Radon and Cancers Other Than Lung Cancer in Underground Miners: a Collaborative Analysis of 11 Studies

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Background: **Exposure to the radioactive gas radon and its progeny (^{222}Rn and its radioactive decay products) has recently been linked to a variety of cancers other than lung cancer in geographic correlation studies of domestic radon exposure and in individual cohorts of occupationally exposed miners.** ***Purpose:*** **This study was designed to characterize further the risks for cancers other than lung cancer (i.e., non-lung cancers) from atmospheric radon.** ***Methods:*** **Mortality from non-lung cancer was examined in a collaborative analysis of data from 11 cohorts of underground miners in which radon-related excesses of lung cancer had been established. The study included 64 209 men who were employed in the mines for 6.4 years on average, received average cumulative exposures of 155 working-level months (WLM), and were followed for 16.9 years on average.** ***Results:*** **For all non-lung cancers combined, mortality was close to that expected from mortality rates in the areas surrounding the mines (ratio of observed to expected deaths [O/E] = 1.01; 95% confidence interval [CI] = 0.95-1.07, based on 1179 deaths), and mortality did not increase with increasing cumulative exposure. Among 28 individual cancer categories, statistically significant increases in mortality for cancers of the stomach (O/E = 1.33; 95% CI = 1.16-1.52) and liver (O/E = 1.73; 95% CI = 1.29-2.28) and statistically significant decreases for cancers of the tongue and mouth (O/E = 0.52; 95% CI = 0.26-0.93), pharynx (O/E = 0.35; 95% CI = 0.16-0.66), and colon (O/E = 0.77; 95% CI = 0.63-0.95) were observed. For leukemia, mortality was increased in the period less than 10 years since starting work (O/E = 1.93; 95% CI = 1.19-2.95) but not subsequently. For none of these diseases was mortality significantly related to cumulative exposure. Among the remaining individual categories of non-lung cancer, mortality was related to cumulative exposure only for cancer of the pancreas (excess relative risk per WLM = 0.07%; 95% CI = 0.01-0.12) and, in the period less than 10 years since the start of employment, for other and unspecified cancers (excess relative risk per WLM = 0.22%; 95% CI = 0.08-0.37).** ***Conclusions:*** **The increases in mortality from stomach and liver cancers and leukemia are unlikely to have been caused by radon, since they are unrelated to cumulative exposure. The association between cumulative exposure and pancreatic cancer seems likely to be a chance finding, while the association between cumulative exposure and other and unspecified cancers was caused by deaths certified as due to carcinomatosis (widespread disseminated cancer throughout the body) that were likely to have been due to lung cancers. This study, therefore, provides considerable evidence that high concentrations of radon in air do not cause a material risk of mortality from cancers other than lung cancer.** ***Implications:*** **Protection standards for radon should continue to be based on consideration of the lung cancer risk alone. [J Natl Cancer Inst 87:378-384, 1995]**

It has been established that working in a mine with a high concentration of radon and its progeny (^{222}Rn and its radioactive decay products) leads to an increased risk of lung cancer (*1*). Excess risks of other cancers have not been established following such exposure. However, increased risks of several cancers have been reported in individual studies of miners (*2-5*), and significant positive associations between mortality and cumulative exposure have been reported for gallbladder cancer, multiple myeloma, and lymphomas (*4,6*). Furthermore, geographic correlations between domestic radon concentrations and leukemia, melanoma, lymphosarcoma, and kidney, prostate, and childhood cancers have recently been noted (*7-14*), as has a correlation between mutant frequency in peripheral lymphocytes and domestic radon concentrations (*15*). Increases in nonrespiratory neoplasms (including kidney cancers, bone sarcomas, and soft-tissue tumors in male rats and mammary tumors in female rats) have also been found in inhalation experiments (*16,17*).

This study was designed to characterize further the risks for cancers other than lung cancer from atmospheric radon.

