CZECH STUDIES OF LUNG CANCER AND RADON

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INTRODUCTION

According to the International Agency for Research on Cancer, there is a significant evidence to classify radon as a carcinogen. Using extrapolations from occupational studies, it can be shown that for some countries environmental exposure to radon is the second most important cause of lung cancer in the general population after cigarette smoking. Czech studies among uranium miners, established in 1970 by Josef Ševc [1], and in the general population aim to contribute to knowledge on the risk from radon, particularly by evaluating temporal factors and interaction of radon exposure and smoking.

METHODS

Definition of cohorts

The study population of occupational cohorts consists of uranium miners exposed in two different periods. The older cohort (S) involves 4339 miners from the Jáchymov region (West Bohemia), who began underground work in 1948-59 [2]. The newer cohort (N) consists of 5621 miners who entered Příbram mines (Central Bohemia) during 1968-74, when hygienic measures had been already fully introduced [3].

The residential study is as a retro-prospective follow-up covering period since 1960. The study area – Middle Bohemian Pluton (241 km^2) is mostly granitoid with considerable breaks. The population includes inhabitants of the area (80 villages) who had resided there for at least 3 years, were alive by 1960 or were born later. The collected data included past residences and smoking habits. Data on 12 002 subjects were collected by trained interviewers. A total of 221 people were excluded from the present analyses for deficient personal data, not permanent residence, or large gaps in their residence histories [4].

Information on vital status and causes of death were obtained from the Czech population registry and the diagnoses from registries of deaths at local administrative offices. Follow-up for each subject started according to the respective definition of each cohort [2, 5]. The present follow-up is limited by the end of 1999.

Estimation of exposure to radon and tobacco smoke

Exposure estimates in the S study were derived from extensive measurements of radon commencing already in 1949 [2]. Each man's annual exposures to radon progeny were estimated combining measurement data with the men's registered employment details, including duration of underground work at different shafts and job category. In the N study, the exposure estimates were based on personal dosimetric records [3]. Occupational exposures are given in Working Level Months (*WLM*) integrating the concentration of radon progeny in air in terms of Working Levels (*WL*) and the duration of exposure in Working Months (170 hours). One *WL* corresponds to 130 000 MeV of potential alpha energy released by the short-lived progeny in equilibrium with radon in one litre of air (3.7 kBq/m^3).

The exposure assessment in the residential cohort was based on measurements of equivalent equilibrium concentrations of radon (radon progeny) in most houses (80%) of the study area. During the period 1991-92, integral detectors (Kodak LR115) were installed for one year in two mostly occupied rooms of the house. The conversion factor between radon progeny and radon gas activities was estimated from 652 simultaneous measurements by both passive track detectors and electrets. Exposure estimates outside the area were derived from radon mapping in the country. In houses of the study area, the community means were used instead of missing values. Concentrations corresponding to residences outside the area (16% of respective residence person-years) were estimated by larger community means in the neighbouring four districts and by district means in other districts [4].

In order to compare the risk in the occupational and residential studies, the indoor exposure was expressed in terms of $kBqm^{-3}\ y$ integrating both the concentration of radon ($kBqm^{-3}$) and the duration of residence in years (*y*), similarly as for the unit WLM.

Information on smoking in the cohorts was different. In the S cohort, data were collected from only 332 cases since 1970 and 502 controls matched by year of birth and attained age. This information was obtained from medical records, relatives, and from alive miners. In the N study, smoking data were routinely collected (85%). As smoking details from these sources were different, collected smoking data were limited to numbers of cigarettes smoked per day and the year of cessation.

Statistical analyses

The statistical analyses were based on the relative risk model. Numbers of cases (*O*) observed at given levels of cumulated exposures and modifying variables (W_k) were supposed to have the Poisson distribution with parameter $iE\ (1+ \Sigma\ b_k\ W_k\ )$, where *E* is the number of cases expected from national mortality data, parameter *i* is an intercept term that allows the background mortality rate for the 'unexposed' cohort to differ from that in the general population, parameters b_k represent specific excess relative risk per unit exposure (ERR/WLM) in each level (*k*) of time since exposure (5-19, 20-34, 35-49), age at exposure (-29, 30-39, 40-), and exposure rate in terms of *WL* (<1, 1-2, 2-4, 4-8, >8). The observed relative risk (*RR*) in the cohort can be estimated by ratio *O/(iE)*.

