Lung Cancer Risk Associated with Low Chronic Radon Exposure: Results from the French Uranium Miners Cohort and the European Project

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INTRODUCTION

Comprehensive results from miners cohort studies had been published on the risk of lung cancer death associated to radon exposure, especially from a joint analysis regrouping 11 cohorts of miners published in 1994 (Lubin et al., 1994; Lubin et al., 1997, BEIR, 1998). This joint analysis was based on more than 1 million person-years and included 2,700 lung cancer cases, including the initial French cohort and the Czech cohort of uranium miners. Each of these cohorts presented individual radon exposure, recorded on an annual basis. All these studies showed a risk of lung cancer increasing linearly with cumulative radon exposure. However, several early cohorts, such as part of the Colorado miners, had no individual registered doses and their miner's doses were estimated on various assumptions. Another point is that a large proportion of these miners had cumulated high radon exposures, often during a short period of exposure corresponding to only few years of underground experience (Figure 1).

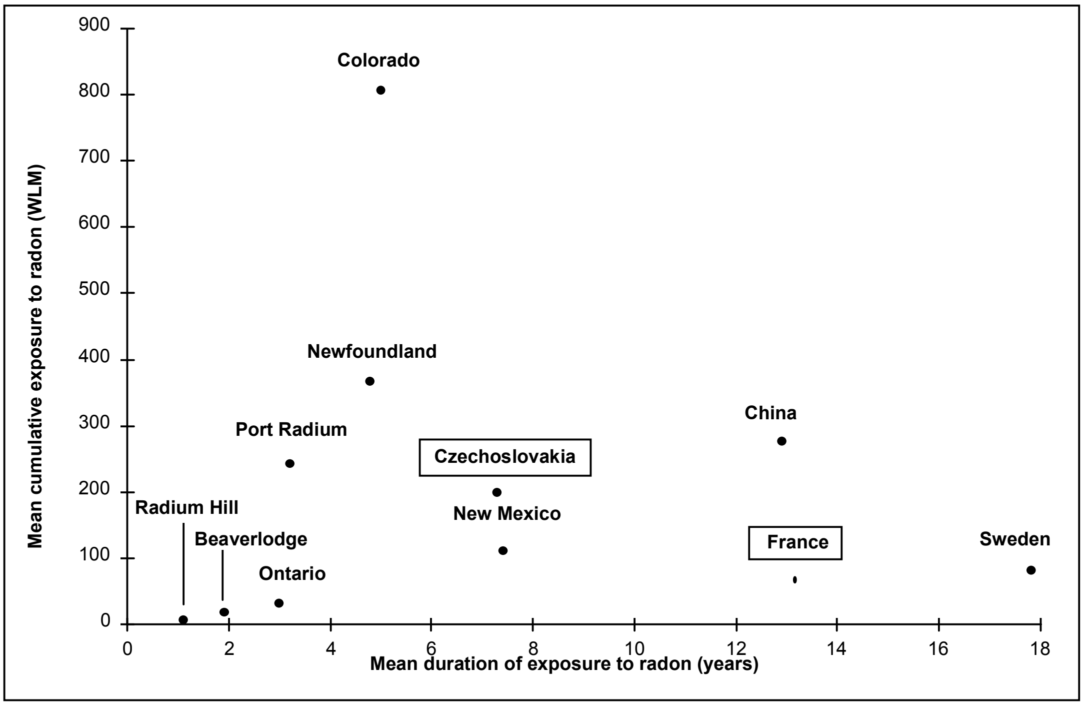

Figure 1. Mean cumulative exposure and mean duration of exposure in each of the 11 cohorts

WLM (Working Level Month) is a unit of exposure multiplying a concentration of radon decay products by the duration of exposure. A yearly exposure to 11 WLM corresponds roughly to a monthly exposure to 1 WL, the monthly exposure being defined as 170 working hours. 1 WL is equivalent to any combination of radon decay products in 1 liter of air, that results in the emission of 130,000 MeV of energy of α *particles.*

An inverse dose-rate effect has been observed in most of these studies, but mainly limited to high cumulative radon exposures. This effect has to be evaluated more precisely, mainly when considering low radon exposure protracted over more than 10 years. If this inverse dose-rate effect is existing for low annual exposures, it may have an important impact in the estimation of the lung cancer risk of the general public exposed to low chronic exposures in dwellings.