Materials and Methods

Study Populations

This analysis includes all published cohort studies of underground miners identified by a literature search with the following: (*a*) complete, or essentially complete, follow-up of the cohort; (*b*) estimates of exposure to radon progeny available in working-level months (WLM)[1] for each cohort member, based on measurements of radon or radon progeny; (*c*) a radon-related excess mortality of lung cancer; and (*d*) at least 40 deaths from cancers other than lung cancer (i.e., non-lung cancers). The fol-

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See "Notes" section following "References."

lowing studies were excluded: studies (e.g., *18*) of miners where follow-up of the cohort was grossly incomplete, studies (e.g., *19*) where there was an excess of lung cancer that may have been radon related but where individual radon measurements were not available, studies (e.g., *20*) where exposures were low and there was no relationship between exposure and lung cancer mortality, and studies (e.g., *21*) where there were fewer than 40 deaths from non-lung cancer. Eleven studies were identified as satisfying the inclusion criteria (Table 1). Details of the methods of data collection and ascertainment of deaths are given in the references cited in Table 1. Six studies were of miners in North America, four in Europe, and one in China. Seven were of uranium miners, two of tin miners, and one each of iron and fluorspar miners. For the Colorado and Cornwall studies, follow-up has been extended over that previously published, to the end of 1984 and to the end of 1989, respectively; for the West Bohemia study, some previously unknown causes of death have been established. To avoid possible confusion with the effects of other carcinogens, we excluded Ontario uranium miners known also to have mined gold, which is associated with arsenic exposure, as well as Cornwall miners with no definite underground exposure or known to have worked at the arsenic-calcining plant located at one of the mines. There were very few female miners, and these are excluded from the present analysis. Ten of the 11 studies included here were also included in a recent joint analysis of lung cancer risk in radon-exposed miners (*33*). The Cornwall study was not included in that analysis but has been included here; the Radium Hill study (*18*), which was included in the joint analysis of lung cancer, has been excluded here, since follow-up was incomplete: 36% of the cohort could not be traced beyond the end of employment at Radium Hill. Exposures were low in the Radium Hill study (average final cumulative exposure, 7.0 WLM), and no deaths from cancers other than lung cancer were known to have occurred in workers with cumulative exposures above 50 WLM.

Method of Analysis

For each study, men were entered into the analysis on the latest date of: start of employment, start of the follow-up period for the study involved (which for some men was well after the start of employment), or at the end of any minimum employment period for that study. Men were removed from the analysis on the earliest date of: death, emigration, loss to follow-up, end of the period of follow-up for the study involved, or, in studies where men over a certain age had been excluded, on reaching the relevant maximum age. For all studies except the China study, the numbers of observed and expected deaths were calculated for a standard set of cancer sites defined according to the 9th revision of the International Classification of Diseases, Injuries, and Causes of Death (ICD-9) (*34*), and equivalent groupings were constructed for earlier revisions of the ICD, where necessary. The cancer sites to be examined were chosen before the analysis was carried out. Expected deaths were calculated using age- and calendar-year-specific national (West Bohemia, Colorado, Cornwall, Newfoundland, France, Beaverlodge, and Port Radium) or regional (Ontario, Malmberget, and New Mexico) rates. Observed and expected deaths were subdivided according to time since the start of employment (0-, 10+ years) and total cumulative radon exposure (<50, 50-, 100-, 200-, 300-,..., 1300-, 1400-, 1500+ WLM) calculated with a 5-year lag for all sites of cancer other than leukemia and with zero lag for leukemia. For each category of interest, significance tests comparing the number of deaths observed with the number expected from external national or regional rates were carried out, and 95% confidence intervals (CIs) for the ratio of observed to expected deaths were calculated assuming that the number of observed deaths followed a Poisson distribution. Tests for heterogeneity of the ratio of observed to expected deaths used the score statistic (*35*). For subtypes of leukemia, national or regional rates were available only for the period in which the 8th and 9th revisions of the ICD had been used; all observed and expected deaths occurring before this period were excluded from the analyses of specific leukemia subtypes. For the West Bohemia study, deaths were coded using only the first three digits of the ICD; thus, where appropriate, either the closest three-digit category was used (primary liver, bladder, and kidney), or the West Bohemia study was omitted from the analysis for that particular site (liver unspecified, leukemia excluding chronic lymphatic, and acute myeloid leukemia).

