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# AN OVERVIEW OF THE NORTH AMERICAN RESIDENTIAL RADON AND LUNG CANCER CASE-CONTROL STUDIES

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Ernest G. Létourneau and Janet B. Schoenberg are retired; Jan A. Stolwijk has emeritus status.

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*Lung cancer has held the distinction as the most common cancer type worldwide since 1985 (Parkin et al., 1993). Recent estimates suggest that lung cancer accounted for 1.2 million deaths worldwide in 2002, which represents 17.6% of the global cancer deaths (Parkin et al., 2005). During 2002, the highest lung cancer rates for men worldwide reportedly occurred in North America and Eastern Europe, whereas the highest rates in females occurred in North America and Northern Europe (Parkin et al., 2005). While tobacco smoking is the leading risk factor for lung cancer, because of the magnitude of lung cancer mortality, even secondary causes of lung cancer present a major public health concern (Field, 2001). Extrapolations from epidemiologic studies of radon-exposed miners project that approximately 18,600 lung cancer deaths per year (range 3000 to 41,000) in the United States alone are attributable to residential radon progeny exposure (National Research Council, 1999). Because of differences between the mines and the home environment, as well as differences (such as breathing rates) between miners and the general public, there was a need to directly evaluate effects of radon in homes. Seven major residential case-control radon studies have been conducted in North America to directly examine the association between prolonged radon progeny (radon) exposure and lung cancer. Six of the studies were performed in the United States including studies in New Jersey, Missouri (two studies), Iowa, and the combined states study (Connecticut, Utah, and southern Idaho). The seventh study was performed in Winnipeg, Manitoba, Canada. The residential case-control studies performed in the United States were previously reviewed elsewhere (Field, 2001). The goal of this review is to provide additional details regarding the methodologies and findings for the individual studies. Radon concentration units presented in this review adhere to the types (pCi/L or Bq/$m^3$) presented in the individual studies. One picocurie per liter is equivalent to 37 Bq/$m^3$. Because the Iowa study calculated actual measures of exposure (concentration × time), its exposures estimates are presented in the form $WLM_{5–19}$ (Field et al., 2000a). $WLM_{5–19}$ represents the working level months for exposures that occurred 5–19 yr prior to diagnosis for cases or time of interview for control. Eleven $WLM_{5–19}$ is approximately equivalent to an average residential radon exposure of 4 pCi/L for 15 yr, assuming a 70% home occupancy.*

## SUMMARIES OF INDIVIDUAL CASE-CONTROL STUDIES

### New Jersey (NJSDH, 1989; Schoenberg et al., 1990, 1992)

The New Jersey study of indoor radon exposure and lung cancer risk was restricted to women and spanned the period 1982–1984. Year-long alpha-track detector measurements of radon were used and extensive data on smoking, occupation, and diet were collected. A larger population-based study of lung cancer had been ongoing for at least 10 yr, from which 433 New Jersey female lung cancer cases and 402 controls were selected for an initial analysis (NJSDH, 1989; Schoenberg et al., 1990). Population controls were selected from three sources depending on the vital status and age of the case: driver license (<65 yr) or health care files (65 yr +) for controls of directly interviewed cases, and death certificates for controls of proxy-interviewed cases. Live cases were frequency-matched to live controls on age and race; deceased cases were frequency matched to deceased controls on age, race, and nearest date of death.

The analysis was limited to those for whom both interview and home monitoring data were available, and included 31% (433) of the eligible cases and 27% (402) of the eligible controls; the possibility of selection bias was one of several author-cited limitations. Due to budget limitations for the initial

analysis, year-long radon measurements were limited to the most recent New Jersey residence of minimum 10 yr duration in the period 5 to 30 yr prior to ascertainment. Covariates included several active-smoking related variables, age (in three categories), education (three levels), "race" (dichotomous), county of residence, occupation (as a dichotomous variable), vegetable consumption (three categories), and source of information (direct versus proxy respondent).

Adjusted odds ratios were 1.1 (90% CI 0.79–1.7), 1.3 (90% CI 0.62–2.9), and 4.2 (90% CI 0.99–17.5) for exposure of 1.0–1.9, 2.0–3.9, and 4.0–11.3 pCi/L, respectively, relative to exposures of less than 1.0 pCi/L, showing a significant trend (one-sided $p = .04$) with increasing radon concentration. The trend was strongest among light smokers (less than 15 cigarettes/day, one-sided $p = .01$). The trend for lung cancer risk with estimated cumulative radon exposure was slightly weaker (one-sided $p = .09$). The increase in relative risk for each unit of cumulative exposure, 3.4% (90% CI 0.0–8.0%) per working level month, was consistent with the range of 0.5–4.0% per working level month generally reported for underground miner studies, supporting the extrapolation of the occupational data to the residential setting. However, the possibility of selection biases, the small number of high exposures, and other uncertainties necessitate caution in the interpretation of these data.

The final analysis of the New Jersey study (Schoenberg et al., 1992) relaxed the eligibility criteria to include all subjects for whom home radon measurements or estimates were available for a minimum of 9 yr over the 25-yr ETW. The latter modification increased the number of studied subjects in final analysis to 922 (480 cases and 442 controls) from 835 (433 cases and 402 controls) in the initial analysis, but did not substantively change the study results or their interpretation in relation to radon-related lung-cancer risk.

### Winnipeg (Létourneau et al., 1994, 1995)

A case-control study of lung cancer in Winnipeg, Manitoba, Canada, was conducted during the period 1983–1990. This investigation involved both males and females:738 individuals with histologically confirmed lung cancer cases (aged 35 to 80 yr) diagnosed between 1983 and 1990 were identified from the Manitoba Cancer Registry and individually matched by age (±5 yr) and sex with potential controls identified by random selection from the Winnipeg telephone directory. Alpha-track radon detectors were placed in all residences in which the study subjects had reported living within the Winnipeg metropolitan area for at least 1 yr. Radon dosimetry was carried out by means of two 6-mo integrated alpha-track measurements averaged to provide a 1-yr measurement. In the homes monitored, the average level of radon-222 was about 120 $Bq/m^3$ in the bedroom area and 200 $Bq/m^3$ in the basement. Although the numbers of nonrespondents to initial contact was unrecorded during recruitment of controls, 97% of those interviewed were retained in the analysis. Of the 1400 cases eligible, 53% were included; reasons for case exclusion were limited to illness of the patient, refusal of the proxy, lack of

permission by the physician, and inability to trace the patient. Year-long radon measurements were sought in all Winnipeg metropolitan area residences in which subjects had reported living for at least 1 yr during the exposure period 5–30 yr prior to recruitment. One-third of reported residences were actually assessed. On average, study subjects experienced a cumulative radon exposure of about 3520 $Bq/m^3$-yr in the living area of their homes during the period 3–30 yr before enrolment in the study. Covariates included age (six categories), active cigarette smoking (ever smoking, age at start, duration, daily and pack-years), occupational exposures (three indicator variables each for job and substances), education (two categories), and country of birth (five categories). After adjusting for cigarette smoking and education, the odds ratios increased markedly with the duration of smoking, the number of packs of cigarettes smoked per day, and the cumulative amount smoked, and decreased with the age at which smoking began.