A European collaborative work on uranium miners has been initiated in 1996, with the objectives to estimate the risk of lung cancer linked to radon when low cumulative exposures are protracted over large periods of time, and to test the influence of other components present in the mining atmosphere. The project includes a total of several tens of thousands of miners from the Czech Republic, France and Germany. This paper presents results from the French cohort and the framework of the European project.

THE EXTENDED FRENCH COHORT OF URANIUM MINERS

In France, uranium mining began at the end of the forties. The French initial cohort of uranium miners included 1,785 uranium miners who began underground work between 1946 and 1972 and were exposed to radon for more than 2 years. A first analysis of this cohort has been published in 1993, based on a follow-up completed to December 1985 (Tirmarche et al., 1993). Since then, important efforts have been made to enlarge the French cohort of miners, by extending the duration of follow-up, and by including other miners. The objective is to obtain an increased statistical power for further analyses of radon risk at low levels of exposure. We also had the opportunity to collect, beside radon decay exposure, parallel exposure to gamma rays and to long-lived uranium dust. Tobacco consumption will be considered through a nested case-control approach.

Enlargement and extension of the cohort

The initial French cohort included 1,785 miners employed before 1972 with at least 2 years of underground work. The enlargement of the cohort has been performed, by including miners employed after 1972 and replacing the inclusion criterion of "2 years of underground exposure" by the less restrictive criterion "at least one year of employment as a miner". The whole cohort includes 5098 males, employed as miners by CEA or COGEMA between 1946 and 1990 for at least one year. Among this cohort, a group of 964 miners with no exposure to radon is present.

In the initial analysis (Tirmarche et al., 1993), miners were followed-up to 1985. Efforts have been made to extend dosimetric and medical follow-up to December 1994, for the whole cohort. Vital status has been ascertained by information from the administrative and medical files of COGEMA. For each miner suspected to have died or with an unknown status, a letter has been sent to the town hall of the place of birth, asking for validation of the vital status. About 2,000 letters have been sent with a quasi 100% response rate. For those miners born out of France, letters have been sent to the ministry of foreign affairs. Vital status has been completed up to 1994 for 98% of the miners. The total number of death is 1,162 (23%). Seventy four percent of the miners are still alive in 1995. The mean duration of follow-up is 26.2 years. Mean age at end of follow-up is 55 years old. The total number of person-years is 133,528.

Information on causes of death have been collected from two complementary sources, depending on the period. For the first period (1946-1985), causes of death were collected through an active research by the occupational medical service of COGEMA. After it became possible in France to use an anonymous linkage procedure with the French national mortality database that gathers information from death certificates for all deaths recorded in France since 1968. All causes of death were coded according to the International Classification of Diseases (ICD). Causes of death have been obtained for 1,092 deaths (94%). The number of lung cancer deaths is 126.

Reconstruction of radon exposure has been completed for the whole cohort of French miners up to 1995. This reconstruction needed a great effort of verification of the exposure database. This work has been performed in close collaboration with COGEMA, present employer of uranium miners in France. The same firm has ensured continuous dosimetric monitoring of all uranium miners since the beginning. For the first period (1946-1955), annual exposures have been retrospectively determined by a working group of experts from available information characterizing the type of and duration of work of each miner and the characteristics of each mine. Since 1956, recording of the annual radon exposure of all workers has been systematic. Each exposure variable was registered in the miner's file as individual annual exposures. Among the 4,134 miners with positive radon exposure, mean cumulative exposure is 36.5 WLM (minimum = 0.1, maximum = 960.1), protracted on a mean duration of 11.5 years (minimum = 1, maximum = 37). Figure 2 presents the distribution of levels of exposure to radon over time in the whole French cohort. The four curves indicate, for each calendar year, the fifth percentile (level under which 5 % of the positive measurements occurred), median (level under which 50 % of the positive measurements occurred), arithmetic mean, and the 95th percentile (level under which 95 % of the positive measurements occurred). It shows a dramatic decrease in radon exposures after 1956, following the introduction of a large-scale ventilation in mines. Mean exposures decreased from more than 20 WLM/y during the period 1946-1955 to less than 4 WLM/y after 1956.

