Paper

ACCOUNTING FOR SMOKING IN THE RADON-RELATED LUNG CANCER RISK AMONG GERMAN URANIUM MINERS: RESULTS OF A NESTED CASE-CONTROL STUDY

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Abstract—**The possible confounding effect of smoking on radon-associated risk for lung cancer mortality was investigated in a case-control study nested in the cohort of German uranium miners. The study included 704 miners who died of lung cancer and 1,398 controls matched individually for birth year and attained age. Smoking status was reconstructed from questionnaires and records from the mining company's health archives for 421 cases and 620 controls. Data on radon exposure were taken from a job-exposure matrix. Smoking adjusted odds ratios for lung cancer in relation to cumulative radon exposure have been calculated with conditional logistic regression. The increase in risk per Working Level Month (WLM) was assessed with a linear excess relative risk (ERR) model taking smoking into account as a multiplicative factor. In addition, the potential impact of temporal factors on the ERR per WLM was examined. Lung cancer mortality risk increased with increasing radon exposure, yielding a crude ERR per WLM of 0.25% (95% CI: 0.13–0.46%). Adjustment for smoking led only to marginal changes of the radon-associated lung cancer risks. The adjusted ERR per WLM was very similar (0.23%, 95%-CI: 0.11–0.46%) to the crude risk and to the risk found in the Wismut cohort study. This stability of the radon-related lung cancer risks with and without adjustment for smoking suggests that smoking does not act as a major confounder in this study and presumably also not in the cohort study.**

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Key words: cigarettes; lungs, human; mining, uranium; radon

INTRODUCTION

Exposure to radon gas and its progeny products increases the risk of lung cancer. This relationship has been consistently shown in studies on underground miners occupationally exposed to radon and its decay products (National Research Council 1999) and also in pooled studies on residential radon (Darby et al. 2005; Krewski et al. 2005).

Recently, first results from the currently largest single cohort study on underground miners — the Wismut cohort including about 59,000 German uranium miners — have been published (Grosche et al. 2006; Kreuzer et al. 2006, 2008, 2009). In accordance with results from other miners studies, a statistically significant linear increase in risk for lung cancer mortality with increasing cumulative exposure to radon progeny has been found in the Wismut cohort (Grosche et al. 2006). Its size, the long duration of follow-up (on average 31 y), the large number of lung-cancer deaths (2,388 up to the end of 1998), and the inclusion of a large internal comparison group make this cohort a particularly important source of knowledge on the relationship between radon exposure and lung cancer mortality. However, information on the smoking behavior of the miners is very limited for the Wismut cohort. Only very coarse information, referring mainly to time periods after 1970, is available for just 38% of the cohort members. Consequently, the role of this important risk factor as a potential confounder has not been addressed in the cohort study. Also, for many other cohorts of uranium miners, information on the smoking behavior of the miners is either very limited or non-existent. In order to explore the role of smoking for radon-related lung cancer risk, case-control studies nested in the cohorts have been carried out (Qiao et al. 1989; Lubin et al. 1990; L'Abbe et al. 1991; Yao et al. 1994; Leuraud et al. 2007).

Since smoking is generally such a strong risk factor for lung cancer and tobacco use is widespread among underground miners, the possible confounding effect of smoking on estimates of radon-induced lung cancer risk needs to be quantified and accounted for in analyses of the Wismut cohort. For this reason, in the present study, the possible contribution of confounding by smoking to the estimated

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radon-induced risk for lung cancer mortality among Wismut miners is investigated with data from a case-control study nested in the Wismut cohort.

MATERIALS AND METHODS

Study subjects

The German cohort

The assembly of the cohort with relevant inclusion criteria and details of the mortality follow-up have been described in detail in previous publications (Kreuzer et al. 2002, 2006, 2009; Grosche et al. 2006). The cohort consists of about 59,000 men employed for at least 180 days by the Wismut Company, established by the Soviet Union for mining uranium in the former German Democratic Republic (GDR) after the Second World War. Cohort members were selected from personnel files, including about 130,000 workers, as a stratified random sample. The sample was stratified by date of first employment, place of work and area of mining to allow risk estimation based on a large range of exposures. Further inclusion criteria for the cohort were date of first employment between 1946 and 1989 and year of birth after 1899.