Odds ratios for the four categories of radon dose relative to the lowest radon dose category in homes were calculated. No increase in the relative risk for any of the histologic types of lung cancer observed among the cases was detected in relation to cumulative exposure to radon ($p > .05$), nor was there any evidence of an increasing trend in the odds ratios as radon exposure increased. In general, the odds ratios for the subset of participants for whom radon measurements were available for a minimum of 75% of the observation period appear to be more consistent with the null hypothesis of no radon effect than those for the full data set. A similar analysis was carried out for the four histologic types of lung cancer observed in this study. None of the odds ratios computed for these histologic subgroups was significantly different from 1.0.

**Missouri-I (Alavanja et al., 1994)**

This population-based, case-control study of incident lung cancer was conducted in Missouri between 1986 and 1992. In total, 538 primary lung cancer cases were identified from those reported to the Missouri cancer registry between June 1, 1986, and June 1, 1991, having been diagnosed between 1986 and 1992; 1183 controls, frequency matched to controls (to a tolerance of 5 yr), were identified during an unspecified time interval from one of two sources depending on case age: the driver's license files (for the 30–64 yr age group) and Health Care Financing Administration Medicare listings (for the 65–84 yr age group). As a proportion of those "eligible," 83% of cases and 78% of controls were included in the analysis. Year-long radon measurements were attempted in at least 1 home that the subjects had occupied during the exposure period 5–30 yr preceding recruitment. Radon measurements covered 78% of the relevant residential period, and women reported being indoors for 84% of this time. Covariates included age, marital status (six categories), active smoking (previous smoking, years since cessation, and pack-years), passive smoking (five levels), preexisting nonmalignant lung disease (dichotomous), education (three categories plus "unknown"), saturated fat intake (quintiles of kilocalorie intake), and source of information (direct versus

proxy). The time-weighted average radon concentrations were exactly the same for case subjects and control subjects (1.8 pCi/L). Radon levels exceeding 4 pCi/L were experienced by 6.5% of the cases and 6.8% of the controls. For all data combined, there was little evidence for a trend of lung cancer with increasing radon concentrations (two-tailed trend test, $p = .99$ continuous data analysis; $p = .19$ categorical data analysis). A positive dose-response trend was suggested for the adenocarcinoma cell type and among directly interviewed women (two-tailed trend test; $p = .31$ continuous data analysis; $p = .04$ categorical data analysis), but not for other histologies or among those who had surrogate interviews. In conclusion, the possibility of detecting a risk from indoor radon in this study was maximized by (a) including a large number of nonsmoking women with high indoor occupancy, (b) conducting a large number of radon measurements near the time of the diagnosis of cancer, and (c) controlling for known causes of lung cancer. However, in contrast with the Iowa Study, an association between lung cancer and the exposure to domestic levels of radon was not convincingly demonstrated. It was concluded therefore that the magnitude of the lung cancer risk from radon levels commonly found in U.S. dwellings appeared low.

**Missouri-II (Alavanja et al., 1999)**

Using two radon dosimetry techniques (annual time-weighted average exposure and the surface monitors), this case-control study, carried out between January 1993 and January 1994, described both standard year-long indoor air radon measurements and measurements with CR-39 alpha-particle detectors (called surface monitors and made from an alpha-sensitive material, polyallydiglycol carbonate), which directly assess long-term (20 yr and more) cumulative exposure by analyzing glass objects in the home. A total of 783 women of White, Black, and other ethnic origins were reported to the Missouri Cancer Registry with lung cancer. The subjects were divided into four categories with respect to smoking (never smoked, former smokers, current light to moderate smokers, and heavy smokers). Five hundred and forty-six control cases were selected randomly and matched to case patients by 5-yr age groups. Both patients and controls completed a control interview and had comprehensive radon dosimetry (i.e., 70% of the previous 25 yr accounted for by air monitors, surface monitors, or both). Multivariate logistic regression models were used to adjust for potential confounding by age, education, previous lung disease, pack-years of smoking, and vegetable intake. Wald confidence intervals were computed on the basis of estimated parameter, beta, and its standard error. Trends in the logistic analysis were evaluated with a score test in which the continuous radon concentration and the mean value within categories were used as the quantitative values for exposure.

The results demonstrated odds ratios of lung cancer among women exposed to higher radon categories—20-yr time-weighted average radon concentrations of 37 to 73, 74 to 147, and 148 Bq/m$^3$ or higher—of 1.11, 1.32, and 3.33, respectively, with reference to women exposed to less than 37 Bq/m$^3$.

A statistically significant exposure-response trend ($p = .02$, continuous exposure variable) was observed. Subjects who did not have a history of previous lung disease had a significantly greater risk from residential radon exposure than those who had such a history (i.e., the $p$ value for homogeneity of trends was .05). There was also significant heterogeneity of radon risk associated with vegetable consumption.

Among women who occupied homes with complete glass-based surface monitor dosimetry during the previous 25 yr, a dose-response trend was observed: (With reference to radon levels below 37 Bq/m$^3$, odds ratios for exposure categories of 37–73, 74–147, and 148 Bq/m$^3$ and higher, were 1.18, 1.39, and 4.29, respectively, with a statistically significant trend ($p = .02$). The slope of the overall dose-response trend was similar to the slope within each cell type (i.e., adenocarcinoma, small-cell carcinoma, squamous carcinoma, and other cell types).