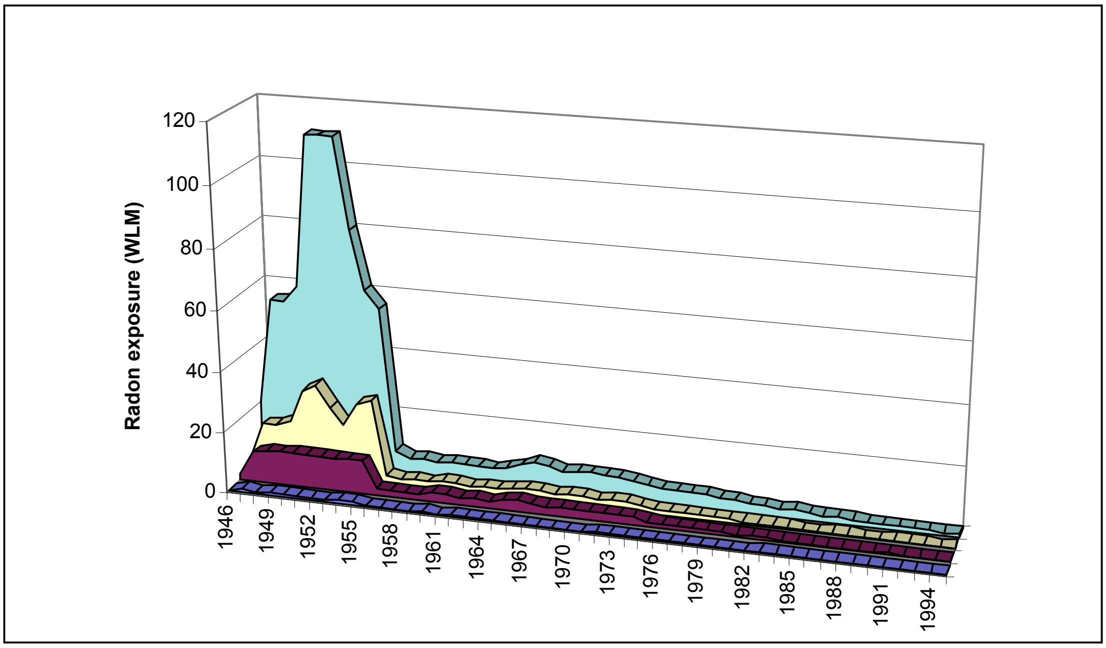

Figure 2. Evolution of annual exposure to radon in the French cohort of uranium miners

Compared to the initial cohort on which previously published results were based, the extension and enlargement of the French cohort of uranium miners allows a great increase in the size and in the number of cases (Table 1), which contributes to an important gain in statistical power.

Table 1. Characteristics of the French cohort of uranium miners, at the time of the first analysis, and after enlargement and extension of the follow-up.

	Initial cohort (Tirmarche et al., 1993)	Enlarged cohort	Difference
End of follow-up	1985	1994	
Number of miners	1,785	5,098	+ 186 %
Person-years	45,000	133,528	+ 197 %
Mean duration of follow-up (years)	25.2	26.2	+ 4 %
Number of deaths	352	1162	+ 230 %
Number of lung-cancer deaths	45	126	+ 180 %
Mean cumulative exposure to radon among exposed miners (WLM)	70.4	36.5	- 48 %
Mean duration of exposure among exposed miners (years)	14.5	11.5	- 21 %

Results: relative risk by cause of death

Compared to expected numbers calculated by applying male national rates, significant excesses are observed for lung cancer (Observed = 126, Expected = 83.7, Standardized mortality ratio (SMR) = 1.51 with 95% Confidence Interval (CI95%) = [1.25 ; 1.79]) and for silicosis (O = 20, E = 3.3, SMR = 6.02, CI95% = [3.68 ; 9.30]). No excess is observed for all types of cancer after subtracting lung cancers. An excess of death from larynx cancer that was observed in the first analysis in 1993 (Tirmarche et al., 1993) is not confirmed in the present cohort (O = 24, E = 20.4, SMR = 1.18, CI95% = [0.75 ; 1.75]).

