-0
Previous results

Leukemia excluding CLL

15-country study (2005)
UK NRRW study (2009)
French CEA-AREVA-EDF study (2013)
US combined study (2015)*
Life Span Study (2012)**

ERR per Gray

* IC95%
** calculated at IRSN using the Hiroshima and Nagasaki A-bomb survivors data restricted to men exposed between 20 and 60 years of age using an ERR stratified for attained age, calendar period and city.
### Characteristics of INWORKS

<table>
<thead>
<tr>
<th></th>
<th>France</th>
<th>USA</th>
<th>UK</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of participants</strong></td>
<td>59,003</td>
<td>101,428</td>
<td>147,866</td>
<td>308,297</td>
</tr>
<tr>
<td><strong>Person-years (millions)</strong></td>
<td>1.47</td>
<td>3.34</td>
<td>3.41</td>
<td>8.22</td>
</tr>
<tr>
<td><strong>Duration of follow-up (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>25 (9)</td>
<td>33 (13)</td>
<td>23 (12)</td>
<td>27 (12)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>23 (18-36)</td>
<td>31 (23-44)</td>
<td>22 (14-32)</td>
<td>26 (18-36)</td>
</tr>
<tr>
<td><strong>Age at last observation (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>56 (13)</td>
<td>65 (13)</td>
<td>54 (15)</td>
<td>58 (15)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>54 (46-66)</td>
<td>66 (55-76)</td>
<td>54 (42-66)</td>
<td>58 (47-70)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>51,567 (87%)</td>
<td>81,883 (81%)</td>
<td>134,812 (91%)</td>
<td>268,262 (87%)</td>
</tr>
<tr>
<td>Female</td>
<td>7,436 (13%)</td>
<td>19,545 (19%)</td>
<td>13,054 (9%)</td>
<td>40,035 (13%)</td>
</tr>
<tr>
<td><strong>Vital status on Dec 31, 2005</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alive</td>
<td>52,565 (89%)</td>
<td>65,573 (65%)</td>
<td>118,775 (80%)</td>
<td>236,913 (77%)</td>
</tr>
<tr>
<td>Died</td>
<td>6,310 (11%)</td>
<td>35,015 (35%)</td>
<td>25,307 (17%)</td>
<td>66,632 (22%)</td>
</tr>
<tr>
<td>Number of deaths from malignant neoplasm of lymphoid and haemopoietic tissues (% of total deaths)</td>
<td>196 (3%)</td>
<td>1,031 (3%)</td>
<td>564 (2%)</td>
<td>1,791 (3%)</td>
</tr>
<tr>
<td>Emigrated or lost to follow-up</td>
<td>128 (-1%)</td>
<td>840 (1%)</td>
<td>3,784 (3%)</td>
<td>4,752 (2%)</td>
</tr>
<tr>
<td><strong>Cumulative red bone marrow dose (mGy)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (range)</td>
<td>11.6 (0.0-415.8)</td>
<td>15.2 (0.0-820.2)</td>
<td>18.2 (0.0-1217.5)</td>
<td>15.9 (0.0-1217.5)</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>1.3 (0.0-10.7)</td>
<td>1.9 (0.2-10.6)</td>
<td>2.6 (0.4-12.9)</td>
<td>2.1 (0.3-11.7)</td>
</tr>
</tbody>
</table>

Data are n (%) unless stated otherwise.

[Leuraud et al, Lancet Haematol 2015]
Dose to Red Bone Marrow

Annual dose : 1.1 mGy (SD 2.6)
Cumulative dose : 15.9 mGy (SD 42.8)  Median : 2.1 mGy ; Min-max : 0.0 - 1217.5

Figure A1. Distribution of cumulative red bone marrow doses among workers. INWORKS, 1943–2005.