Using traditional radon gas measurements, the relative risk of lung cancer among women exposed to the highest category as compared to the lowest category of radon exposure (<37 Bq/m$^3$) was 0.71 (95% CI 0.3, 1.3), and the $p$ value for trend was not significant. Similar patterns of odds ratios were observed for subjects stratified by age, educational level, previous lung disease, and smoking status. However, among individuals who consumed seven or more servings of vegetables per week, the lung cancer risk rose with radon exposure and the gradient of risk was significantly different than for those who consumed fewer vegetables. A positive dose-response gradient of lung cancer risk was observed with increasing radon exposure among heavy smokers, but the number of cases in each strata was relatively small, and the pattern of risk in heavy smokers was not statistically different from that in light to moderate smokers or those who had never smoked.

**Iowa (Field et al., 2000a, 2000b)**

The Iowa Radon Lung Cancer Study was a population-based, case-control epidemiologic study performed in the state of Iowa (United States) during the period 1993 to 1999. The Iowa Radon Lung Cancer Study had several strengths: (1) An expert independent pathology review was performed for 96% of the cases (Field et al., 2004), (2) the study was carried out in the state with the highest mean screening radon concentrations in the United States, (3) the high radon concentrations in conjunction with a strict quality assurance protocol (Field et al., 1998a) contributed to accurate and precise radon gas and progeny measurements, (4) the study's criterion requiring occupancy in the current home for at least the last 20 yr eliminated the need to impute radon measurements from missing homes, (5) the linkage between radon measurements and retrospective participant mobility, both inside and outside the home, allowed for a refined exposure estimate, and (6) Iowa has a high-quality, National Cancer Institute-supported Surveillance, Epidemiology, and End Results (SEER) registry for cancer reporting, which allowed initial contact via a rapid-reporting mechanism yielding a high percentage (69%) of living

cases. An important feature of this study was its enhanced dosimetry, including retrospective mobility assessment, measurements in multiple rooms of each house, and radon measurements outdoors and in work areas. The Iowa study also used both traditional alpha-track detectors to measure contemporary radon gas and a novel glass-based retrospective radon gas and progeny detector. Investigators enrolled a total of 413 lung cancer cases among female Iowa residents who had occupied their current home for at least 20 yr and 614 age-frequency-matched controls.

The odds ratio for lung cancer in women who had smoked at least 100 cigarettes or who had smoked for a period of at least 6 mo in their lifetimes versus women who never smoked was 13.2 (95% CI 9.5–18.3). In addition, ORs of 8.1 (95% CI 5.6–11.7) and 29.0 (95% CI 19.1–43.9) were observed in light and heavy smokers (defined as below or above a median pack-year rate of 208.2 pack-years), respectively, compared with never smokers. Pack-year rate was defined as the average number of packs smoked per year from birth until 5 yr prior to study enrollment (assumed latency period for lung cancer) for controls or lung cancer diagnosis for cases. After adjustment for age, smoking (duration and intensity), and education, there was a statistically significant positive trend ($p = .05$) in lung cancer risk with increasing categories of cumulative radon gas exposure. Analyses restricted to the 283 live cases and 614 living controls demonstrated both strong categorical ($p = .01$) and continuous ($p = .03$) trends. For 15–yr cumulative radon exposure at 11 $WLM_{5–19}$ (roughly equaling 15 yr of residential exposure at 148 $Bq/m^3$), excess odds of 0.24 (95% CI –0.05–0.92) and 0.50 (95% CI 0.004–1.81) were calculated for all cases using continuous and categorical exposure variables, respectively. Higher excess odds of 0.49 (95% CI 0.03–1.84) and 0.83 (95% CI 0.11–3.34) were noted per 11 $WLM_{5–19}$ for the subset of live cases for the continuous and categorical risk estimates, respectively.

There was no evidence of heterogeneity for age, education, and smoking status using either continuous or categorical analyses. Large-cell carcinoma exhibited a statistically significant trend for both the continuous ($p = .04$) and categorical ($p = .03$) risk estimates. A suggestive dose-response trend was also observed for the squamous cell carcinoma subset (categorical $p$ for trend = .06) with a significant categorical risk estimate of 3.17 (95% CI 1.08–10.06) for the highest exposure category. However, the differences in the linear excess odds between histologic types were not statistically significant (continuous $p = .58$, categorical $p = .65$).

The Iowa findings suggest that the ability to detect an association between cumulative radon exposure and lung cancer requires both a rigorously designed study minimizing radon exposure misclassification (Field et al., 2002) and a study location with relatively high radon concentrations. Overall, the risk estimates obtained in this study suggested that prolonged cumulative radon progeny exposure in the residential environment is significantly associated with lung cancer risk. Furthermore, these risk estimates are in general agreement with the National Research Council's predicted lung cancer risk associated with indoor radon exposure.

### Connecticut/Utah/Southern Idaho (Sandler et al., This Issue)

Cases aged 40–79 yr with incident-confirmed lung cancer were identified through cancer registries and medical record review. Based on a screening telephone interview, all cases who had never smoked (never smokers) or who had not smoked for at least 10 yr (nonsmokers) and a random sample of others were selected for study. Persons who smoked cigars or pipes, but not cigarettes, were excluded. Controls were selected using randomized recruitment (Weinberg & Sandler, 1991) to achieve a sample that was effectively matched on smoking status 10 yr prior to interview, age, and sex, but without the resulting analytical limitation of matching. They were identified through random telephone screening and listings of Medicare recipients provided by the Health Care Finance Administration (HCFA) (for controls aged 65 yr or older in Utah/southern Idaho). In total, 1474 cases (963 in Connecticut and 511 in Utah/southern Idaho) and 1811 controls (949 in Connecticut and 862 in Utah/southern Idaho) completed the study. Only 9% of the cases and 14% of the controls had never smoked. Nearly all (>97%) of the study subjects were White. Overall 57% of the case and control subjects were males.

Radon measurements were performed on multiple levels of past and current homes. The mean radon concentrations were lover than anticipated, with median values of 23 Bq/$m^3$ in Connecticut and 45 Bq/$m^3$ in Utah/southern Idaho. Radon values from measured control homes, information about the residence, and external factors were used to identify factors that predicted measured radon levels. These factors were in turn used to define informative strata to "impute" radon values for similar homes that could not be measured. Regression trees were constructed separately for Connecticut and Utah/southern Idaho using measured control homes to identify categories of residences that were similar in their radon concentration. Predictors used in constructing the tree included the relative (to ground) position of the index level, housing characteristics, and geological characteristics (e.g., altitude, groundwater radon, soil permeability, atmospheric radiation) obtained by linking geocoded study residences to available geographic databases. An index level radon value for each unmeasured home was imputed from the mean radon value for all measured control homes in the appropriate stratum identified from the tree. Time-weighted average radon concentrations took into account time spent on each level of a home as well as the number of years of residence in each home.

