

Radon exposure in residences and lung cancer among women: combined analysis of three studies

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Lung cancer risk in relation to indoor radon was examined in three case-control studies in Stockholm (Sweden), New Jersey (United States), and Shenyang (People's Republic of China). Year-long measurements of radon gas were made in current and past homes of 966 women who developed lung cancer and of 1,158 control women, included in the combined analysis. Nearly 14 percent of the participants were estimated to have a time-weighted, mean, radon concentration in their homes of more than 4 pCi/l (150 Bq/m³) during the period from five to 35 years prior to the date of lung cancer diagnosis (or comparable date for controls). There was a tendency for risk to increase with increasing levels of radon in NJ and Stockholm, but the trends for individual studies and overall were not statistically significant. The estimates of the excess relative risk for indoor exposure per pCi/l were 0.18 (95 percent [CI] = - 0.04-0.70) in NJ, 0.06 (CI = - 0.05-0.34) in Stockholm, and -0.02 (CI = - 0.03-0.03) for Shenyang; these estimates did not differ significantly from each other. The overall excess RR per pCi/l was 0.00 (CI = - 0.05-0.07); the confidence limits were sufficiently broad, however, that the overall estimate was still compatible with extrapolations of risks from miners. Cigarette smoking was the predominant cause of lung cancer with the RR significantly elevated in all studies. Within smoking categories, the trend in risk with increasing mean radon concentration was inconsistent. Analyses of data from several studies are complicated by the possibility that there may exist important differences in study bases which might affect results, and which may be controlled only partially through adjustment procedures. Future efforts to combine various residential studies will need to be attentive to the intrinsic limitations of studies to detect low levels of risk as well as the unique uncertainties associated with estimating, accurately, cumulative exposure to indoor radon. *Cancer Causes and Control* 1994, 5, 114-128

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Introduction

Radon (radon-222) is an inert gas that can percolate through the earth's crust and accumulate in underground tunnels and residential dwellings. At sufficiently high concentrations, radon and its particle-emitting decay products (polonium-214, polonium-218) have been shown to cause lung cancer among underground miners, especially those who smoke cigarettes.¹ There is concern that residential exposures might be responsible for a considerable number of lung cancer deaths in the general population.^{2,3} However, because there are substantial differences between an underground mine and a domestic residence, estimates of risk derived from studies of miners must be applied cautiously to the indoor environment.⁴ Direct assessments of risk from residential radon thus are being sought through epidemiologic studies of lung cancer in the general population.^{5,6} Such studies, though, are not without methodologic problems which can severely limit their accuracy and ability to demonstrate, convincingly, a radon risk.⁷ Until large investigations of sufficient precision can be conducted, available studies will have to be combined and analyzed in parallel to provide direct evidence of the level of risk from residential radon. We report the first such attempt in pooling results from three, recent case-control studies of lung cancer where cumulative exposure was estimated from year-long measurements of radon gas in at least one residence of each subject.

Although numerous descriptive or ecologic surveys have attempted to correlate estimates of radon exposure with rates of lung cancer,⁵ results are of limited usefulness because radon exposure and cigarette-smoking status are not known for individuals and effects of nondifferential misclassification can be substantial.⁸ When we began the current analysis, three comprehensive, analytic, case-control studies had been conducted: in Shenyang (People's Republic of China);⁹ New Jersey (United States);^{10,11} and Stockholm (Sweden).¹² Each study estimated cumulative exposure to radon based on year-long residential measurements. Exposure concentrations were compared between women with lung cancer and control subjects, and cigarette smoking was evaluated in the analysis. No association of lung cancer with indoor radon was found in China, whereas increases were suggested in NJ and Sweden.

Units measuring radon concentration differ between homes and mines. In mines, the Working Level (WL) unit is a measure of α -particle energy released by radon and its short-lived decay products. The measure of cumulative exposure to radon progeny in the mine is the Working Level Month (WLM); one WLM is equiv-

alent to 170 hours of exposure to one WL. One WLM would result in a dose to lung tissue of approximately 0.5 rad.¹³ Based on studies of underground miners, exposure to one WLM would be predicted to increase the relative risk (RR) of lung cancer by 1.34 percent (95 percent confidence interval [CI] = 0.9-2.6),¹ i.e., RR = 1.013 for one WLM cumulative exposure to radon, compared with 'unexposed' miners.

In the US, residential concentrations are expressed in units of activity (rate of atomic decays) of radon gas, in picocuries per liter (pCi/l). When radon is in equilibrium with its decay products, one pCi/l equals 0.01 WL. However, because of ventilation and air exchange in homes, the equilibrium of radon with its decay products, and therefore the energy available, is about 50 percent, although this can vary widely.¹⁴ Thus, in a home environment, one pCi/l corresponds to about 0.005 WL. Assuming 75 percent occupancy, a typical residential exposure for one year would be about 0.2 WLM (= 0.005 WL x 365 d x 24 h/170 h x 0.75). Depending upon various assumptions, a typical residential exposure to one pCi/l for one year could result in a lung dose-equivalent of between two and four rem.¹⁵

In other countries, residential radon is expressed in becquerels per cubic meter (Bq/m³). Under equilibrium conditions, one pCi/l is equivalent to 2.2 decays per minute of radon progeny in one liter of air, and one pCi/l equals 37 Bq/m³. The distribution of indoor radon is approximately log normal, with arithmetic mean concentration in the US of about one to 1.5 pCi/l in living areas.^{16,17} Concentrations, however, vary widely; in Sweden the mean is about 2.6 pCi/l,¹⁸ while in Great Britain, the mean is 0.5 pCi/l.¹⁹ The US Environmental Protection Agency (EPA) has recommended that remedial action be taken for home concentrations exceeding four pCi/l and should be considered between two pCi/l and four pCi/l.²⁰ Other countries have established different guidelines. In Sweden, the recommended action level for radon mitigation corresponds to about 10 pCi/l in existing homes, and four pCi/l for new construction,²¹ while in the United Kingdom, the action level is five pCi/l.¹⁹

Materials and methods

Stockholm

Study subjects. The methods of the Swedish investigation have been described elsewhere.¹² Women suspected of having lung cancer on admission between 1983 and 1985 to the three clinical departments of pulmonary medicine and the only department of thoracic surgery in Stockholm County were interviewed. Those subsequently diagnosed as having lung cancer

were classified as cases ($n = 210$), while those subsequently found not to have lung cancer were classified as hospital controls ($n = 191$). Population controls ($n = 209$) were obtained from Stockholm County population registers. For each case, one control was selected randomly from among the women born on the same day as the case.