Results: Relationship between risk of death and cumulative exposure to radon

The analysis of the relationship between mortality risk and cumulative exposure to radon was performed using linear Poisson regression models of the excess relative risk (ERR), both internally and with external reference (regression on the SMR's). A lag time of 5 years was applied.

For lung cancer risk, the results are as follow :

- internal regression : ERR/WLM = 0.82% CI95% = [0.24% - 1.40%], p = 0.003
- external regression : SMR (WLM) = 1.10 (1+ 0.0088 WLM)
  ERR/WLM = 0.88% CI95% = [0.30% - 1.47%], p = 0.002

The estimated ERR is significantly different from zero. This relationship is illustrated by figure 3.

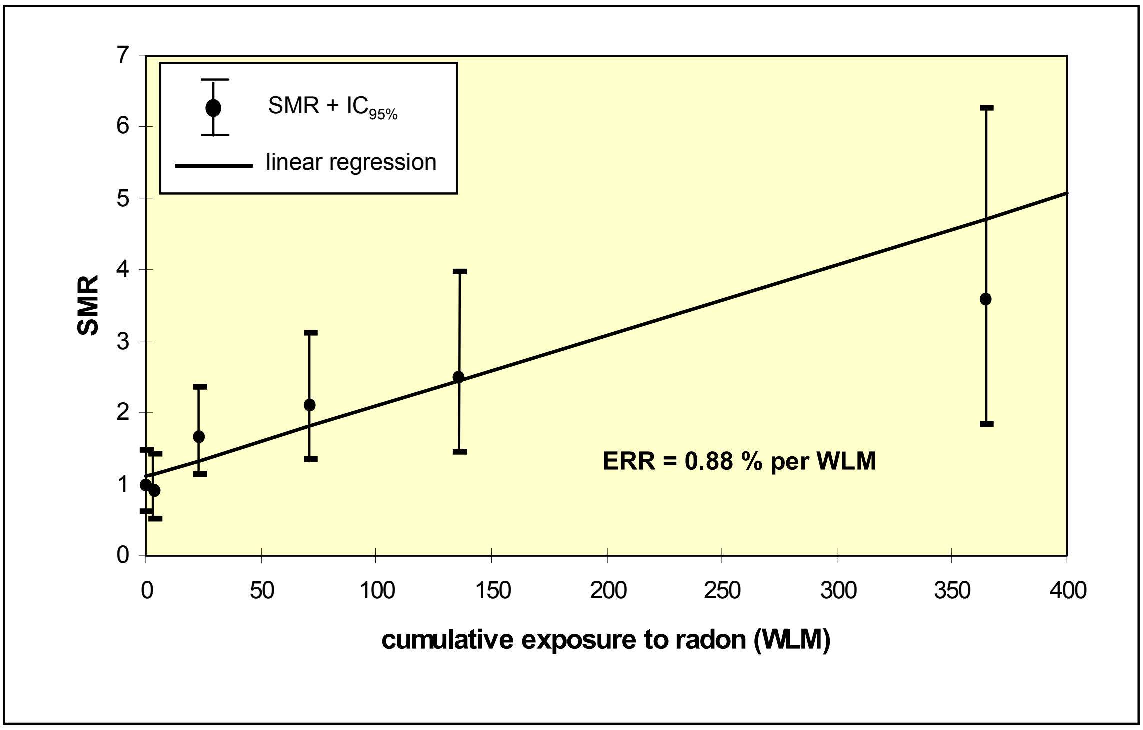

Figure 3. Relationship between lung cancer mortality risk and cumulative exposure to radon in the French cohort of uranium miners

These results confirm those previously published from the initial French cohort (Tirmarche et al., 1993 ; Tirmarche et al., 1997) and from the international joint analysis of 11 cohorts (Lubin et al., 1994). No other significant relationship with cumulative exposure to radon is observed for mortality from any other type of cancer.