To test for an association between mortality and cumulative exposure, we assumed that the number of deaths observed in the jth category of exposure for the ith study had a Poisson distribution with the following expected value:

$$E_{ij}\exp(\alpha_i + \beta x_j),$$

where E_{ij} is the number of deaths expected from external national or regional rates, α_i is a study-specific parameter allowing for an excess or deficit compared with the external expected value at zero cumulative exposure, x_j is the midpoint of exposure category j and 1550 for the 1500+ WLM category, and the parameter β is the increase per unit WLM in the logarithm of the ratio of observed to expected deaths, assumed common to all studies. Tests of $\beta = 0$ were two-sided and were based on the score statistic (*35*), as were tests for heterogeneity of β between studies. Significance levels were calculated with the use of the normal approximation, but all values found to be significant with $P<.05$ were checked with the use of simulation. The 95% CIs were also based on the score statistic (*35*). Estimation of β was carried out by maximum likelihood with the use of the computer program AMFIT (*36*). The estimated value of β was taken to be the excess relative risk (i.e., the increase in relative risk) per unit WLM (excess relative risk [ERR]/WLM); i.e., it was assumed that $\exp(\beta x_j) \approx 1 + \beta x_j$. Analyses were carried out for the whole time period and separately for the periods less than and 10 years or more since first employment. The period less than 10 years since first employment was examined separately, since mortality during this period would be expected to be

Table 1. Study populations included in joint analysis together with number of men, period of follow-up, length of employment, final exposure, and length of follow-up for each cohort

Study (ref. No.)	Location of mine	Substance mined	No. of men in the study	Period of follow-up	Average length of follow-up, y	Average length of employment at mine, y	Average final cumulative exposure, WLM
West Bohemia (*4,22,23*)	Jáchymov area, Czech Republic	Uranium	4320	1952-1990	24.8	7.9	219
Ontario (*24,25*)	Canada	Uranium	17 833	1955-1986	14.2	2.6	30
Malmberget (*3,26*)	Northern Sweden	Iron	1415	1951-1989	23.6	18.7	89
Colorado (*27,28*)	Colorado Plateau, USA	Uranium	3347	1950-1984	23.1	5	821
Cornwall (*29*)	Southwest England	Tin	2535	1941-1989	26.4	11	65
Newfoundland (*2*)	Canada	Fluorspar	1772	1950-1984	28.2	5.7	383
France (*5*)	Massif Central, Vendée, and Hérault areas	Uranium	1785	1948-1985	25.2	14.5	70
Beaverlodge (*30*)	Saskatchewan, Canada	Uranium	8487	1950-1980	13.9	1.7	11*
Port Radium (*31*)	Northwest Territories, Canada	Uranium	2103	1950-1980	25.2	3.2	164
New Mexico (*32*)	Grants area, New Mexico, USA	Uranium	3469	1958-1985	17.9	7.4	111
China (*6*)	Yunnan Province, southern China	Tin	17 143	1976-1987	10.2	10.3	221
Total			64 209		16.9	6.4	155

*Recent dosimetry revision has suggested that exposures may be underestimated, possibly by a factor of around 0.7.

low because of the selection of healthy men for employment in the mines.

For the Chinese data (*6*), no external mortality rates were available, and deaths in the study were classified into 11 non-lung cancer sites (nasopharynx, esophagus, stomach, colon, rectum, liver, bladder, and brain cancers, and lymphoma, leukemia, and other non-lung cancers) according to the Chinese Health Ministry coding system. Observed deaths for these cancers and person-years were stratified by attained age in 5-year groups subdivided by cumulative exposure and time since start of employment. Each age stratum of the Chinese data for which there was one or more observed death was included in the analysis of association between mortality and cumulative exposure for the 11 ICD-defined categories to which it corresponded most closely by setting E_{ij} to be the number of person-years in the jth exposure category of the stratum and allowing α_i to vary over strata. This assumes that, within each stratum, the risk of a death occurring within each exposure category is proportional to the person-years in that category, but allows the risk to vary freely between strata.