Data collection. Subjects were interviewed by physicians using a structured questionnaire. For cases and hospital controls, information was obtained on admission. Population controls were interviewed by personal visit or by telephone. Information was obtained on smoking, exposure to environmental tobacco smoke, occupational history, and consumption of foods rich in vitamins A and C. Also obtained was a history of all residences in which the subject lived for two or more years since birth or arrival in Sweden. The residential history included information on type of house, building material, and year of construction. Data from parish registries on past residences were used to verify and supplement the residential histories.

Methods of radon concentration measurement. Measurements were sought for all dwellings where the subject resided for two years or more between 1945 and the end of observation, 1983-85. For the hospital-based subjects, the end of observation was five years prior to the date of the study interview; for the population controls, it was five years prior to the interview of the corresponding case. In the 2,118 residences so identified, no measurements could be made in 27.4 percent: in 11.2 percent because the house no longer existed; in 4.4 percent because the house was located abroad; in 3.2 percent because the current house owner refused; and in 8.6 percent for various other reasons (Table 1).¹²

Year-long radon-concentration measurements were made in 1,339 dwellings using two a-track detectors (Terradex Corp., Type SF).²² Generally, one detector was deployed in the livingroom and one in the bedroom. In another 234 dwellings (15 percent), measurements were made for two weeks during the winter season using thermoluminescence detectors (TLDs) designed by the Swedish Institute of Radiation Protection. The TLD was placed in the livingroom for one week and in the bedroom for another week (Table 1). The two methods gave readings that had correlations above 0.8, although the TLD values were higher on average, reflecting decreased ventilation in the colder months. In the estimation of radon concentrations, the TLD values were adjusted empirically before being included with the a-track detector data.²³ The radon-concentration value assigned to a house was either the

mean of the two a-track readings or the adjusted TLD reading (Table 2). The higher level for the TLD mean value is because this type of measurement was performed more often in dwellings which were in areas with a greater likelihood of high radon-gas emanation from the ground.²⁴

New Jersey

Study subjects. The technical aspects of the NJ study have been presented elsewhere.^{10,11} The cases were 1,306 NJ female residents who were newly diagnosed with histologically confirmed lung cancer from August 1982 through September 1983. They were identified from hospital pathology records and from the NJ State Cancer Registry and death certificate files. Interviews were obtained for 994 women (76 percent). For cases who were interviewed in person ($n = 532$), controls were selected from the New Jersey driver's license file for those under age 65 and from the Health Care Financing Administration file for those aged 65 and over; these groups were frequency-matched to the cases on race and age. For cases with next-of-kin respondents ($n = 462$), controls were selected at random from death certificates with no mention of respiratory disease, and individually matched to cases by race, age, and closest date of death. Altogether 1,449 controls were identified from these sources, and interviews were obtained for 995 women (69 percent).

Data collection. Subjects or surrogate respondents were interviewed by trained staff of the NJ Department of Health using a structured questionnaire. The subjects themselves provided 53 percent of the interviews; spouses provided 17 percent; and other next-of-kin, 29 percent. Information was obtained on lifetime smoking history, smoking among other household members, lifetime residential and occupational histories, and consumption of food high in vitamin A. Information on specific street-address of past residences was collected several years after the original interview through subsequent telephone contacts. During visits to the residences eligible for radon measurement, information was obtained on house characteristics, including heat circulation and changes involving construction, heating, and ventilation.

Methods of radon measurement. The NJ radon study included a sub-sample of the original lung-cancer study groups (Table 1). Houses to be measured were included in the study in two phases. In Phase I, a single 'index' residence per subject was chosen in which the subject lived for at least 10 years in the 10- to 30-year period prior to diagnosis or selection. In Phase II, the residence criteria were broadened, adding additional

Table 1. Comparison of subjects by study and methods of measurement of radon concentration

	Stockholm			New Jersey			Shenyang	
	Cases	Hospital controls	Population controls	Cases	Live controls	Deceased controls	Cases	Live controls
Number of female subjects								
Case-control study	210	191	209	994	532	467	520	557
Radon study	210	191	209	480	240	202	308	356
Present analysis	200	179	196	480	240	202	286	341
Index date								
Date	Interview	Interview	Interview of matching case	Diagnosis	Interview	Diagnosis of matching case	Interview	Interview
From (mo/yr)	9/83	9/83	9/83	8/82	11/82	8/82	3/85	2/86
To (mo/yr)	12/85	12/85	12/85	9/83	7/84	9/83	6/87	6/87
Radon exposure period								
Radon study	1945 to 5 yrs before index date			5-30 yrs before index date			Last residence of 5+ yrs duration	
Present study	5-35 yrs before index date			5-35 yrs before index date			5-35 yrs before index date	
Total number of residences								
Radon study								
All	725	679	714		Unavailable		1,017	1,262
Measured ^a	536	487	550	584	295	238	301	355
Present study								
All	654	626	652		Unavailable		936	1,133
Measured	482	450	492	584	293	238	286	341
Number of measured residences per subject, present study								
Mean \pm SD ^b	2.3 \pm 1.2	2.3 \pm 1.3	2.3 \pm 1.2	1.2 \pm 0.4	1.2 \pm 0.4	1.2 \pm 0.4	1.0 \pm 0.0	1.0 \pm 0.0
Median	2.0	2.0	2.0	1.0	1.0	1.0	1.0	1.0
Maximum	6	7	7	3	3	3	1	1
Years covered with measurements, present study								
Mean \pm SD ^b	24 \pm 7.6	22 \pm 8.4	24 \pm 7.7	22 \pm 6.1	22 \pm 6.0	23 \pm 6.0	18 \pm 10.5	18 \pm 10.1
Median	27	25	27	23	22	24	21	20
Maximum	30	30	30	30	30	30	30	30
Where detectors located (see Table 2)								
	Livingroom & bedroom or one room only			Main upstairs living area (floors 1-2 or levels 1-3) and/or basement			Livingroom & bedroom	
Source and duration of radon concentration measurement, present study ^c								
Living area	86.9%	82.4%	86.7%	76.7%	75.8%	74.8%	100.0%	100.0%
α -track, 1 yr ^d								
Basement area	—	—	—	5.0%	5.8%	5.9%	—	—
α -track, 1 yr ^d								
Basement & living area canister, 4 d ^e	—	—	—	5.7%	7.2%	7.6%	—	—
Living area canister, 4 d ^e	—	—	—	1.5%	1.0%	1.7%	—	—
Apartment > 2nd floor	—	—	—	11.1%	10.2%	10.1%	—	—
Thermolumin, 2 w ^d	13.1%	17.6%	13.3%	—	—	—	—	—

^a Stockholm values include 36 dwellings with less than 5 yrs of residence before radon measurement.

^b SD = standard deviation.

^c Percentages are based on measured houses.

^d As measured, see Table 2.

