Risk of lung cancer and other cancers in the German uranium miners cohort study

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Abstract: To evaluate the risk of cancer associated with low and high levels of radon exposure one of the largest single cohort studies on uranium miners is being conducted in Germany. It includes 58,940 men who were employed for at least 6 months between 1946 and 1989 at the former Wismut uranium company in Eastern Germany. Information on job histories was collected from the original pay rolls. Exposure to radon and its progeny, long-lived radionuclides and gamma radiation was estimated by using a detailed job-exposure matrix. For 94% of the cohort members the vital status has been ascertained from the date of entry to 31 December 1998. For 87% of the deceased cohort members causes of death were identified. The different causes of death were compared with the age- and calendar-year specific national death rates of Eastern Germany, formerly GDR. Standardized mortality ratios (SMR) with 95% confidence limits (CI) were calculated. The total number of person-years under observation was 1,795,195, with a mean duration of follow-up of 30 years. In this period a total of 4,692 malignant cancer deaths including 2,335 lung cancer deaths occurred. The observed overall mortality in the cohort was significantly lower than that expected from national rates (SMR=0.93, 95% CI: 0.91-0.94), demonstrating a possible healthy worker effect. The SMR for lung cancer was 1.83 (95% CI: 1.76-1.91), showing a clear increase with increasing cumulative radon exposure. When other sites of cancer were considered, a non-significant excess was observed for cancers of larynx and liver. These results were consistent to the results of the joint analyses of the 11 miner cohort studies. A potential limitation of this first analysis concerns the comparison group. Therefore internal risk analyses will be performed in a next step.

1. Introduction

An increased risk of lung cancer associated with exposure to radon and its progeny among underground miners is well established and has been summarized by the Committee on the Biological Effects of Ionizing Radiation of the US National Research Council [1]. Uncertainty, however, still remains with regard to the dose-response relationship at low levels of radon exposure and other risk or modifying factors for lung cancer. This is of particular importance in estimating the lung cancer risk due to radon exposure in homes in the general population. Another uncertainty concerns a possible relation of radon to cancers other than the lung as it has been suggested by Darby et al.[2] and Tomásek et al.[3].

The aim of the German uranium miners study, which includes about 60,000 former Wismut employees, is to further evaluate the lung cancer risk associated with radon and its progeny due to cumulative radon exposure, exposure rate, duration of exposure, time since last exposure, attained age, and the interactions with smoking, dust and arsenic exposure. Moreover, particular concern will be given to the lung cancer risk associated with low levels of radiation and the risk of extra-pulmonary cancers. This paper presents the results of the follow-up of the Wismut cohort to 1998. In this first analysis, an external comparison group is used and standardized mortality ratios for different causes of death are presented, while internal risk analysis will be performed later.

2. Materials and Methods

2.1 Historical background

The Erzgebirge (Ore Mountains) of Saxony (Germany) and Bohemia (Czech Republic) have a long history of underground mining. As early as in the 12th century silver mining was performed, while later on other metals such as iron, bismuth, cobalt, nickel and tungsten and in the beginning of the 19th century uranium were mined in the Schneeberg area. In 1946, after the Second World War, the Soviet Union established the "Wismut" company, aiming to exploit uranium in Saxony. The old silver mines were reopened. Later on mining was expanded to areas in Thuringia. During the operation period of the Wismut company (1946 to 1989) a total of 220,000 tons of uranium was produced. Thus the former GDR became the third largest producer of uranium worldwide. Three different time periods of mining activities can be distinguished. In the period 1946 to 1954, the so-called 'wild years', exposure to radiation and dust was at its peak due to dry drilling and the lack of forced ventilation. Between 1955 and 1970 the miners' working conditions improved. Dry drilling was replaced by wet drilling, leading to a reduced dust exposure. Radon concentrations decreased due to a more efficient ventilation technique and other measures. After 1970 international radiation protection standards were introduced, and the working conditions were stable at a high safety level. With the German unification in 1990, mining was abandoned.

2.2 Definition of the cohort

The development of the cohort has been described in previous publications[4,5]. Briefly, the selection of cohort members was based on three personnel files of the Wismut company which consisted of some 130,000 workers, and provided sufficient personal and occupational data for a follow-up and for estimation of exposure. A stratified random sample of 64,311 workers was drawn from these data. In order to reflect the different mining conditions at the Wismut company the sample was stratified by the date of first employment (1946-1954, 1955-1970, 1971-1989), place of work and area of mining. Criteria for inclusion in the cohort study were as follows: 1) minimum duration of employment of at least 6 months, 2) date of first employment between 1946 and 1989, 3) year of birth after 1899 and 4) male gender. After collection and subsequent evaluation of the occupational data, which were extracted from the original pay rolls, a total of 5,371 individuals were excluded from the initial cohort, who did not meet the inclusion criteria. The final cohort for the analysis thus consists of 58,940 men.

