Cancer risk associated to radon after exposure in mines or in homes

Research programs under EU coordination
Implications for risk management

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In charge of ICRP C1 Task Group 64 « Cancer risk from alpha emitters »
The “Uminers + Animal data” European project

Uminers + Animal data
Contract no. FIGH-CT1999-00013
Duration: Feb 2000 – July 2003
Coordinator: M Tirmarche (IRSN)

Quantification of lung cancer risk after low radon exposure and low exposure rate:
synthesis from epidemiological and experimental data

- Epidemiology (cohorts of U miners in Europe)
- Modelling (confrontation of classical and TSCE modelling)
- Animal experiments

8 partners
- IRSN (France), BfS (Germany), NRPI (Czech Republic), GSF (Germany), CEA (France),
  AEAT (UK), NRPB (UK), RIVM (The Netherlands)

Final report: www.irsn.org
The Alpha-risk European project

Specific targeted research or innovation project (STREP)
Contract no. 516483 (FI6R)
Duration: July 2005 – June 2008
Coordinator: M Tirmarche (IRSN)

Quantification of cancer and non-cancer risks associated with multiple chronic radiation exposures
- Epidemiological studies (U miners, nuclear workers) and radon in homes
- Organ dose calculation
- Risk assessment

18 partners
IRSN (France), BfS (Germany), NRPI (Czech Rep), CR-UK (UK), IARC (France), WSC (UK), AWE (UK), HPA (UK), U Salzburg (Austria), GSF (Germany), RIVM (The Netherlands), ISS (Italia), BAuA (Germany), CAATS (France), UK-AEA (UK), SCK-CEN (Belgium), U Ottawa (Canada), RWE NUKEM (UK)

Web site: www.alpharisk.org
Reference documents

1988
IARC 43 « Man-made Mineral Fibres and Radon »

1993
ICRP 65 « Protection against radon-222 at home and at work »

1999
BEIR VI « Health effects of radon exposure »

2001
IARC 78 « Some internally deposited radionuclides »

2007
UNSCEAR R-654 « Sources-to-effects assessment for radon in workplaces and homes »
BEIR VI Report

11 cohorts

- > 60000 miners
- > 2600 lung cancer deaths

Results

- ERR/100 WLM 0.49 [0.2 – 1.0]
- Agreement with a linear model
- ERR ↘ with Time Since Exposure
- ERR ↘ with Age at Exposure
- inverse exposure rate effect
- sub-mutiplicative interaction with tobacco
- no increased risk except lung cancer
Lung cancer risk among miners

All data combined

RR = 1 + 0.0049 x WLM

(from Lubin et al, NIH 1994)
## BEIR VI preferred models

<table>
<thead>
<tr>
<th>TSE age duration model</th>
<th>TSE age concentration model</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ERR/WLM</strong></td>
<td><strong>ERR/WLM</strong></td>
</tr>
<tr>
<td><strong>TSE (years)</strong></td>
<td><strong>TSE (ans)</strong></td>
</tr>
<tr>
<td>5-14</td>
<td>5-14</td>
</tr>
<tr>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>15-24</td>
<td>15-24</td>
</tr>
<tr>
<td>0.72</td>
<td>0.78</td>
</tr>
<tr>
<td>25-</td>
<td>25-</td>
</tr>
<tr>
<td>0.44</td>
<td>0.51</td>
</tr>
<tr>
<td><strong>Attained age (years)</strong></td>
<td><strong>Attained age (years)</strong></td>
</tr>
<tr>
<td>-54</td>
<td>-54</td>
</tr>
<tr>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>55-64</td>
<td>55-64</td>
</tr>
<tr>
<td>0.52</td>
<td>0.57</td>
</tr>
<tr>
<td>65-74</td>
<td>65-74</td>
</tr>
<tr>
<td>0.28</td>
<td>0.29</td>
</tr>
<tr>
<td>75-</td>
<td>75-</td>
</tr>
<tr>
<td>0.13</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>Exposure duration (years)</strong></td>
<td><strong>Concentration (WL)</strong></td>
</tr>
<tr>
<td>-4</td>
<td>-0.5</td>
</tr>
<tr>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>5-14</td>
<td>0.5-1</td>
</tr>
<tr>
<td>2.78</td>
<td>0.49</td>
</tr>
<tr>
<td>15-19</td>
<td>1-3</td>
</tr>
<tr>
<td>4.42</td>
<td>0.37</td>
</tr>
<tr>
<td>20-24</td>
<td>3-5</td>
</tr>
<tr>
<td>4.42</td>
<td>0.32</td>
</tr>
<tr>
<td>25-34</td>
<td>5-15</td>
</tr>
<tr>
<td>6.62</td>
<td>0.17</td>
</tr>
<tr>
<td>35-</td>
<td>15-</td>
</tr>
<tr>
<td>10.2</td>
<td>0.11</td>
</tr>
</tbody>
</table>

