

Lung Cancer Risk From Residential Radon: Meta-analysis of Eight Epidemiologic Studies

Jay H. Lubin, John D. Boice, Jr.*

Background: Studies of underground miners exposed to radioactive radon and its decay products have found that exposure increases risk of lung cancer. Consequently, when radon was found to accumulate in houses, there was concern about the public health impact from exposure to a known carcinogen. Estimates on the basis of studies of underground miners suggest that indoor radon may account for 6000-36 000 lung cancer deaths each year in the United States. Because of differences between working in underground mines and living in houses, estimates are subject to major uncertainties. Numerous case-control studies were launched to assess directly the lung cancer risk from indoor radon. Some studies report positive or weakly positive findings, while others report no increased risk. Thus, the potential hazard from indoor radon remains answered only indirectly through miner studies, experimental animal studies, and cellular studies. **Purpose:** To provide more information on the risk of lung cancer from indoor radon, we conducted a meta-analysis of all case-control studies that included at least 200 case subjects each and that used long-term indoor radon measurements. **Methods:** Eight studies were available and included a total of 4263 lung cancer case subjects and 6612 control subjects. From the published results of each study, confounder-adjusted relative risk (RR) estimates and 95% confidence intervals (CIs) for categories of radon concentration were obtained, and weighted linear regression analyses were performed. **Results:** The combined trend in the RR was significantly different from zero (two-sided $P = .03$), and an estimated RR of 1.14 (95% CI = 1.0-1.3) at 150 Bq/m³ was found. An influence analysis indicated that no single study dominated the combined results. The exposure-response trend was similar to model-based extrapolations from miners and to RRs computed directly from miners with low cumulative exposures. However, there were significant differences in the study-specific estimates of the exposure response (two-sided $P < .001$), which were not explained by study differences in percent of the defined exposure interval covered by radon measurements, mean number of residences per subject, and other factors. **Conclusions:** Meta-analyses are valuable for identifying differences among studies and for summarizing results, but they should be interpreted cautiously when expected RRs are low as with indoor radon exposure, when there is study heterogeneity and where there is the potential for confounding and exposure misclassification. Nonetheless, the results of this meta-analysis suggest that the risk from indoor radon is not likely to be markedly greater than that predicted from miners and indicate that the negative exposure response reported in some ecologic studies is likely due to model misspecification or un-

controlled confounding and can be rejected. **Implications:** Until ongoing case-control studies of indoor radon are completed and the data are pooled and analyzed, the studies of underground miners remain the best source of data to use to assess risk from indoor radon. This meta-analysis provides support for their general validity. [J Natl Cancer Inst 1997; 89:49-57]

Eleven comprehensive studies of underground miners exposed to radioactive radon gas and its alpha-particle emitting decay products all found that exposure increases the risk of dying of lung cancer [reviewed in (1)]. As a consequence, when it was found that radon could accumulate in houses, albeit at concentrations usually much lower than in mines, there was concern about a possible significant public health hazard from exposure to a known human carcinogen (2).

With the use of miner-based risk models and after adjustment for effects of exposure in mines as compared with homes (3), indoor radon may account for 6000-36 000 lung cancer deaths each year in the United States (4). Because of the major differences between working in underground mines and living in houses, some have questioned the validity of extrapolating risks from male miners to home residents, particularly to females and to children, and have taken issue with current estimates of radon-attributable lung cancers (5,6). Miners experienced higher exposure rates and were frequently exposed to other potential lung carcinogens and lung irritants, such as arsenic and silica. In addition, a high proportion of miners were smokers.

To address concerns about extrapolating risk from miners, numerous epidemiologic case-control studies were launched in the past decade to assess directly lung cancer risk from indoor radon. Major studies have now been published (7-15), and results seemingly are equivocal (16,17). Some studies (7,9,13,14) report positive or weakly positive findings, while others (8, 11,12,15) report no increased risk, even at the highest indoor radon level. A pooled analysis of three studies with nearly 1000 lung cancer cases estimated no trend overall. The estimated relative risk (RR) for long-term residence in a house with a radon concentration of 150 Bq/m³ was 1.0 (95% confidence interval [CI] = 0.8-1.3) (18). Thus, the question concerning whether indoor radon poses a significant health hazard, particularly for

*Affiliations of authors: J. H. Lubin, Epidemiology and Biostatistics Program, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD; J. D. Boice, Jr., International Epidemiology Institute, Rockville, MD.

Correspondence to: Jay H. Lubin, Ph.D., National Institutes of Health, Executive Plaza North, Rm. 403, Bethesda, MD 20892.

See "Notes" following "References."

people living in homes with high radon concentrations, remains answered only indirectly, through miner studies, experimental animal studies, and cellular and molecular studies (19).

The mixed results from indoor radon studies may be the consequence of inherent limitations, principally low expected RRs, estimated at 1.1-1.3 at 150 Bq/m³, a concentration that is equaled or exceeded in about 6% of U.S. houses (20), and the extreme uncertainty in estimating accurately individuals' past exposure based on current radon measurements of houses. An analysis of study power and exposure uncertainty indicates that a single case-control study in excess of 5000-15 000 lung cancer cases may be needed to have sufficient power to detect an exposure response equal to the trend estimated from miner studies (21).

Pooling of original data from existing studies offers an alternative to conducting a single large study. Efforts at pooling completed and ongoing radon studies are under way; however, results are unlikely within the next several years (22). Until studies are pooled, meta-analysis offers the best opportunity for characterizing existing information. In this article, we present a meta-analysis of completed case-control studies of indoor radon.

Subjects and Methods

There have been eight case-control studies of indoor radon and lung cancer that enrolled a minimum of 200 case subjects and measured one or more houses for radon concentrations for all, or nearly all, subjects, by use of long-term alpha-track detectors (Table 1). [Two studies have been reported from Finland; the earlier study (7) is denoted Finland-I, and the more recent study (8) is denoted Finland-II.] Each of the studies had particular strengths and weaknesses. Because it is not possible to know how the impact of any perceived weakness might actually influence results and because knowing results of a study may color any assessment of study quality, all studies were included in the meta-analysis.

From the published results of each study, confounder-adjusted RR estimates and 95% CIs for categories of radon concentration in Bq/m³ were obtained. Mean or median concentrations within categories were used as the quantitative value for regression modeling. If means or medians were not available, mid-points of categories or, for open-ended categories, representative values were used as the quantitative values for radon level. To evaluate study heterogeneity, a number of study-related factors were examined. These included the following: overall mean radon level, percent of the defined exposure interval covered by radon measurement data, mean number of residences per subject within the exposure interval, mean number of measured residences per subject, percentage of case subjects who smoked, percentage of eligible case subjects included in the radon analysis, percentage of homes with year-long radon measurements, percentage living case subjects, and percentage female case subjects.

Weighted linear regression analyses of the natural logarithm of the confounder-adjusted RR estimates were carried out, using inverse variances as weights (23). Thus, each study contributed in relation to the precision of its estimate, which was related to the numbers of case and control subjects and the distribution of exposure. For each study, we fit a log-linear RR model that passed through the quantitative value for the base-line category. For radon at level x , the regression model was

$$\log[RR(x;x_0)] = \beta(x - x_0), \quad [1]$$

where x_0 was the quantitative value for the referent category and β the exposure-response parameter.