Selection of the cases

Selection of cases for the nested case-control study was based on information from the first follow-up of the cohort, determining the vital status of cohort members up to 31 December 1998 (Kreuzer et al. 2002, 2006). Causes of death were identified mainly on the basis of death certificates from Public Health Administrations. Additional sources of information for the follow-up were the Wismut Pathology Archives and District Archives. As results from a previously conducted pilot study for the nested case-control study had shown that it was particularly difficult to obtain information on smoking behavior for cohort members born before 1927, only lung cancer cases born 1927 or later were included. By the end of June 2002, a total of 706 lung cancer cases fulfilling these criteria could be identified in the cohort. Later, two cases had to be excluded: one because of a wrong birth year, and the other because of missing exposure information. Finally, 704 lung cancer cases have been included in the case-control study.

Selection of the controls

Two controls were matched individually to each case in a two-step process. In the first step for each case, a set of all eligible cohort members born in the same year as the case and alive at the time of the case's death was defined. In the second step, two controls were selected randomly from each of these sets. Later, 10 of these controls had to be excluded, either because exposure estimation was not possible for them or because violation of inclusion criteria was detected on the basis of newly-emerging information. Hence, the sample comprised 1,398 controls (1,043 alive, 355 deceased at the end of the first follow-up for the cohort, i.e., at the end of 1998), and therefore for 10 cases the matching rate was 1:1.

Radon exposure

Data on exposure to radon and its progeny were the same as used in the cohort study. Annual exposures have been estimated by using a job-exposure-matrix (JEM) (Lehmann et al. 1998). This JEM provides annual exposure values for each calendar year of employment between 1946 and 1989, each place of work and each type of job. More than 900 different jobs and several mining facilities have been evaluated. Measurements of radon are available only from 1955 onwards. For the time periods without measurements, these concentrations were estimated based on first available measurements, taking into account previous working conditions in the mines, mine architecture and so on. Further details are given elsewhere (Lehmann et al. 1998; Kreuzer et al. 2002, 2009). Complete daily information on the type of job and type of mining facility and information on periods of absence were available for nearly all cohort members. The cumulative exposure to radon and its progeny is expressed in Working Level Months (WLM). A working level (WL) is defined as 1.3×10^5 MeV of potential alpha energy per liter of air. A working level month equals exposure to 1 WL for 170 h.

Smoking history

Information on smoking habits was extracted from two different sources: (1) from self-administered questionnaires sent to living controls and to next-of-kin of cases and deceased controls; (2) from the Wismut Health Archives, containing the files of the company's own Health System, which was responsible for the health care of the employees and their next-of-kin (i.e., documents from hospitals, cures, regular medical check-ups, etc.). The smoking history of all subjects was extracted from these files in a standard fashion.

Questionnaire data

Current addresses of living controls and next-of-kin (mainly widows or children) of deceased miners were obtained from local registration offices. These persons were invited to take part in the study by mail and were asked to send back a written informed consent form in a pre-stamped envelope. Non-responders were reminded by mail twice, 3 weeks apart. Persons who agreed to participate were sent a questionnaire inquiring about whether the study subject ever smoked (regularly or

occasionally) and if so which type of tobacco product had been used. If possible, respondents were asked to detail smoking history in separate phases defined by a change in amount smoked. In the case that these questions could not be answered, the possibility was provided to describe the smoking habits of the study subject at least roughly.

Completed questionnaires were sent back by 183 cases and 527 controls (26% and 38%, respectively). All of the questionnaires for cases and 173 questionnaires for controls had been filled in by next-of-kin (mostly wives or children), the rest by the miners themselves. In most of the questionnaires completed, information on tobacco use was available (for 180 cases and 518 controls).

For 18% (n = 125) of the cases and 11% (n = 156) of the controls, no next-of-kin were found or could be contacted. A total of 16% of the cases (n = 115) and 18% (n = 249) of the controls did not answer at all, while 39% (n = 281) of the cases and 33% (n = 466) of the controls explicitly refused to take part. Reasons for refusal were inability (10% of the cases and 4% of the controls)—for example because of bad health or lack of knowledge—or rejection (7% of the cases and 6% of the controls), mainly because of emotional distress. Twenty-two percent of the cases and 24% of the controls refused to take part without stating reasons.