^e Used to estimate living area concentration as measured by 1 yr α -track.

subjects and additional houses. The eligibility period for the 'index' residence was extended to cover the

period from five to 30 years prior to diagnosis, and all houses were enrolled in which a subject resided for

Table 2. Mean radon concentration (pCi/l) by type of measurement for study residences and by study

Type of measurement	No.	Arithmetic mean (SD) ^a	Geometric mean (GSD) ^a	Value used in analysis
Stockholm				
α-track, livingroom & bedroom	1,098	3.3 (2.9)	2.5 (2.2)	(LR + BR)/2
α-track, one room only	120	3.2 (2.8)	2.4 (2.1)	LR or BR
Thermoluminescence detector only	206	4.6 (4.0)	3.7 (1.8)	2 week cumulative: 0.91 × TLD + 44.0
New Jersey				
α-track above basement				
1st floor or level	506	0.8 (1.0)	0.5 (2.4)	As measured or (Rm1 + Rm2)/2
2nd floor or level	331	0.7 (0.6)	0.5 (2.3)	As measured or (Rm1 + Rm2)/2
3rd+ level	11	1.0 (0.8)	0.7 (2.2)	As measured or (Rm1 + Rm2)/2
Total	848	0.7 (0.8)	0.5 (2.0)	—
α-track for basement				
Forced air heating;	10	0.4 (0.1)	0.4 (1.3)	0.155 + 0.389 × bsmt _{α-track}
< 1 pCi/l				
Forced air heating;	10	0.8 (0.4)	0.7 (1.5)	0.085 + 0.230 × bsmt _{α-track} +
≥ 1 pCi/l, and/or canisters				0.044 × bsmt _{canstr} + 0.171 × upst _{canstr}
Other heating types;	35	0.4 (0.2)	0.4 (1.3)	0.158 + 0.2476 × bsmt _{α-track}
< 2 pCi/l				
Other heating types;	5	0.7 (0.2)	0.7 (1.4)	0.075 + 0.191 × bsmt _{α-track} -
≥ 2 pCi/l, and/or canisters				0.033 × bsmt _{canstr} + 0.265 × upst _{canstr}
Canister only				
Forced air heating;	24	0.6 (0.3)	0.6 (1.5)	0.265 + 0.133 × bsmt _{canstr} +
basement and above				0.191 × upst _{canstr}
Forced air heating;	4	0.8 (0.4)	0.7 (1.8)	0.170 + 0.536 × upst _{canstr}
upstairs only				
Other heating types;	48	0.5 (0.2)	0.4 (1.5)	0.142 + 0.068 × bsmt _{canstr} +
basement and above				0.318 × upst _{canstr}
Other heating types;	12	0.6 (0.1)	0.6 (1.2)	0.356 + 0.387 × upst _{canstr}
upstairs only				
Apartments above 2nd floor	119	0.4 (0.0)	0.4 (1.4)	0.4 pCi/l
Shenyang				
α-track, livingroom & bedroom	597	3.3 (3.7)	2.6 (2.0)	(LR + BR)/2
α-track, one room only	30	2.2 (1.4)	1.8 (2.1)	As measured

^a Based on time-weighted mean per subject, SD = standard deviation.

four or more years in the six NJ counties with high average radon-levels, or for seven or more years in the rest of the state (Table 1). Of the 994 cases and 995 controls with completed interviews, 661 cases (66 percent) and 667 controls (67 percent) had residences which were eligible under the Phase II criteria.

Terradex Type SF detectors were deployed for one year. In each dwelling, one detector was placed in the living area, usually the master bedroom, and another in the lowest habitable level, usually the basement. In addition, four-day screening measurements were made under closed-house conditions during the heating season, using charcoal canister detectors placed near the a-track detectors. The screening measurements were used primarily as a backup if long-term measurements could not be completed and to identify homes requiring immediate mitigation. The radon concentration assigned to the house in this analysis is the non-basement, primary living area α-track measurement, when

available (76 percent of houses). When unavailable, the non-basement radon concentrations were estimated from other measurements in descending order of priority: (i) basement α-track (5.4 percent); (ii) basement charcoal canister with upstairs canister (6.5 percent); (iii) upstairs charcoal canister (1.4 percent). The estimates were derived from regression equations based on complete sets of measurements which also took into account the heating system (forced air *cf* other). Canister readings below minimum detectable concentration (MDC) were assigned the MDC value. Apartments above the second floor (10.6 percent) were assigned a value of 0.40 pCi/l (Table 1, Table 2). Usable measurements were obtained for 480 cases, and 422 controls, or 74 and 72 percent respectively, of those eligible under the Phase II criteria.

Shenyang

Study subjects. The methods and results of this study

have been described elsewhere.^{9,25} Candidate cases were female residents of Shenyang, between 30 and 69 years old, identified in the Shenyang Cancer Registry through diagnoses of primary lung cancer between September 1985 and September 1987. A rapid-ascertainment system during the study period expedited review of diagnostic materials. A population-based, age-matched control group of women was selected from the Shenyang general population as follows. A population-weighted, probability sample was obtained from 1,400 geographic administrative units of Shenyang. In each selected administrative unit, one household was chosen at random, with replacement, and its members were listed. A five-year age group was selected with a probability weight determined so as to reflect the age distribution of the cases. Finally, one woman in that age group was chosen at random from among those on the household list. A total of 397 cases and 391 control subjects had detectors placed in their houses; these numbers represent 95 and 99 percent of eligible cases and controls, respectively. These subjects represent a subset of the entire study population; for budget reasons, the radon-measurement component of the study ended prior to the termination of case acquisition.

Data collection. Nurses trained in interviewing sought personal interviews with the subjects, except for those who were too ill or deceased. Participation rates were 95 percent for cases and 97 percent for controls. For most patients, the time between diagnosis and interview was less than one month. A structured questionnaire was used in an interview to inquire about smoking by the subject and other household members, occupation, prior medical conditions, residential history, and housing characteristics such as indoor air pollution. A time-weighted index of lifetime air-pollution exposure was determined from these characteristics which included type of heating, fuel used for cooking, and whether cooking facilities were located in a separate kitchen or combined with livingroom or bedroom.²⁵

Methods of radon measurement. Two a-track Type SF detectors were placed for one year in the current residence of each case and control. One detector usually was located in the livingroom and one in the bedroom. Nearly all homes were single-story. For individuals who lived in the current house less than five years, a prior Shenyang residence was tested, provided that it was accessible and that the subject lived there at least five years. Detectors were collected for 308 cases (78 percent) and 356 controls (91 percent).