(From Beir VI, 1999)
Uranium mines in Europe

- Vendée
- Forez
- Auvergne
- Hérault
- Schneeberg
- Jachymov
- Pribram
Points of research and objectives

Extended follow-up and new cohorts:
- Increase statistical power for risk assessment of lung cancer deaths at low doses
- Allows modelling of the exposure-risk relationship (non parametric approaches, modifying factors, exposure rate effect…)
- Cohort studies give information on causes of death other than lung cancer
- Adjustment on other risk factors (arsenic, silica, diesel exhaust, smoking)
- External gamma radiation, LLRn dust inhalation: interaction on target organ?
- Organ dose calculation and dose-risk modelling
- Incidence rather than mortality data: available?

- Exposure-dose correspondence?
- Lifetime risk estimates?
- ICRP recommendations?
The Czech-French joint study: risk modifiers

Strong decrease of risk with time since exposure
No inverse dose-rate effect
Relative lung cancer risk of lung cancer associated to a radon cumulated exposure of 90 WLM (6 WLM per year during 15 years)

2 scenarii:
Exposure at age 20-34 years (solid lines)
Exposure at age 35-49 years (dashed lines)

2 models:
BEIR VI-age-concentration model (broken lines)
Cz-Fr preferred model (M3) (smoothed lines)

[Tirmarche et al, 2003]
Uranium miners studies

Cohorts of uranium miners (WP1)
- France, Czech Republic and Germany
- (> 40,000 miners)
- Nested case-control studies (tobacco, lung cancer and leukemia risk)
- Good quality reconstruction of multiple exposures (radon, gamma, ore dust)

Methodology
- Dosimetric models (WP5)
- Parametric statistical methods and biologically-based modelling approaches
- Consideration of measurement errors and uncertainty

Objectives
- Time-modifier of the radon-lung cancer risk relationship
- Risk associated to tobacco, radon and other radiation sources in the mines
- Risk of cancers other than lung (leukemia, kidney…)
- Non cancer mortality risk
- Lifetime lung cancer risk estimates (WP6)
- Parallel analysis with indoor radon studies (WP6)
Radon and decay products in homes

1. Epidemiology: Analytical versus ecological studies

a. Risk of lung cancer:
   - Results from a large number of national case-control studies,
   - Major information from joint analyses:
     ▪ European,
     ▪ North American studies
     ▪ Future world pooling analysis
   - Experience through extrapolation from miners studies

b. Leukemia risk?
   - Studies in adults, in childhood leukemia
Radon and decay products in homes

1. Risk management
   a. Radon is a typical domestic pollutant, to be managed in parallel to other domestic agents
      ➔ General public : risk per Bq.m$^3$

   b. Risk from chronic alpha exposure should be expressed in working environment, compared with risk from external exposure :
      ➔ multiple exposure, occupational exposure

   - Comparing risk at the same organ level :
     - input from dosimetry expertise
     - cumulated exposure : external and internal : dose expressed in Gy ?
     - discussion of quality factor, dose rate effect, experience from Uminers studies
     - differences of background rates as we are comparing different populations (ERR versus EAR, cofactors......)
     - Management through mSv limits ?
Radon risk at low annual exposure in houses?