RESULTS

By 1999, a total of 4008 deaths were observed in both cohorts of uranium miners. Among these deaths, a total of 922 cases of lung cancer were diagnosed (Table 1). Increased mortality from lung cancer in occupational cohorts corresponds to cumulative exposures experienced in the two cohorts.

In the residential study, a total of 4090 subjects (35%) of the cohort have died by the end of 1999, 465 of them in ages over 85, and 18 subjects emigrated. A total of 218 lung cancers have been observed. The present figures suggest increased mortality from lung cancer (O/E=1.15) in contrast to 600 cancers other than lung (O/E=0.87). The association of the risk and average radon exposure of preceding periods 5-34 years was significant. The estimate of excess relative risk (ERR) per unit radon concentration (100Bq m^3) was 0.085 (90%CI: 0.015-0.205). This estimate did not substantially change by adjustment for smoking (ERR/100Bq m^3 = 0.076, 90%CI: 0.010-0.191), calendar period or gender.

Table 1. Cohorts of Czech uranium miners and residents by 1999

	S	N	S+N	Residents
Number of subjects	4 339	5 621	9 960	11 801
Alive by 1999	20%	84%	56%	65%
Mean cumulated exposure	152 WLM	7 WLM	70 WLM	24 $kBqm^3y$
PY weighted exposure 5-34 y ago	111 WLM	5 WLM	54 WLM	11 $kBqm^3y$
Person-years of follow-up	116 366	143 709	260 075	299 810
Lung cancers	841	81	922	218
Standardized mortality (O/E [a])	4.64	1.43	3.88	1.15
Relative risk (RR [b])	3.93	1.23	3.29	1.35

[a] O/E - ratio of observed numbers to numbers expected from national mortality data

[b] RR - relative risk – ratio of observed cases to internally estimated numbers expected at zero exposure

Lung cancer risk in the occupational cohort (S+N) shows linear trend in dependence on cumulated exposures below 400 WLM (Figure 1). The obvious departure from linearity in exposures over 400 WLM is attributed to the so-called inverse exposure rate effect. This is accounted for by including exposure rate specific terms in the model (Table 2). Similar effects were observed in most studies of highly exposed miners [6]. In our analyses, the total cumulated exposure for each miner was differentiated according to the exposure rate in each year of employment. The exposure rate effect is present only at exposure rates over 4WL. In general, the effect from exposures received at very high rates (>8WL) is roughly 1/3 when compared to rates <8WL.

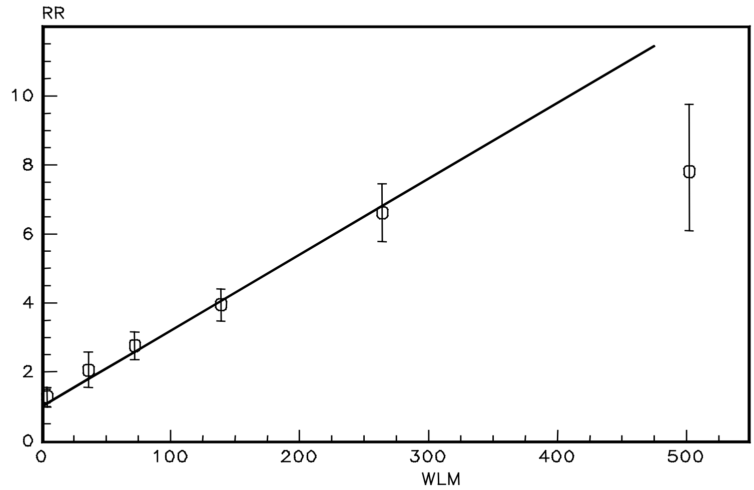

Figure 1. Relative risk of lung cancer (RR) in the cohort of U miners by cumulative exposure (WLM); solid line - RR = 1+ 0.02 WLM for exposure rates <8WL