Model [1] was fit to each study, and estimates of β_i , $i = 1, \dots, 8$ were obtained. Under a fixed-effects model, it is assumed that the true exposure-response parameter β is the same for all studies. However, because of differences in study design, type of living environment, populations, and other factors, the effects of exposure could be expected to vary from study to study. The random effects model, where β_1, \dots, β_8 is assumed to be a random sample from a normal distribution with mean β , was therefore used to compute summary exposure-response estimates. Details are given in the "Appendix" section. In a

random effects model, the variance of the estimate of β accounts for variability among studies, so that precision is not overstated (24,25). The 95% CI for the estimate of the RR for a unit increase in exposure is $\exp[b^* \pm 1.96 \times \sqrt{\text{var}(b^*)}]$, where b^* denotes the summary estimate under a random effects model.

Analyses of radon progeny exposure among miners are usually based on linear models in the excess RR of the form $RR = 1 + \beta x$, as opposed to the log-linear form of model [1]. In this analysis, we departed from the linear excess RR modeling for two reasons. First, for the indoor radon data, RRs are small, so differences between linear and log-linear models are minimal. Analyses using a linear excess RR model did not affect conclusions. Second, with linear excess RR models, the (asymptotic) variance estimate of the exposure response (β) can be seriously in error when data are limited (26,27). In contrast, with a log-linear model, exposure-response estimates are unconstrained, ranging from minus infinity to plus infinity, and the surface of the likelihood function is usually more symmetric. As a result, the (asymptotic) variance estimate for the logarithm of the exposure response is more accurate when data are limited. Because the summary exposure-response estimate relies on weights based on study-specific variances, we used model [1] to minimize possible distortions from less accurate variance estimates from a linear excess RR model.

Note that all related figures (i.e., Figs. 1-3) use the same scales for the axes to allow direct comparisons.

Results

Overall, 4263 lung cancer case subjects and 6612 control subjects contributed to the meta-analysis. RRs and 95% CIs for each study are shown in Fig. 1. The figure also shows an RR of 1 and extrapolated RRs for indoor exposures on the basis of a recent combined analysis of miner data (4). The miner extrapolation assumes 25 years of exposure to indoor radon at a constant concentration for a 65-year-old male. The estimate of RR is similar to the estimate on the basis of the BEIR IV risk model developed earlier by the National Research Council's Committee on the Biological Effects of Ionizing Radiation (BEIR) (19). The figure suggests that RRs from indoor studies are consistent with the extrapolation based on miner studies. The CIs for the individual RRs are large, and most overlap an RR of 1, suggesting that results may also be consistent with no effect of radon. However, although there is a wide range of RRs, more of the RRs exceed 1 than are 1 or less, and there appears to be a general tendency for elevated RRs with higher radon levels. In the meta-analysis, we formally assess results from the various studies.

Model [1] was fit to each study with radon concentration as the regressor variable. Except for the Finland-I study, log-linear models in radon level provided good fits to the data (Fig. 2), and there were no significant deviations from linearity. For the Finland-I study, a quadratic term significantly improved the fit of the model ($P = .03$). For simplicity when computing summary estimates, the estimate of β from model [1] using only radon level was used for the Finland-I study. The study-specific values for the exponential of the estimates in units of 150 Bq/m³, i.e., $\exp(\beta_i \times 150)$, are shown in Table 2. The fitted RRs at 150 Bq/m³ ranged from 0.8 to 1.8 and were in good agreement with the estimates provided in or derived from the original reports. For four studies, the lower limit of the 95% CIs for the estimates of $\exp(\beta)$ was greater than 1 (suggesting a significant exposure response); for one study, the CI for the estimate of $\exp(\beta)$ was entirely below 1. For three studies, the CIs for the estimates of $\exp(\beta)$ included 1, suggesting no significant radon effect. Since data on individual subjects were not available and we fit model [1] rather than a linear excess RR model, these estimates differed, although only slightly, from estimates provided in the original publications.

Table 1. Summary of the eight principal lung cancer case-control studies with long-term measurements of indoor radon concentration*

Study and site (reference No.)	Subjects	Radon concentration†	Radon extremes	Summary of overall results
Finland-I (7)	Males: 238 case subjects and 434 control subjects	Mean of 220 Bq/m ³	40% > 174 Bq/m ³	Quintile categories <80, 80-126, 127-173, 174-274, and ≥275 Bq/m ³ with RRs of 1.0, 1.1, 1.7, 1.9, and 1.1, respectively. <i>P</i> value for test trend >.05
Finland-II (8)	517 matched case and control pairs, among residents of one single-family home for ≥ 19 y	Medium of 66.6 Bq/m ³ , means of 103 and 96 Bq/m ³ for case subjects and control subjects, respectively	9% > 200 Bq/m ³	Categories <50, 50-99, 100-199, 200-399, and ≥400 Bq/m ³ with RRs of 1.0, 1.0, 1.0, 0.9, and 1.3, respectively
New Jersey, United States (9,10)	Females: 433 case subjects and 402 control subjects	Median of 22 Bq/m ³ , mean of 26 Bq/m ³	1% > 148 Bq/m ³	Categories <37, 37-73, 74-147, and ≥148 Bq/m ³ with RRs of 1.0, 1.1, 1.3, and 4.2, respectively. <i>P</i> value for test of trend .04; highest category had 6 case patients and 2 control subjects
Shenyang, China (11)	Females: 308 case subjects and 362 control subjects	Median of 85 Bq/m ³ , mean of 118 Bq/m ³	20% > 148 Bq/m ³	Categories <74, 74-147, 148-295, and ≥296 Bq/m ³ with RRs of 1.0, 0.9, 0.9, and 0.7, respectively
Winnipeg, MB, Canada (12)	Females: 250 case subjects and 250 control subjects; males: 488 case subjects and 488 control subjects	Means of 120 and 200 Bq/m ³ for bedrooms and basements, respectively	24% > 144 Bq/m ³	Categories (estimated) <72, 72-144, 145-287, and ≥288 Bq/m ³ with RRs of 1.0, 1.0, 0.8, and 1.0, respectively, using bedroom and 1.0, 0.8, 0.9, and 0.6 using basement measurements
Stockholm, Sweden (13)	Females: 210 case subjects and 191 hospital and 209 population control subjects	Mean of 128 Bq/m ³	28% > 150 Bq/m ³	Categories <75, 75-110, 111-150, and 151 Bq/m ³ with RRs of 1.0, 1.2, 1.3, and 1.7, respectively. <i>P</i> value for test of trend .05. No trend after adjustment for residential occupancy or BEIR IV weighting of exposure‡
Sweden (14)	Males and females: 1281 case subjects and 2576 control subjects	Mean of 107 Bq/m ³	25% > 117 Bq/m ³	Categories ≤50, 51-80, 81-140, 141-400, and >400 Bq/m ³ with RRs of 1.0, 1.1, 1.0, 1.3, and 1.8, respectively. <i>P</i> value for test of trend <.05
Missouri, United States (15)	Female nonsmokers: 538 case subjects and 1183 control subjects	Mean of 67 Bq/m ³ for case subjects and control subjects	7% > 148 Bq/m ³	Quintile categories <30, 30-43, 44-63, 64-91, and ≥91 Bq/m ³ with RRs of 1.0, 1.0, 0.8, 0.9, and 1.2, respectively

*RR = relative risk.