Gas: concentration is depending of underground characteristics, changes on geographical level, seasonal corrections are needed.

Habits of live should be taken in account, residence level...

1. Exposure is present everywhere, but at different concentrations.
2. It is a chronic exposure, cumulated over life time.

⇒ Individual measurement of exposure is necessary.

⇒ Best approach: case-control study.
Case-control study of indoor radon and lung cancer in France

Results:

• Past exposure to radon reconstructed over a mean duration of 20 years
• Lung cancer risk increases with exposure to radon
  \[ RR = 1.04 \text{ per } 100 \text{ Bq.m}^{-3} \quad CI 95\% = [0.99 - 1.11] \]
  (adjusted on age, sex, region, smoking and occupational exposure)
  \[ RR = 1.07 \text{ per } 100 \text{ Bq.m}^{-3} \quad CI 95\% = [1.00 - 1.15] \]
  (if limited to those with all houses measured)
• This risk is low when compared to the risk associated to smoking
• This result is concordant with those from previous studies and with the risk extrapolated from miners studies
  • publication in Epidemiology (Nov 2004, vol15, 6:709-716)
  Integration in the European joint analysis (France, Belgium, Germany, UK, Sweden, Italy,...)
  ➔ 7148 cases and 14208 controls included (in Darby et al : BMJ.2005;330:223-7)
Comparison of Risk from French U Miners and Case-control Study

Relative risks of lung cancer by time-weighted average radon concentration during 5-30 period of exposure (4 regions)

- **French case-control study**: $RR=1.04$ [0.99:1.11] per 100 Bq/m$^3$
- **French cohort study of miners**: $RR=1.09$ per 100 Bq/m$^3$

25 WLM $\rightarrow$ 230 Bq/m$^3$ for 25 years

$\Rightarrow$ $RR=1.008$ per WLM

$\Rightarrow$ $RR=1.09$ per 100 Bq/m$^3$
From miners risk coefficient to indoor risk coefficient

If 1 WLM annual exposure in a mine is equivalent to an exposure to 230 Bq per m$^3$ over one year in a home

This assumes

Exposure duration : 2000 hours in mines versus 7000 hours in homes

Different breathing rates

Different equilibrium factors, particles sizes, attached fraction

Different co-factors : dust/smoking particles, others
Case-control studies in general population

- Comment: no other domestic pollutant has been studied in a more detailed way:
  - Evidence from animal experience, even at « low » doses
  - Evidence from occupational exposure
  - Evidence from 13 epi studies in Europe, 7 from North-America and two from China (plus 2 from Ural region)

Major input of case-control studies:

- in field epi studies, able to adjust precisely on individual tobacco consumption, including male and females, smokers and non-smokers
- meta-analysis
- joint analysis: increase of statistical power
### European case-control studies of residential radon and lung cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of subjects with lung cancer</th>
<th>Number of control subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>183</td>
<td>188</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>171</td>
<td>713</td>
</tr>
<tr>
<td>Finland: nationwide</td>
<td>881</td>
<td>1435</td>
</tr>
<tr>
<td>Finland: south</td>
<td>160</td>
<td>328</td>
</tr>
<tr>
<td>France</td>
<td>571</td>
<td>1209</td>
</tr>
<tr>
<td>Germany: Eastern</td>
<td>945</td>
<td>1516</td>
</tr>
<tr>
<td>German: Western</td>
<td>1323</td>
<td>2146</td>
</tr>
<tr>
<td>Italy</td>
<td>384</td>
<td>405</td>
</tr>
<tr>
<td>Spain</td>
<td>156</td>
<td>235</td>
</tr>
<tr>
<td>Sweden: nationwide</td>
<td>960</td>
<td>2045</td>
</tr>
<tr>
<td>Sweden: never-smokers</td>
<td>258</td>
<td>487</td>
</tr>
<tr>
<td>Sweden: Stockholm</td>
<td>196</td>
<td>375</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>960</td>
<td>3126</td>
</tr>
</tbody>
</table>