Table 2. Effect of exposure rate in relative risk model $RR = 1+ \Sigma c_k W_k$

		Estimate [a]	*90%CI*	Estimate [b]	*90%CI*
ERR/WLM [c]	overall	0.012	*0.009 – 0.016*	0.017	*0.012 – 0.023*
	Deviance [c]		*7090.23*		*7053.42*
ERR/WLM	0-1WL	0.020	*0.009 – 0.035*	0.015	*0.004 – 0.031*
ERR/WLM	1-2WL	0.026	*0.017 – 0.037*	0.027	*0.018 – 0.041*
ERR/WLM	2-4WL	0.022	*0.015 – 0.032*	0.027	*0.018 – 0.039*
ERR/WLM	4-8WL	0.009	*0.003 – 0.018*	0.011	*0.004 – 0.021*
ERR/WLM	8- WL	0.005	*0.001 – 0.010*	0.007	*0.002 – 0.013*
	Deviance [c]		*7056.23*		*7023.93*
ERR/WLM	0-4WL	0.024	*0.017 – 0.034*	0.029	*0.021 – 0.041*
ERR/WLM	4-8WL	0.010	*0.003 – 0.017*	0.013	*0.005 – 0.024*
ERR/WLM	8- WL	0.005	*0.002 – 0.010*	0.008	*0.003 – 0.014*
	Deviance [c]		*7057.03*		*7027.21*

[a] crude estimates
[b] estimates adjusted for time since exposure and age at exposure
[c] excess relative risk per WLM
[d] deviance represents measure of fit of each model

Factors modifying the linear relative risk model

In addition to the inverse exposure rate effect (Table 2), lung cancer risk from cumulated exposure to radon is strongly influenced by time since exposure (chi-squared 264, 2 degrees of freedom), being less than 1/13 after more than 34 years since exposure in comparison to the period of 5-19 years (Table 3). The evaluation of the modifying effect of age at exposure is related to the effect of time since exposure. For instance, when exposures are considered only in time windows 5-34 and 35-49, the effect of age at exposure is diluted in this longer period.

If time since exposure factor is omitted at all, the risk is paradoxically higher for miners exposed in older ages, however such exposures represent at the same time more recent exposures.

Table 3. Model of relative risk and modifying effect of time since exposure, age at exposure, and exposure rate $RR = 1 + b \Sigma\Sigma\Sigma t_i a_j c_k W_{ijk}$

Modifying factor	Parameter of model		Estimate	95%CI	chi-sq	p-value
	ERR/WLM [a]	b	0.111	0.077 – 0.160		
Time since exposure	5-19	t_1	1.000		264.02	0.0001
	20-34	t_2	0.174	0.127 – 0.221		
	35-49	t_3	0.073	0.036 – 0.110		
Age at exposure	-29	a_1	1.000		40.52	0.0001
	30-39	a_2	0.676	0.449 – 0.903		
	40-	a_3	0.388	0.282 – 0.494		
Exposure rate	0-4 WL	c_1	1.000		15.08	0.0005
	4-8 WL	c_2	0.697	0.285 – 1.110		
	8- WL	c_3	0.360	0.098 – 0.621		

[a] Excess relative risk per WLM corresponding to first categories of each modifying factor

Comparison between the occupational and residential studies

Relative risk in relation to cumulated exposures below 150 WLM and the risk from residential radon are shown in Figure 2. A significant elevation of the risk is observed at low exposures of 10-20 WLM or 10-20 kBq $m^{-3}y$ in both studies. Risk coefficients related to cumulated exposure in mines and houses are compared in Table 4. The considerable effect of time since exposure seen in the occupational study can also be observed in the residential study. The analysis of temporal modification of the risk suggests that the risk results mainly from exposures experienced in previous period 5-19 years. However, in the residential study the statistical power to detect such differences is limited. The risk coefficient from exposures in the distant past (35-49 years) is negligible (about 1/7 in comparison to the period 5-34).

Table 4. Time since exposure (TSE) specific risk coefficients
Estimates from occupational and residential studies

	Uranium Miners (922 cases)		Residential (218 cases)	
TSE	*ERR/WLM*[a]	90%CI	*ERR/kBq* $m^{-3}y$	90%CI
5-19	0.059	0.043 – 0.075	0.045	-0.000 – 0.153
20-34	0.015	0.010 – 0.021	0.013	-0.000 – 0.123
35-49	0.008	0.003 – 0.012	*not estimated*	
5-34	0.028	0.020 – 0.035	0.028	0.005 – 0.069
35-49	0.004	0.001 – 0.008	0.003	-0.000 – 0.071