Overall, there was no statistically significant association between the estimated time-weighted average radon concentration within the 20-yr time window (5–25 yr prior to diagnosis or interview) and lung cancer risk. The excess relative risk (ERR) associated with a 100-Bq/$m^3$ increase in radon concentration was 0.002 (95% CI –0.21, 0.21) in the overall population, 0.134 (95% CI –0.23, 0.50) in Connecticut and –0.112 (95% CI –0.34, 0.11) in Utah/Idaho. Higher ERRs were noted for some subgroups less prone to misclassification. Nonetheless, there was no group with a statistically significant linear increase in risk.

## COMPARISON OF ATTRIBUTES OF THE CASE-CONTROL STUDIES

This review highlights some of the major components and findings of the seven major North American case-control residential radon studies conducted to date. The major papers detailing each of the seven studies described in this article are: New Jersey (NJSDH, 1989; Schoenberg et al., 1989a; Schoenberg et al., 1992), Winnipeg (Létourneau et al., 1994), Missouri-I (Alavanja et al., 1994), Missouri-II (Alavanja et al., 1999), Iowa (Field et al., 2000a), Connecticut (Sandler et al., this issue), and Utah/southern Idaho (Sandler et al., this issue). In addition to the seven included studies, a smaller independent residential radon case-control study has been performed in Worcester, MA (Shalat et al., 2000a, 2000b). Since neither the study methodology nor findings of this smaller case-control study have been published, it has not been included herein. The New Jersey study was the first of its kind to be conducted either in the United States or Canada. The last of the seven studies included residential case-control studies conducted in Connecticut and in Utah/southern Idaho.

### Study Subject Selection

Study subject selection for each of the seven studies is detailed in Table 1. With respect to case selection, all studies used state or provincial cancer registries. The Connecticut, Utah/southern Idaho studies supplemented case ascertainment through a rapid-reporting system in each state and by a review of medical records. The New Jersey study identified cases through a rapid-reporting system with hospital pathology departments, pathology records, and death certificate files as well as the state registry. Three of the studies (Connecticut, Utah/southern Idaho, and Winnipeg) identified controls randomly by telephone. In the Iowa, Missouri-I and -II, and New Jersey studies, driver license and Medicare files were the source of control selection. In Utah/southern Idaho, Medicare files were used to recruit controls that were 65 yr or older. For the New Jersey study, in which cases and controls were matched with respect to vital status, death certificates were used as the source of control subjects for deceased cases. All studies matched with respect to age and sex. The control selection period for each study mirrored the case selection time frame. The Iowa, Missouri-I, Missouri-II, and New Jersey study groups were comprised of females only. The Missouri-II, Connecticut, and Utah/southern Idaho studies used randomized recruitment (Weinberg & Sandler, 1991) procedures to increase the percentage of ever-smoking controls. In the Connecticut and Utah/southern Idaho studies, selection probabilities were based on smoking status 10 yr prior to interview, as well as on age and gender. The only other study on which smoking status was matched was Missouri-II. Race was included in the pair matching applied in the New Jersey study, while the Winnipeg study applied pair matching on the basis of age and sex. With respect to attained age, all except the latter two studies either undertook frequency matching or used randomized recruitment to achieve stochastic matching.

**TABLE 1.** Participant Selection, Matching, Histologic Confirmation, and Response Rates

| Study | Dates of ascertainment subject selection | | Matching respondent type | Histologic confirmation | Number and Sex of Subjects Response Rates | |
|---|---|---|---|---|---|---|
| | Cases | Controls | | | Cases | Controls |
| NJ | Dx: 1982–1984<br>1. Rapid reporting system with hospital pathology departments.<br>2. hospital pathology records, state cancer registry, and death certificate files | 1982–1983<br>1. Live cases: driver license (<65 yr); Medicare files (65+)<br>2. Deceased cases: death certificates | 1. Live (Direct): age and race (FM) (P)<br>2. Deceased (proxy): age, race, closest date of death (P) | Histologic typing relied on outside pathology reports | 480 F 48% of 994 interviewed, 37% of 1306 eligible | 442 F 44% of 995 interviewed, 30% of 1449 eligible |
| Winn | Dx: 1983–1990 Manitoba Registry | 1983–1990 phone directory | Age (P) Sex (P) | Histologic confirmation relied on outside pathology reports | 488 M, 250 F 53% of 1400 eligible | 488 M, 250 F <54% of eligible |
| MO-I | Dx: 1986–1991 Missouri Cancer Registry | 1986–1991 Driver license (30–64 yr), Medicare files (65–84 yr) | Age (FM) | Precise histologic confirmation by independent review of 76% of the cases | 538 F 83% of 650 eligible completed phone questionnaire and had dosimetry from at least 1 home | 1183 F 78% of the 1587 eligible completed phone questionnaire and had dosimetry from at least 1 home |
| MO-II | Dx: 1993–1994 Missouri Cancer Registry | 1993–1994 Driver license (30–64 yr), Medicare files (65–84 yr) | Two-stage randomized recruitment procedure; age, sex, smoking status (F) | Precise histologic confirmation by over independent review of over 80% of the cases. | 512 F 69% of 742 eligible cases completed questionnaires and had some dosimetry[a] | 553 F 3886 initially eligible, 75% of 730 targeted had both interview and some dosimetry[a] |

| | | | | | | |
|---|---|---|---|---|---|---|
| IA | Dx: 1993–1996 Iowa SEER Cancer Registry with 90% of subjects rapidly-reported | 1993–1996 Driver license (40–64 yr), Medicare files (65–84 yr) | Age (FM) | Precise histologic confirmation by independent review of 96% of the cases | 413 F 68% of 603 eligible completed questionnaires and had complete dosimetry | 614 F 53% of 1337 eligible completed questionnaires and had complete dosimetry[b] |
| CT | Dx: 1989–1992 Cancer registries and medical record review | 1990–1993 Random telephone screening | Randomized recruitment was used to identify cases and controls that were similar in age, sex and smoking status (FM) | Histologic confirmation relied on outside pathology reports | 527 M, 436 F 75% of 5216 cases screened for eligibility 963 (79%) qualifying cases completed the study[a] | 442 M, 507 F 83% of households screened; of 1542 eligible after screening and randomization, 62% completed the study[a] |
| UT/ID | Dx: 1989–1992 Cancer registries and medical record review | 1989–1992 Random telephone screening and listings of Medicare recipients | Randomized recruitment was used to identify cases and controls that were similar in age, sex, and smoking status (FM) | Histologic confirmation relied on outside pathology reports | 319 M, 192 F 81% of 1388 cases screened for eligibility 511 (85%) of eligible cases completed the study[a] | 587 M, 275 F <65, 3 steps (i) 94% of phone numbers enumerated; (ii) 96% of the potential controls identified were screening for eligibility and randomization; (iii) interviewed 84% of those found eligible. 65+, screened 91% of potential controls for eligibility and randomization; then 78% of those found eligible were interviewed |

*Note*. Dx, diagnosis; F, female-restricted study; M & F, males and females included; FM, frequency matching; P, pair-matching.