Combined analysis

In the present analysis, exposures to radon were estimated for subjects who resided in at least one measured house during the period from five to 35 years prior to the index date. This time interval was chosen because studies of underground miners indicate that a minimum latency period of five years before radiogenic lung cancer would develop, and that the risk decreases with time since exposure. Further, it was important to limit the historical reconstruction of exposures, since we are concerned that estimates of radon exposure become increasingly inaccurate as the interval of time between the measurement date and years to which the measurement pertained lengthened. Ten Stockholm cases and 25 controls were excluded because no house measurements were available in the time period covered. Because of the criteria under which the NJ subjects were recruited into the radon component, all met the five- to 35-year time-window requirement. In Shenyang, 13 cases and 15 controls did not reside in the measured residence during the five- to 35-year period considered here. Nine additional Shenyang subjects were excluded because of incorrect data, so that 286 cases and 341 controls are included in this analysis.

Several measures were computed to assess radon exposure. One measure was time-weighted, mean, radon concentration in pCi/l for all measured residences. For subjects with a single measured home, the exposure estimate was the value ascribed to the home (Table 2). When more than one home was measured, the exposure estimate was the mean radon-concentration of all measured homes weighted by the time spent in the home. We also computed a measure of cumulative exposure to radon gas in pCi/l-y in the five-to 35-year period of interest. Because, for some subjects, radon gas measurements could not be obtained in all prior residences in the five- to 35-year period, we imputed radon concentration values for missing time intervals. We used the mean radon concentration for subjects of the same case-control status, study location, and smoking group. Except for a comparison with miners' studies, we present results only for time-weighted, mean, radon concentration; analyses using estimated cumulative exposure produced essentially the same results.

The data were analyzed using a multiple regression program for binary data, as implemented in the EPI-CURE package of programs for personal computers.²⁶ To control for confounding, most analyses were stratified on study location (Stockholm, NJ, Shenyang), age (0-54, 55-64, 65+ years), smoking status, and cigarette consumption (nonsmoker; former smoker; and two levels of current cigarette consumption, 1-19 and 20+ cigarettes per day). In addition, we also adjusted for an

index of the degree of air pollution (score values 0, 0.1-1.5, >1.5 as described in Xu *et al*²⁵) for the Shenyang data and for residency (Stockholm, elsewhere) for the Stockholm data. For regression analyses with continuous radon exposure, the odds of disease outcome ($D = 1$ denotes a case and $D = 0$ denotes a control) was modeled

$$\frac{P(D = 1 | x, r)}{P(D = 0 | x, r)} = e^{\alpha(1 + \beta r)}$$

where x was a vector of adjustment variables, r was radon exposure and α and β were their associated parameters. In most analyses presented here, r was time-weighted, mean, radon concentration in pCi/l and β was the exposure-response parameter, interpretable as excess RR for exposure at a mean concentration of one pCi/l. Two-sided trend tests were carried out using a score test, i.e., a test of $\beta = 0$ in the above model. This score test is equivalent to a score test under an exponential model in r , since the regression under the null hypothesis was the same and with stratification on the x variables equivalent to the standard Mantel-extension test of trend. The P -values for the test of trend were conducted by including r as a continuous variable or as a median exposure within exposure cate-

gory. In some instances, the P -values were quite different. The reasons for this will be considered in the Discussion.

Results

The mean years of residence for which direct measurements were available during the period five to 35 years prior to the reference date were 23 years in Stockholm, 22 years in NJ, and 18 years in Shenyang (Table 1); these years correspond to 77, 73, and 60 percent of the designated exposure period. Few subjects in the Stockholm and Shenyang studies were exposed to estimated, mean, time-weighted concentrations of radon below two pCi/l, while in NJ, few were exposed in excess of two pCi/l (Table 3). After adjustment for smoking, age, air pollution, and residency, the relative risks (RR) of lung cancer increased slightly with increasing radon exposure in Stockholm and in NJ, but not in Shenyang; trends in the RRs were not statistically significant. The trend for Stockholm based on category medians, however, was nearly significant, $P = 0.07$. The highest exposure group in the Stockholm data, ≥ 4 pCi/l, had an RR of 1.6, about equal to that in the highest exposure group in the NJ data, ≥ 2 pCi/l. For all data

Table 3. Relative risks of lung cancer (RR^a), 95% confidence intervals (CI) and numbers of subjects by time-weighted mean Rn concentration

	Mean concentration (pCi/l)						Total	P ^b	P ^c
	<0.5	0.5-0.9	1.0-1.9	2.0-2.9	3.0-3.9	4.0+			
Stockholm									
Cases	0	9	33	57	38	63	200	—	—
Controls	1	7	77	112	71	107	375	—	—
RR	(— 1.0 —)			1.2	1.4	1.6	—	0.46	0.07
(CI)	—	—	—	(0.7-2.1)	(0.8-2.5)	(0.9-2.7)	—	—	—
New Jersey									
Cases	241	158	58	14	4	5	480	—	—
Controls	227	136	66	8	4	1	442	—	—
RR	1.0	1.1	1.0	(— 1.5 —)			—	0.13	0.37
(CI)	—	(0.8-1.6)	(0.7-1.6)	(0.7-3.2)			—	—	—
Shenyang									
Cases	4	14	97	70	56	45	286	—	—
Controls	2	17	101	95	56	70	341	—	—
RR	(— 1.0 —)			0.8	1.1	0.7	—	(0.47)	(0.28)
(CI)	—	—	—	(0.5-1.2)	(0.7-1.7)	(0.5-1.2)	—	—	—
Combined analysis^d									
Cases	245	181	188	141	98	113	966	—	—
Controls	230	160	244	215	161	178	1158	—	—
RR	1.0	1.1	1.0	1.0	1.2	1.1	—	0.94	0.48
(CI)	—	(0.8-1.6)	(0.7-1.5)	(0.7-1.6)	(0.8-2.0)	(0.7-1.8)	—	—	—

^a RR for radon concentration, with multiplicative adjustment for age at interview, smoking status, residency for Stockholm and air pollution for Shenyang.

^b P -value for test of trend using continuous concentration variable. Parentheses indicate negative trends.

^c P -value for test of trend using category median value. Parentheses indicate negative trends.

^d RRs as in footnote ^a with additional adjustment for study.

combined, there was no increase in RRs with mean concentration ($P = 0.94$). Overall, RRs showed no significant increase with exposure concentration.

Within smoking groups, there were no consistent trends among the studies in the RR of lung cancer with increasing estimated radon-concentration (Table 4). In Stockholm, the steepest gradient in risk occurred among those smoking 20 or more cigarettes per day, although the trend was not significant ($P = 0.20$). There were no comparable increasing trends in the highest smoking category of the other groups. Among nonsmokers, RRs exhibited no significant trend; for concentrations of 2.0 pCi/l and greater, all RRs were elevated but the gradient was flat. In NJ, there was no trend in RRs with exposure among nonsmokers; however, there was a suggestive positive relationship between radon exposure and lung cancer risk among former smokers ($P = 0.12$), due to an elevated RR in the highest pCi/l category, which included only eight cases and one control. A positive trend also was suggested among "smokers of one to nineteen cigarettes/day" ($P = 0.15$). In contrast with the Stockholm findings, in NJ there was a negative relationship in the highest smoking category, although that also was not significant ($P = 0.21$). The Shenyang data showed no clear trends with amount of estimated exposure for any

smoking category. In the combined analysis, among former smokers there was only an irregular trend with radon exposure ($P = 0.11$); trends in the other groups were unremarkable.