2.3 Information on exposure to radiation and other variables

Exposure to radon and its progeny, external γ radiation and long-lived alpha-particle emitters were estimated by using a job-exposure-matrix (JEM). The JEM provides annual dose values for each calendar year of employment between 1946 to 1989, each place of work and each type of job. More than 900 different jobs and several mining facilities have been evaluated. Radon measurements are available only from 1955 onwards. For the period 1946 to 1954, radon concentrations were estimated based on measurements from 1955, taking into account ventilation rate, vein space, uranium content and so on. Further details are given elsewhere [5-8]. For nearly all cohort members complete information on the type of job and type of mining facility was available on a daily basis, and additionally, information on periods of absence. The cumulative exposure to radon and its progeny was calculated as the sum of the annual radon exposures estimated by the JEM weighted by the duration of work in days. It 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 hours.

Active smoking habits were derived from annual medical examination files, which were available since 1972. Yet, this annual information does not allow the calculation of cumulative tobacco consumption (pack-years), but only determining smoking status (never/ever smoker) and years since quitting smoking. The levels of exposure to total dust, fine dust, quartz fine dust and arsenic, which were

registered by the Wismut company since 1963, have been evaluated and extrapolated for the time period from 1946 to 1962 by the Research Institute for Hazardous Substances in Bochum[9]. A computerized job-exposure matrix that provides information on exposure to dust and arsenic for each calendar year and several job categories and mining facilities for the years from 1946 to 1989 is in preparation.

2.4 Follow-Up and identification of causes of death

The first mortality follow-up determined the vital status of cohort members as of 31st December 1998. Information on the vital status of the cohort members was obtained from local registration offices. For deceased cohort members copies of the certificates of deaths were obtained from the responsible Public Health Administrations. In addition, a record linkage was performed with the pathology archive of the Wismut company. In this archive more than 28,000 autopsy files of former Wismut employees and their relatives are kept and a total of 3,217 cohort members could be identified. All causes of death from either the certificates of deaths or the autopsy files were coded based on the 10th revision of the International Classification of Diseases.

2.5 Statistical Methods

The present analysis is based on an external comparison of the cohort with the national mortality rates. The method of indirect standardization was used to compare the mortality observed in the cohort with the mortality of the general male population of the same age over the same calendar year period in Eastern Germany. External rates had been available from 1960 onwards, while rates from 1946 to 1959 were estimated based on data from 1960. The expected mortality is calculated by applying national mortality rates per calendar year and per 5-year age group to the number of person-years corresponding to the cohort. The Standardized Mortality Ratio (SMR) is given by the ratio of O/E, where O is the number of observed deaths in the cohort, and E is the number expected. 95% confidence limits were calculated based on the assumption that the number of observed deaths O follows a Poisson variable. In accordance to other miners cohort studies a five year lag time for lung cancer has been used, i.e. exposures are integrated only up to 5 years before the specified age, assuming that the risk of cancer for a given year depends on radon exposure cumulated up to 5 years before.

3. Results

Table I shows characteristics of the study population. In order to reflect the different mining conditions in the three above mentioned time periods of the Wismut company operation, all results are presented stratified by year of first employment. Of the 58,940 cohort members, 41% started to work at the Wismut company in the years between 1946 and 1954 (so-called sub-cohort A), 30% between 1955 to 1970 (sub-cohort B), and 29% after 1970 (sub-cohort C). As of 31 December 1998, 66.6% of the cohort members are determined as being alive, 27.8% as being deceased, while 5.6 % were lost to follow-up. Loss-to follow up was the highest for miners of sub-cohort A who left the Wismut company before the sixties. The mean age at death among the 16,404 deceased cohort members was 62 years. The total number of person-years under observation was 1,795,195, which corresponds to a mean duration of follow-up of 30 years (Table I). The mean duration of follow-up was higher in sub-cohort A and B with 37 years and 33 years, respectively, as compared with 18 years in sub-cohort C. Causes of death were available for 14.306 persons (87%) of the 16,404 deceased cohort members. Most of the causes of death were related to circulatory disorders (37%), followed by malignant neoplasms (33%), respiratory diseases (11%) and injuries and poisoning (9%). Overall a total of 35% of all causes of death were based on autopsy files. This percentage was higher for malignant neoplasms with 44% and the highest for lung cancer (58%).