Total number of subjects 7148 14,208
North American and Chinese case-control studies of residential radon and lung cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of subjects with lung cancer</th>
<th>Number of control subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Jersey</td>
<td>480 f</td>
<td>442 f</td>
</tr>
<tr>
<td>Winnipeg</td>
<td>488 m; 250 f</td>
<td>488 m; 250 f</td>
</tr>
<tr>
<td>Missouri 1</td>
<td>538 f</td>
<td>1183 f</td>
</tr>
<tr>
<td>Missouri 2</td>
<td>512 f</td>
<td>553 f</td>
</tr>
<tr>
<td>Iowa</td>
<td>413 f</td>
<td>614 f</td>
</tr>
<tr>
<td>Connecticut</td>
<td>527 m; 436 f</td>
<td>442 m; 507 f</td>
</tr>
<tr>
<td>Utah; southern Idaho</td>
<td>319 m; 192 f</td>
<td>587 m; 275 f</td>
</tr>
</tbody>
</table>

China

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of subjects</th>
<th>Number of control subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shenyang</td>
<td>308</td>
<td>356</td>
</tr>
<tr>
<td>Gansu</td>
<td>768</td>
<td>1659</td>
</tr>
</tbody>
</table>
Joint European study: Protocol and results

- **Protocol**
  - 13 studies / 9 countries:
  - Standardized protocol, same inclusion criteria, common questionnaire, reconstruction of exposure over last 35 years, inter-comparison of methods of measurements, 7,148 cases / 14,208 controls

- **Results: linear dose-response relationship**

  > Clear evidence of association: Lung cancer risk is increasing with cumulated radon exposure.
  > 
  > RR = 1.08 for 100 Bq/m³ [1.03 – 1.16]

  > Significant relationship if limited to those exposed <= 200 Bq/m³
  > Significant increase for nonsmokers

[Darby et al, *BMJ* 2005]
### EUROPEAN POOLING Study: non-smokers

<table>
<thead>
<tr>
<th>Measured radon (Bq/m³)</th>
<th>% who were lifelong non-smokers</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100</td>
<td>39</td>
</tr>
<tr>
<td>100-199</td>
<td>40</td>
</tr>
<tr>
<td>200-399</td>
<td>41</td>
</tr>
<tr>
<td>400-799</td>
<td>46</td>
</tr>
<tr>
<td>800+</td>
<td>48</td>
</tr>
</tbody>
</table>

*p for trend* 0.001

Percentages calculated after stratification for study, age, sex, and region of residence
## EUROPEAN POOLING Study:

Effect of stratification for smoking

<table>
<thead>
<tr>
<th>Stratification</th>
<th>% increase in lung cancer risk per 100 Bq/m³ measured radon</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Study, age, sex, region, smoking in 20 groups</td>
<td>8.4</td>
<td>(3.0, 15.8)</td>
<td>0.0007</td>
</tr>
<tr>
<td>B. Study, age, sex, region, smoking in 7 groups</td>
<td>5.2</td>
<td>(1.1, 10.7)</td>
<td>0.009</td>
</tr>
<tr>
<td>C. Study, age, sex, region only</td>
<td>2.3</td>
<td>(-0.5, 6.1)</td>
<td>0.64</td>
</tr>
</tbody>
</table>
Joint European analysis

Lung cancer risk

- Non smokers
- Ex smokers > 10 years
- Ex smokers <10 years
- Smokers 15-24 cig per day

Relative risk vs Radon Concentration (Bq.m$^{-3}$)
European pooling: Contribution of each study

1. No evidence that effect of radon differed between studies

2. Influence analysis: analysis repeated by omitting each study in turn (ref Darby et al, table 10, Scan J Work Environ Health 2006, vol32 suppl 1)
   
   Estimated linear relationship (after stratification by study, age, sex, region of residence and smoking history) changed by less than 10% for 11 of the 13 studies