Results

The 11 studies included 64 209 men followed for 16.9 years on average (Table 1). The overall average length of employment in the mines was 6.4 years, but it varied from 1.7 years at Beaverlodge to 18.7 years at Malmberget. The average final cumulative exposure was 155 WLM and also varied widely. In the 10 studies where external rates were available, 1179 non-lung cancer deaths were observed, close to the number expected (O/E [observed/expected] = 1.01; 95% CI = 0.95-1.07) (Table 2). O/E was lower in the period less than 10 years since first employment, as would be expected because of the selection of healthy men for employment (O/E = 0.87; 95% CI = 0.72-1.04). O/E was slightly higher in the period 10 or more years since first employment, but it was still close to unity (O/E = 1.03; 95% CI = 0.97-1.09). In the period 10 or more years since first employment, O/E varied between the studies (P for heterogeneity = .004). For the Ontario study, it was significantly less than unity (O/E = 0.80; 95% CI = 0.67-0.95); in contrast, in the West Bohemia and Malmberget studies, it was significantly raised (West Bohemia—O/E = 1.16; 95% CI = 1.03-1.30 and Malmberget—O/E = 1.23; 95% CI = 1.04-1.43). The increase in the West Bohemia study is due to liver and gallbladder cancers (*4*), and the increase in Malmberget is due to stomach and rectal cancers (*3*). A possible explanation for the low mortality in the Ontario study is that some deaths were missed in men with unknown Social Insurance numbers (*25*). Excluding Ontario, the O/E ratios are 1.04 (95% CI = 0.97-1.10) and 1.07 (95% CI = 1.00-1.14) for all years and 10 or more years since first employment, respectively.

Repeating the external comparison for 28 individual cancer sites, there were statistically significant overall increases for stomach (O/E = 1.33; 95% CI = 1.16-1.52) and primary liver (O/E = 1.73; 95% CI = 1.29-2.28) cancers and statistically significant deficits for tongue and mouth (O/E = 0.52; 95% CI = 0.26-0.93), pharynx (O/E = 0.35; 95% CI = 0.16-0.66), and colon (O/E = 0.77; 95% CI = 0.63-0.95) cancers (Table 3). Results 10 or more years since starting employment were similar to those for all years. There were no statistically significant deficits less than 10 years since first employment, but there was a statistically significant excess for leukemia (O/E = 1.93; 95% CI = 1.19-2.95). Among the leukemia subtypes, O/E for acute myeloid leukemia exceeded that for all leukemias, but the numbers were small and the increase was not statistically significant (O/E = 2.42; 95% CI = 0.50-7.07).

When mortality from all non-lung cancers combined was considered in all 11 studies, including the China study, there was little evidence of a trend with cumulative exposure when all years were considered (ERR/WLM = 0.01%; 95% CI = –0.01-0.03) or 10 or more years since first employment (ERR/WLM = 0.01%; 95% CI = –0.01-0.02). There was no evidence of heterogeneity of trend between the studies 10 or more years since first employment (P = .14), and the O/E ratios calculated under the hypothesis of no

Table 2. Numbers of deaths observed from cancers other than lung cancer (O), ratio of observed to expected deaths (O/E), and 95% CI by time since first employment for each cohort

Study	Time since first employment								
	<10 y			≥10 y			All y		
	O	O/E*	95% CI	O	O/E	95% CI	O	O/E	95% CI
West Bohemia	15	0.77	0.43-1.27	283	1.16†	1.03-1.30	298	1.13†	1.01-1.27
Ontario	48	1.20	0.88-1.59	124	0.80†	0.67-0.95	172	0.89	0.76-1.03
Malmberget	0	0.00	0.00-2.02	162	1.23†	1.04-1.43	162	1.21†	1.03-1.41
Colorado	15	0.94	0.53-1.55	115	1.08	0.89-1.30	130	1.06	0.89-1.26
Cornwall	7	0.96	0.39-1.98	94	1.07	0.86-1.31	101	1.06	0.86-1.29
Newfoundland	5	0.95	0.31-2.22	81	0.96	0.76-1.19	86	0.96	0.77-1.19
France	4	0.69	0.19-1.77	69	1.03	0.80-1.30	73	1.00	0.78-1.26
Beaverlodge	14	0.65	0.36-1.09	52	0.76	0.57-1.00	66	0.73‡	0.56-0.93
Port Radium	1	0.13§	0.01-0.72	48	0.85	0.63-1.13	49	0.76	0.56-1.00
New Mexico	7	0.86	0.35-1.77	35	1.08	0.75-1.50	42	1.04	0.75-1.41
Chinall	4	—	—	190	—	—	194	—	—
All studies (excluding China)	116	0.87	0.72-1.04	1063	1.03	0.97-1.09	1179	1.01	0.95-1.07

*Expected deaths calculated from external national or regional mortality rates.
†.05≥P>.01.
‡.01≥P>.001.
§P<.001 (two-sided tests).
‖Expected deaths not available for Chinese study.