Information on smoking habits is available for 38% of the total cohort. This proportion is considerably lower for members of sub-cohort A (20%) and B (33%) than for subjects of sub-cohort C (64%), since smoking habits were recorded only after 1970. More than 50% of the miners with known smoking habits were heavy smokers of cigarettes, while the proportion of non-smokers is about 26%.

Table I: Characteristics of the study population stratified by sub-cohorts

	Total Cohort	**Begin of employment between**		
		1946 – 54	**1955 – 70**	**1971 – 89**
		A	**B**	**C**
Number of miners	58,940	23,871	17,936	17,133
Vital Status as of 31/12/1998				
Alive	39,253	9,880	13,211	16,162
Deceased	16,404	11,853	3,927	624
Loss-to-Follow-Up	3,283	2,138	798	347
Mean age of those being alive (years)	54	71	59	40
Mean age at death (years)	62	65	58	36
Person-Years	1,795,195	890,225	593,739	311,231
Mean duration of follow-up (years)	30	37	33	18
All known causes of death	14,306	10,312	3,443	551
Malignant cancers	4,692	3,529	1,076	87
Circulatory disorders	5,290	4,022	1,186	82
Respiratory diseases	1,523	1,306	202	15
Injuries and poisoning	1,245	487	480	278
Others	1,556	968	499	89
Unknown causes of death	2,098	1,541	484	73
Cumulative exposure to radon				
Not exposed (0 WLM)	8,236	2,326	3,671	2,239
< 10 WLM	16,590	2,635	3,992	9,963
≥ 10 – < 50 WLM	11,149	2,127	4,173	4,849
≥ 50 – < 100 WLM	3,288	973	2,233	82
≥ 100 – < 500 WLM	8,971	5,786	3,185	-
≥ 500 – < 1,000 WLM	6,024	5,433	591	-
≥ 1,000 WLM	4,862	4,591	91	-
Exposed only (> 0 WLM)	50,704	21,545	14,265	14,894
Mean cumulative exposure (WLM)	280	583	104	9
Median cumulative exposure (WLM)	33	441	37	59
Mean duration of exposure (years)	11	14	12	7
Mean age at first exposure (years)	25	28	24	21

WLM: Working level month

Table I also gives information on the exposure to radon and its progeny. A total of 50,704 individuals had been exposed to radiation at some time, while 8,236 have never been exposed. Among exposed miners the average age at first exposure was the lowest in sub-cohort C (21 years) and the highest in sub-cohort A (28 years). Duration of radiation exposure among individuals who were exposed for the first time between 1946 and 1970 (sub-cohort A and B) was considerable longer than among those exposed for the first time after 1970. Due to the higher radon concentrations in the earlier years and the longer duration of exposure among individuals of sub-cohort A, the mean cumulative radon exposure is substantially higher in members of sub-cohort A (583 WLM) than among those of sub-cohort B (104 WLM) and C (9 WLM), respectively. The maximum exposure value for an individual miner is 3,224 WLM. Overall, 16,590 workers were exposed to less than 10 WLM. This group, however, is dominated

by the very young sub-cohort C with a first exposure to radon after 1970. Radon levels above 100 WLM occurred in sub-cohorts A and B only.

For each calendar year between 1946 to 1980 Figure 1 shows the 75th, 50th and 25th percentiles of the actual individual exposures to radon and its progeny among exposed miners. The individual exposures per year were given in WLM and reflect both the levels of radon progeny concentration and the duration of exposure in this year. The highest exposure values for cohort members are found for the time period from 1953 to 1958 (median = 106 WLM/year), when the mines had been in operation for some years. Since the late 1970s radon exposure was very low (median = 2 WLM/year), reflecting the fact that international radiation protection standards had been successfully introduced.

