Lung Cancer Risk Associated with Low Chronic Radon Exposure:
Results from Epidemiology and Animal Experiments in France

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Abstract
An increased lung cancer risk associated with radon exposure has been reported both in underground miner cohort studies and in animal experiments. However a large proportion of these results came from populations who received high radon exposure for a short period of time. Our aim is to analyse the effects of radon in populations exposed to low level and low rates over long periods. In France, research was developed in parallel both in the field of epidemiology through the cohort of uranium miners, and in that of animal experiments. We present here recent results underlying the points of agreement between epidemiological and experimental approaches.

The French cohort of uranium miners includes 5098 miners with low cumulative radon exposure protracted over a long duration. Results show a significant increase of lung cancer risk with cumulative exposure to radon. Period of exposure appears as an important modifier of the exposure-risk relationship (reflecting historical changes in radiation protection and measurement methods), but no effect of exposure rate is observed.

Recent animal experiments were conducted in France by CEA and COGEMA at low levels of exposure. More than 4600 rats have been exposed to various exposure rates and durations under controlled conditions, and followed-up over their life span. Results show that the risk increases with cumulative exposure. In this experiments, an inverse exposure rate effect is observed at the highest level of exposure. Such effect is not observed at the lowest level.

Epidemiological and animal data are consistent to show an increase of risk with cumulative exposure protracted at low exposure rates. Animal data are also consistent with previous studies of underground uranium miners showing an inverse exposure rate effect at high level, but this effect disappears at low levels of exposure.
1. Introduction

Radon is a radioactive gas produced during the decay of uranium 238 that is present in soil. It can concentrate in stuffy atmospheres like in mines. Elevated concentrations can be measured in some buildings, depending on the nature of the subsoil, type of construction, building material, inhabitants habits of life, etc. Radon is inhaled, and its daughters may induce irradiation of lung and bronchial cells. Radon is classified by WHO as a human lung carcinogen [1]. This statement is based on evidence coming from animal data and from uranium miner studies with high levels of exposure to radon.

Since the 1970s, a large number of miner cohort studies have been published. A comprehensive joint analysis of 11 cohorts has been published [2, 3]. The Czech and French cohorts of miners were already involved in this joint analysis [4, 5]. The results consistently demonstrate an excess risk of lung cancer death associated with radon exposure. However, a large proportion of these results are based on high radon exposures, received during a short period of exposure. Furthermore, the existence of an inverse exposure rate effect on the relationship between radon exposure and lung cancer risk was suggested. This effect was reduced when analyses were performed on data restricted to low exposure ranges [6]. An inverse exposure rate effect was also observed in previous analyses of animal experiments performed at high levels of exposure and exposure rates [7, 8].

Our aim is to analyse the effects of radon in populations exposed to low level of exposure during a long period of time. In France, research was developed in parallel both in the field of epidemiology through the cohort of uranium miners, and in that of animal experiments. We present here recent results underlying the points of agreement between epidemiological and experimental approaches.

2. Material and methods

2.1. The French cohort of uranium miners

The French cohort of uranium miners is conducted in collaboration between the IRSN and the Occupational Medical Service of COGEMA, the company in charge of the mines in France. The analysis started in 1980, with a first cohort analysed in 1993 [4], based on 1785 miners. Since then, enlargement and extension of the follow-up of the cohort were performed [9, 10, 11]. The cohort now includes 5098 males employed at least one year as a miner since 1946, and followed up to 1994. Before 1956, annual individual exposure was reconstructed retrospectively by a group of experts, both from environmental measurements in the mining atmosphere and from information about the type and place of work. Since 1956, annual individual exposure to radon, gamma rays and uranium ore dust was recorded systematically. Forced ventilation was introduced in the mines in 1956, which led to a dramatic decrease in the level of exposure to radon (mean annual exposure of 15 to 30 WLM before 1956 to less than 4 WLM after). Causes of death were obtained from the National Mortality Database, which gathers all information from death certificates in France since 1968. Cause-of-death information from the COGEMA Occupational Medicine Department was used as a complementary source.