Health archives

In the health archives, files for 649 cases (92%) and 1,266 controls (91%) have been retrieved. In these files, information relevant to smoking habits was found for 477 cases (68%) and for 777 controls (56%). For 353 cases (50%) and for 441 controls (32%), the health archives were the only source of information on smoking.

Most of the information contained in the files refers to the years after 1970, when regular medical checkups had been introduced by the health system. Smoking information collected in these checkups referred only to the current situation, and the predefined categories simply include "non-smoker" as a category, but not "never-smoker." Thus information from these archives usually only covers the time period between 1971 or start of employment and closure of the Wismut Company or end of employment. Therefore certain differentiations with respect to smoking status are not possible based on the files from the health archives. For example, for a miner whose first record in the archives dates back to 1970 and who is consistently declared as "non-smoker," no reliable distinction between lifelong non-smoker and long-term ex-smoker is possible, as he might have been a smoker before 1970. Similarly, a current smoker cannot be distinguished from an ex-smoker having stopped after his last entry in the archives.

Definition of smoking status

The data from the health archives served as the main source of information on smoking for the study because of the low response rate from the questionnaires. To deal with the above-mentioned problems, smoking was treated as a dichotomous variable, with the two categories "smoker," defined as persons who ever smoked in the last 20 y before death (for cases) or the reference case's death (for controls), and "non-smoker," defined as persons who never smoked or stopped smoking at least 20 y before death or the reference case's death. Smoking status for controls was determined by truncating smoking information at the time of the corresponding case's death; i.e., a control having started to smoke after the case's death was categorized as "non-smoker." In some rare cases, information from the health archives contradicted that from the questionnaire. If the health archives provided several congruent statements contradicting the information from the questionnaire, smoking status was derived from the health archives, otherwise from the questionnaire.

For 171 cases (24%) and 449 controls (32%), information on smoking was neither available from the questionnaires nor from the health archives. For 27 cases and 69 controls, the only available information was too old or too vague to allow classification of smoking status as defined above. Consequently, smoking status was determined for 506 cases (72%) and 880 controls (63%). Restrictions due to matching led to the exclusion of another 85 cases and 260 controls, resulting in a study sample with 421 cases and 620 controls for the consideration of smoking in the analyses. This study sample comprises 60% of the cases and 44% of the controls of the initial sample, which consists of 704 cases and 1,398 controls.

Statistical methods

The cumulative exposure to radon and its progeny was calculated as the sum of the annual exposures estimated by the JEM, from the first year of exposure up to 5 years before death for cases and 5 years before death of the corresponding case for controls. Hence, a minimum lag time of 5 years between exposure and death from lung cancer was assumed for consistency with other miners' studies (National Research Council 1999; Tomasek 2002).

Conditional logistic regression for individually matched data was used to calculate odds ratios (ORs) for lung cancer death in the six categories of cumulative radon exposure (>0–<50, 50–<100, 100–<500, 500–<1,000, 1,000–<1,500 and ≥1,500 WLM) in comparison to the reference category of unexposed (0 WLM). These categories of WLM agree with those chosen for

the analyses of the cohort (Kreuzer et al. 2006, 2008). For all ORs, 95% confidence intervals (CIs) were computed. In addition, the increase in risk per WLM was estimated by fitting a linear excess relative risk (ERR) model with cumulative radon exposure in WLM as a continuous variable (Lubin 1988; Leuraud et al. 2007). Likelihood-based 95% CIs were calculated for the ERR (Moolgavkar and Venzon 1987). The crude risk for lung cancer mortality related to radon exposure was analyzed in the study sample (with smoking information) and in the initial sample to investigate whether the reduction of the initial sample to the study sample introduced any selection bias.

