Cancer risk from radon exposure: recent results from uranium miners studies

ICRP Symposium on the International System of Radiological Protection

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Margot Tirmarche
ICRP Committee 1
Radioactive gas of natural origin, present everywhere, concentrates in confined places

- Emitter of α particles
- Inhalation leads to irradiation of the bronchial epithelium
- Classified as a pulmonary carcinogen by the International Agency for Research on Cancer in 1988

Quantification of the exposure-risk relationship at relatively low annual doses:
  - Answer from miners and indoor epidemiological studies
  - Interaction with tobacco

Atmosphere
- Lead 206 (stable)
- Lead 210
- Polonium 214
- Bismuth 214
- Lead 214
- Polonium 218
- Radon 222
- Uranium 238
- Radium 226

Earth’s crust
- Lead 206
- Polonium 214
- Bismuth 214
- Lead 214
- Polonium 218
- Radon 222
- Uranium 238
- Radium 226

Decay times
- Lead 206: 3,8 d
- Polonium 214: 160 µs
- Bismuth 214: 20 min
- Lead 214: 27 min
- Polonium 218: 3 min
- Radon 222: 3,8 d
- Uranium 238: 22,3 y
- Radium 226: (stable)
The Alpha-Risk European Research Project

Uranium Miners

- Three European cohorts of uranium (U) miners
  - France, Czech Republic, Germany
- Individual smoking information
  - not available for the whole cohorts
  - studied under a nested lung cancer case-control approach

Alpha-Risk
FP6 Project no. 516483 (2005-2009)
www.alpha-risk.org
Miners cohort studies

The Alpha-Risk Project
(EC FP6, 2005-09, Contract n° 516483
Quantification of cancer and non-cancer risks associated with multiple chronic radiation exposures

http://www.alpha-risk.org

<table>
<thead>
<tr>
<th>Population size</th>
<th>5,086</th>
<th>9,979</th>
<th>35,084</th>
<th>50,149</th>
</tr>
</thead>
<tbody>
<tr>
<td>Person-years</td>
<td>153,047</td>
<td>262,507</td>
<td>908,661</td>
<td>1,324,215</td>
</tr>
<tr>
<td>Duration of follow-up (y)</td>
<td>30.1</td>
<td>26.3</td>
<td>25.9</td>
<td>26.4</td>
</tr>
<tr>
<td>Number of death</td>
<td>1,467</td>
<td>3,947</td>
<td>4,519</td>
<td>9,933</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>159</td>
<td>922</td>
<td>462</td>
<td>1,543</td>
</tr>
<tr>
<td>Radon Cumulative exposure (WLM)</td>
<td>36.6</td>
<td>72.8</td>
<td>55.9</td>
<td>58.0</td>
</tr>
<tr>
<td>Duration of exposure (y)</td>
<td>11.7</td>
<td>6.9</td>
<td>8.9</td>
<td>8.8</td>
</tr>
</tbody>
</table>

**Working Level Months (WLM):** unit of radon exposure. any combination of radon progeny in 1l of air which results in the emission of 130,000 MeV of energy from alpha particles x a monthly working time of 170 hours)  
(Tirmarche et al., Alpha-Risk 2010)
# Exposure-risk relationship at low levels of exposure

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Whole cohorts</th>
<th>Low exposure rate period *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ERR/ 100 WLM</td>
<td>95% CI</td>
</tr>
<tr>
<td>Czech</td>
<td>1.13</td>
<td>0.74-1.53</td>
</tr>
<tr>
<td>French</td>
<td>0.60</td>
<td>0.17-1.03</td>
</tr>
<tr>
<td>German</td>
<td>0.41</td>
<td>0.27-0.55</td>
</tr>
<tr>
<td>Joint</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

models stratified on the birth year and the country

* exposures since 1953, 1956 and 1967, respectively in the Czech, French and German cohort

(Tirmarche et al., Alpha-Risk 2010)