The total number of death is 1162, including 395 cancers and 125 lung cancer deaths. Mean cumulative exposure to radon is 36.5 WLM, protracted over a mean duration of 11.5 years (Table I).

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1 WLM (Working Level Month): unit of exposure multiplying a concentration of radon decay products by the duration of exposure. A monthly exposure of 1 WLM is defined as 170 working hours in an atmosphere of 1 WL. 1 WL is equivalent to any combination of radon decay products in 1 litre of air, which results in the emission of 130,000 MeV of energy of α particles.
Table I. Characteristics of the French cohort of uranium miners.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of workers</td>
<td>5098</td>
</tr>
<tr>
<td>Non-exposed miners</td>
<td>964</td>
</tr>
<tr>
<td>Number of person-years</td>
<td>133521</td>
</tr>
<tr>
<td>Number of lung cancer deaths</td>
<td>125</td>
</tr>
<tr>
<td>Average cumulative exposure (WLM)*</td>
<td>36.5</td>
</tr>
<tr>
<td>Average annual exposure (WLM)*</td>
<td></td>
</tr>
<tr>
<td>&lt;1956</td>
<td>23.9</td>
</tr>
<tr>
<td>≥ 1956</td>
<td>1.5</td>
</tr>
<tr>
<td>Average duration of exposure (years) *</td>
<td>11.5</td>
</tr>
<tr>
<td>Person-years by lagged cumulative exposure (WLM)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>49408</td>
</tr>
<tr>
<td>]0;10[</td>
<td>35817</td>
</tr>
<tr>
<td>]10;50[</td>
<td>27778</td>
</tr>
<tr>
<td>]50;100[</td>
<td>11358</td>
</tr>
<tr>
<td>]100;200[</td>
<td>6213</td>
</tr>
<tr>
<td>≥200</td>
<td>2947</td>
</tr>
</tbody>
</table>

*among exposed miners (n=4134)

In addition to the cohort study, a nested case-control study has been launched among the French uranium miners to investigate the respective impact of radon and smoking on lung cancer risk. This study will include 100 lung cancer cases and 500 controls. Collection of data on past tobacco consumption is ongoing [12], and the analysis of this study is expected during 2004.

2.2. The CEA animal experiments

Experimental animal studies were used in addition to epidemiological studies to investigate the effects of exposure, exposure rate and other factors in predicting risks resulting from human radon exposures. This review summarises data on lung cancer risk from radon experimental studies performed by our group at CEA-COGEMA (France) with emphasis on the most recent findings and analyses on the influence of dose-rate and that of fatal versus all malignant lung cancers. The advantage of animal data is that animals can be exposed under carefully controlled conditions. Despite the fact that significant cumulative exposures at typical residential exposure rates of about 0.001 WLM per day cannot be tested in a short-lived species like the rat, the rat model is valuable for confirming the conclusions acquired from human data particularly in regard to the exposure-rate effect.

Different analyses of various animal data sets have already been performed and the importance of categorization of lung tumours as fatal or incidental to the death of the animals was extensively discussed. The experiments conducted at CEA-COGEMA were lifespan studies in which, after exposure, rats were kept and regularly observed until death and killed when moribund. Rats do not, generally, die from lung cancer. Thus, so-called fatal tumours that are thought to grow faster and to cause more serious health effects than incidental tumours, were determined on the basis of histopathological criteria. Moreover, close similarities exist between fatal tumours in rats and human lung cancers. An analysis of fatal and incidental lung tumours was performed in rats for which sufficiently detailed information was available. In this analysis, a tumour was considered as fatal if one of the following criteria was satisfied [13]:
- presence of a single metastasis or multiple metastases,
- tumour size depending on the structure affected, but generally larger than 15 mm in diameter,
- presence of marked necrosis affecting more than 50% of the lesion,
- extensive invasion into pleura, bronchi and/or blood vessels.
As a whole 4,682 rats were analysed, including 2,662 rats exposed at cumulative exposures ≤ 107 WLM and potential alpha energy concentration (PAEC) varying from 2 to 188 WL, 499 rats exposed at cumulative exposures ≥ 200 WLM and high PAEC (1,200 WL) and 1,521 unexposed or sham-exposed controls. It comprised 209 malignant rat lung cancers among which 101 were considered as fatal. The background incidence of fatal lung cancers in controls was very low: 1 among 1521 rats (0.07 %). This represents the most important existing data set of rats exposed to radon and its progeny at low cumulative exposures.