†Most studies incorporated 1-year measurements as the principal source of exposure data. The Swedish study used 3-month winter measurements, and the Finland-I used 2-month winter measurements. The New Jersey and Stockholm studies used measurements of less than 1-year duration for 9% and 13% of subjects, respectively.

‡Residential exposures were weighted, with exposures 5-14 years prior to the index date given full weight and greater than or equal to 15 years before given half weight. BEIR = Biological Effects of Ionizing Radiation.

For all studies combined, the summary estimate of exposure-response trend differed significantly from zero ($P = .03$). The fitted RR at 150 Bq/m³ was 1.14 (95% CI = 1.0-1.3). A test of homogeneity of the estimates was rejected ($\chi^2[7 df] = 52.8$; $P < .001$). A detailed radon effects analysis indicated that between-study variability was substantial relative to within-study variability.

Definitions for base-line categories for calculating RRs differed for the various studies, necessitating an adjustment of the study-specific RRs before they could be used to obtain RRs for specific categories for all studies combined. By use of the fitted, study-specific log-linear models, RRs for each study were shifted to a base-line concentration of "zero" radon level by multiplying each RR by $\exp(b_i x_{0i})$, where x_{0i} was the concentration for the base-line category for the i th study and b_i the estimate of β_i . By use of mean radon concentrations for all studies and all categories, five categories were created on the basis of quintiles, <55.4, 55.5-88.7, 88.8-142.2, 142.3-250.8, and ≥250.9 Bq/m³. By use of model [1] with $\beta(x - x_0)$ replaced by an intercept parameter and four parameters for four indicator variables for radon categories, estimates of RR (95% CIs) for the radon categories were 1.0, 1.06 (0.9-1.3), 1.06 (0.9-1.3), 1.28

(1.0-1.6), and 1.20 (1.0-1.5). We adjusted these RRs to a base-line of zero radon level by multiplying by $\exp(b^* \times x_0)$, where b^* is the random effects estimate of β , and x_0 was the mean concentration for the lowest radon category 34.2 Bq/m³. Fig. 3 shows the adjusted RRs (solid squares) and the line $\exp(b^* \times x)$, where x is radon level. The model [1] provided a good fit to the combined data, with no significant departure from linearity.

Mean cumulative exposure in the miner studies was more than 20 times greater than exposure from living 25 years in an average U.S. house, which has an estimated arithmetic mean concentration of 46 Bq/m³ (20). In pooled miner data, there were 223 000 person-years of follow-up and 107 lung cancer cases among nonexposed miners and 506 474 person-years of follow-up and 358 lung cancer cases among miners exposed to fewer than 50 Working Level Months¹ (WLM) (4), which is a level of cumulative exposure that might be experienced by long-term residents in houses with radon levels in excess of 400 Bq/m³. The correspondence between exposures for miners in WLM and radon concentrations in homes in Bq/m³ was made assuming 25 years of exposure, standard residential occupancy assumptions (i.e., living for 1 year in a house at 37 Bq/m³ is approximately equal to 0.2 WLM of exposure), and a 0.8 correction factor that

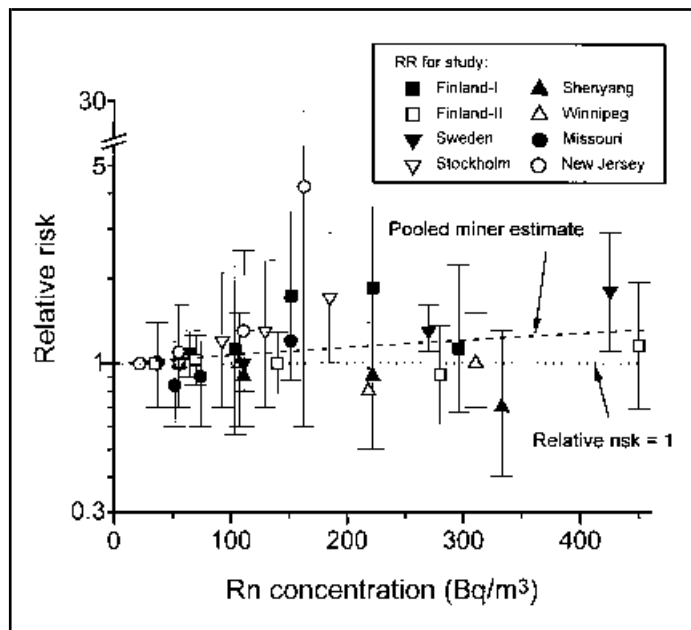


Fig. 1. Relative Risks (RRs) from eight lung cancer case-control studies of indoor radon levels. Dashed line = extrapolation of RR from miners (4), while the dotted line depicts a RR of 1.

accounts for a reduced delivery of dose for indoor exposure as compared with mine exposure (3). For example, a miner exposed to 25 WLM was assumed to have approximately the same exposure as an individual living 25 years in a house with a radon concentration of 231 Bq/m³ [= 37 × 25 WLM/(25 years × 0.2 × 0.8)]. In the miner data, RRs were calculated for categories 0, 1-9, 10-19, 20-29, 30-39, and 40-49 WLM. Fig. 3 shows RRs and 95% CIs from the miner data (open squares).

A log-linear model was fit to the miner RRs under 50 WLM. The model-based estimate of RR was 1.13 at 150 Bq/m³ (95% CI = 1.0-1.2), essentially the same as the 1.14 estimate from the meta-analysis of residential studies. As suggested from a comparison of Fig. 3 with Fig. 1, the RRs for miner exposures under 50 WLM were similar to extrapolations using the miner-based risk model, which was developed in data with generally higher exposures than in residential studies.

The indoor studies were carried out in five countries, Canada, China, Finland, Sweden, and the United States. To investigate the influence of any single study on the overall parameter estimate and its CI, Fig. 4 shows the results of an influence analysis, in which eight summary estimates were computed on the basis of subsets of seven studies, omitting each study in turn. The figure indicates that the overall estimates changed very little when any single study is omitted. When the Finland-I, New Jersey, Stockholm, or Sweden studies were omitted, 95% CIs included 1.