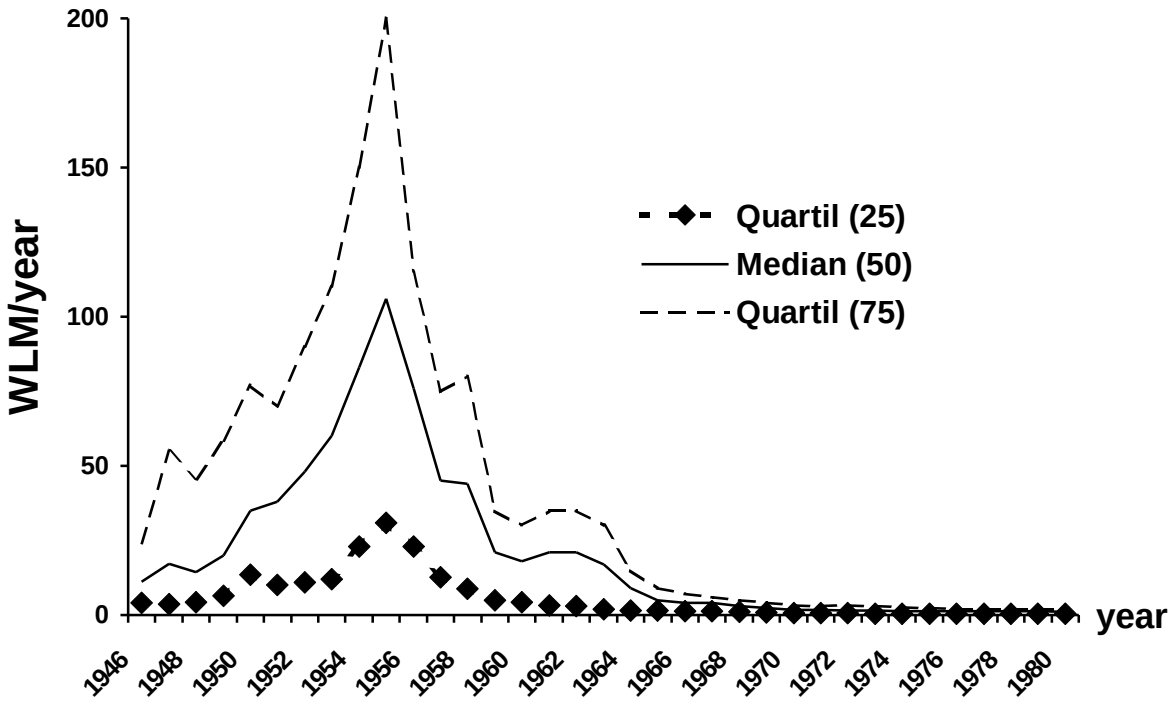

Figure 1: Quartiles of individual exposure to radon and its progeny per year in WLM for exposed cohort members (WLM > 0) from 1946 to 1980

Table II gives the number of observed and expected deaths based on the male Eastern German population, as well as the corresponding SMR and its 95% confidence intervals for all causes of deaths, cancer deaths and all sites of cancer with more than 50 observed cases. When all causes of deaths were considered, the number of observed deaths (n=16,404) was significantly lower than that expected from the population (n= 17,674), resulting in an SMR of 0.93 (95% CI: 0.91-0.94). There was a statistically significant excess in the mortality of all types of cancer (SMR=1.15; 95% CI: 1.12-1.18) mainly due to lung cancer. Fifty percent of all observed cancer deaths were cancers of the lung. Since information on the external rates was available only for cancer of lung and trachea combined, both sites of cancer were combined in the analyses. Yet there were only 2 observed cases of tracheal cancer , while the remaining 2,333 cases were deaths of lung cancer. An excess of deaths was observed for the following sites of cancer: lung and trachea (SMR=1.83; 95% CI :1.76.-1.91); larynx (SMR=1.08; 95% CI: 0.83-1.39) and liver (SMR=1.11; 95% CI: 0.91-1.34). Statistically significant reduced numbers of death were found for leukemia (SMR=0.75), cancer of the tongue, mouth and pharynx (SMR=0.66), bladder (SMR=0.70), rectum (SMR=0.74) and brain (SMR=0.75).

Table II: Observed (O) and expected (E) number of deaths and ratio of observed to expected deaths (SMR = O/E) for selected causes of death

Causes of death	**O**	**E[1]**	**SMR [2]**	**95 % CI[3]**
All causes	16,404	17,674	0.93	0.91 – 0.94
All types of cancer	4,692	4,088	1.15	1.12 – 1.18
Tongue, mouth, pharynx (C00-C14)	67	102	0.66	0.51 – 0.84
Esophagus (C15)	87	92	0.94	0.75 – 1.16
Stomach (C16)	454	484	0.94	0.85 – 1.03
Colon (C17-C18)	219	234	0.94	0.82 – 1.07
Rectum (C19-C21)	164	221	0.74	0.63 – 0.86
Liver (C22)	108	98	1.11	0.91 – 1.34
Gallbladder (C23-C24)	56	65	0.85	0.65 – 1.11
Pancreas (C25)	156	177	0.88	0.75 – 1.03
Larynx (C32)	61	56	1.08	0.83 – 1.39
Lung and trachea (C33-C34) [4]	2,335	1,275	1.83	1.76 – 1.91
Prostate (C61)	160	230	0.70	0.59 – 0.81
Kidney (C64)	104	n.a.	n.a.	n.a.
Bladder (C67)	120	n.a.	n.a.	n.a.
Brain and other nervous system (C71)	80	113	0.75	0.60 – 0.93
Leukemia (C91-95)	95	127	0.75	0.61 – 0.92
All cancers other than lung	2,357	2,813	0.84	0.80 – 0.87

Sites of cancer with less than 50 deaths not listed

[1] Expected on the basis of calender year and age specific national male mortality rates between 1650 to 1998 in Eastern Germany.