3. Results

3.1. The French cohort of uranium miners

A significant excess of lung cancer deaths was observed (Standardised Mortality Ratio = 1.5, 95% confidence interval = [1.2 – 1.8]). Regression showed a significant linear increase of lung cancer risk with cumulative exposure to radon (Excess Relative Risk (ERR) = 0.8 per 100 WLM, 95% CI = [0.3 – 1.4], p<0.001, Figure 1).

![FIG. 1. Relationship between lung cancer mortality risk and cumulative exposure to radon in the French cohort of uranium miners (vertical bars represent 95% confidence intervals).](image)

Analysis showed a decrease of the risk with time since exposure [14]. Period of exposure (before or after 1956) also appeared as an important modifier of this relationship: estimated ERR per WLM was 8 times higher for exposure received after 1956 than before (p<0.01). After adjustment on this difference, no modifying effect of time since exposure or age at exposure can be shown, and no effect of exposure rate was observed (p=0.11) [15, 16]. No association with radon exposure was observed for other causes of death.

3.2. The CEA animal experiments

It has been demonstrated that exposure to radon and its progeny induces lung cancer in rats [8]. An excess risk of lung cancers was observed in rats at cumulative exposure as low as 25 WLM performed at relatively high PAEC of about 100 WL [7]. A dose-effect relationship was established showing that the incidence of lung cancers in rats exposed to radon/radon progeny increased with cumulative exposure [17]. Figure 2 shows the incidence of all malignant and fatal lung cancers in rats exposed at cumulative exposures up to 6,000 WLM. The proportion of both total and fatal lung cancers in rats
increased for cumulative exposures ranging from 25 WLM up to 3,000 WLM, and decreased thereafter. At cumulative exposures of about 50 to 100 WLM, the proportion of fatal lung cancer is about 80% that of all malignant lung cancers. However, in rats that were exposed at cumulative exposure of 200 WLM or higher, the proportion of fatal lung cancer is about half that of all malignant lung cancers.

For medium and high cumulative exposures, the pattern of this dose-effect relationship was very similar to that observed in underground uranium miners in whom a significant excess of lung cancers was observed for cumulative exposure ranging from about 100 WLM to 400 WLM and above [2]. However, excess respiratory tract tumours were produced in rats at exposures considerably lower than 100 WLM, even at cumulative exposures (although not exposure rates) comparable to typical lifespan exposures in homes at about 25 WLM. A cumulative exposure of 25 WLM, at a high PAEC of 100 WL resulted in a three to four-fold increased lung cancer frequency in male Sprague-Dawley rats as compared to unexposed control rats [18].

Figure 3 shows the lifetime excess absolute risk (LEAR) of fatal lung cancers in rats exposed to radon and its progeny at various cumulative exposures and PAEC. The LEAR increases with cumulative exposures up to 3,000 WLM, and decreased thereafter. The highest LEAR values are observed in groups exposed at high cumulative exposures of about 100 WLM and higher and high PAEC of 188 WL and 1200 WL, respectively. In contrast the lowest LEAR values (≤ 5%) are observed in rats exposed at cumulative exposures lower than 100 WLM and PAEC lower than 100 WL. When dividing by the corresponding cumulated exposure, LEAR of fatal lung cancers per WLM ranges between $6 \times 10^{-6}$ and $5.5 \times 10^{-4}$. LEAR per WLM increases up to cumulated exposures of 100 WLM. For cumulative exposures higher than 100 WLM, and PAEC higher than 150 WL, the risk of fatal lung cancer per WLM decreases with increasing cumulative exposure and increasing PAEC.
FIG. 3. Lifetime excess Absolute Risk (%) of fatal lung cancers in rats exposed at various cumulative exposures (WLM log transformed) and PAEC (WL).