Table 3. Numbers of deaths observed (O), ratio of observed to expected deaths (O/E), and 95% CI by time since first employment for selected sites of cancer (all studies except China)

Cancer site (ICD-9 code)	Time since first employment								
	<10 y			≥10 y			All y		
	O	O/E*	95% CI	O	O/E	95% CI	O	O/E	95% CI
Tongue and mouth (141,143-145)	2	0.97	0.12-3.51	9†	0.47	0.22-0.89	11†	0.52	0.26-0.93
Salivary gland (142)	1	2.91	0.07-16.38	3	1.21	0.25-3.52	4	1.41	0.39-3.62
Pharynx (146-149)	1	0.40	0.01-2.20	8§	0.34	0.15-0.67	9§	0.35	0.16-0.66
Esophagus (150)	4	1.12	0.30-2.86	41	1.05	0.75-1.42	45	1.05	0.77-1.41
Stomach (151)	17	0.93	0.54-1.48	200§	1.38	1.20-1.59	217§	1.33	1.16-1.52
Colon (152-153)	10	0.80	0.38-1.47	85†	0.77	0.62-0.95	95†	0.77	0.63-0.95
Rectum (154)	3	0.47	0.10-1.38	57	0.90	0.68-1.17	60	0.86	0.66-1.11
Liver, primary (155.0,155.1)	3	1.19	0.24-3.47	47§	1.78	1.31-2.37	50§	1.73	1.29-2.28
Liver, unspecified (155.2)	0	0.00	0.00-4.79	3	0.48	0.10-1.42	3	0.43	0.09-1.26
Gallbladder (156)	0	0.00	0.00-3.35	19	1.33	0.80-2.07	19	1.23	0.74-1.92
Pancreas (157)	6	0.75	0.28-1.64	85	1.08	0.86-1.34	91	1.05	0.85-1.29
Nose (160)	0	0.00	0.00-7.38	3	0.78	0.16-2.28	3	0.69	0.14-2.02
Larynx (161)	0	0.00	0.00-1.42	38	1.32	0.94-1.82	38	1.21	0.86-1.67
Bone (170)	0	0.00	0.00-1.68	10	1.35	0.65-2.48	10	1.04	0.50-1.91
Connective tissue (171)	0	0.00	0.00-3.21	5	1.01	0.33-2.36	5	0.82	0.27-1.91
Malignant melanoma (172)	4	1.11	0.30-2.84	14	0.87	0.48-1.46	18	0.92	0.54-1.45
Other skin (173)	1	1.20	0.03-6.63	8	1.67	0.72-3.28	9	1.60	0.73-3 03
Prostate (185)	4	1.12	0.31-2.87	79	0.87	0.69-1.08	83	0.88	0.70-1.09
Testis (186)	1	0.26	0.01-1.44	5	1.12	0.36-2.60	6	0.72	0.26-1.57
Bladder (188, 189.3-189.9)	0	0.00	0.00-1.12	39	0.92	0.65-1.26	39	0.85	0.61-1.16
Kidney (189.0-189.2)	3	0.67	0.14-1.97	41	0.93	0.67-1.27	44	0.91	0.66-1.22
Brain and central nervous system (191,192)	5	0.46	0.15-1.07	47	1.08	0.79-1.43	52	0.95	0.71-1.25
Thyroid gland (193)	0	0.00	0.00-7.38	2	0.54	0.07-1.94	2	0.47	0.06-1.71
Non-Hodgkin's lymphoma (200,202)	6	0.81	0.30-1.77	30	0.79	0.54-1.13	36	0.80	0.56-1.10
Hodgkin's disease (201)	5	0.77	0.25-1.80	12	1.01	0.52-1.77	17	0.93	0.54-1.48
Multiple myeloma (203)	2	1.18	0.14-4.25	24	1.31	0.84-1.95	26	1.30	0.85-1.90
Leukemia (204-208)	21‡	1.93	1.19-2.95	48	0.99	0.73-1.31	69	1.16	0.90-1.47
Leukemia excluding chronic lymphatic (204-208 except 204.1)‖	7	1.28	0.51-2.64	29	1.08	0.72-1.55	36	1.11	0.78-1.54
Myeloid leukemia (205,206)‖	3	1.53	0.32-4.47	24	1.39	0.89-2.07	27	1.41	0.93-2.05
Acute myeloid leukemia (205.0,205.2,206.0,206.2)‖	3	2.42	0.50-7.07	9	0.99	0.45-1.87	12	1.16	0.60-2.02
Other and unspecified	17	1.50	0.87-2.40	101	1.08	0.88-1.31	118	1.12	0.93-1.35
All cancers other than lung (140-161,163-208)	116	0.87	0.72-1.04	1063	1.03	0.97-1.09	1179	1.01	0.95-1.07