[a] Many subjects were excluded who did not pass smoking randomization and other study criteria.

[b] Follow-up study found similar demographics between responders and nonresponders.

Cancer cases were categorized by histologic type for the New Jersey, Winnipeg, Connecticut, and Utah/southern Idaho studies by use of outside pathology reports. The Missouri-I, Missouri-II, and Iowa studies obtained more precise consensus diagnoses performed by a panel of blinded expert pathologists. Histologic panel review was available for 76% of cases in the Missouri-I study, over 80% of the cases in the Missouri-II study, and 96% of the cases in the Iowa Study. When histologic material was not available for review by the panel, the outside pathologist's opinion, with additional medical file review, was used for categorization of the cancer subtype. Comparison of response rates between the various studies is problematic because of the differences between subject selection criteria (e.g. randomized recruitment) for cases and controls.

### Vital Status of Interview Respondents

Table 2 presents information on the vital status of the subjects enrolled in the various studies. Recall bias is of particular concern in case-control studies, which often base exposure assessment and evaluation of potentially confounding variables, such as smoking status, on information from interviews. Usually the subjects themselves provide more accurate information on lifestyle factors, health history amount of time spent at home, residential history, and other information relevant to epidemiologic study than could a proxy respondent such as a relative or friend. Since 31% (Iowa) to 68% (Missouri-II) of the lung cancer cases in the included studies were deceased at the time of interview, it was necessary to use proxy respondents for the deceased cases. Even for deceased cases, however, the use of live controls is generally preferable to the use of deceased controls (Wacholder et al., 1992). Except for the New Jersey (47% control proxy) and Winnipeg studies (11% control proxy), the included studies limited eligible controls to live subjects who were directly interviewed. Analyses restricted to direct respondents (live cases and controls) increased the ERR estimates for the Missouri-I, Connecticut, Utah/southern Idaho, and Iowa studies.

### Radon Dosimetry

Table 3 summarizes the radon exposure data available from the seven included studies. With the exception of the Winnipeg study, most of the studies utilized year-long indoor radon gas measurements recorded using Landauer, Inc., alpha-track detectors placed in the subjects' current and (where undertaken) former homes. The accuracy and precision of the Landauer, Inc., detector have been described elsewhere (Field et al., 1998a). For the Winnipeg study, alpha-track detectors were supplied by a government entity. The alpha-track detectors used in Winnipeg reportedly (Létourneau et al., 1994) exhibited less precision (COV = 20%) as compared to the precision (COV = 8%) noted for the Landauer alpha-track detectors (Field et al., 1998a). In the New Jersey study, short-term charcoal detector tests and thermal luminescent dosimeters were used to reconstruct exposure histories when year-long alpha track measurements were unavailable.

**TABLE 2.** Vital Status of Subjects and Related Analysis

| Study | Subjects included direct[a] and proxy[b] | | Adjustment for vital status | Proxy-specific analysis | Comments |
|---|---|---|---|---|---|
| | Cases | Controls | | | |
| NJ | Direct 267 (56%)<br>Proxy 213 (44%) | Direct 240 (54%)<br>Proxy 202 (46%) | Yes | No | Both the main effect of respondent type and its interaction with smoking status were retained in the final model. |
| Winn | Direct 481 (65%)<br>Proxy 257 (35%) | Direct 660 (89%)<br>Proxy 78 (11%) | No | Yes | Analysis restricted to the 471 case-control pairs who were directly interviewed failed to provide evidence of increased risk with radon. |
| MO-I | Direct 197 (37%)<br>Proxy 341 (63%) | Direct 1183 (100%) | No | Yes | A marginally significant ($p = .06$) dose-response trend was noted when analysis was limited to direct interview subjects. |
| MO-II | Direct 512 (68%)<br>Proxy 164 (32%) | Direct 553 (100%) | No | No | |
| IA | Direct 283 (69%)<br>Proxy 130 (31%) | Direct 614 (100%) | No | Yes | Analyses restricted to direct cases and controls found a statistically significant dose-response using both continuous and categorical analyses. |
| CT | Direct 574 (60%)<br>Proxy 389 (40%) | Direct 940 (99%)<br>Proxy 9 (1%) | No | Yes | Proxy status found to have little effect and dropped from final models. Analysis restricted to self-respondents resulted in increased estimate of effect—but no evidence for significant linear effect. |
| UT/ID | Direct 262 (51%)<br>Proxy 249 (49%) | Direct 843 (98%)<br>Proxy 19 (2%) | No | Yes | Proxy status found to have little effect and dropped from final models. Analysis restricted to self-respondents resulted in increased estimate of effect—but no evidence for significant linear effect. |

[a] Subject alive and well enough to be interviewed.
[b] Family member or knowledgeable friend provided information.