Higher risk coefficients at low levels of exposure
Good coherence between estimates from the 3 cohorts
Mean Annual Exposures in the Studies

Cut points correspond to largest difference in period specific estimates of ERR/WLM.
# Pooled nested case control study

<table>
<thead>
<tr>
<th></th>
<th>France</th>
<th>Czech Rep.</th>
<th>Germany</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases / controls</td>
<td>100 / 500</td>
<td>672 / 1491</td>
<td>704 / 1398</td>
<td>1476 / 3389</td>
</tr>
<tr>
<td>Cases / controls with smoking information</td>
<td>60 / 310</td>
<td>672 / 1491</td>
<td>314 / 691</td>
<td>1046 / 2492</td>
</tr>
</tbody>
</table>

Leuraud et al, Health Phys 2007

Tomasek, Rad Prot Dosim 2011

Schnelzer et al, Health Phys 2010
# European cohort of uranium miners

<table>
<thead>
<tr>
<th></th>
<th>France</th>
<th>Czech Republic</th>
<th>Germany</th>
<th>Combined Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>5086</td>
<td>9979</td>
<td>35084</td>
<td>50149</td>
</tr>
<tr>
<td>Person-years</td>
<td>153,047</td>
<td>262,507</td>
<td>908,661</td>
<td>1324,215</td>
</tr>
<tr>
<td>Follow-up duration</td>
<td>30.1</td>
<td>26.3</td>
<td>25.9</td>
<td>26.4</td>
</tr>
<tr>
<td>Attained age (y)</td>
<td>58.9</td>
<td>56.6</td>
<td>48.6</td>
<td>51.2</td>
</tr>
<tr>
<td>Number of deaths</td>
<td>1467</td>
<td>3947</td>
<td>4519</td>
<td>9933</td>
</tr>
</tbody>
</table>

**Nested case-control study**

*ICRP* INTERNATIONAL COMMISSION ON RADI OLOGICAL PROTECTION
**Lung cancer risk associated to radon exposure and smoking**

<table>
<thead>
<tr>
<th>Cumulative radon exposure (5-year lagged, WLM)</th>
<th>Never smoker</th>
<th>Ex-smoker ≥ 10 y</th>
<th>Ex-smoker &lt; 10 y + current smoker</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50</td>
<td>1</td>
<td>1.9 (0.8-4.3)</td>
<td>7.2 (3.6-14.6)</td>
</tr>
<tr>
<td>50-100</td>
<td>2.1 (0.8-5.2)</td>
<td>3.9 (1.6-9.8)</td>
<td>12.0 (5.7-25.2)</td>
</tr>
<tr>
<td>100-200</td>
<td>2.0 (0.8-5.0)</td>
<td>5.0 (2.1-11.6)</td>
<td>18.6 (9.0-38.6)</td>
</tr>
<tr>
<td>200-400</td>
<td>4.9 (1.9-12.5)</td>
<td>6.3 (2.6-15.2)</td>
<td>21.0 (10.0-44.1)</td>
</tr>
<tr>
<td>≥ 400</td>
<td>7.1 (2.4-20.6)</td>
<td>16.8 (6.8-41.6)</td>
<td>36.7 (16.9-279.6)</td>
</tr>
</tbody>
</table>

WLM: Woking Level Month

Risk increases with both smoking and cumulative radon exposure
### Excess relative risk of lung cancer associated to radon exposure

<table>
<thead>
<tr>
<th></th>
<th>ERR per WLM (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Unadjusted on smoking</strong></td>
<td>0.010 (0.006-0.018)</td>
</tr>
<tr>
<td><strong>Adjusted on smoking</strong></td>
<td>0.008 (0.004-0.014)</td>
</tr>
<tr>
<td>Among never and long term ex-smokers</td>
<td>0.012 (0.005-0.026)</td>
</tr>
<tr>
<td>Among short term ex- and current smokers</td>
<td>0.007 (0.003-0.013)</td>
</tr>
</tbody>
</table>