[a] for exposure rates below 8WL

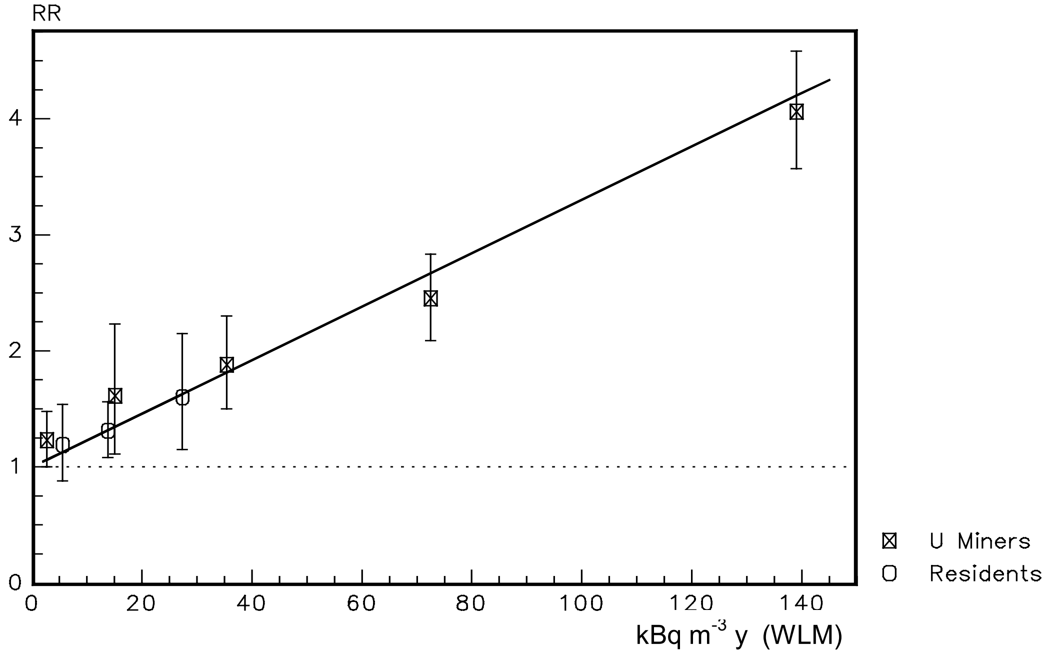

Figure 2. Relative risk (RR) by exposure cumulated in the preceding period of 5-34 years in the occupational (WLM) and residential (kBq m^{-3} y) studies

Smoking

With the exclusion of the S cohort, smoking data were collected from most cohort members. When the S cohort of miners was identified in 1970, the mines had already closed and so a direct investigation in the study was not possible. As most informative results in this respect can be expected in highly exposed miners, a retrospective investigation was recently initiated. Data were collected from medical records and from relatives of miners. So far, information on 834 miners from the S cohort is available. Since the relative risk among long term ex-smokers was not different from never smokers (RR=0.80, 95%CI: 0.39 - 1.65), subjects who quitted smoking before more than 20 years (14 cases) were combined with never smokers. Preliminary results (Table 5) exhibit a considerable consistency in risk coefficients. Results from the Czech residential study [4] are given for comparison.

Table 5. Excess relative risk per unit exposure among smokers and non-smokers

	UE [a]		Cases	*ERR/UE* [b]	90%CI	p-value [c]
Occupational	WLM	Smokers	362	0.018	0.010 – 0.030	*0.214*
		Non-smokers [d]	43	0.040	0.014 – 0.140	
Residential	kBq m^{-3} y	Smokers	173	0.023	0.000 – 0.064	*0.768*
		Non-smokers [d]	42	0.043	-0.006 – 0.444	

[a] UE unit of exposure

[b] Excess relative risk per unit exposure

[c] Test for heterogeneity of risk coefficients between smokers and non-smokers

[d] Including 14 and 6 ex-smokers who quitted smoking before more than 20 years

Because of low numbers of non-smoking lung cancer cases, the comparison of the risk coefficients between smokers and non-smokers has not resulted in significant differences in either cohorts, however, higher relative risk is suggested among non-smokers in both studies. In addition to smoker specific estimated risk, the relative risk of lung cancer for smokers in comparison to non-smokers in the cohort was also estimated (RR=11.1). This value is consistent with amount of cigarettes smoked per day among miners. Using these estimates, combined effect from radon and smoking can be summarized (Table 6). For instance, exposure to radon progeny at 200 WLM roughly corresponds to the relative risk among non-exposed smokers (assuming 20 cigarettes a day). However, the simultaneous exposure to radon progeny and tobacco smoke does not result in the product of the risks, but is about half. These patterns are consistent with sub-multiplicative interaction.

Table 6. Relative risk of lung cancer from radon progeny and smoking

	Non-smoker	Smoker
Not exposed	1	11
Exposed (200WLM)	10	55

Relative risk among residents from lifetime exposure to 1 kBq/m^3 (which is comparable to exposure lasting only recent 30 years) is about 2.3 for non-smokers and 1.7 for smokers. This approximately 'doubling' exposure would correspond to 2 cigarettes per day.