*Expected deaths calculated from national or local mortality rates.
†.05≥*P*>.01.
‡.01≥*P*>.001.
§*P*≤.001 (two-sided tests).
‖For each study, only the time period for which the 8th or 9th ICD revisions were in use nationally is included.

trend were close to unity for all cumulative exposure categories (Table 4). In contrast, less than 10 years since first employment, mortality from all non-lung cancer increased with cumulative exposure (ERR/WLM = 0.15%; 95% CI = 0.06-0.23; *P* = .002), and O/E was 9.52 in those with cumulative exposure of 1500 WLM or more (Table 4).

For individual cancer sites, using all years or 10 or more years since first employment, mortality increased significantly with increasing cumulative exposure only for pancreatic cancer (*P*<.05 for both periods). There was no evidence of heterogeneity of trend between studies (*P* = .76 for both periods), and the ERR/WLM for all years was 0.07% (95% CI = 0.01-0.12) and for 10 or more years was 0.06% (95% CI = 0.002-0.12). For more than 10 years since first employment, the O/E ratios calculated under the hypothesis of no trend were less than 1 in the two lowest cumulative exposure categories and 2.37 at 1500 WLM or more (based on eight deaths) (Table 4). In contrast, for stomach and primary liver cancers, although there was an overall excess compared with external rates, there was little evidence of a trend with cumulative exposure, and the O/E ratios (calculated assuming no trend) were close to unity for all cumulative exposure categories (Table 4).

In the remainder category, other and unspecified cancers, there was a significant association between mortality and cumulative exposure less than 10 years since first employment (ERR/WLM = 0.22%; 95% CI = 0.08-0.37; *P* = .002), with two deaths at 1500 WLM or more and only 0.02 expected (Table 4). Both deaths were certified as being due to carcinomatosis (widespread disseminated cancer throughout the body). One man had previously been registered with lung cancer in the New Mexico Tumor Registry. The other man was in the Colorado study, where lung cancer had increased less than 10 years since first employment (O/E = 2.10; *P*<.05); among 28 deaths

Table 4. Observed deaths (O) and ratio of observed to expected deaths (O/E) for selected sites of cancer by cumulative radon exposure (all studies, including China)

Cancer site		Cumulative radon exposure (WLM)*							P†
		<50	50-99	100-499	500-999	1000-1499	≥1500	Total	
		Less than 10 y since start of employment							
Leukemia	O	14	3	5	0	0	0	22	.91
	O/E‡	0.86	1.27	1.79	0.00	0.00	0.00	1.00	
Leukemia except chronic lymphatic	O	5	2	0	0	0	0	7	.72
	O/E	0.79	4.88	0.00	0.00	0.00	0.00	1.00	
Myeloid	O	1	2	0	0	0	0	3	.32
	O/E	0.38	8.00	0.00	0.00	0.00	0.00	1.00	
Acute myeloid	O	1	2	0	0	0	0	3	.34
	O/E	0.38	7.69	0.00	0.00	0.00	0.00	1.00	
Other and unspecified§	O	13	2	2	0	0	2	19	.002
	O/E	0.98	0.99	0.66	0.00	0.00	100.00	1.00	
Cancers other than lung or other and unspecified	O	77	7	13	4	0	0	101	.17
	O/E	0.95	0.89	1.21	3.88	0.00	0.00	1.00	
All cancers other than lung	O	90	9	15	4	0	2	120	.002
	O/E	0.95	0.91	1.08	2.84	0.00	9.52	1.00	
Person-years at risk	0 lag*	271 956	31 971	53 017	5906	1483	1484		
	5-y lag*	323 086	20 255	21 379	2211	402	375		
		At least 10 y since start of employment							
Stomach	O	82	35	88	18	2	6	231	.95
	O/E	1.07	1.04	0.90	1.24	0.62	1.33	1.00	
Primary liver	O	22	12	39	16	3	0	92	.81
	O/E	1.05	1.03	0.86	1.38	1.67	0.00	1.00	
Pancreas	O	26	7	36	7	1	8	85	.04
	O/E	0.95	0.63	1.01	1.29	0.50	2.37	1.00	
Kidney	O	12	7	21	0	0	1	41	.61
	O/E	0.95	1.11	1.10	0.00	0.00	1.37	1.00	
All cancers other than lung	O	405	183	515	93	25	32	1253	.56
	O/E	0.98	1.04	0.99	1.02	1.11	1.10	1.00	
Person-years at risk	5-y lag	295 078	87 286	222 305	42 231	10 686	12 108		