Risk increases with cumulative radon exposure among smokers and non-smokers (submultiplicative interaction, ref. Leuraud et al. Rad Research 09/2011,176,3)
Context for risk assessment

- Radon associated risk estimated by the ICRP in report 65 (1993)
- New results from epidemiological studies (miners and general population) since ICRP 65
- Evidence of a significant relationship between exposure to radon and radon decay products and lung cancer risk
- Evidence for modifying factors of the exposure-risk relationship from miners studies (age, time since exposure)

TASKGROUP64 of C1 summarizes available knowledge and proposes new calculation of lifelong risk

What is the impact of new results compared to the ICRP 65?
Are results from miner studies and indoor studies coherent?
What is the coherence with recent position of Unscear and WHO
Risk coefficient
7 miners mortality studies

Projection model
multiplicative model
modifying effect of age at exposure and time since exposure

Lifetime
cumulated risk up to age 90

Background rates
mixed population (ICRP 60) : both sexes, 5 countries

Exposure scenario
chronic exposure to 2 WLM from age 18 to 64

Lifetime Excess Absolute Risk : 2.8 \times 10^{-4} \text{ per WLM}
(fatality coefficient)

Working Level Months (WLM): unit of time-integrated radon exposure. any combination of radon progeny in one liter of air which results in the ultimate emission of 130,000 MeV of energy from alpha particles x a monthly working time of 170 hours)
11 cohorts

- > 60,000 miners
- > 2600 lung cancer deaths
- mean exposure 164 WLM (max > 10000 WLM)

Results

- ERR/100 WLM 0.49 [0.2 – 1.0]
- Agreement with a linear model
- ERR \( \propto \) with Time Since Exposure
- ERR \( \propto \) with Age at Exposure
- inverse exposure rate effect
- ERR/100 WLM below 50 WLM 1.18 [0.2 – 2.5]
Calculation of Lifetime Excess Absolute Risk (LEAR)

**Lifetime risk calculation:** LEAR (Thomas D et al. Health Phys 1992)  
(also called REID, Risk of Exposure Induced Deaths)

**Risk model**
Derived from published combined analyses  
Relative risk models with modifying effects

**Lifetime**
90 y old (No risk before age 18)

**Background rates:** ICRP 103 2007  
Mean M/F-Asian/Euroamerican  
average population: 2 sexes, Euro-American / Asian

**Exposure scenario:** ICRP 65 1993  
2 WLM per y from age 18 to 64 (cumulated 94 WLM)
### Czech-French joint model

*(Tomasek et al. Rad Res 2008)*

**Combined analysis of low exposed miners**

<table>
<thead>
<tr>
<th>Name-place</th>
<th>Country</th>
<th>Type of mine</th>
<th>Follow-up period</th>
<th>Nb miners</th>
<th>Nb lung cancer deaths</th>
<th>Cumul expo WLM</th>
<th>Person-years</th>
<th>ERR per 100 WLM</th>
</tr>
</thead>
<tbody>
<tr>
<td>West Bohemia</td>
<td>Czech Republic</td>
<td>Uranium</td>
<td>1956-95</td>
<td>5002</td>
<td>449</td>
<td>57</td>
<td>133 521</td>
<td></td>
</tr>
<tr>
<td>CEA-AREVA</td>
<td>France</td>
<td>Uranium</td>
<td>1946-94</td>
<td>5098</td>
<td>125</td>
<td>37</td>
<td>115 261</td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td></td>
<td></td>
<td></td>
<td>10 100</td>
<td>574</td>
<td>47</td>
<td>248 782</td>
<td>1.6 [1.0 – 2.4]</td>
</tr>
</tbody>
</table>

- Agreement with a linear model
- ERR \( \uparrow \) with Time Since Exposure
- ERR \( \uparrow \) with Age at Exposure
- no inverse exposure rate effect
Scenario: 2 WLM per y from age 18 to 64