As smoking data were available only for the study sample, all analyses related to smoking were restricted to this data set. The crude smoking-related OR for lung cancer death for "smokers" ("current smokers and ex-smokers having stopped less than 20 years ago") in comparison to "non-smokers" ("never-smokers and ex-smokers having stopped smoking at least 20 years ago") in the study sample was estimated with conditional logistic regression. To adjust the radon-related lung cancer risk for smoking, a multiplicative model, including smoking in these two categories and cumulative radon exposure either in the above-listed seven categories or as continuous variable, was fitted. The choice of a multiplicative model is in accordance with Leuraud et al. (2007) and Brüske-Hohlfeld et al. (2006). An additive model was also fitted, and the fit of both models was compared by the Akaike Information Criterion (AIC) (see Walsh 2007 for a review). Since the AIC indicated that the additive model (deviance 632.73) fits the data significantly worse than the multiplicative model (p = 0.994), the multiplicative model was used.

In a next step, the potential impact of several temporal factors upon the exposure-response relation between cumulative radon exposure and the risk of lung cancer death was examined. ERR/WLM was calculated for two different categories of each of these temporal factors, and their heterogeneity was tested. In addition these ERR/WLM risks were adjusted for smoking by fitting a multiplicative model, and their heterogeneity was also tested. The temporal factors considered in these analyses were attained age at the reference case's death, age at first exposure, duration of exposure, average radon exposure per year in WLM, time since last exposure and time since first exposure. The median for the controls was used as cut-point for each variable.

The SAS version 9.1 (SAS Institute Inc., Cary, NC) was used for calculating descriptive statistics, and regression analyses were performed with the PECAN program from the software package EPICURE (Preston et al. 1990). All statistical tests are two-sided, with a type I error of 5%.

RESULTS

Study population

The study sample concurs very well with the initial sample in characteristics which are not related to exposure (see Table 1). The proportion of exposed miners was also virtually the same in the study sample and the initial sample. However on average, miners in the study sample have been employed for 4.5 (cases) or 5.6 y (controls) longer than those in the initial sample, and they have also been exposed to radon for 3.7 (cases) or 4.7 (controls) years longer than those in the initial sample. Moreover, their exposure ended on average more recently (4.4 y for cases and 5.6 y for controls), and they accumulated on average 67 WLM more radon exposure than those in the initial sample, both of which probably reflect the longer time of employment. However, per year they received on average 3.5 WLM (cases) or 4.9 WLM (controls) less radon exposure than cases and controls in the initial sample, which might reflect the drop of radon concentration in the later years.

Although there are some discrepancies in exposure characteristics between the study sample and the initial sample, differences between cases and controls are practically the same in the study sample and the initial sample (see Table 1). Even the cumulative frequency distribution of the cumulative radon exposure is very similar in the study and the initial sample (see Fig. 1). Mean cumulative radon exposure is 207 WLM higher for cases than for controls in both samples. Further relevant differences between cases and controls are emerging in the length of the time interval since the end of exposure and the average exposure received per year: On average, for cases the period of exposure dates back longer than for controls (8.1 y and 9.3 y in the study sample and the initial sample, respectively), and their annual exposure was higher (10.8 WLM and 9.4 WLM in the study sample and the initial sample, respectively). The proportion of non-smokers was considerably lower among cases (5.2%) than among controls (25.3%) in the study sample.

Risk analysis

Lung cancer mortality risk increases with increasing radon exposure in both samples (see Table 2 and Fig. 2). In the study sample, as well as in the initial sample, it is elevated significantly in all exposure categories above 100 WLM of cumulative radon exposure compared to the non-exposed group. The ERR/WLM estimated in the linear regression model was equal to 0.25% (95% CI:

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Table 1. Description of the study population and its exposure.