When nonsmokers were used as the referent category (Table 4), the RRs for smoking categories, adjusted for age, air pollution residency, and radon exposure, were similar between Stockholm and NJ; but the RRs for former smokers was somewhat lower in Stockholm (RR = 2.0) than in NJ (RR = 3.8). The RRs for Shenyang were lower in both current smoking groups than those in the other two study areas.

The excess relative risks (ERRs) per pCi/l, overall and within categories of several variables, are shown in Table 5. As suggested by Tables 3 and 4, the overall ERR/pCi/l was greatest for the NJ study; lower, but positive, for Stockholm; and slightly negative for Shenyang. No exposure-response trend was significantly different from zero. For each study, tests of non-linearity in the exposure-response relationship were not significant. Within study, ERR/pCi/l were homogeneous (and not different from zero) across categories of age and smoking status (Tables); for Stockholm and NJ, there was a suggestion of a greater ERR/pCi/l at the youngest ages. As suggested by the RRs in Table 4, in Stockholm the exposure-response trend was flat

Table 4. Relative risk of lung cancer (RR^a) for time-weighted mean Rn concentration by smoking status

Smoking status	Mean concentration (pCi/l)						Smoking			P ^c	P ^d
	<0.5	0.5-0.9	1.0-1.9	2.0-2.9	3.0-3.9	4.0+	RR ^a	Cases	Controls		
Stockholm											
Nonsmoker	(—1.0—)						1.0	38	181	0.95	0.26
Former ^e	(—1.0—)						2.0	29	66	0.94	0.87
1-19 cig/d	(—1.0—)						5.1	109	117	0.57	0.31
20+ cig/d	(—1.0—)						13.2	24	11	0.20	0.43
New Jersey											
Nonsmoker	1.0	0.9	1.1	(—0.4—)			1.0	66	231	0.32	0.61
Former	1.0	0.9	0.8	(—7.3—)			3.8	91	91	0.12	0.13
1-19 cig/d	1.0	2.0	1.8	(—3.7—)			7.7	123	63	0.15	0.08
20+ cig/d	1.0	1.0	0.7	(—0.5—)			14.6	200	57	(0.21)	(0.25)
Shenyang											
Nonsmoker	(—1.0—)						1.0	114	215	(0.33)	(0.37)
Former	(—1.0—)						2.3	20	18	0.19	0.40
1-19 cig/d	(—1.0—)						2.3	87	70	(0.15)	(0.25)
20+ cig/d	(—1.0—)						3.3	65	38	0.60	0.98
Combined analysis											
Nonsmoker	1.0	0.9	1.1	0.9	1.4	0.9	1.0	218	627	(0.43)	(0.27)
Former	1.0	0.9	1.1	1.1	1.1	1.8	2.4	140	175	0.11	0.19
1-19 cig/d	1.0	1.9	1.6	1.6	1.5	1.8	4.2	319	250	(0.65)	0.59
20+ cig/d	1.0	1.0	0.6	0.9	0.6	0.7	7.5	289	106	0.73	(0.64)

^a RR for radon concentration, with multiplicative adjustment for age at interview and, for Shenyang, air pollution.

^b RR for smoking, with multiplicative adjustment for age at interview, radon concentration, residency for Stockholm and air pollution for Shenyang.

^c P-value for test of radon exposure response trend using continuous concentration variable. Parentheses indicate negative trends.

^d P-value for test of radon exposure response trend using category median value. Parentheses indicate negative trends.

^e Stopped smoking 2 or more years before index date.

Table 5. Excess relative risk of lung cancer and 95% confidence interval (CI) for time-weighted mean Rn concentration, by age at interview, smoking status and study^a. Models adjusted for age, smoking status, residency for Stockholm, air pollution for Shenyang and, where applicable, study

	Excess relative risk per pCi/l			
	Stockholm	New Jersey	Shenyang	Combined
Overall	0.06	0.18	- 0.02	0.00
(CI)	(- 0.04- 0.34)	(- 0.04- 0.70)	(Undef.-0.03)	(- 0.05- 0.07)
Specific for:				
Age				
< 55	0.06	1.03	- 0.04	- 0.03
55-64	0.15	0.16	0.02	0.06
65 +	0.03	0.12	- 0.05	- 0.04
Smoking status				
Nonsmoker	0.03	0.14	- 0.20	0.03
Former	0.03	0.39	0.29	0.04
1-19 cig/d	0.04	0.91	- 0.05	- 0.05
20 + cig/d	1.17	- 0.21	0.04	- 0.04
Study				
Stockholm	—	—	—	0.05
New Jersey	—	—	—	0.17
Shenyang	—	—	—	- 0.02

^a All tests of homogeneity of excess relative risk across levels of age, smoking status and study were not significant.

among nonsmokers. The largest ERR/pCi/l was 1.17 in the >=20 cig/d group, but was based on 24 cases and 11 controls and was not statistically different from the others. In the combined data, the overall ERR/pCi/l was 0.00 (95 percent confidence interval [CI] = - 0.05-0.07) and did not vary by age or smoking status. With indicator variables for study included as adjustment variables, the ERR/pCi/l estimates were homogeneous across the studies.

Figure 1 shows a comparison of the observed RRs for each study (a-c), and all data combined (d), fitted estimates from the linear ERR models, and the constant ERR model from the BEIR IV Report.¹ Although known to be inappropriate because of the variation of exposure effects with attained age and time since exposure occurred, the BEIR IV Committee fitted a constant ERR model to four studies of miners and estimated an overall summary ERR/WLM of 1.34 percent. This ERR/WLM estimate however was not directly comparable to estimates from the indoor exposure data. For the figures, the estimated ERR/WLM for the miners was taken as 0.96 percent; the 1.34 percent was multiplied by 0.8 to adjust for differences between exposures in miners and homes (the K-factor for adults defined in National Research Council⁴) and by 0.9 to reflect an older mean age at lung cancer (incidence) for the case-control studies, 62 years, as compared with the mean age at lung cancer (death) for the miners, 57 years. No adjustment was made for extrapolation from males

(miners) to females. For the indoor radon series, the time-weighted, mean concentration was converted to WLM assuming a 30-year exposure period, an equilibrium factor of 0.5, and a home occupancy factor of 75 percent, resulting in the standard conversion that occupancy in a home at one pCi/l roughly corresponds to an exposure to radon progeny of about 0.2 WLM/y. In panel (a), the category-specific RRs for Stockholm lay entirely above the fitted line. This is a consequence of the choice of categorization for exposure (see Discussion); there was no significant lack of fit or curvilinearity in the exposure-response. The estimates and CIs for ERR/WLM for Stockholm, NJ, and Shenyang data were therefore 1.2 percent (CI = -0.8-6.8), 3.6 percent (CI = -0.8-14.0) and 0 percent (CI = -∞-1.4), respectively, compared with 0.96 percent for the miners. The estimate of ERR/WLM for the Stockholm data was similar to the estimate from the miners' data, while the NJ estimate was about four times larger; however, when combined with the Shenyang data, no positive trend was seen. The figures indicate that each study and all data combined are consistent both with the miners' data and with no effect of exposure. Similarly, the confidence limits for the individual, category-specific, RR estimates were wide and all RRs, save one from the Shenyang data, were statistically consistent with the studies of underground miners and with no effect of exposure.