*5-year lag for cancers other than leukemia; 0 lag for leukemia.

†Two-sided significance level for trend calculated using cumulative WLM categories 0-, 50-, 100-, 200-, 300-, ... 1300-, 1400-, 1500+. Sites shown include all those for which $P<.05$.

‡Expected deaths calculated under the null hypothesis of no trend, and assuming that the total number of deaths expected in each study was equal to that observed; i.e., within each study the number of deaths expected from external rates has been multiplied by the ratio of total observed to total expected deaths.

§Disease group defined as in Table 3.

certified as cancer in this period, 13 were certified as lung cancer. It therefore seems likely that the primary site in this man was also lung. The category of other and unspecified cancers was entirely responsible for the significant trend in the combined category of all non-lung cancer less than 10 years since first employment. When the analysis for this period was repeated, excluding these deaths, there was little evidence of a trend in mortality with cumulative exposure for the 27 specified sites of cancer combined (ERR/WLM = 0.09%; 95% CI = –0.04-0.23; P = .17) or for the individual sites, including leukemia (Table 4).

Discussion

Direct evidence that radon progeny can cause non-lung cancer, provided doses to the appropriate cells are sufficient, is available from observations of people who ingested radium, in whom radon accumulated in the sinuses led to increases in the risk of carcinoma of the paranasal sinuses and mastoid air cells (*1*). Recent biokinetic models, taking into account the high solubility of radon in fat (*37*), indicate equivalent doses of 1.6, 0.5, 0.3, and 0.3 mSv per WLM underground for kidney, bone surface, bone marrow, and liver, respectively (derived from James' values for indoor exposure [(*38*); James AC: personal communication]. The kidney has a high value as it takes up lead and bismuth from the blood, but even this value is low compared with 120 mSv per WLM for the lungs (*39*). Increased body burdens of lead-210 and polonium-210 have been found in uranium miners (*40*); activity was concentrated in the skeleton with lesser amounts in lung, liver, muscle, lymph nodes, kidney, and stomach.

Radon-related lung cancer excesses have been established for all cohorts in this analysis; in the 10 studies with external mortality rates, 1659 lung cancer deaths occurred compared with 516.31 expected, indicating that about 1000 radon-related excess lung cancer deaths have occurred. In contrast, in all non-lung cancer combined (for all years and ≥10 years since starting employment), the total numbers of deaths observed were close to the numbers expected (Table 2). Furthermore, for both time periods, the ERR/WLM was close to, and statistically compatible with, zero. In the period less than 10 years since starting employment, the number of deaths observed was lower than expected; although mortality increased with cumulative exposure, this

result was entirely due to cancers with unspecified primary site, most of which were probably lung cancer.