DISCUSSION

The present results from the residential cohort study in terms of excess relative risk per 100 Bq/m^3 are in line with findings in other studies (all case-control) as summarized in [7].

In comparison to our previous publications [2, 5], results from the occupational study based on the extended follow-up showed that factors that modify the general linear model became more discernible. The present analyses confirmed the decreasing effect with time since exposure, observed in many studies of miners [6]. It is worth noticing that a similar pattern was observed in the residential study. Although the confidence intervals for the time specific risk coefficients in the residential study are relatively wide, these estimates suggest that using time window of 5-34 years is appropriate in evaluating risk from lifetime exposures.

The evaluation of age at exposure depends both on numbers of miners employed at young ages (say below 30) and simultaneously on the critical period about two decades after such exposure. As the background rates below age of 50 are generally relatively low in comparison to older age categories, the observed absolute excess is low, too, and so the detection of age at exposure effect is limited in most studies [6].

The issue of smoking in evaluation lung cancer risk is essential. Although the design to evaluate smoking in the S and N cohorts is different, the results are consistent with general knowledge on the risk of smokers compared to non-smokers. Smoking prevalence among miners is higher than in the general population. For instance, in the N study, the proportion of current smokers in the period 1970-85 was 77%, which is more than in the Czech male population (55-60%) of similar age (20-44) [8, 9]. The assessment of combined effects of smoking and radon is an obvious issue in occupational studies. However, only few had been evaluated. The crucial point is the sufficient number of cases in the non-smoking group. Results obtained in six combined uranium miners studies (64 non-smoking cases) are in line with our findings [6]. Generally, it is presumed that the difference in risk coefficients is due to different patterns of lung deposition and clearance in smokers and non-smokers.

The evidence of lung cancer risk from radon is based mainly on studies of men employed underground in mines. Direct estimation of the risk from residential radon is more complex than in occupational studies. In addition, exposure estimates in residential studies show higher uncertainty than in studies of miners. Estimates of cumulated exposure in occupational studies are generally more precise; not only because the radon measurements in mines were conducted already in the past, but also because the duration of stay of workers in the radon environment was recorded with a higher precision than in houses. In spite of these weak points, the results of Czech occupational and residential studies exhibit considerable similarities. Virtually identical coefficients were estimated when exposures were limited to preceding period of 5-34 years and very similar coefficients were obtained in the smoking and non-smoking sub-cohorts. The exposure units used in the occupational and residential studies are different, though. According to ICRP-65 [10],

1 WLM = 3.5 mJh/m^3,
1 kBq m^{-3} y = 15.6 mJh/m^3 (at F=0.4),
1 kBq m^{-3} y = 11.7 mJh/m^3 (at F=0.3).

The important point in the estimation of potential alpha energy intake is the estimation of breathing rates at various activities. Such values were estimated by the Panel on dosimetric assumptions affecting the application of radon risk estimates [11]. Using Table 9-5 [10] and assuming 45% heavy exercise, 45% light exercise, and 10% rest for miners and 30% sleep, 25% rest, 25% light exercise, and 20% outdoor (corresponding to annual 7000 hours for residents), we can estimate the annual intake of 7.4 mJ and 8.1 mJ corresponding to 1WLM and 1kBq/m^3, respectively (Table 7). Our findings in terms of relative risk per unit exposure correspond to these estimates.

Table 7. Estimates of potential alpha energy intake from occupational and resdidential radon

			Uranium miners			Residents	
ICRP-65:	1WLM		=3.5 mJhm^3	1kBq m^{-3} y		=15.6 mJhm^3	F=0.4
						=11.7 mJhm^3	F=0.3
			men			*men+women*	
activities and breathing rates [a]	heavy	45%	3.0 m^3/h	light	25%	1.38 m^3/h	
	light	45%	1.5 m^3/h	rest	25%	0.46 m^3/h	
	rest	10%	0.5 m^3/h	sleep	30%	0.38 m^3/h	
				outdoor[b]	20%		
mean breathing rates			2.1 m^3/h			0.7 m^3/h	
potential alpha energy			7.4 mJ			8.1 mJ	

[a] according to NRC, Comparative Dosimetry of Radon in Mines and Homes, 1991

[b] corresponding to 7000 hours annually (ICRP-65)

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