	Study sample		Initial sample	
	Cases (n = 421)	Controls (n = 620)	Cases (n = 704)	Controls (n = 1398)
All miners				
Birth year				
Mean	1932	1932	1932	1932
Range	[1927–1956]	[1927–1956]	[1927–1956]	[1927–1956]
Attained age (y)[a]				
Mean	57.4	57.4	58.0	58.0
Range	[33.8–71.7]	[33.9–71.0]	[33.8–71.7]	[33.9–71.3]
Start of employment				
Mean	1953	1955	1953	1954
Range	[1946–1987]	[1946–1985]	[1946–1987]	[1946–1985]
Age at first employment (y)				
Mean	21.1	22.2	21.0	21.8
Range	[14.5–47.5]	[14.1–48.9]	[14.5–47.5]	[13.0–48.9]
Duration of employment (y)[a]				
Mean	24.5	23.4	20.0	17.8
Range	[0.5–42.8]	[0.5–43.5]	[0.5–42.8]	[0–43.5]
Proportion of 'smokers'[d]	94.8%	74.7%	—	—
Exposed miners				
n (%)	401 (95%)	554 (89%)	659 (94%)	1239 (89%)
Age at first exposure (y)[b]				
Mean	21.6	22.8	21.4	22.3
Range	[14–48]	[15–49]	[14–48]	[14–49]
Duration of exposure[a,b] (y)				
Mean	21.3	19.3	17.6	14.6
Range	[0–42]	[0–43]	[0–42]	[0–43]
Time since end of exposure[a,b] (y)				
Mean	14.7	22.8	19.1	28.4
Range	[0–43]	[1–49]	[0–44]	[1–49]
Cumulative radon exposure (WLM)[a,b,c]				
Mean	716.3	509.4	649.1	442.4
Range	[0.2–2947.4]	[0–2686.7]	[0.1–2947.4]	[0–2686.7]
Average annual exposure rate (WLM y^{-1})[a,b]				
Mean	41.7	31.0	45.3	35.9
Range	[0–256.2]	[0–223.6]	[0–256.2]	[0–264.0]

[a] At the time of death of the corresponding case (index year) for controls.
[b] For exposed miners only.
[c] 5-y lagged.
[d] 'smokers' are defined as persons who ever smoked in the last 20 y before death (for cases) or the reference case's death (for controls).

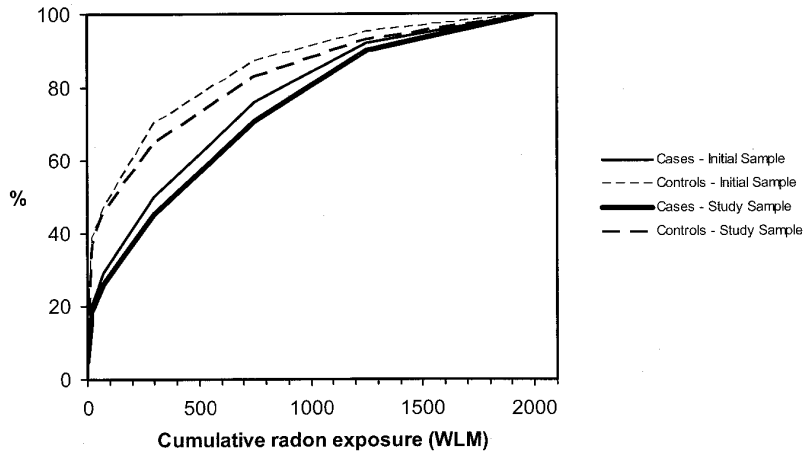

Fig. 1. Cumulative frequency distribution of the cumulative radon exposure among cases (bold solid line) and controls (bold dashed line) in the study sample and among cases (fine solid line) and controls (fine dashed line) in the initial sample.

Table 2. Risk estimates for lung cancer death by categories of cumulative radon exposure and estimated linear increase in risk per WLM for the study sample and the initial sample.