Meta-analyses are used to evaluate similarities and differences among studies, as well as to summarize results. In our analysis, study-specific, exposure-response estimates were heterogeneous. To examine these differences, values for overall mean radon level, percent of exposure interval covered by radon measurement data, mean number of homes per subject, mean number of measured homes per subject, percentage of case subjects who smoked, percentage of eligible case subjects included in the radon analysis, percentage of homes with year-long radon

measurements, percent of living case subjects, and percentage of female case subjects were obtained for each study. Fig. 5 plots these data by the study-specific, exposure-response estimates. Correlation coefficients, which are also shown, were not significantly different from zero. None of the variables, individually or jointly, significantly improved the regression model. With these variables in the regression, the test of homogeneity of b_1, \dots, b_8 was still significant ($\chi^2[7 \text{ df}] = 27.5; P < .001$), although the chi-squared value was much reduced. The summary estimate of exposure response changed only slightly and was 1.13 at 150 Bq/m³ (95% CI = 1.0-1.3). The sign of the correlation coefficients suggested that studies with higher exposure-response estimates were those with lower coverage of the exposure-time window, mean number of residences, lower percentage of living case subjects, and lower percentage with 1-year radon measurements of houses and with higher percentage of smokers, higher percentage of females, higher inclusion of eligible subjects, higher measured residences per subject, and higher overall mean radon concentration.

Analyses of miner data indicate that the joint RR for smoking and radon progeny exposure is most likely intermediate between a multiplicative and additive association, although the joint association is consistent with a multiplicative relationship. This implies that RRs in nonsmokers should be greater than those in smokers. The New Jersey, Shenyang, Stockholm, Sweden, and Missouri studies either enrolled only nonsmokers or presented RRs by radon levels for nonsmokers; the studies included 61, 123, 38, 178, and 538 nonsmoking lung cancer case subjects, respectively. For nonsmokers in the five studies, fitted RRs at 150 Bq/m³ on the basis of model [1] were 0.97, 0.77, 8.51, 1.21, and 1.12, respectively. There were no significant trends with RR level, either for the individual studies or for the combined studies. The summary exposure-response estimate for nonsmokers gave an RR at 150 Bq/m³ of 1.18 (95% CI = 0.8-1.6), similar to the estimate for these five studies, 1.24 (95% CI = 1.0-1.5), when smoking was ignored. The summary estimate for nonsmokers should be viewed cautiously, since it was strongly influenced by results from a single study, the Stockholm study. In an influence analysis, the summary estimate dropped to 1.02 when the Stockholm study was omitted.

Discussion

In the meta-analysis, an increased RR was observed with greater radon level, and the summary exposure-response trend was statistically significant. In addition, the summary exposure-response estimate for the indoor studies was similar to extrapolations using miner-based models and similar to the exposure response fitted to RRs from miner studies, using data only from miners with low total cumulative exposure, less than 50 WLM. Thus, this analysis supports a deleterious effect of high indoor radon levels that is consistent with extrapolations of risk using miner-based models.

Although overall results showed a significant trend, results must be cautiously interpreted, since meta-analyses have known limitations (28-32). Although publication bias is unlikely to be a problem, data for the analysis are limited to published RRs and CIs. Indoor radon studies define an exposure-time window, usu-

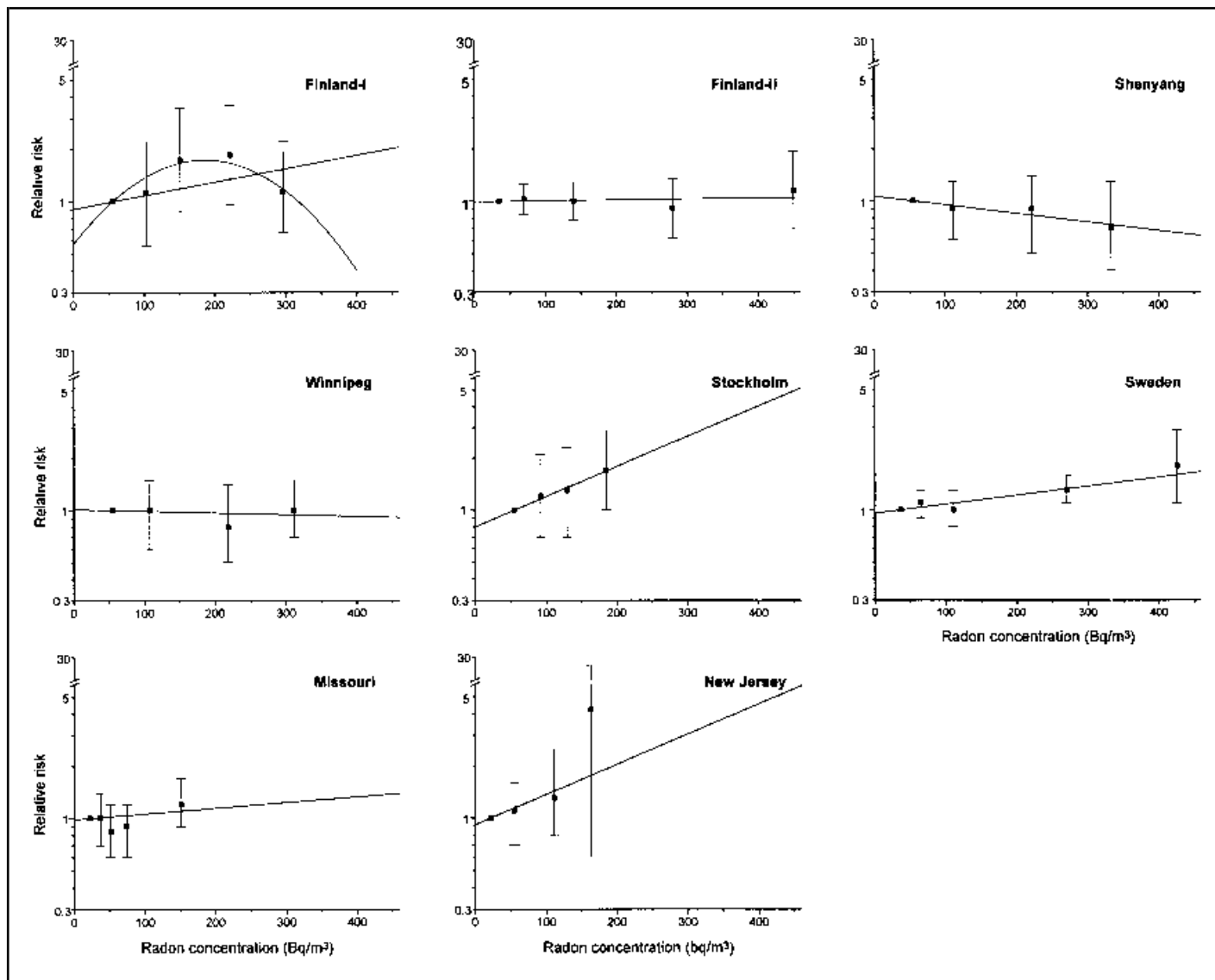


Fig. 2. Relative risks (RRs) for radon concentration categories and fitted exposure-response models for each case-control study. Fitted lines are adjusted to pass through the quantitative value for the baseline category. Models fit to the logarithm of the RRs are linear with respect to radon. There was a significant departure from linearity in the Finland-I data, and also shown is the model which is linear and quadratic with respect to radon.

ally 30-40 years prior to the subject's enrollment date, so that including a 5-year lag interval the relevant exposure period covers 25-35 years. Radon measurements in houses typically cover 60%-70% of the exposure window, and various methods are used to impute missing measurements. Improper imputation methods for residential gaps can introduce bias (33), but in a meta-analysis, it is not possible to evaluate imputation procedures. We also could not explore the robustness of RR trends by studying effects of choice of cut-points. The Missouri (15) and Stockholm (13) studies reported *P* values for tests for linear trend that sometimes differed markedly, depending on whether a continuous radon concentration or a category-specific mean was used as the quantitative score variable. With summary data, such sensitivity cannot be evaluated. Examinations of potential confounding variables or subtle variations of effects are also not possible, except for those presented in the original reports. Finally, some studies were of lung cancer incidence, while others were of lung cancer mortality, and different exposure windows

would exist for 5 years prior to incidence versus 5 years prior to death.