Estimates of cumulative radon exposure included imputation of exposure values for residence time in unmeasured houses. The cumulative-exposure measure showed similar relationships to lung cancer risk as the mean time-weighted concentration, and results therefore are not presented in detail. The trends in the RRs using the continuous exposure variable were not significant for the Stockholm data ($P = 0.50$), or those from Shenyang ($P = 0.32$), while the trend in the NJ data was of marginal significance ($P = 0.07$). No trend was evident in the joint analysis.

Adenocarcinomas were the most common histologic type in all three studies. When controlling for age, smoking, residency in Stockholm, and air pollution in Shenyang, there were no significant trends in histologic-specific RRs with increasing mean pCi/l or cumulative radon exposure in the individual studies (except for 'other histologic types' in NJ) or in the combined data (Table 6).

Discussion

Studies of underground miners and laboratory animals leave little doubt that exposure to high levels of radon can increase markedly the risk of lung cancer.¹ Radon is also the largest contributor to radiation exposure of the

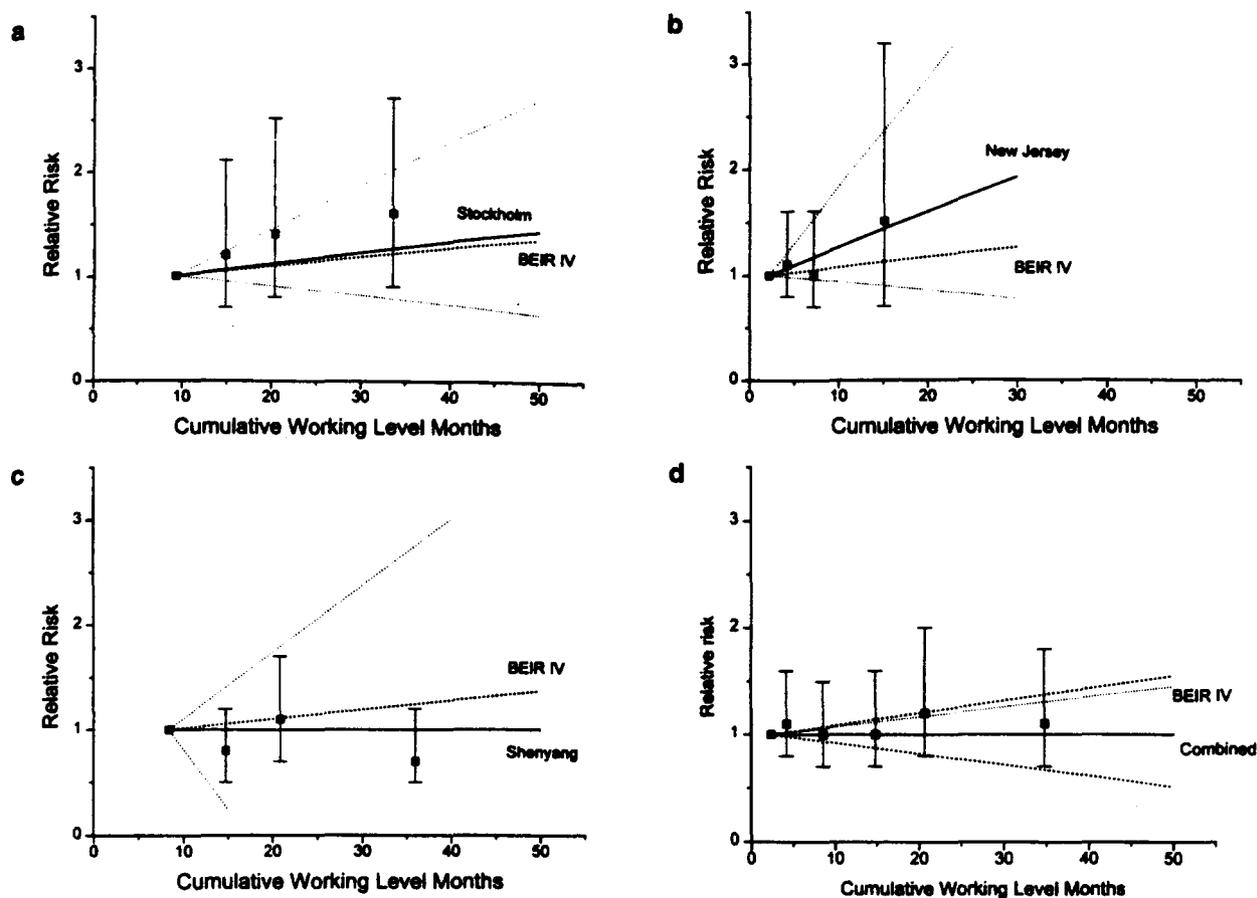


Figure 1. Relative risk (RR) of lung cancer and 95% confidence interval (CI) by categories of cumulative working level months (WLM) and fitted excess relative risk models and their 95% CI for each indoor radon study [Stockholm (a); New Jersey (b); Shenyang (c)] and for all data combined (d), and for the constant excess RR model from the BEIR IV Report⁷ of four cohorts of underground miners. The miners' model was adjusted for extrapolation from mines to homes and for age differences between miners and the indoor studies; see text for details. For Shenyang (c), lower CI is undefined.

public and has been estimated to cause many thousands of lung cancer deaths per year.^{2,20} However, despite a comprehensive analysis of nearly 1,000 women with lung cancer and a similar number of controls, we were unable to demonstrate a clear and consistent relationship between indoor radon and lung cancer. Further, analyses among miners suggest that, because the joint radon-exposure and smoking-RR relationship is likely intermediate between a multiplicative and additive association,¹ RRs for radon exposure should be greater in nonsmokers than in smokers; no such patterns were observed. In Stockholm and NJ, there was a suggestion of an increased risk with exposure within selected subgroups; however there was little consistency, as subgroups differed. The lack of consistent results may be due to the inherent difficulties in exposure assessment and in control of potent confounding influences such as cigarette smoking, as well as to the statistical diffi-

culties in detecting relatively small increases in lung cancer risk. This latter issue is complicated further by uncertainties in the extrapolation of lung cancer risk from studies of underground miners.