3. No significant difference
   a. when considering lung cancer diagnosis over clinical versus death certificates
   b. Study with hospital or population based studies
   c. Whether or not surrogates interviews were used
   d. Radon measurements detectors were open or closed
   e. No effect of « windows of exposure »
   f. If linear or log-linear or linear quadratic RR models were used: quite comparable results were obtained
Combined analysis from North American studies
Krewski, Lubin et al, J TOX ENV H)

- Odds ratio trend consistent with linearity (p= 0.10)
- Excess OR : 0.10 per 100 Bq per m$^3$ (CI 95 %: -0.01,0.26)
- If limited to residence of one or two houses and with alpha track measurements over at least 20 years :
  
  EOR = 0.18 per 100 Bq per m$^3$ (0.02,0.43)

Estimates are compatible with an EOR of 0.12 per 100 Bq per m$^3$ (0.02,0.25) predicted by extrapolation from miners studies
Quantification of cancer and non-cancer risks associated with multiple chronic radiation exposures: Epidemiological studies, organ dose calculation and risk assessment

http://www.alpha-risk.org
Quantitative Risk Assessment

Methodology:
Exposure–risk relationship
Models used
- European joint analysis
  [Darby et al, BMJ 2005]
- Miners studies
  [BEIR VI, 1999; Tirmarche et al, 2005]

Modifying factors
- Age at exposure
- Time since exposure
- Radon and tobacco interaction

Population data used
- national census (Insee)
- Mortality rates (Inserm)
- percentage of smokers (Insee/Credes)

Exposure data of French population
Correction of seasonal variations, type of houses, population density
- 12,261 measurements used

[Billon et al, Rad Prot Dosim 2005]
Quantitative Risk Assessment

25 134 lung cancer deaths in France (Inserm, 1999)

Considering the different models, uncertainty of risk coefficients and variation of radon measurements:

between 4.9% (uncertainty interval at 90% : 2.4 – 9.0) and 12.3% (11.3 – 12.8) of the Lung cancer deaths are attributable to radon in France

[Catelinois 2004]

By taking in account interaction of tobacco-radon and percentage of smokers in France

75% of cases attributable to radon are smokers
Results in France

Concentration categories (Bq.m\(^{-3}\))

- **0 - 99**: 76% (47% of 1,497 deaths)
- **100 - 199**: 15% (26% of 815 deaths)
- **200 - 399**: 7% (18% of 598 deaths)
- **400 +**: 2% (9% of 277 deaths)

- **Percentage of person**
  - 100%
  - 80%
  - 60%
  - 40%
  - 20%
  - 0%

- **Percentage of risk**
  - 100%
  - 80%
  - 60%
  - 40%
  - 20%
  - 0%
Radon and leukemia risk

Review [Laurier, 2001]: no evidence for an association between radon exposure and leukemia

3 recent studies:

Retrospective case-cohort study - Czech uranium miners - incidence [Rericha, 2006]
- 84 leukemia cases (53 CLL)
- leukemia risk associated with cumulative radon exposure
- CLL risk associated with cumulative radon exposure

Cohort study - Czech uranium miners – mortality [Tomasek, 2006]
- 30 deaths from leukemia
- risk increased with duration of work
- risk not significantly associated with cumulative radon exposure
- calculation of equivalent RBM dose: LLRn > 60%, radon < 10%
- risk of leukemia associated with cumulated equivalent RBM dose

Case-control study - Former uranium miners, East Germany - incidence [Mohner, 2006]
- 377 leukemia cases and 980 controls
- elevated risk for employees with a very long duration of work
- calculation of equivalent RBM dose: radon > 75%
- no association with exposure to short-lived radon progeny
Radon and leukemia risk

- Some evidence of an increased risk of leukemia among miners.
- Increased risk associated with a long duration of exposure.
- Association with cumulative radon exposure not yet confirmed.
- Need for considering the different components of exposure (radon, gamma, LLRn).
- Need for considering the uncertainties in exposure and dose assessment.
Radon and childhood leukemia in France (1990-2001)
ref PhD 2006: Envir. exp. to radiation and childhood leukemia, AS Evrard and Health Physics 2006