**TABLE 3.** Radon Dosimetry

| Study | Duration and method | Residence inclusion criteria | Location of dosimeter placement | Exposure time window | Exposure time window (ETW) coverage | Analysis | Method of imputing missing data |
|---|---|---|---|---|---|---|---|
| NJ | 1 yr ATD T, some short-term charcoal canister detectors | Last NJ residence of ≥10 yr during the period 10–30 yr prior to Dx or selection. Criteria varied slightly for final analysis | Living area (76%); basement (5%); 4-day charcoal canister (8%) | 5–30 yr prior to diagnosis or selection | Only 1 residence monitored first phase of study; median ETW residence time in years: 20 years (cases) and 21 years (controls); 82% cases and 79% controls resident >15 yr | CONC CUM IMP | Median value of controls assigned for periods not residing in index home; apartments assigned 0.4 pCi/L |
| Winn | 1 yr ATD G | All Winnipeg residences of ≥1 yr during index period | Bedroom and basement (reported separately) | 5–30 and 5–15 yr prior to interview | 33% of eligible residences monitored; mean years covered: 17 in 5–30 yr ETW (68% of person-time); 8 in the 5–15 yr ETW (80% of person-time) | CUM IMP | Calibration to bedroom or basement monitored; if no measurement, average study value for all subjects |
| MO-I | 1 yr ATD T | All in-state index period residences | Bedroom and kitchen area | 5–30 yr prior to interview | Average coverage of 20 yr; ETW coverage: l iving cases: 78.5%; deceased cases: 76%; controls: 78.8% | TWAC CUM IMP | Stratum-specific mean (cases and controls assigned the respective group mean) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| MO-II | 20+ yr RSM, 1 yr ATD | All in-state index period residences | Bedroom and kitchen; no dose-response noted for gas measurements, but findings using RSM found statistically significant dose-response | 5–25 yr prior to diagnosis for cases and interview for controls | Average coverage of 18.2 yr in ETW; ETW coverage: 91% for cases and controls using at least one of the detectors; only 9% of pertinent years in need of imputation for missing radon values. | TWAC IMP | Annual means for measured values were used for imputation of missing values for both measure methods |
| IA | 1 yr ATD T RRD, outdoor ATD M | Current home only—inclusion criteria limited subjects to those subjects occupying the current home for at least the past 20 yr. | Each level of home, bedrooms and work areas of home including outdoor regional radon concentrations. RRD results will be available in near future. | 5–19 yr prior to diagnosis for cases and interview for controls | 100% coverage of ETW; all homes were measured; median coverage 32 yr | CUM Accounts for all exposure time past 19 years. | No missing home radon measurement periods over ETW; no imputation |
| CT | 1 yr ADT T | All homes occupied for at least 1 yr since age 25 | Bedroom, another room on lowest living area and some basements depending on occupancy. A sample of homes measured every level. | Age 25 up to 5 yr prior to diagnosis | Maximum window, age 25 up to 5 yr before diagnosis/interview; analysis window, 5–25 yr prior to diagnosis/interview; average coverage for eligible homes was 57% for the maximum window and 69% for the analysis window | TWAC IMP | The percent time coverage for the maximum window was 69% and 79% for the analysis window; regression trees aided in providing stratum-specific control means for imputation |

(Continued)

**TABLE 3.** *(Continued)*

| | | | | | | |
|---|---|---|---|---|---|---|
| UT/ID 1 yr ATD T | All homes occupied for at least 1 yr since age 25 | Bedroom, another room on lowest living area and some basements depending on occupancy. A sample of homes measured every level. | Age 25 up to 5 yr prior to diagnosis | Maximum window, age 25 up to 5 yr before diagnosis/ interview; analysis window, 5–25 yr prior to diagnosis/ interview; 62% of homes in maximum window and 78% of homes in analysis window measured | TWAC IMP | The percent time coverage for the maximum window was 73% and 82% for the analysis window; regression trees aided in providing stratum-specific control means for imputation |

*Note*. ATD T: alpha-track detector manufactured and read by Terradex Corporation; ATD G: government office responsible for dosimeter provision; ATD M: alpha-track detector manufactured and read by the Minnesota Radon Project; CONC: only radon concentration in the one monitored home considered; CUM: exposures were cumulated over the ETW; ETW: exposure time window; RRD: glass-based retrospective reconstruction detector; RSM: glass-based retrospective surface monitor; TWAC: analysis was by time-weighted (by residence time) averaging of measured concentrations; IMP: results were analyzed with imputation of missing data as described.

In addition to assessing ambient radon levels, the Missouri-II and Iowa studies utilized detection methods that assess levels of the long-lived radon decay product $^{210}$Pb accumulated in glass products in the home (such as mirrors or picture glass) over time. The Missouri-II study utilized a glass-based retrospective surface monitor (RSM) (Mahaffey et al., 1993, 1996, 1999), and the Iowa study, a retrospective reconstruction detector (Steck et al., 1993, 2002; Steck & Field, 1999). Because of the long half-life of the radon decay product $^{210}$Pb (22 yr), glass-implanted $^{210}$Pb measurement provides a long-lasting marker for retrospective radon determination. Glass-based retrospective radon detectors also readily detect levels of the shorter lived decay product, $^{210}$Po, arising from the decay of $^{210}$Pb. The glass-based measurements in Missouri-II study provided estimates of cumulative radon exposure, and when divided by the number of years that the subject had owned the particular glass object, provided annual time-weighted average exposure estimates. Additional details regarding the glass-based retrospective radon gas and progeny detectors used in these two studies can be found elsewhere (Field et al., 1999).

With the exception of phase I of the New Jersey study, measurements were also made in most in-state homes occupied for at least 1 yr during the designated ETW. The New Jersey study included radon measurements from a single residence, that being the most recent residence of minimum 10 yr of occupancy in the period 10–30 yr prior to diagnosis. The Utah/Connecticut study also obtained measurements for 1+-yr residences outside of the states.

All studies measured radon gas concentrations in several areas of the homes, focusing on the areas in which subjects were most likely to spend the majority of their time. One of the advantages of the Iowa study was the linkage between multiple radon measurements (Fisher et al., 1998) both inside the house and outside the house (Steck et al., 1999) with the subjects' past personal mobility patterns (Field et al., 1998b). For the purpose of measuring outdoor radon levels, the Iowa study utilized regional outdoor alpha-track detectors manufactured and read by the Minnesota Radon Project (Steck et al., 2002).

Due to the 20-yr residency requirement in the Iowa study, the coverage of the ETW was 100%. The Missouri-II study had an average of 91% coverage of the exposure window by at least one of the two types of detector employed. The majority of the remaining studies had at least 70% coverage in the ETW.

As presented in Table 3, the individual studies employed a variety of different techniques to impute values for missing radon concentrations. These methods included the potentially bias-inducing method of using status (case vs. control)-specific mean imputation (Missouri-I), the use of median (New Jersey) or average (Winnipeg) radon values from all subjects' (cases and controls) measured homes, and, most preferable of all, the use of control-only means, either from all control subjects (Missouri-II) or within strata defined by regression tree methods (Connecticut and Utah/southern Idaho).