Studies of miners show that the exposure-response relationship for radon progeny exposure decreases with attained age, time since exposure occurred, and exposure rate or exposure duration and that the exposure response is larger in never-smokers than in smokers (4). These patterns could not be adequately evaluated in the meta-analysis, further suggesting a cautious interpretation of the result.

The combined data from the meta-analysis of indoor radon are consistent with extrapolations based on data from studies on underground miners. This is reassuring, since at one time it was suggested that residential radon exposure might be relatively more hazardous than radon exposure in mines because of a lower exposure rate (34,35). Studies of miners (4,34,36,37) have reported an inverse exposure-rate effect, i.e., for equal total exposure, lung cancer risk increased as exposure rate diminished and duration of exposure increased. However, for miners, the in-

Table 2. Estimates of the relative risk (RR) at 150 Bq/m³ and the 95% confidence interval (CI) for each study and for all studies combined

Study	RR*	95% CI	Reported in original paper†
Finland-I‡	1.30	1.09-1.55	NA
Finland-II	1.01	0.94-1.09	1.02
New Jersey	1.83	1.15-2.90	1.77
Shenyang	0.84	0.78-0.91	0.92§
Winnipeg	0.96	0.86-1.08	0.97
Stockholm	1.83	1.34-2.50	1.79
Sweden	1.20	1.13-1.27	1.15
Missouri	1.12	0.92-1.36	NA
Combined	1.14	1.01-1.30	

*Values shown are estimated RR at 150 Bq/m³, i.e., $\exp(b \times 150)$, where b was the estimate of β obtained from a weighted linear regression fitting the model $\log(\text{RR}) = \beta(x - x_0)$, where x_0 is the quantitative value for the lowest radon category and x is the category-specific radon level.

†RR at 150 Bq/m³, based on or computed from exposure-response relationship provided in original reports. Exposure response was not available (NA) in Finland-I and Missouri studies.

‡For Finland-I, there was a significant departure from linearity ($P = .03$). The estimated RR for 150 Bq/m³ under a linear-quadratic model was 1.71.

§Taken from results in pooled analysis (18).

||Combined estimate and CI based on a random effects model. Fixed effects estimate was 1.11 (95% CI = 1.07-1.15).

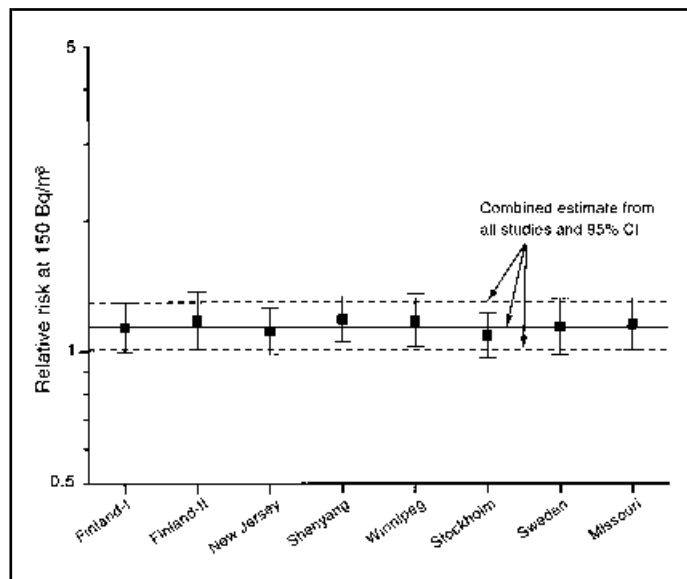


Fig. 4. Results of an influence analysis showing estimated summary relative risks and 95% confidence intervals (CIs) at 150 Bq/m³, computed by omitting each study in turn. Also shown is the summary estimate for all eight studies (solid line) and its 95% CI (dashed lines).

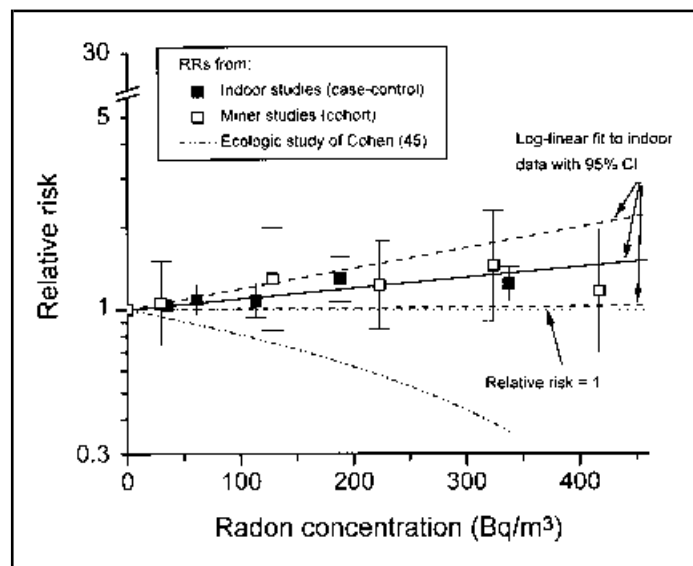


Fig. 3. Summary relative risks (RR) from the meta-analysis of indoor radon studies and RRs from the pooled analysis of underground miner studies, restricted to exposures under 50 Working Level Months (4). Also, included are a RR of 1, the fitted exposure response and its 95% confidence interval (CI) from the indoor radon studies, and the estimated linear RR based on the ecologic analysis by Cohen (47).

crease in the effectiveness of exposure, due to the inverse exposure-rate effect, diminished at total exposures below about 50-100 WLM (38,39). This diminution can be explained, since a cell cannot “experience” an exposure-rate effect if the probability of more than one traversal of a cell by an alpha particle is low (38).

There was significant heterogeneity in the exposure-response estimates, further suggesting a cautious interpretation of results. The Finland-I, New Jersey, Stockholm, and Sweden studies suggested positive exposure-response relationships, while no trends

were evident in the other four data sets. These differences could have arisen for many reasons, since the studies were carried out in many countries, source populations differed, and adjustment for important confounding factors may have been incomplete. For example, environmental pollution was likely severe in Shenyang, although results were similar within and across categories of an air pollution index (11). The apparent positive trend in the Stockholm data occurred only among residents of the city of Stockholm (13), while there was no trend with exposure among the women who resided outside of the city (40). Also, trends diminished when more weight was given to recent exposures, suggesting that RRs were heavily influenced by past exposures, contradicting results in miners. In the Missouri data, the trend in the RRs was greater when the interview respondent was the subject rather than a next-of-kin, suggesting possible recall bias. However, substantial recall bias seems unlikely, since radon exposure was based on physical measurements, and data suggested that the ability of surrogates to recall past residences was good (15). The Finland-I (7) and Stockholm (13) studies measured winter radon levels for 2 and 3 months, respectively, and comparability of the exposure-response estimates with other studies is uncertain.