THE EUROPEAN PROJECT

This chapter presents the framework of the collaborative work on uranium miners in Europe that has been initiated in 1996, with the support of the European Union (DG XII). The main partners involved in this

European program were :

Bernd Grosche, BfS, Munich, Germany,

Matthias Moehner, GSF, Munich, Germany,

Colin Muirhead NRPB, Chilton, Didcot, United Kingdom,

Dominique Laurier, IPSN, Fontenay aux roses, France,

Ladislav Tomasek NRPI, Prague, Czech Republic,

Coordination : Margot Tirmarche, IPSN, Fontenay aux roses, France.

The objectives of the European project were to estimate the risk of lung cancer linked to radon when low cumulative exposures are protracted over large periods of time, and to test the influence of other components present in the mining atmosphere. A joint analysis of European miners will increase the statistical power for the demonstration of a potential lung cancer risk linked to low levels of exposure. The analysis will be restricted to miners having experienced only low exposure rates, with a precise individual measurement of this exposure. Furthermore, the European project will allow to consider the modifying effects of confounding factors, present in the mines but absent in houses, such as gamma rays or uranium dust. Also smoking consumption will be considered.

This project comprised two workpackages, each of them being characterised by a different epidemiological and statistical approach, but both were involved in the estimation of cancer risk, mainly lung cancer risk linked to cumulated radon exposure. The populations used for the risk assessment were the uranium miners having worked in France, Germany and Czech Republic. The two main objectives were :

- estimation of lung cancer risk linked to radon decay products when low cumulative exposures are protracted over large periods, and test of the influence of other components present in the mining atmosphere that may influence the dose-response relationship, on the basis of a joint analysis of the European cohorts,
- test of the feasibility of case-control studies nested within the cohorts, and modelling of lung cancer risk through the application of multi-stage mechanistic models of carcinogenesis.

The final report in the frame of the European contract has been finalised in January 2000 (Tirmarche et al., 2000).

Workpackage 1: Joint analysis of European cohort studies

In the first workpackage, the objective of our European collaborative work on uranium miners cohorts was to estimate the risk of lung cancer linked to radon when low cumulative exposures are protracted over long periods, and to test the influence of other components present in the mining atmosphere, especially gamma rays and uranium dust. The final objectives in the frame of the European contract is the preparation of a joint analysis of the French, Czech and German cohorts, restricted to miners with low levels of exposure (Tirmarche and Tomasek, 1996).

A preliminary joint analysis of the French and Czech cohorts has been performed. Data included the enlarged cohort of French uranium miners described above. The Czech studies of miners (Tomasek and Placek, 1999) included two cohorts: an old one including 1,920 uranium miners at the Jachymov region firstly exposed in 1953-59, and a second one including 5,630 uranium miners who entered the Pribram uranium mines in 1968-74, when radiation protection measures had been fully introduced. The mean radon cumulative exposure in the joint two Czech cohorts is 29 WLM, and corresponds thus to that of the French cohort. Both French and Czech studies show a significant increase of lung cancer mortality with cumulative exposure to radon, with estimated excess relative risks varying between 0.9% and 2% per WLM. The joint analysis of the French and Czech cohorts permits to increase the power and the ability to analyse modifying factors, it confirms previous analyses and provides a higher precision to estimates of risk coefficients.

From the total cohort of French miners, a subcohort of miners employed after the implementation of forced ventilation in the mines in 1956 has been defined. This cohort includes 3,388 miners with precise individual records of exposure to radon, to gamma rays and to ore dust. The mean level of exposure to radon is low: among miners with positive radon exposure, mean cumulative exposure is 17.8 WLM, protracted on a mean duration of 11.5 years. Restriction of the joint analysis to such low exposed miners gives us the opportunity to study the risk of lung cancer death linked to low levels of radon exposure, protracted at low rate over a long duration, and taking into account multiple exposures to gamma rays and to ore dusts.