[2] Standardized mortality ratio (SMR=O/E)

[3] CI: Confidence limits

[4] 2,333 observed deaths of lung cancer and two observed deaths of cancer of trachea

Table III presents the standardized mortality ratios for lung cancer in relation to the cumulative exposure to radon and its progeny in WLM with a five year lag time. The mean exposure is calculated from the exposure of the individuals having passed through this exposure group. The lung cancer mortality in the exposure category of 0 WLM was similar to that in the population (SMR=0.97; 95% CI: 0.84-1.12). There was an increasing risk with increasing cumulative radon exposure, showing a fourfold increased SMR in the exposure group of 2000 WLM or more.

4. Discussion

The main strengths of the German cohort study are its size, a wide range of exposure levels, a long duration of exposure and a large number of cases of lung cancer and other diseases. This first analysis was based on external comparisons and provided information on the risk of lung cancer and other cancers in the cohort of Wismut miners compared with the general population. It is well established that lung cancer is caused by radon.[1] This evidence mainly comes from cohort studies in miners[10-23], but meanwhile there is also suggestive evidence from case-control studies of lung cancer and indoor radon.[24-26] The present study confirmed a statistically significant excess of lung cancer mortality in the cohort and a trend of increasing risk with increasing cumulative radon exposure.

Table III: Observed (O) and expected (E) number of deaths of cancer of the lung and trachea by cumulative radon exposure (5 year lag time)

Cumulative Exposure (WLM)	Mean cumulative exposure	Person-years	O	E[1]	SMR[2]	95 % CI[3]
0	0	235,660	186	191.6	0.97	0.84 – 1.12
> 0 - 9	1.8	639,051	147	184.0	0.80	0.68 – 0.94
10 - 19	14.4	103,357	63	61.7	1.02	0.79 – 1.31
20 – 49	32.4	127,949	86	78.7	1.09	0.87 – 1.35
50 - 99	72.3	94,010	96	66.1	1.45	1.18 – 1.77
100 - 199	146.7	112,164	149	98.3	1.52	1.28 – 1.78
200 - 499	332.9	181,096	317	193.3	1.64	1.46 – 1.83
500 - 999	730.8	180,685	637	227.6	2.80	2.59 – 3.02
100 - 1999	1321.6	106,692	564	152.2	3.70	3.41 – 4.02
2000 +	2373.7	14,532	90	21.6	4.16	3.35 – 5.13
Total	221.6	1,795,195	2,335[4]	1,274.9	1.83	1.76 – 1.91

WLM: Working level months
[1] Expected on the basis of calender year and age specific national male mortality rates between 1960 to 1998 in Eastern Germany.
[2] Standardized mortality ratio (SMR=O/E)
[3] CI: Confidence limits
[4] 2,333 observed deaths of lung cancer and two observed deaths of cancer of trachea

With respect to cancer sites other than lung cancer, we found an excess mortality for cancer of the liver and larynx. The observed increased mortality of liver cancer in our study (SMR=1.11; 95% CI: 0.91-1.34) is consistent to the results of other miner studies [2,21]. In the collaborative analysis of the 11 miner studies an even higher statistically significant increased SMR was found (SMR=1.73, 95% CI:1.29-2.28). The effect is unrelated to the cumulative exposure to radon, but seems to be no chance finding. One possible explanation is the high consumption of alcohol among miners. In the early years, the Wismut company offered the miners alcohol and cigarettes free of charge. There was a non-significant excess of the mortality of cancer of larynx in the Wismut cohort.

The observed overall mortality in the cohort as well as the mortality from all cancers other than lung cancer was significantly lower than that expected from the general population. One possible explanation is a healthy worker effect. Other potential limitations of this study concern the relatively high proportion of missing causes of deaths (13%) and limited accuracy of the causes of death since only 35% of them were based on autopsy files, while the remaining were based on certificates of death. Also the validity of external deaths rates, particularly in the early years, are a potential limitation. Therefore, in a next step internal analyses will be performed.

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