As suggested by Greenland (29), we carried out an objective, although limited, comparison of studies, using data on quality-related factors abstracted from the published reports. None of the variables considered were significantly correlated with the results of the studies or explained the heterogeneity of the studies. Nevertheless, the direction of the correlations suggested some interesting possibilities, as well as some results that were counter-intuitive, that could be explored in future pooling of data. For example, improved exposure assessment and less exposure misclassification may result in less attenuation of the exposure response (41). This pattern is suggested by the positive correlation coefficients for the exposure-response estimates with the mean number of measured residences per subject and with the per-

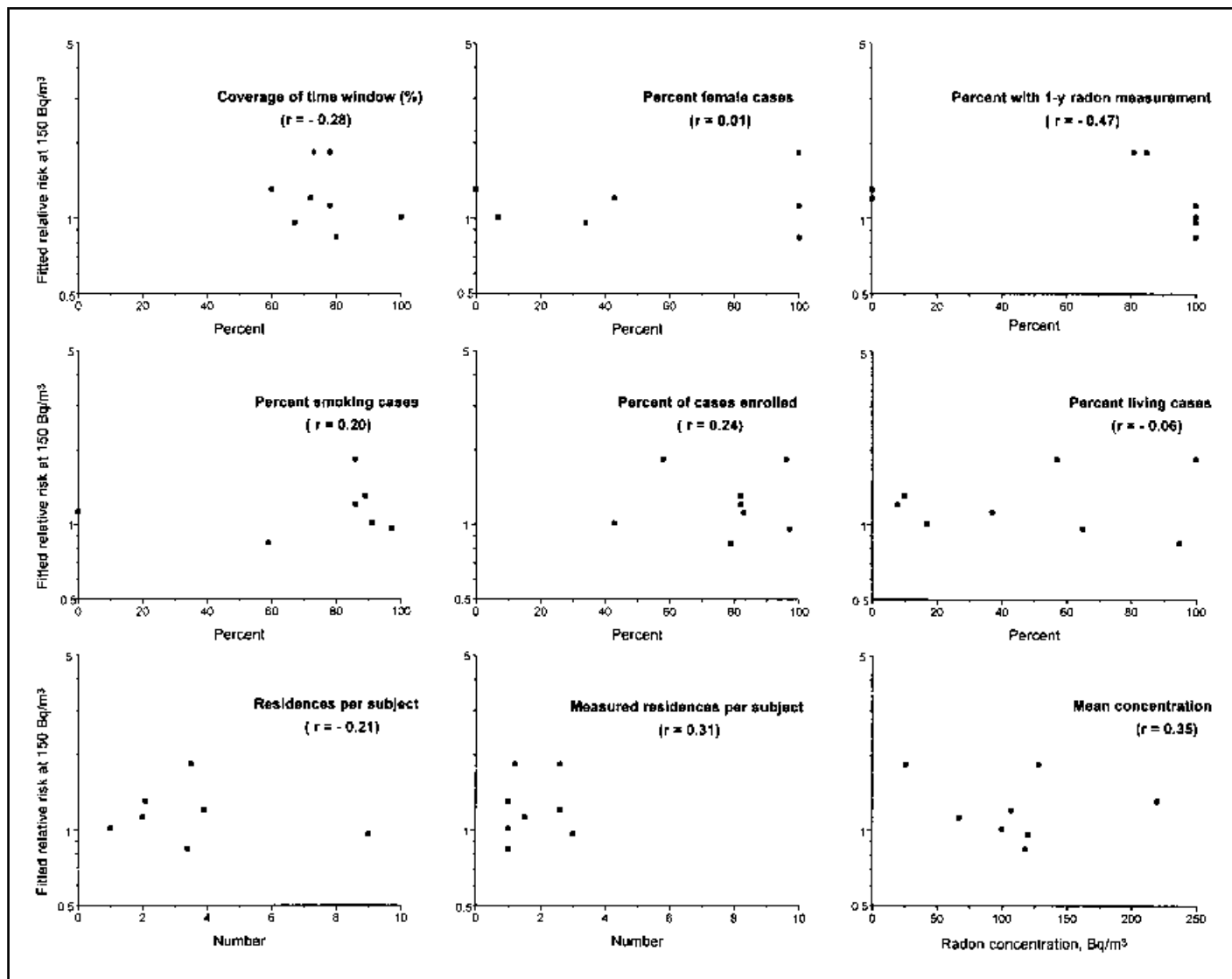


Fig. 5. Fitted relative risk estimates at 150 Bq/m³ and summary variables for each study of indoor radon and lung cancer, and the correlation coefficients (r).

centage of case subjects identified who were actually enrolled, and by the negative correlation coefficient for the number of residences per subject (the more residences, the greater potential for missing data and increased exposure misclassification). However, this pattern is not entirely consistent, because a greater percent coverage of the exposure-time window and percentage of subjects with 1-year measurements of radon would be expected to result in less exposure misclassification and therefore be positively correlated with exposure-response estimates, but negative correlations were observed for these variables. Finally, with the evidence of linearity at residential ranges of exposure, there is no obvious reason why the magnitude of the exposure-response estimate should be positively correlated with mean radon level.

Data from three of the studies considered in this meta-analysis, the New Jersey, Shenyang, and Stockholm studies, have been previously pooled and included nearly 1000 lung cancer cases (18). The study-specific estimates of RR (95% CI) at 150 per Bq/m³ were 1.7 (0.8-3.8), 0.9 (0.0-1.2), and 1.2 (0.8-2.4), respectively; the pooled exposure-response relationship was flat, with an RR estimate (95% CI) at 150 per Bq/m³ of 1.0 (0.8-1.3). In our meta-analysis, the study-specific RR estimates

at 150 Bq/m³ were 1.8 for New Jersey, 0.8 for Shenyang, and 1.8 for Stockholm, with a summary estimate of 1.1, and were within the range of estimates from the pooled analysis. The differences, although slight, were likely because of the different data that were used in the two analyses. Our meta-analysis relied on RRs and CIs from the published reports. In contrast, in the pooled analysis, original data were used, and to ensure comparability, definitions of the exposure-time window and cut points for the exposure categories were standardized, resulting in different numbers of case and control subjects than in the original reports.

Because radon data on individuals are obtained in case-control studies, they are intrinsically superior to ecologic studies, in which lung cancer rates are compared with summary measures of exposure using linear regression models. For example, with ecologic data, it is not known whether persons who die in a specific county actually lived there for a meaningful period of time, smoking histories are not known, and individual radon progeny exposure cannot be determined. As seen in surveys, radon levels in homes in the same geographic area can vary by several orders of magnitude (20,42), essentially negating the value of average county-wide estimates for individuals re-

siding in the county, when the age-adjusted disease rates are not a simple linear function of exposure.