For the German cohort, the main achievement is the collection of personal data and reconstruction of working histories for approximately 60,000 uranium miners and controls (Kreuzer et al., 1999). An internal validation of all records have been performed, and a first descriptive analysis of the cohort has been achieved. The average duration of exposure among exposed persons is 10 years. Vital status is reconstructed up to 1997. The reconstruction of radon exposures and other occupational exposures and the research for causes of death have been started. The German cohort study, that has been initiated later than the French and Czech studies, will be included in the joint analysis in a second step, when the data of the subgroup, exposed after 1960 will be validated and analyzed.

Workpackage 2: Nested case-control approach

For a precise estimate of lung cancer risk from radon progeny exposure, tobacco consumption and occupational exposure to carcinogenic substances as potential confounding or interacting factors have to be considered. Smoking is a well known and powerful risk factor for lung cancer mortality, but this factor has rarely been taken into account in the analysis of lung cancer risk in miners cohorts. For this purpose, a nested case-control approach was envisaged among European miners cohorts. With sufficient data on radon exposure and on amount of tobacco consumption and its time-related changes, modelling of lung cancer risk can be approached with application of multi-stage mechanistic models of carcinogenesis.

The implementation of nested case-control approaches has been realised as a pilot study in Germany and France. Fruitful discussions were raised between partners to examine the methodology of nested case-control studies, for use in defining a common approach to analyse uranium miner data. Among the French cohort of uranium miners, a group of 100 cases deceased from lung cancer between 1980 and 1994 has been selected. For each, five controls have been randomly selected, matched on the age at death of the case and on the period of birth. Research of information about smoking is ongoing for these subjects. For the German nested case-control study, the procedure of data collection has been established and a self-administered questionnaire has been developed. A feasibility study has been performed, that permits to assess the recruitment efficacy. According to these results, the study population has been defined. The approach combines data from the indoor radon case-control study and from the Wismut cohort of miners, which allows to evaluate the consistency of the information about smoking habits.

Models that attempt to describe mechanisms of carcinogenesis have been fitted to updated data on lung cancer mortality among Colorado Plateau uranium miners in the USA. Statistical aspects associated with the design of nested case-control studies of uranium miners were examined. In particular, modelling of the above data indicated that the ratio of controls to cases needs to be of the order of 10 or more in order to obtain reliable results from mechanistic modelling on radon-associated lung cancer risks. In practice, it may not always be possible to obtain such high control-case ratios, in which case analyses would be best restricted simply to the estimation of a simple relative risk, rather than fitting detailed risk models. Using the best-fitting mechanistic model, predictions of lung cancer risk were made under various exposure scenarios. A notable feature was the inter-relation between the effects of factors such as radon exposure rate, duration of exposure, age and time since exposure, as well as the effect of smoking. Although interpretation of these predictions is complex, they should have a stronger basis than predictions based on empirical models fitted solely to provide a good fit to epidemiological data. Furthermore, mechanistic modelling should provide further insights into the carcinogenic process.

CONCLUSION

Data on European uranium miners constitute a unique tool for estimation of the cancer risk linked to low chronic exposure to radiation. Together, the French, Czech and German cohorts of uranium miners when completed will constitute a total population of low exposed miners of about 20,000 individuals, with similar working conditions and comparable quality of dosimetric data. This collaboration will be continued during the next years. The consequent step could be the same approach of modelling of the low exposed European cohorts, once finished the collection of the data of the nested case-control approach. Results of these studies are necessary both for a better understanding of the ongoing mechanism involved in daily alpha exposure of the human cells and for a validation of the risk evaluation linked to low chronic exposure in absence and in presence of concomitant lung carcinogens. These results are expected to be quite informative for the estimation of lung cancer risk following domestic exposures. A parallel analysis of human and animal data is also planned in this framework.

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