To account for the induction period for lung cancer, the 5-yr period prior to diagnosis was excluded from the exposure assessment in all studies. The

Missouri-I and -II, Connecticut, and Utah/southern Idaho studies all estimated radon exposure as time-weighted average radon concentrations. Cumulative radon exposure was estimated with imputed values for missing historical data in analyses of the New Jersey, Winnipeg, and Missouri-I investigations. The Iowa study estimated cumulative radon exposure in units of working level months (WLM) and because of the 20-yr current home residency inclusion criterion, there were no historical exposure gaps requiring imputed estimates.

### Radon Concentrations

As can be seen in Table 4, the highest geometric mean radon concentrations in measured homes were reported in Winnipeg and Iowa. In fact, living-area radon concentrations exceeded the U.S. Environmental Protection Agency action level of 148 Bq/m$^3$ in approximately 25% of the studied homes in Winnipeg and Iowa. In addition, over 59% of basement radon gas measurements in Iowa exceeded 148 Bq/m$^3$. The percent of living area radon concentrations exceeding 148 Bq/m$^3$ in the other study sites ranged from 1% in New Jersey to 7% in both Missouri-I and Connecticut/southern Idaho. In Missouri-II, the estimated retrospective radon concentrations obtained from the glass-based retrospective surface monitor radon measurements were slightly higher than those obtained from alpha track measurements for cases, but not for controls (66.0 and 57.1 Bq/m$^3$ for cases for retrospective surface monitor and alpha track measurements, respectively, and 57.1 and 59.6 Bq/m$^3$ for controls).

### Control of Potentially Confounding Factors

Table 5 presents information on restrictions on inclusion criteria and factors examined to control for potential confounding. Each of the seven studies controlled for age and various measures of past cigarette usage. The individual studies explored a variety of other factors that were potentially predictive of lung cancer risk, such as occupation, environmental tobacco smoke, country of birth, and preexisting lung disease. The predictive model used by Schoenberg et al. (1990) included adjustment for number of cigarettes per day, time since smoking cessation, age, occupation, respondent type, and the interaction between respondent type and number of cigarettes per day.

Winnipeg's final predictive model (conditional on age and gender) was the most limited among the seven studies, selecting only factors that materially affected the radon odds ratios in this site: education and smoking status. The final model in New Jersey did, however, include adjustment for occupation. A similar set of factors was included in Iowa's final model, which adjusted for the effects of age, active smoking (in pack-years), and attained education level.

The Missouri and Iowa studies were unique in considering dietary factors and previous nonmalignant lung disease in the prediction of lung cancer risk. The Missouri-I study of nonsmoking women observed saturated fat consumption to be predictive, in a model also containing age, marital status, previous smoking, passive smoking, education, and respondent type. The Missouri-II study, which was unrestrictive on smoking status included in its final model

**TABLE 4.** Radon Exposure Estimates

| Study | Geometric mean radon concentration[ab] in Bq/m$^3$ (geometric standard deviation) by level of home | Percent[c] of homes exceeding a time-weighted average radon concentration of 148 Bq/m$^3$ | Type of exposure estimate reported | Central in-home exposure estimate for study time window[c] |
|---|---|---|---|---|
| NJ | 26.2 (2.2) Level 2<br>19.0 (2.3) Level 1 | 1 % > 148 Bq/m$^3$ | TWA[c] and cumulative | The mean exposure for cases: 26.3 Bq/m$^3$, for controls 23.8 Bq/m$^3$, median for each 14.8 Bq/m$^3$ |
| Winn | 90.7 (2.4) Living area<br>161.3 (2.0) Basement | 24 % > 144 Bq/m$^3$ | Cumulative | Mean 32,250 Bq/m$^3$-years for 5–30 yr time window[d] |
| MO-I | 44 (1.9) Level 2<br>44 (2.2) Level 1<br>89 (2.1) Basement | 7% > 148 Bq/m$^3$ | TWA and cumulative[e] | Median exposure 58 Bq/m$^3$ for cases and controls for 25-yr time window 3–30 yr before cancer diagnosis |
| MO-II | 44 (2.2) Level 2<br>44 (2.2) Level 1<br>89 (2.1) Basement | 4% > 148 Bq/m$^3$ | TWA | Median exposure 59 Bq/m$^3$ for cases and controls for 20-yr time window 5–25 yr before cancer diagnosis |
| IA | 74 (2.1) Level 2<br>93 (2.2) Level 1<br>170 (2.2) Basement | 25% > 148 Bq/m$^3$ | Cumulative and TWA | Median for 15-yr ETW was 8.6 WLM for cases and 7.9 WLM for controls[d] |
| CT | 15 (2.7) Level 2<br>19 (2.8) Level 1<br>56 (2.7) Basement | 3% > 148 Bq/m$^3$ | TWA | Median for ETW averaged for both cases and controls was 23 Bq/m$^3$ |
| UT/ID | 37 (2.2) Level 2<br>44 (2.2) Level 1<br>67 (2.3) Basement | 7% > 148 Bq/m$^3$ | TWA | Median for ETW averaged for both cases and controls was 46 Bq/m$^3$ |

*Note*. TWA, time-weighted average radon concentration.

[a] Radon concentrations reflect available measured values without imputation.

[b] Values from Field (2001).

[c] Includes imputed values for some studies and generally represents living area concentrations unless otherwise specified.

[d] Cumulative working level month (WLM) exposure occurring within the home and outside the home.

**TABLE 5.** Prevention and Control of Confounding

| Study | Restriction[a] | Potential confounders investigated | Matching with adjustment | Variables adjusted for in the final model [b] |
|---|---|---|---|---|
| NJ | F | Age; active smoking (several variables); "race"; education; county of residence (NEF); occupation; vegetable consumption (NEF); respondent type. | Respondent type: No<br>Age: Yes<br>Race: No<br>Closest date of death (proxy): No | Age; lifetime nonsmoking, years since quit smoking; cigarettes per day; occupation; respondent type; respondent type × smoking. |
| Winn | Age: 35–80 yr (cases) | Age; sex; smoking; education; country of birth (NEF); occupation (NEF). | Age: Yes<br>Sex: No | Age; smoking status; education level |
| MO-I | F<br>Age 30–84<br>Nonsmokers<br>White "race" | Age; marital status; previous smoking; passive smoking, preexisting nonmalignant lung disease; education; saturated fat; respondent type. | Age: Yes | Age; smoking<br>Odds ratios were also presented with adjustments for other factors like education, saturated fat, passive smoking, pack-year, etc. |
| MO-II | F<br>Age 30–84 | Age, education, previous lung disease, pack-years of smoking, vegetable intake. | Age: Yes | Age; consumption of vegetables, intensity of smoking, educational level, and previous lung disease |
| IA | F<br>Age: 40–84<br>Years residence >20 in current home | Age; active smoking; education, previous nonmalignant lung disease (NEF), occupation (NEF), and family health history (NEF), environmental tobacco smoke (NEF), dietary practices, and others (NEF). | Age: Yes | Age; years since smoking cessation; cigarette pack-year rate; educational level |