Ecologic studies are used primarily as hypothesis-generating studies, because there are recognized limitations that can seriously compromise their validity (43-45). Results from ecologic studies of lung cancer and residential radon (46) have been mixed and offer limited insights into the consequences of residential radon effects. Unfortunately, a good deal of publicity has been given to the results of a large ecologic study (47), that found a negative exposure-response relationship between county lung cancer rates and county radon levels. Greenland and Robins (48) demonstrated how the inclusion of area level regressors variables, for example, smoking, may not entirely adjust for confounding at the level of the individual when the risk model is nonlinear and smoking effects are multiplicative, as is approximately the case with radon progeny exposure. An evaluation by Gilbert (49) supported the potential residual confounding by smoking, showing negative coefficients for the regression of disease rates for several smoking-related cancers, not including lung cancer, on radon concentration. The ecologic analysis by Cohen (47) fitted a linear model, which resulted in a declining linear excess RR trend of 0.002 per Bq/m³ (Fig. 3). Comparing the ecologic regression line to RRs from residential studies and from miner studies, it is clear that the negative exposure response is contradicted by both the miner data and by indoor radon studies.

In summary, there was a significant exposure-response relationship in the current analysis with an estimated RR at 150 Bq/m³ of 1.14, and results were generally confirmatory of miner-based extrapolations of risk. However, meta-analyses are known to have numerous limitations, including an inability to explore adequately the consistency of results within and between studies and to control for potentially important confounding factors. Thus, results should be interpreted cautiously, until additional studies are reported and the pooling of original data from multiple studies is completed. Nonetheless, our results are consistent with a small effect on lung cancer associated with exposure to indoor radon progeny.

Appendix

Model [1] was fit to each study, and an estimate of β_i , denoted b_i , was obtained. Under a fixed effects model, the true β is considered fixed and the same for all studies. A summary estimate is computed as a weighted mean of the study-specific estimates, with weights w_i , the inverse variance of the b_i . The summary estimate is

$$b = \sum w_i b_i / \sum w_i$$

The summary RR, relative to zero radon level, is $RR(x;0) = \exp(\beta x)$, with β estimated by b . Since the studies, and therefore the b_i , are independent, the fixed effects variance of b is $1/\sum w_i$.

In the analysis, however, we use a random effects approach, in which the exposure-response parameter is assumed to be a radon variable. We assume that β_1, \dots, β_8 is an independent sample from a normal distribution with mean β and variance τ^2 , denoted $\beta_i \sim N(\beta, \tau^2)$, and that each study-specific b_i is normally distributed with mean β_i and variance $1/w_i$, $b_i \sim N(\beta_i, 1/w_i)$

(24,25). Marginally, $b_i \sim N(\beta, 1/w_i + \tau^2)$. The variance of the summary estimate b is

$$\begin{aligned} \text{var}(b) &= \frac{\sum w_i^2 \text{var}(b_i)}{(\sum w_i)^2} \\ &= \frac{\sum w_i^2 (1/w_i + \tau^2)}{(\sum w_i)^2} \\ &= \frac{1}{\sum w_i} + \frac{\tau^2 \sum w_i^2}{(\sum w_i)^2} \end{aligned}$$

An estimate of τ^2 is obtained from the expression

$$\tau^2 = (Q - k + 1) / [\sum w_i - (\sum w_i^2) / \sum w_i],$$

where Q is the test statistic for the test of homogeneity (25). The variance estimate is the sum of two terms, the sampling variation within study, and the variation between studies. An updated summary estimate based on the $1/w_i + \tau^2 = 1/w_i^*$ for the variance of b_i is used, namely,

$$b^* = \sum w_i^* b_i / \sum w_i^*$$

with variance $1/\sum w_i^*$.

In the meta-analysis, $\text{var}(b^*) = 0.0006 + 0.0032$, where the first term is the within-study variance and the second term is the between-study variance. The result suggests substantial between-study variability.

References

- (1) Lubin JH, Boice JD Jr, Edling C, Hornung RW, Howe G, Kunz E, et al. Lung cancer and radon: a joint analysis of 11 underground miner studies. Bethesda (MD): National Cancer Institute, 1994: DHS Publ No. (NIH)94-3644.
- (2) US Environmental Protection Agency. Technical support document for the 1992 citizen's guide to radon. EPA 400-R-92-011. May 1992.
- (3) National Research Council. Comparative dosimetry of radon in mines and homes. Washington (DC): National Academy Press, 1991.
- (4) Lubin JH, Boice JD Jr, Edling C, Hornung RW, Howe GR, Kunz E, et al. Lung cancer in radon-exposed miners and estimation of risk from indoor exposure. J Natl Cancer Inst 1995;87:817-27.
- (5) Abelson PH. Mineral dusts and radon in uranium mines [editorial] [see comment citation in Medline]. Science 1991;254:777.
- (6) Cole LA. Elements of risk: the politics of radon. Washington (DC): AAAS Press, 1993.
- (7) Ruosteenoja E. Indoor radon and risk of lung cancer: an epidemiological study in Finland [dissertation]. Department of Public Health, University of Tampere, 1991, Finnish Government Printing Centre, Helsinki.
- (8) Auvinen A, Makelainen I, Hakama M, Castren O, Pukkala E, Reisbacka H, et al. Indoor radon exposure and the risk of lung cancer: a nested case-control study in Finland. J Natl Cancer Inst 1996;88:966-72.
- (9) Schoenberg JB, Klotz JB, Wilcox GP, Gil-del-Real MT, Stenmagen A, Mason TJ. Case-control study of residential radon and lung cancer among New Jersey women. Cancer Res 1990;50:6520-4.
- (10) Schoenberg JB, Klotz JB, Wilcox HB, Szmancias SF. A case-control study of radon and lung cancer in New Jersey women. In: Cross FT, editor. Proceedings of the 29th Hanford Symposium: Indoor Radon and Lung Cancer: Reality or Myth? Part 2. Columbus (OH): Battelle Press, 1992:905-17.
- (11) Blot WJ, Xu ZY, Boice JD Jr, Zhao DZ, Stone BJ, Sun J, et al. Indoor radon and lung cancer in China [see comment citation in Medline]. J Natl Cancer Inst 1990;82:1025-30.
- (12) Letourneau EG, Krewski D, Choi NW, Goddard MJ, McGregor RG, Zielinski JM, et al. Case-control study of residential radon and lung cancer in