The parameters that influence fatal lung cancer risk are cumulative exposure, PAEC, exposure-rate, and protraction of exposure. The highest fatal lung cancer risk per WLM is observed in rats exposed at about 100 WLM, at high PAEC in the range of 150-200 WL, and/or high exposure-rate from about 3.5 to 5 WLM/day, delivered over a short period (30 days). At cumulative exposures lower than 50 WLM, the risk decreases with decreasing PAEC, decreasing exposure rates and increased protraction of exposure. At very high cumulative exposures of about 500 WLM and higher, the risk decreases with increasing cumulative exposure, decreasing exposure rates and increased protraction of exposure.

4. Discussion

Several differences have to be taken into account when comparing results from human and animal data. The average duration of life among rats is approximately 900 days. This relatively short duration implies generally short exposure periods and elevated rates of exposure. Also, previous studies suggested that rats have a higher sensitivity to radon, for the same level of exposure [19]. Therefore, levels of exposure and exposure rates have to be considered differently among human and animal data. Another difference is that rats were followed up over their total lifespan until death. In the French miner cohort, as the mean age at end of follow-up is 55 years old, we are far from a lifetime coverage of risk. Therefore lifetime risk estimates have to be constructed to allow a parallel with the results of animal experiments [16]. If we accept a correspondence for ageing between rats and men of 1 day for 1 month, then 900 days for a rat approximately corresponds to an age of 74 years old for a man. Another important difference lies in the endpoint: rats are not dying of lung cancer, and the occurrence of a lung tumour was diagnosed at necropsy. Among miners, lung cancer is determined as the cause of death on the basis of death certificates, but no information is available on incidence. The development of histo-pathological criteria to determine the fatality of a tumour among rats was therefore a key step to allow a comparison of risk estimates between animal and human data.

Given the above restrictions, the following results can be drawn. Epidemiological results obtained from the French cohort of uranium miners are consistent with results obtained from the CEA animal experiments to show an increase of risk with cumulative exposure protracted at low exposure rate. At
low cumulative exposures, no exposure rate effect is observed among miners, and in animals the excess relative risk per WLM increases with exposure rate [20]. Animal data are also consistent with previous studies of underground uranium miners showing an inverse exposure rate effect at high cumulative exposures, but this effect disappears at low cumulative exposures [6].

The combination of both approaches – epidemiology and animal experiments – permits to take advantage from both sources of data. Even if they can’t support a direct estimation of the risk associated with radon exposure among human populations, the results obtained from animal data are useful in bringing support to the results obtained among miner studies. Nevertheless, to go further in the comparison of risk estimates between human and animal data, additional work is needed, especially for rescaling the effect of age and the differences in organ dose [19].

These studies were part of the collaborative work “UMINERS+ANIMAL DATA” conducted during the Fifth Framework Programme of the European Community. The project, coordinated by M. Tirmarche, involved 7 teams from 5 different countries. The objective was to derive a synthesis from human and animal data, bringing together researchers involved in three different fields: epidemiology, animal experiments and mechanistic modelling. Especially, the project included a joint analysis of Czech and French uranium miners, including a total of more than 10 000 miners, and a joint analysis of CEA and AEAT rats experiments, including more than 5500 rats. Results provided a sound basis for assessment of risk associated with low radon exposures [16].

French, German and Czech miners nested case-control studies, which are conducted under the same protocol, will be analysed jointly, once the collection of smoking data has been finished in each country.

5. Conclusion

In France, research was developed in parallel both in the field of epidemiology through the cohort of uranium miners, and in that of animal experiments. These works lead to the constructions of large datasets to allow analysis of the effects of radon on risk of lung cancer, at low levels and low rates of exposure. The combination of both approaches – epidemiology and animal experiments – permitted to take advantage from both sources of data. Results provided a sound basis for assessment of risk associated with low radon exposures.

From these data, it appears that epidemiological and animal results are consistent to show an increase of risk with cumulative exposure protracted at low exposure rates. Animal data are also consistent with previous studies of underground uranium miners showing an inverse exposure rate effect at high cumulative exposures, but this effect disappears at low cumulative exposures.

Acknowledgement

This work was supported partly by the European Community in the frame of the fifth Framework Program for Research and Technological Development (Contract FIGH-CT1999-0013). We also thank COGEMA for financial support.
References