[Leuraud et al, Lancet Haematol 2015, appendix]
Relative risk of non-CLL leukemia associated with red bone marrow dose
Relative risk of non-CLL leukemia associated with red bone marrow dose

ERR per Gy = 2.96; 90%CI [1.17 – 5.21]
**ERR per Gy for leukemia, lymphoma, multiple myeloma**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Deaths</th>
<th>ERR per Gy</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukaemia excluding CLL*</td>
<td>531</td>
<td>2.96</td>
<td>1.17 to 5.21</td>
</tr>
<tr>
<td>Chronic myeloid leukaemia*</td>
<td>100</td>
<td>10.45</td>
<td>4.48 to 19.65</td>
</tr>
<tr>
<td>Acute myeloid leukaemia*</td>
<td>254</td>
<td>1.29</td>
<td>-0.82 to 4.28</td>
</tr>
<tr>
<td>Acute lymphoblastic leukaemia*</td>
<td>30</td>
<td>5.80</td>
<td>NE to 31.57</td>
</tr>
<tr>
<td><strong>CLL</strong></td>
<td>138</td>
<td>-1.06</td>
<td>NE to 1.81</td>
</tr>
<tr>
<td>Multiple myeloma†</td>
<td>293</td>
<td>0.84</td>
<td>-0.96 to 3.33</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma†</td>
<td>710</td>
<td>0.47</td>
<td>-0.76 to 2.03</td>
</tr>
<tr>
<td>Hodgkin’s lymphoma†</td>
<td>104</td>
<td>2.94</td>
<td>NE to 11.49</td>
</tr>
</tbody>
</table>

* lag 2 years, † lag 10 years

[Leuraud et al, Lancet Haematol 2015]
Relative risk of non-CLL leukemia over restricted dose ranges

[Leuraud et al, Lancet Haematol 2015]
## Homogeneity between countries

<table>
<thead>
<tr>
<th>Leukemia excluding CLL</th>
<th>Deaths</th>
<th>ERR per Gy</th>
<th>90%Ci</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excluding France (57)</td>
<td>474</td>
<td>2.95</td>
<td>1.13-5.24</td>
</tr>
<tr>
<td>Excluding UK (164)</td>
<td>367</td>
<td>2.32</td>
<td>0.03-5.33</td>
</tr>
<tr>
<td>Excluding USA (310)</td>
<td>221</td>
<td>3.68</td>
<td>1.09-7.29</td>
</tr>
</tbody>
</table>

CLL = chronic lymphocytic leukaemia

[Leuraud et al, Lancet Haematol 2015]
Sensitivity analyses

**Non-CLL leukemia**
- No substantial improvement in the fit of the dose-response with addition of nonlinear (quadratic) term in model
- Little between-country heterogeneity
- Alternative lag assumptions changed results little
- Excluding neutron-exposed workers: ERR per Gy 4.19, 90% CI 1.42-7.80
- Adjusting for internal contamination: ERR per Gy 3.39, 90% CI 1.39-5.93

**Multiple myeloma**
- ERR per Gy increased when excluding UK: ERR per Gy 3.32, 90% CI 0.27-7.64
Comparison of the leukemia ERR per Gy with other studies

- **15-country study**: 1.93 (196)
- **INWORKS**: 2.96 (531)
- **Life Span Study** (men exposed 20-60 years): 2.63 (94)

* Excluding CLL
Conclusions

Non-CLL Leukemia

- Dose-risk relationship observed with cumulative RBM dose. Not statistically significant below 300 mGy
- Larger dose-risk relationship observed for Chronic Myeloid Leukemia
- Relationship appears stable (small heterogeneity between countries, small variation in sensitivity analyses)
- Risk coefficient similar to that derived from the A-bomb survivors study

Chronic Lymphocytic Leukemia

- No association with cumulative RBM dose

Lymphoma and Myeloma

- Positive but imprecise dose-response for deaths caused by Hodgkin’s lymphoma, non-Hodgkin lymphoma, and multiple myeloma
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)
Implications

- INWORKS provides direct evidence of an association between protracted low dose radiation exposure and leukaemia mortality
- Would not have been possible without 25 years of data collection work, and collaboration with nuclear operators. Cohort needs to be extended in the future
- Results contribute to improving knowledge about radiation low dose effects, in complement to dosimetry, biology, genetics, toxicology...
- Contributes to the validation of a major hypothesis of the radiation protection system, which is transposition of risk models derived from acute exposure to low dose rate exposure
- Strengthen the justification for radiological protection of exposed populations (workers, medical uses, general population)
Publications


- Other papers in preparation
INWORKS partners

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