Among the individual cancer sites, the increases for stomach and liver cancers for all years and for 10 or more years since starting employment are highly significant and unlikely to be chance findings (Table 3). However, mortality from these cancers is not related to cumulative exposure (Table 4); thus, the increases are unlikely to be caused by radon. One possible explanation for the liver increase is that the miners had a high alcohol consumption. There is some evidence for this from the West Bohemia study, since mortality from cirrhosis was clearly increased (*23*), although in the present analysis there was no excess of other alcohol-related cancers (O/E for tongue, mouth, pharynx, esophagus, and larynx combined, 0.87). Another possible explanation for the liver increase is that some secondary cancers from primary cancers of the lung may have been misdiagnosed as primary cancers of the liver. Increased rates of stomach cancer have been observed in miners of several substances [e.g., (*41*) and (*42*)], and it is possible that mining in general may be associated with an increased risk of stomach cancer, although the precise factor involved is not yet known. A relationship between pancreatic cancer and radon exposure has not previously been suggested, and there was little overall excess (Table 3). Thus, the association between pancreatic cancer and cumulative radon exposure seems likely to be a chance finding, as might be expected when 28 sites are examined. It is also possible that some deaths certified as being due to pancreatic cancer were actually due to metastatic lung cancers.

In populations exposed to x rays, leukemia induction periods are short, and relative risks reach their maximum within 5 years of exposure (*43*). Therefore, a leukemia increase less than 10 years after starting employment (Table 3) is consistent with an occupational cause, as is the concentration of any risk during this period (since average employment length was only 6 years). There are also a priori reasons for considering leukemia as a candidate for radon-induced cancer, including geographic studies (*7,9-12,14*), high relative risks for leukemia compared with other cancers following exposure to x rays and gamma rays (*43,44*), the suggestion that uptake of radon by fat cells in bone marrow might cause irradiation of hematopoietic stem cells (*45*), and evidence that irradiation by alpha particles can increase leukemia risk (*46*). However, since leukemia mortality was not significantly related to cumulative exposure either less than 10 years since starting employment or overall, it seems unlikely that radon is the cause of the increase. These miners may also have been exposed to diesel fumes, dusts containing silica, arsenic, or other minerals. Evaluations of the risks of exposure to these carcinogens have not suggested that they are leukemogens (*47-49*). Exposure of the men to gamma radiation in the mines might also be a possible explanation. Exposures to gamma rays and radon will not be highly correlated, since gamma-ray exposures are not affected by ventilation introduced to reduce radon levels. Current models of risks following gamma-ray exposure suggest that leukemia risk would be doubled following an exposure rate of 0.06 Sv per year for 6 years (*50*). Precise data for gamma-ray exposures are not available for most studies, although among Ontario miners monitored since 1981, average annual exposures were only 0.003 Sv (Sont WN, Ashmore JP: personal communication).

This study was motivated by reports of geographic associations between domestic radon concentrations and non-lung cancers (*7-14*) and by associations between non-lung cancers and cumulative radon exposure in individual studies of miners (*4,6*). These associations have not been confirmed in this large study of men occupationally exposed to high concentrations of radon and its progeny. In addition, mortality from kidney cancer, which dosimetric calculations indicate will have the highest doses after the lung (*38*) and which has been related to radon exposure in animal studies (*16,17*), was slightly lower than expected from external mortality rates (Table 3); mortality did not increase with cumulative exposure (Table 4). Nevertheless, the possibility that atmospheric radon causes non-lung cancers cannot be completely ruled out. In this study, the possibility that some deaths may have been missed cannot be ignored, and the study was based on death certificates, so the diagnoses are of limited accuracy. A study (*51*) of basal cell cancer among uranium miners in the Czech Republic suggested a radon-related increase but, since the case fatality is low, this study provides little additional evidence on this issue. No women and very few children were included in this study, so it provides no evidence on the effects of childhood exposure to atmospheric radon or on the risk of female cancers (including breast cancer). In addition, caution must be exercised in generalizing from this study to environmental exposures, since exposure conditions in mines differ considerably from those elsewhere. However, these results provide considerable evidence that neither inhaled radon nor radon progeny deposited on the skin cause a material risk of mortality from cancers other than lung cancer. It therefore seems appropriate that protection standards against atmospheric radon should continue to be based on consideration of the lung cancer risk alone.

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Notes

[1]The working level is defined as any combination of radon daughters in 1 L of air that will result in the emission of 1.3×10^5 MeV potential alpha energy. Exposure of a miner to this concentration for 170 hours (or twice this concentration for half as long, and so on) is defined as a working-level month (WLM). In terms of basic Système International units, 1 WLM = 0.0035 Joule hours per cubic meter.

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