Variation of RR over time

RR lung cancer

- Blue line: Beir 6 c
- Red line: CzFr 2008
Lifetime Excess Absolute Risk \( (10^{-4} \text{ per WLM}) \)

<table>
<thead>
<tr>
<th>Mean Population (m+f/asian+euroamerican)</th>
<th>Beir 6 c</th>
<th>CzFr 2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-89</td>
<td>5.38</td>
<td>4.84</td>
</tr>
</tbody>
</table>

To be compared to the ICRP 65 value of \(2.8 \times 10^{-4}\) per WLM

Scenario 1: 2 WLM per y from age 18 to 64
## Lifetime Excess Absolute Risk \((10^{-4} \text{ per WLM})\)

<table>
<thead>
<tr>
<th>Mean Population (m+f/asian+euroamerican)</th>
<th>Beir 6 c</th>
<th>CzFr 2008</th>
<th>Fr post56</th>
<th>Eldorado 2006</th>
<th>Wismut 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-89</td>
<td>5.38</td>
<td>4.84</td>
<td>7.60</td>
<td>6.77</td>
<td>3.09</td>
</tr>
</tbody>
</table>

### Sensitivity to risk model

Scenario 1: 2 WLM per y from age 18 to 64
### Lifetime Excess Absolute Risk ($10^{-4}$ per WLM)

<table>
<thead>
<tr>
<th>Mean Population (m+f/Asian+Euroamerican)</th>
<th>Beir 6 c</th>
<th>CzFr 2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-69</td>
<td>3.69</td>
<td>3.25</td>
</tr>
<tr>
<td><strong>18-89</strong></td>
<td><strong>5.38</strong></td>
<td><strong>4.84</strong></td>
</tr>
<tr>
<td>18-94</td>
<td>5.41</td>
<td>4.85</td>
</tr>
</tbody>
</table>

**Sensitivity to lifetime duration**

Scenario 1: 2 WLM per y from age 18 to 64
### Lifetime Excess Absolute Risk ($10^{-4}$ per WLM)

**Mean Population (m+f/asian+euroamerican)**

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Beir 6 c</th>
<th>CzFr 2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-89</td>
<td>5.38</td>
<td>4.84</td>
</tr>
</tbody>
</table>

**Male Euroamerican Population**

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Beir 6 c</th>
<th>CzFr 2008</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-89</td>
<td>7.18</td>
<td>6.40</td>
</tr>
</tbody>
</table>

**Sensitivity to background rates**

Scenario 1: 2 WLM per y from age 18 to 64
**Pooled residential studies**

*Indoor data – primary risk coefficients*

<table>
<thead>
<tr>
<th>Joint analysis</th>
<th>Number of studies included</th>
<th>Cases</th>
<th>Controls</th>
<th>Relative risk per 100 Bq m(^{-3})</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chinese (Lubin et al., Int J Cancer 2004)</td>
<td>2</td>
<td>1050</td>
<td>1995</td>
<td>1.13</td>
<td>(1.01-1.36)</td>
</tr>
<tr>
<td>European (Darby et al., BMJ 2005)</td>
<td>13</td>
<td>7148</td>
<td>14208</td>
<td>1.08</td>
<td>(1.03-1.16)</td>
</tr>
<tr>
<td>North American (Krewski et al., Epidemiol 2006)</td>
<td>7</td>
<td>3662</td>
<td>4966</td>
<td>1.10</td>
<td>(0.99-1.26)</td>
</tr>
</tbody>
</table>

Very good coherence of results from different indoor studies
Comparison miner studies – indoor studies

Domestic radon- case control studies : European pooling
No modifying effect of attained age, age at exposure or time since exposure
Age at diagnosis: approx 70 y old
25 years of exposure reconstruction: 5 to 30 y before diagnosis (approx age 40 to 64)

Miner studies
Modifying effect of age at exposure and time since exposure
Men

Comparison of LEAR: if miners conditions similar to case-control studies
Lifetime age 70
Exposure scenario: 0.43 WLM (100 Bq/m$^3$) per y from age 40 to 64 (11 WLM)
Indoor primary coefficient for men