Research on indoor radon is subject to several inherent methodologic limitations.⁷ Estimates of radon exposure are based on recent measurements which may not accurately reflect levels in previous years. In addition, even accurate characterizations of radon concentrations in homes may be poor predictors of individual exposures, which depend upon actual time spent indoors, living habits, and house alterations.²⁷ To estimate exposures in homes where measurements were not possible, several methods were used to 'impute' exposures that occurred as far back in time as World War II. These imputation procedures induce great uncertainties in estimating past exposures, and any misclassification of exposure would result in a loss of-

Table 6. Relative risk (RR^a) by histologic type of lung cancer for time-weighted mean Rn concentration

Histologic type	Mean concentration (pCi/l)						Total	P ^b	P ^c
	< 0.5	0.5-0.9	1.0-1.9	2.0-2.9	3.0-3.9	4.0 +			
Stockholm									
Squamous cell	0	1	11	16	11	16	54	—	—
RR	(—1.0—)			1.2	1.6	1.6	—	0.94	0.14
Small cell	0	4	5	13	10	18	50	—	—
RR	(—1.0—)			1.2	1.9	2.1	—	0.24	0.11
Adenocarcinoma	0	3	12	23	11	19	68	—	—
RR	(—1.0—)			1.2	1.0	1.2	—	0.86	0.72
Other type	0	1	6	5	6	10	28	—	—
RR	(—1.0—)			0.5	1.3	1.3	—	0.79	0.25
Controls	1	7	77	112	71	107	375	—	—
New Jersey									
Squamous cell	64	44	12	3	0	1	124	—	—
RR	1.0	1.1	0.7	(—0.9—)			—	0.62	(0.71)
Small cell	62	31	8	4	1	1	143	—	—
RR	1.0	0.8	0.6	(—1.2—)			—	0.65	0.51
Adenocarcinoma	72	47	18	3	2	1	105	—	—
RR	1.0	1.1	1.1	(—2.1—)			—	0.30	0.54
Other type	43	36	20	4	1	2	108	—	—
RR	1.0	1.6	2.1	(—1.6—)			—	0.04	0.03
Controls	227	136	66	8	4	1	442	—	—
Shenyang									
Squamous cell	1	4	22	21	9	10	67	—	—
RR	(—1.0—)			1.1	0.6	0.7	—	(0.52)	(0.31)
Small cell	0	3	11	7	6	8	35	—	—
RR	(—1.0—)			0.6	0.9	1.1	—	(0.92)	0.93
Adenocarcinoma	1	3	32	21	19	10	86	—	—
RR	(—1.0—)			0.8	1.2	0.5	—	(0.24)	(0.16)
Other type ^d	1	1	8	5	6	3	24	—	—
RR	(—1.0—)			0.6	1.3	0.5	—	(0.62)	(0.56)
Controls	2	17	101	95	56	70	341	—	—
Combined analysis									
Squamous cell	65	49	44	40	20	27	245	—	—
RR	1.0	1.1	0.8	0.9	0.7	0.9	—	(0.56)	(0.28)
Small cell	72	54	34	24	17	27	228	—	—
RR	1.0	1.3	0.9	1.0	1.1	1.5	—	0.52	0.22
Adenocarcinoma	63	37	52	48	31	31	262	—	—
RR	1.0	0.8	0.8	0.9	0.8	0.7	—	(0.59)	(0.66)
Other types	44	38	34	13	14	14	157	—	—
RR	1.0	1.5	1.8	1.3	2.1	1.9	—	0.70	0.16
Controls	230	160	244	215	131	178	1,158	—	—

^a RR for radon concentration with multiplicative adjustment for age at interview, smoking status and air pollution for Shenyang and residency for Stockholm.

^b P-value for test of radon exposure response trend using continuous concentration variable. Parentheses indicate negative trends.

^c P-value for test of radon exposure response trend using category median value. Parentheses indicate negative trends.

^d Excludes 74 cases with unknown type.

power to demonstrate a radon effect. Also, increased mobility, which forces a narrowing of the exposure distribution for individuals,⁷ can influence the ability to detect an effect, with substantial loss of power as the mean number of residences rises.

As expected, cigarette smoking was the most striking cause of lung cancer in each of the study groups, with RRs in Stockholm and NJ almost 14-fold for women smoking 20 or more cigarettes per day. The RRs for

smoking were noticeably lower in Shenyang, reaching threefold in the highest smoking category. Although much lower than for the other two study populations, the smoking results for the Shenyang data were consistent with the larger parent study of lung cancer in 729 males and 520 females,²⁵ where smokers had an overall threefold higher risk than nonsmokers, and with other lung cancer case-control studies conducted throughout China,²⁸⁻³¹ where RRs were typically of this

magnitude. Because the anticipated level of risk from indoor radon is in the order of 1.1- to 1.5-fold, a slight misclassification of individuals with regard to smoking duration or quantity could cloud or confound a possible association between radon and lung cancer risk.

As mentioned, there was (seemingly) a lack of consistency in results for the three studies, making the joint analysis problematic and results difficult to interpret. However, the major function of a joint analysis is to assess formally the variation of effects among the studies. In no instance among the three studies was there significant heterogeneity of effects. Thus, differences among studies could have been due to chance alone. However, in the evaluation of subtle differences, such as between studies or variations of trend across level of other factors, large numbers of subjects are required to achieve high power.⁷

In a statistical sense, as suggested by the confidence limits for the RRs and for the fitted exposure-response models in Figure 1, the data from the three studies of indoor radon are not inconsistent with extrapolations based on investigations of underground miners. Moreover, even this figure is misleading, since the sampling and non-sampling variability in the estimates from the studies of miners, perhaps as great as a factor of two to four,⁷ have not been depicted. Because of the wide confidence limits, the possibility of an association between indoor exposure to radon gas and lung cancer cannot be excluded. In addition, because of the wide confidence limits about the risk estimates for the indoor studies and the absence of an effect for all data combined, the possibility that the level of lung cancer risk from indoor radon is less than the level predicted studies of miners cannot be excluded. It is informative to discuss why these differences might arise.

There are notable differences in host and exposure characteristics between the combined series and studies of underground miners which might limit comparability of findings. The combined series of indoor radon was large, but included only women; 37 percent of cases were nonsmokers; exposure occurred over many years at a relatively low rate; and exposure estimates were based on recent conditions in the home. Analyses of underground-miner studies,¹ however, included 360 lung cancers, involved only men, mainly cigarette smokers, in a very dusty and polluted environment, with exposure to a wide range of radon levels over a limited number of years, and cumulative exposure estimated from intermittent sampling.