Cumulative radon exposure (WLM)	Study sample						Initial sample			
			Unadjusted		Adjusted[c]					
	Cases (%)	Controls (%)	OR[b]	95%-CI[d]	OR[b]	95%-CI[d]	Cases (%)	Controls (%)	OR[b]	95%-CI[d]
0	20 (4.8%)	60 (9.7%)	1	—	1	—	45 (6.4%)	151 (10.8%)	1	—
>0–<50	58 (13.8%)	172 (27.7%)	0.98	0.53–1.81	0.86	0.45–1.65	101 (14.4%)	392 (28.0%)	0.84	0.55–1.26
>50–<100	32 (7.6%)	51 (8.2%)	1.63	0.83–3.19	1.34	0.65–2.73	59 (8.4%)	114 (8.2%)	1.55	0.98–2.45
>100–<500	79 (18.8%)	117 (18.9%)	2.36	1.28–4.34	2.14	1.12–4.09	146 (20.7%)	316 (22.6%)	1.72	1.15–2.58
>500–<1000	111 (26.4%)	112 (18.1%)	4.12	2.20–7.73	3.63	1.86–7.08	183 (26.0%)	237 (17.0%)	3.12	2.07–4.72
>1000–<1500	77 (18.3%)	66 (10.7%)	5.09	2.60–9.98	4.59	2.25–9.37	113 (16.1%)	119 (8.5%)	4.05	2.59–6.36
≥1500	44 (10.5%)	42 (6.8%)	4.07	2.00–8.29	3.61	1.70–7.68	57 (8.1%)	69 (4.9%)	3.49	2.09–5.81
ERR[a] WLM^{-1}			0.25%	0.13–0.46%	0.23%	0.11–0.46%			0.23%	0.15–0.34%

[a] Excess relative risk.
[b] Odds ratio obtained from a conditional logistic regression, relative to the reference level non-exposed miners.
[c] Adjusted for smoking in the two categories 'smoker' (i.e. smoked in the last 20 years before death/reference case's death) and 'non-smoker' (i.e. never smoked or stopped smoking at least 20 years before death/reference case's death).
[d] Confidence interval.

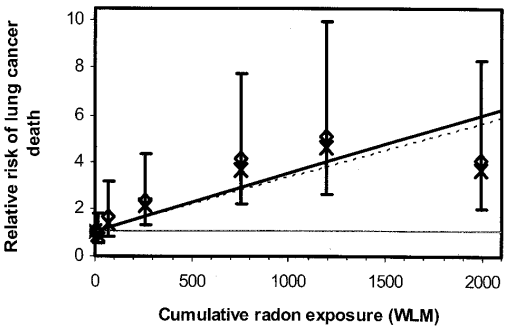

Fig. 2. ORs for lung cancer death within cumulative radon exposure categories and fitted relative risk regression lines. ◇ = OR and associated 95%-confidence interval; X = OR, adjusted for smoking; solid line = RR = 1.0 + 0.0025 × WLM; dashed line = RR = (1.0 + 0.0023 × WLM) × 7.61^{smk} where smk = 0 for non-smokers and smk = 1 for smokers.

0.13–0.46%) in the study sample and thus very similar to that in the initial sample (ERR/WLM = 0.23%, 95% CI: 0.15–0.34%). Adjustment for smoking results in an ERR/WLM of 0.23% (95% CI: 0.11–0.46%). In the categorical analysis estimates for the ORs for lung cancer death in the six categories of cumulative radon exposure also did not change appreciably after adjustment for smoking (see Table 2).

Current smokers or ex-smokers having stopped less than 20 years ago ("smokers") showed a 7.6-fold higher risk compared to never-smokers or ex-smokers having stopped at least 20 years ago ("non-smokers") (95% CI: 4.4–13.1). The model, which takes the influence of smoking and the cumulative radon exposure into account (deviance 622.73), fits the data significantly better than a model containing smoking only ($p < 0.001$, deviance 659.53) or a model containing cumulative radon exposure only ($p < 0.001$, deviance 698.26). The radon-adjusted OR for lung cancer death associated with smoking was 7.5 (95% CI: 4.3–13.0).

A modifying effect on the relation between cumulative radon exposure and risk of lung cancer death was tested for attained age, age at first exposure, duration of exposure, annual radon exposure per year, time since last exposure and time since first exposure. The crude ERR/WLM was significantly lower for miners who had been first exposed to radon at least 44 years ago compared to those exposed first less than 44 years ago (see Table 3). A statistically non-significant indication for a modifying effect was present for attained age ($p = 0.13$), average annual exposure per year ($p = 0.07$) and time since last exposure ($p = 0.09$). No significant influence on the exposure-response relation between cumulative radon exposure and the risk of lung cancer death was identifiable for age at first exposure ($p = 0.51$) or duration of exposure ($p = 0.38$). Adjustment for smoking gave the same pattern of results (data not shown).