(Assuming 1 WLM == 1 year at 230 Bq.m$^3$ indoor (ICRP 65, 1993))
Mean Population (m+f/asian+euroamerican)

<table>
<thead>
<tr>
<th></th>
<th>Beir 6 c</th>
<th>CzFr 2008</th>
<th>Darby 2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-59</td>
<td>1.64</td>
<td>1.30</td>
<td>0.73</td>
</tr>
<tr>
<td>18-69</td>
<td>3.53</td>
<td>2.72</td>
<td>2.71</td>
</tr>
<tr>
<td>18-89</td>
<td>5.58</td>
<td>4.68</td>
<td>7.58</td>
</tr>
</tbody>
</table>

Good agreement of estimated cumulated risk
High sensitivity to lifetime duration

Scenario: 0.43 WLM (100 Bq/m3) per y from age 40 to 64
ICRP considered Lifetime Excess Absolute Risk of $5 \times 10^{-4}$ per WLM
(to be compared with $2.8 \times 10^{-4}$ per WLM estimated by ICRP 65)

For risk communication, explain sensitivity to background rates and risk model (ERR value, modifying factors of the ERR) + duration of lifetime

Good coherence between risk estimates from miners and indoor studies (under appropriate conditions)

ICRP recommendations in line with those from other international committees (WHO, UNSCEAR…)
ICRP-C1-TG64 members involved in this radon risk assessment:

- From IRSN (France): Eric Blanchardon, Dominique Laurier, François Paquet, Margot Tirmarche
- From HPA (UK): John Harrison, James Marsh

Future plans: risk assessment for other alpha emitters
### Period specific ERR/WLM (in two exposure windows)

$$RR = 1 + b_{before} \ W_{before} + b_{after} \ W_{after}$$

<table>
<thead>
<tr>
<th>Study</th>
<th>Cut points</th>
<th>ERR/WLM before</th>
<th>90%CI</th>
<th>ERR/WLM after</th>
<th>90%CI</th>
<th>p</th>
<th>CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Czech</td>
<td>1953</td>
<td>0.0069</td>
<td>0.0041 – 0.0107</td>
<td>0.0210</td>
<td>0.0147 – 0.0305</td>
<td>0.012</td>
<td>14%</td>
</tr>
<tr>
<td>French</td>
<td>1956</td>
<td>0.0016</td>
<td>-0.0009 – 0.0057</td>
<td>0.0219</td>
<td>0.0120 – 0.0358</td>
<td>0.985</td>
<td></td>
</tr>
<tr>
<td>German</td>
<td>1964</td>
<td>0.0027</td>
<td>0.0017 – 0.0038</td>
<td>0.0206</td>
<td>0.0142 – 0.0282</td>
<td>0.0167 – 0.0261</td>
<td></td>
</tr>
</tbody>
</table>

Lower ERR/WLMs from more distant periods (before) reflect higher uncertainty of earlier exposures (less measurements), potential overestimation of exposures (measurements conducted at workplaces with higher concentrations), exposure rate (cell killing because of high doses), and potential decrease with time since exposure.

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Perspectives

International collaboration will continue

Aim: pooling studies to better quantify risks at low exposure
- Residential exposure: World pooling project
- Miners: Euro-Canadian initiative

Correction for measurement errors
(Tirmarche, Alpha-Risk 2010; Allodji 2010)

Continuation of collaboration between internal dosimetrists and epidemiologists
- Analyses based on organ dose-risk relationships
  - may contribute to new exposure-dose conversion convention coefficients for ICRP
- Close collaboration with members of ICRP committee2 (biokinetics models)

Development of molecular epidemiology among miners studies
(Zolzer, ERRS 2010; Kreuzer, BfS 2010)

Launching of studies on exposures during childhood
- Studies on childhood leukaemia risk in the UK and France