Circumstances associated with underground mines have led some to question whether extrapolations from miner studies have direct relevance to residential situations.³² The role of concomitant exposures and lung cancer risk among underground miners has not been

clearly elucidated. Cigarette smoking appears to interact with radon in a manner that greatly enhances the development of lung cancer. Conceivably, other carcinogenic mine-exposures and lung irritants, such as airborne particulate, also might heighten the carcinogenic potential of continuous radon exposure. Some examples of such exposures are arsenic,^{30,31} silica,³³ and diesel and blasting fumes.³⁴ It has been suggested that exposures that damage or irritate lung tissue and promote cell proliferation might potentiate the carcinogenic effect of radon,⁴ and this is supported by recent experimental evidence.³⁵ It is unknown to what degree such factors were present among the cohorts used to develop the BEIR IV risk model, although silica, arsenic, and asbestos were not thought to present major hazards.¹

On the other hand, there is some evidence to suggest that the home radon exposure might be relatively more hazardous than radon exposure in the mine because of a lower exposure rate. Three miner studies,^{30,36,37} have reported an inverse dose-rate effect, i.e., the lung cancer risk was seen to increase as dose rate diminished. Such an effect is supported somewhat by data on high-dose in animals³⁸ and by an independent evaluation of several miner studies.³⁹ The exposure levels over which the inverse dose-rate effect has been seen, however, have been quite large, and the possible role of high-dose cellular killing cannot be discounted. Dose-rate effects may prove to be important determinants of lung cancer risk, although it has been hypothesized that such effects may taper off at the much lower radon-exposure rates experienced in residential settings.⁴⁰

There are several other biologic and dosimetric possibilities for differences between domestic studies and miner predictions. Radon gas (pCi/l) was measured in the homes whereas exposure measurements for miners were of radon progeny (WL). Conversions of pCi/l to WLM would be incorrect if the equilibrium factor between radon and its decay products was less than the 0.5 value commonly used. The amount of time actually spent in the home is critical and a 75 percent occupancy is usually assumed. If the actual occupancy was less, e.g., 65 percent,^{15,18,27} and radon exposure at other locations varied appreciably, then considerable error would be introduced into cumulative exposure estimates. Finally, based on physical characteristics of inhaled radon and the biologic features of the respiratory tract, it has been suggested recently⁴ that exposure to radon in the home should be less effective in causing lung cancer than in the mine and that risk estimates based on miner studies should be reduced by about 30 percent.

The studies from NJ and Stockholm suggested positive exposure-response relationships, while no such

trend was evident in the Shenyang data; however, the heterogeneity was not statistically significant. Provided such differences were not due to chance, it may be informative to discuss why they might have arisen. In contrast to Stockholm and NJ, environmental pollution was more severe in Shenyang. For females, smoky indoor air, primarily from coal-burning stoves, and smoky outdoor air, from living in proximity to industrial factories, were associated with a twofold greater risk of lung cancer. Incomplete control of confounding from air pollution could have affected results. High indoor-particulate concentrations could have played a role by reducing the fraction of unattached radon progeny and the effects of the measured radon-gas exposure. However, there was no evidence in the data that the presence of indoor air pollution influenced results. The relationship between estimate radon-gas exposure and lung cancer in Shenyang was similar within and across categories of an air pollution index.

It may also be useful to compare the RR trends within the Stockholm and NJ data although differences in trend within and between the data sets were not statistically significant and could have arisen by chance. The magnitude of the exposure-response estimate was threefold larger in the NJ data than the Stockholm data. The exposure-response trend in the NJ data was due principally to the RR in the highest exposure category, 2.0 pCi/l or higher, which included 23 cases and 13 controls. The suggested positive trend in risk with radon exposure occurred in moderate smokers (1-19 cig/day), while RRs declined among heavy smokers (20+ cig/day). In the Stockholm data, the suggested trend with exposure was greatest in heavy smokers. The apparent positive trend in the Stockholm data occurred only among residents of Stockholm, while there was no trend with exposure among the women who resided outside of Stockholm.⁴¹ The reasons for this difference are not clear.

Although all studies relied primarily on year-long α -track detectors, the accuracy of estimated exposure may have differed. For the Shenyang data, subjects had a shorter mean occupancy-time in measured homes which may have reduced accuracy. In Stockholm, about 13 percent of the α -track measurement data were supplemented by two-week TLD measurements; in NJ, about 23 percent of the α -track data for living areas was supplemented with basement-area data or with short-term charcoal-canister measurements. The supplementation procedures were based on multiple linear-regression equations, thus adding random error to the exposure estimate. The relative magnitude and impact of these various sources of measurement error are uncertain.

Because of the need for comparability among the three studies in the definition of exposure to indoor radon, our analyses differed slightly from the individual reports. These differences, however, did not affect inference. The negative results from Shenyang and the trends with exposure in the Stockholm and NJ reports, overall and within various sub-groups, were generally similar to those reported. Differences between the current and published results were likely due to several factors: (i) slightly different sets of data; (ii) different procedures for defining the exposure period of interest; (iii) a different categorization of pCi/l; and (iv) different procedures for the imputation of missing radon measurements and of unmeasured time periods.

Interestingly, in a few instances, the level of statistical significance of tests of trend in indoor radon and lung cancer risk exhibited a difference between the analyses based on continuous and categorical exposure variables, particularly for the Stockholm data (Tables 3,4, and 6). The reason for this difference is partly the result of the choice of categorization and the use of median values for the tests of trend. The analysis using a continuous exposure variable has the advantage of avoiding the arbitrariness involved in the choice of cut-points. On the other hand, trend statistics based on categorical medians reduce the influence of extreme values. The influence of choice of categorization and use of continuous exposure variables on *P*-values for tests of trend indicates a lack of robustness in inference and thus suggests cautious interpretation of results. The lack of consistency within and across studies for a radon effect overall and within smoking categories also reflects, perhaps, the small exposure effects to be detected together with uncertainties in estimation of exposure.

Each of the three studies had limitations which were addressed in the individual publications. The Shenyang series was conducted in an area of high indoor pollution, although analyses were unaffected by adjustment for the index of air pollution. The NJ series had a limited range of exposures and included few nonsmokers (14 percent). The Stockholm series also included few nonsmokers (19 percent), and adjustment for home occupancy or by the BEIR IV time-since-exposure weights, which emphasize more recent exposures, weakened the evidence for an association.¹² In the analysis of exposure to radon, we adjusted RRs for age, cigarette use, an air pollution index (for Shenyang), and residency status (for Stockholm). However, it is uncertain to what extent other, unknown limitations in the individual studies influenced our results.

In summary, the results from the individual studies are statistically consistent with each other, consistent

with extrapolation from miners, and consistent with no observed effects of exposure. Future efforts to combine similar studies are needed to clarify the carcinogenic potential of indoor radon.

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