A significant positive association between indoor radon and AML incidence, remained significant in multivariate analysis, including either terrestrial gamma dose or total gamma dose

<table>
<thead>
<tr>
<th>Radon Level (Bq/m³)</th>
<th>All acute leuk. (O/exp)</th>
<th>ALL (0/exp)</th>
<th>AML (0/exp)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35 Bq/m³</td>
<td>1 (1055/1100,9)</td>
<td>1 (860/896,8)</td>
<td>1 (183/189,1)</td>
</tr>
<tr>
<td>35-46 Bq/m³</td>
<td>1.01 (1042/1080,8)</td>
<td>1.00 (848/881,7)</td>
<td>1.01 (181/184,6)</td>
</tr>
<tr>
<td>48-61 Bq/m³</td>
<td>1.05 (1084/1079,3)</td>
<td>1.07 (906/880,6)</td>
<td>0.9 (161/184,1)</td>
</tr>
<tr>
<td>61-92 Bq/m³</td>
<td>1.11 (1086/1022,2)</td>
<td>1.12 (895/833,6)</td>
<td>1.06 (179/174,8)</td>
</tr>
<tr>
<td>&gt;-93 Bq/m³</td>
<td>1.06 (1063/1046,7)</td>
<td>1.02 (837/853,2)</td>
<td>1.20 (208/179,4)</td>
</tr>
</tbody>
</table>
Radon and childhood leukemia in France (1990-2001)
ref PhD 2006: Envir. exp. to radiation and childhood leukemia, AS Evrard and Health Physics 2006

1. Association with AML seems limited to those less than 14 years old

2. After adjustment on rural areas, proportion of managers, proportion of university graduates, average net income:

⇒ association between radon and childhood leukemia persists
SIR is multiplied by 1.20 for 100 Bq/m³ increase
UK Childhood Cancer Study: domestic radon exposure (ref BJC(2002)86)

No evidence of increased risk in relation to domestic radon

Radon concentrations considered were close to time of diagnosis: 2226 cases and 3773 control homes

- But houses of controls have intrinsic features resulting in higher than average indoor radon concentrations.
- If radiation risk estimates (Com. Medical Aspects of Radiation in Env.) suggests that approximately 14% of leukemia incidence in childhood in UK may be linked to natural background radiation, what is the power of a case-control study to demonstrate clearly this excess?
- Number of cases in high exposed regions may be too small?
- Adjustment on co-factors? Yet unknown
Radon and diseases other than cancer

1. **Cardiovascular diseases**:
   a. large Wismuth study: no increase of risk with radon exposure
   b. New Foundland study: suggested an increase, not confirmed in a recent publication

2. **Multiple sclerosis, Alzheimer**:
   a. Ecological study in Norway (Bolviken, 2003)
   b. Cluster in a specific part of the country, correlation with radon or other geochemical characteristics?

3. **Conclusion**: at present no evidence of a clear link
Radon in homes and cancer: Conclusion

1. Clear evidence of lung cancer risk
   a. Calculation of attributable risk does not mean that we are able to reduce all of those theoretically estimated diseases
   b. Interaction between radon and tobacco should be studied further
   c. Risk management is possible without converting in mSv

2. Leukemia: no clear evidence to-day,
   a. but further survey and studies necessary
   b. calculation of RBM dose, Uminers studies, other studies?
   c. mechanism, different for induction in childhood or exposure in adults?
   d. animal data: not in favour of a leukemia risk linked to radon
   e. radon gas or WLM
   f. Other cofactor, unknown
ICRP C1 Task group an cancer risk in relation to alpha emitters

4 years program:

Radon, thorotrast, plutonium, uranium

Discussion of convincing evidence from epidemiological studies, low dose risk, dosimetric component, contribution by ICRP C2 members, evidence from animal experiments.....

Special mandate for a radon statement during next six months: close to risk management approach (contribution by C4)