- Winnipeg, Manitoba, Canada [see comment citations in Medline]. *Am J Epidemiol* 1994;140:310-22.
- (13) Pershagen G, Liang ZH, Hrubec Z, Svensson C, Boice JD Jr. Residential radon exposure and lung cancer in Swedish women. *Health Phys* 1992;63:179-86.
- (14) Pershagen G, Akerblom G, Axelson O, Clavensjo B, Damber L, Desai G, et al. Residential radon exposure and lung cancer in Sweden [see comment citations in Medline]. *N Engl J Med* 1994;330:159-64.
- (15) Alavanja MC, Brownson RC, Lubin JH, Berger E, Chang J, Boice JD Jr. Residential radon exposure and lung cancer among nonsmoking women [see comment citation in Medline]. *J Natl Cancer Inst* 1994;86:1829-37.
- (16) Lubin JH. Lung cancer and exposure to residential radon [see comment citation in Medline]. *Am J Epidemiol* 1994;140:323-32.
- (17) Samet JM. Indoor radon and lung cancer: risky or not? [editorial] [see comment citation in Medline]. *J Natl Cancer Inst* 1994;86:1813-4.
- (18) Lubin JH, Liang Z, Hrubec Z, Pershagen G, Schoenberg JB, Blot WJ, et al. Radon exposure in residences and lung cancer among women: combined analysis of three studies. *Cancer Causes Control* 1994;5:114-28.
- (19) National Research Council, Committee on the Biological Effects of Ionizing Radiation. Health effects of radon and other internally deposited alpha-emitters: BEIR IV. Washington (DC): National Academy Press, 1988.
- (20) Marcinowski F, Lucas RM, Yeager WM. National and regional distributions of airborne radon concentrations in U.S. homes. *Health Phys* 1994;66:699-706.
- (21) Lubin JH, Boice JD Jr, Samet JM. Errors in exposure assessment, statistical power and the interpretation of residential radon studies. *Radiat Res* 1995;144:329-41.
- (22) Samet JM. Pooling of data from radon investigations. *Radiat Res Notes* 1995;16:1-2.
- (23) Draper NR, Smith H. Applied regression analysis. New York: John Wiley & Sons, 1966.
- (24) Laird NM, Mosteller F. Some statistical methods for combining experimental results. *Int J Technol Assess Health Care* 1990;6:5-30.
- (25) Whitehead A, Whitehead J. A general parametric approach to the meta-analysis of randomized clinical trials. *Stat Med* 1991;10:1665-77.
- (26) Moolgavkar SH, Venzon DJ. Confidence regions for case-control and survival studies with general relative risk functions. In: Moolgavkar S, Prentice RL, editors. *Modern statistical methods in chronic disease epidemiology*. Society for industrial and applied mathematics. New York: John Wiley & Sons, 1986:104-20.
- (27) Prentice RL, Mason MW. On the application of linear relative risk regression models. *Biometrics* 1986;42:109-20.
- (28) Greenland S. Quantitative methods in the review of epidemiologic literature. *Epidemiol Rev* 1987;9:1-30.
- (29) Greenland S. Can meta-analysis be salvaged? [see comment citation in Medline]. *Am J Epidemiol* 1994;140:783-7.
- (30) Oakes M. On meta-analysis. In: *Statistical inference*. Chestnut Hill (MA): Epidemiology Resources Inc, 1990:157-63.
- (31) Pettiti DB. Of babies and bathwater [see comment citation in Medline]. *Am J Epidemiol* 1994;140:779-82.
- (32) Shapiro S. Meta-analysis/Shmeta-analysis [see comment citation in Medline]. *Am J Epidemiol* 1994;140:771-8.
- (33) Weinberg CR, Moledor ES, Umbach DM, Sandler D. Imputation for exposure histories with gaps. *Epidemiology* 1996;7:490-7.
- (34) Darby SC, Doll R. Radiation and exposure rate [letter]. *Nature* 1990;344:824.
- (35) Puskin JS. The inverse dose-rate effect and the extrapolation of radon risk estimates from exposures of miners to low-level exposures in homes [letter] [see comment citation in Medline]. *Radiat Res* 1994;138:143-5.
- (36) Hornung RW, Meinhardt TJ. Quantitative risk assessment of lung cancer in U.S. uranium miners. *Health Phys* 1987;52:417-30.
- (37) Sevc J, Kunz E, Tomasek L, Placek V, Horacek J. Cancer in man after exposure to Rn daughters. *Health Phys* 1988;54:27-46.
- (38) Brenner DJ. The significance of dose rate in assessing the hazards of domestic radon exposure. *Health Phys* 1994;67:76-9.
- (39) Lubin JH, Boice JD Jr, Edling C, Hornung RW, Howe G, Kunz E, et al. Radon-exposed underground miners and inverse dose-rate (protraction enhancement) effects. *Health Phys* 1995;69:494-500.
- (40) Lagarde F. Statistical aspects of the influence of indoor radon exposure and smoking on the risk of lung cancer. Institute of Actuarial Mathematics and Mathematical Statistics, Report No. B:21. Stockholm: University of Stockholm, 1992.
- (41) Pierce DA, Stram DO, Vaeth M. Allowing for random errors in radiation dose estimates for the atomic bomb survivor data. *Radiat Res* 1990;123:275-84.
- (42) White SB, Bergsten JW, Alexander BV, Rodman NF, Phillips JL. Indoor ²²²Rn concentrations in a probability sample of 43,000 houses across 30 states. *Health Phys* 1992;62:41-50.
- (43) Brenner H, Savitz DA, Jockel KH, Greenland S. Effects of nondifferential exposure misclassification in ecologic studies. *Am J Epidemiol* 1992;135:85-95.
- (44) Greenland S. Divergent biases in ecologic and individual-level studies [see comment citations in Medline]. *Stat Med* 1992;11:1209-23.
- (45) Piantadosi S, Byar DP, Green SB. The ecologic fallacy. *Am J Epidemiol* 1988;127:893-904.
- (46) Stidley CA, Samet JM. A review of ecologic studies of lung cancer and indoor radon [see comment citation in Medline]. *Health Phys* 1993;65:234-51.
- (47) Cohen BL. Test of the linear-no threshold theory of radiation carcinogenesis for inhaled radon decay products [see comment citation in Medline]. *Health Phys* 1995;68:157-74.
- (48) Greenland S, Robins J. Invited commentary: ecologic studies—biases, misconceptions, and counterexamples [see comment citations in Medline]. *Am J Epidemiol* 1994;139:747-60.
- (49) Gilbert ES. Smoking as an explanation for the negative relationship between exposure to radon and certain types of cancer [letter] [see comment citation in Medline]. *Health Phys* 1994;67:197-8.

Notes

¹One Working Level (WL) equals any combination of radon progeny in 1 L of air, which results in the ultimate emission of 130 000 MeV of energy from alpha particles. WLM is a time-integrated exposure measure and is the product of time, in units of working months, which is taken to be 170 hours, and WL. In terms of SI units, 1 WLM corresponds to $2.08 \times 10^{-5} \text{ (J m}^{-3}\text{)} \times 170 \text{ hours} = 3.5 \times 10^{-3} \text{ J h m}^{-3}$ (3).

We thank Dr. Jonathan Samet and Ms. Ruth Kleinerman for useful discussions on these and related topics. We also thank Drs. Christer Edling, Richard Hornung, Geoffery Howe, Emil Kunz, Robert Kusiak, Howard Morrison, Edward Radford, Margot Tirmache, Ladislav Tomasek, Alistair Woodward, and Shu Xiang Yao for their collaboration in the analyses of the pooled miner data.

Manuscript received June 4, 1996; revised September 5, 1996; accepted September 27, 1996.