DISCUSSION

The present study shows a clear increase in risk for lung cancer death with increasing cumulative radon exposure. This increase, as well as the pattern of influence of risk-modifying factors found, corresponds very well to the results from the Wismut cohort study (Grosche et al. 2006), in which the case-control study was nested. In contrast to the cohort study, the present study allowed consideration of the influence of smoking on the risk of radon-induced lung cancer mortality. This risk was not found to be appreciably influenced by confounding due to smoking. The evidence is that the estimated

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Table 3. Excess relative risk of lung cancer death per WLM (ERR/WLM) by categories of different temporal factors (using the median for controls as cut-point).

Temporal factor	Cases	Controls	ERR/WLM % (95% CI)	*p*
Attained age (y)				
<59	217	326	0.45 (0.18–1.14)	0.13
≥59	204	294	0.16 (0.06–0.36)	
Age at first exposure (y)				
<22	255	290	0.22 (0.10; 0.43)	0.50
≥22	146	264	0.15 (0.04; 0.38)	
Duration of exposure (y)				
<18	169	308	0.34 (0.16–0.67)	0.38
≥18	252	312	0.22 (0.11–0.43)	
Average annual radon exposure (WLM y^{-1})				
<12	146	310	1.19 (0.43–2.68)	0.07
≥12	275	310	0.32 (0.17–0.60)	
Time since last exposure (y)				
<20	265	270	0.31 (0.15–0.62)	0.09
≥20	136	284	0.13 (0.04–0.29)	
Time since first exposure (y)				
<44	323	270	1.54 (0.83–3.07)	0.001
≥44	78	284	0.01 (−0.02–0.10)	

increase in lung cancer risk with cumulative radon exposure was virtually unchanged with control for smoking status. Likewise, adjustment for smoking neither led to any remarkable changes in the relative risks in different categories of radon exposure nor in the influence of risk modifying variables.

The increase in lung cancer risk with radon exposure observed in the present study (ERR/WLM = 0.23%, 95% CI: 0.15–0.34%) is very similar to the overall ERR for the Wismut cohort, which was 0.21% (95% CI: 0.18–0.24%) (Grosche et al. 2006). This ERR/WLM decreased with increasing time since exposure, with increasing attained age and with increasing exposure-rate in the cohort study. In the present nested case-control study, the ERR/WLM decreased moderately with time since last exposure and strongly with time since first exposure. Moreover evidence was also found for a decrease in risk with attained age and for an inverse relationship between average annual radon exposure and ERR/WLM. No significant risk-modifying effect of duration of exposure was observed either in the cohort study or in the nested case-control study. The correspondence of these results indicates that, for the subjects in the nested case-control study, a similar relation between radon exposure and lung cancer risk holds as for the entire cohort.

The proportion of smokers was very high among the miners; i.e., 95% of the cases and 75% of the controls were smokers. Taking information on this important risk factor into account changes the ERR/WLM only from 0.25% (95%-CI: 0.13–0.46%) to 0.23% (95%-CI: 0.11–0.46%). Risk estimates in different categories of cumulative radon exposure are somewhat lower after adjustment (see Table 2), but the pattern of risks remains virtually the same (see Fig. 2). With regard to the influence of time-dependent effect-modifying variables, adjustment for smoking also shows no effect. Hence the results of this study suggest that the crude estimates of radon-related lung cancer mortality risk are not affected substantially by confounding due to smoking. As the relationship between radon exposure and lung cancer in the case-control study seems to be very similar to that in the cohort study (see above), the present results also suggest that the lack of information on smoking does not introduce serious bias in the estimates for radon-induced lung cancer risk in the Wismut cohort.

A possible confounding effect of smoking on the risk of radon-induced lung cancer was also investigated in other case-control studies among miners (Samet et al. 1989; L'Abbe et al. 1991; Brüske-Hohlfeld et al. 2006; Leuraud et al. 2007) and was found to be small.

Potential limitations

Since the smoking status was obtained only for a subset of the initial case-control sample, there could be differences between this subset and the initial sample. In fact, there are certain differences with respect to radon exposure between the study sample and the initial sample, which are probably due to the fact that quantity and quality of information in the Wismut Health Archives—the main source of information—tends to be better for miners exposed longer and more recently. The unadjusted ERR/WLM estimated from the study sample (ERR/WLM = 0.25, 95%-CI: 0.13–0.46%) is, however, very close to that estimated from the initial sample (ERR/WLM = 0.23%, 95%-CI: 0.15–0.34%). Hence, the population for which

sufficient information on smoking was available for the categorization of smoking habits seems to be representative for the entire population.

Another potential problem was that smoking status had to be treated as a binary variable: never-smokers together with ex-smokers for at least 20 y vs. current smokers together with ex-smokers for less than 20 y. These categories had to be chosen because of the low response to the questionnaires (26% for cases and 38% for controls) and the fragmentary character of the information in the Wismut Health Archives. However, there is evidence that in occupational studies, smoking status alone allows satisfactory control of the potential confounding effect of smoking, presumably because it is unlikely that quantitative measures of the exposure of primary interest in occupational environments are associated with detailed aspects of smoking habits, e.g., intensity, duration and time since cessation (Richiardi et al. 2005). Moreover, there is also evidence that combining long-term ex-smokers with never-smokers in one category may allow more effective control of confounding than using the categories "ever" vs. "never." Brüske-Hohlfeld et al. (2004) observed that adjusting for smoking in the categories "ever"-"never" resulted in a risk estimate more strongly biased toward the crude estimate than adjustment with the reference category "never-smokers together with ex-smokers >20 y." Nevertheless, the small number of non-smokers among the cases observed in this study, as in many other case-control studies on lung cancer (e.g., Brüske-Hohlfeld et al. 2006; Leuraud et al. 2007), and the restriction to only two categories of smoking might hamper the detection of small confounding effects of smoking on the risk of lung cancer mortality due to radon exposure. Major confounding, however, is unlikely.

A major potential limitation concerns the validity of the smoking information collected in this study. The smoking-associated lung cancer mortality risk found in the present study (OR = 7.6) lies in the middle of the range of smoking associated lung cancer mortality risks reported in other case-control studies on uranium miners (Samet et al. 1989; L'Abbe et al. 1991; Brüske-Hohlfeld et al. 2006; Leuraud et al. 2007). These range from 2.5 (L'Abbe et al. 1991) for miners from the Colorado Plateau to 13.0 (Samet et al. 1989) for miners from New Mexico. Hence, smoking information used in the present study may be regarded as reasonably valid. Most notably, it is compatible with the estimated lung cancer risk associated with ever-smoking (compared to never-smoking) found in the above-mentioned case-control study on incident lung cancer cases among a different sample of Wismut miners, which was 11.6 (95% CI 5.6–23.8) (Brüske-Hohlfeld et al. 2004). In this study, risk estimates were based on very detailed information on smoking obtained in personal interviews from the miners directly.

A further potential problem is one that is frequently encountered in retrospective studies on rapidly fatal diseases with a long latency (e.g., lung cancer), namely the validity of surrogate information. In the present study, smoking information in the questionnaires for all of the cases and for 33% of the controls was obtained from next-of-kin. The use of smoking information from next-of-kin is common (e.g., L'Abbe et al. 1991; Leuraud et al. 2007), as a number of studies have established that the quality of information from surrogate interviews is generally high (Rogot and Reid 1975; Kolonel et al. 1977; Pershagen 1984; Lerchen and Samet 1986), particularly with respect to information which is not too detailed, as is the case for smoking status.

Finally, residual confounding caused by non-differential misclassification of smoking status cannot be completely ruled out, even though a great effort was put in to the identification of the smoking status of the miners to avoid this problem.

CONCLUSION

The present nested case-control study shows a clear linear increase in the risk of lung cancer due to cumulative radon exposure, which was modified to some extent by attained age, annual radon exposure, time since last exposure, and more strongly by time since first exposure. Adjustment for smoking led to only marginal changes of the corresponding radon-related lung cancer risks. Thus, it is unlikely that smoking acts as a major confounder in the relationship between radon and lung cancer in the case-control study. Since the observed radon-associated lung cancer risk in the case-control study is very similar to that observed in the whole cohort study, it can also be assumed that the lack of information on smoking will not introduce a major bias when determining the radon-related lung cancer risk in the whole cohort without taking smoking into account.

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