| | | | | |
|---|---|---|---|---|
| CT[c] | Age: 40–79 | Age, state, gender, education, mobility, hours spent at home, altitude, population density, adolescent smoking, smoking pack-years by decade, proxy status (NEF), income (NEF), and others (NEF). | Age: Yes<br>Sex: Yes | Age, state, gender, education, mobility, hours spent at home, altitude, population density, adolescent smoking, and smoking (pack-years by decade) |
| UT/ID[c] | Age: 40–79 | Age, state, gender, education, mobility, hours spent at home, altitude, population density, adolescent smoking, smoking pack-years by decade, proxy status (NEF), income (NEF), and others (NEF). | Age: Yes<br>Sex: Yes | Age, state, gender, education, mobility, hours spent at home, altitude, population density, adolescent smoking, and smoking (pack-years by decade) |

*Note*. NEF, no effect on model fit; F, female.

[a] Aside from residency restrictions.

[b] Adjustment refers to inclusion in a multiple regression model.

[c] Controls selected via randomized recruitment. Selection probabilities for age/sex strata and smoking status included in final models.

vegetable consumption, smoking intensity, educational level, and the presence of previous lung disease.

The Connecticut and Utah/southern Idaho studies included a large number of covariates in their final model: age, state, gender, educational level, mobility, hours spent at home, altitude, population density, adolescent smoking, and smoking pack-years by decade. This latter analysis accounted for the randomized recruitment by including a constant for the selection probabilities, and by including stratification variables for phase of the study. The phase variable was included because the selection probabilities used in randomized recruitment were changed partway through the study.

### Potential Modifiers of Radon Risk

Table 6 presents information on the form of the model used for each study as well as the potential modifiers of radon risk. The New Jersey, Winnipeg, Missouri-I, Missouri-II, and Iowa studies all employed multivariate logistic regression analysis; Winnipeg's analyses were conditional on the pair-matched variables of age and gender. The Iowa study also provided analyses employing

**TABLE 6.** Effect Modification

| | | | Stratum-specific results | | |
|---|---|---|---|---|---|
| Study | Model form | Variables reportedly investigated[a] | Smoking | Age | Histological type |
| NJ | Unconditional logistic regression | (I) Smoking × respondent type | Yes<br>4 levels | No | Yes |
| Winn | Conditional logistic regression | (S) Respondent type | No | No | Yes |
| MO-I | Multivariate logistic regression | (S) Smoking<br>(S) Age | Yes<br>2 levels | Yes<br>6 levels | Yes |
| MO-II | Multivariate logistic regression | (S) Age<br>(S) Education level<br>(S) Previous lung disease<br>(S) Smoking status | Yes<br>4 levels | Yes<br>3 levels | Yes |
| IA | Multivariate logistic regression and linear excess odds (excess relative risk) | (S) Age<br>(S) Active smoking<br>(S) Education | Yes<br>3 levels | Yes<br>3 levels | Yes |
| CT | Product additive excess risk | (I) State<br>(I) Gender<br>(I) Smoking | Yes | No | Yes |
| UT/ID | Product additive excess risk | (I) State<br>(I) Gender<br>(I) Smoking | Yes | No | Yes |

[a]Estimation of an interaction term (I) or stratum-specific analyses (S).

linear excess odds models. Product additive excess risk models were employed in the Connecticut and Utah/southern Idaho studies.

The Missouri-I and Iowa studies presented radon risks by age strata. Gender-specific effects were reported in the Connecticut and Utah/southern Idaho studies. The potentially modifying effect of respondent type was investigated in the New Jersey and Winnipeg studies. Proxy responses were observed to significantly affect smoking effects in the New Jersey analysis. The Connecticut and Utah/southern Idaho study explored the effect of proxy respondents by carrying out a separate analysis in which persons with proxy respondents were excluded. All but the Winnipeg study reported investigating the potential modifying effect of smoking on the risk of lung cancer associated with radon exposure. The Missouri-II and Iowa studies investigated the potentially modifying effects of education level on radon risk. The Winnipeg study provided stratum specific results by area monitored (bedroom and basement). All studies whose results have been published have provided radon risks stratified by histologic type.

### Treatment of Attained Age

Table 7 details study inclusion criteria regarding, and analytical treatment of attained age. All of the included studies with the exception of New Jersey study restricted subject eligibility on age at ascertainment. The range of age criteria varied a minimum of 30 yr to a maximum of 84 yr at subject ascertainment.

The age distributions of cases and controls differed between studies according to their age restriction criteria, with the Winnipeg subjects being youngest on average, and those in Missouri-I being the oldest. Only 1.6% of Winnipeg cases and 4.7% of controls had an attained age exceeding 75 yr at ascertainment. By contrast, the proportion of Missouri-I subjects with ages exceeding 75 yr were 46% and 42% for cases and controls, respectively. Matching (or selection strata used in randomized recruitment) by age was relatively consistent across studies with most using 5-yr age groups. No significant heterogeneity in radon risk across age groups has been reported for any of the studies.

### Smoking-Specific Analyses

Table 8 provides information regarding the proportion of smokers among case and control series by study and smoking-specific analyses performed in each of the seven studies. The Winnipeg study had the highest proportion (97%) of ever-smoking controls. Because of the randomized recruitment efforts in the Missouri-II, Connecticut, and Utah/southern Idaho studies, a similarly high proportion of ever-smokers were included within case and control series, exceeding 90% in all three studies. Only the Missouri-I study was restricted to current nonsmokers.

Exposure-response trends between lung cancer risk and time-weighted averaged radon concentrations were observed among current smokers in the Missouri-II and New Jersey studies. In the New Jersey study, however, the

**TABLE 7.** Treatment of Attained Age

| | Design | | | | | |
|---|---|---|---|---|---|---|
| | Restriction | | | Analysis | | |
| Study | Age inclusion criteria | Proportion in highest age category | Matching | Adjustment for confounding | Stratum-specific r esults | Comments |
| NJ | No age restrictions noted | 25% of the cases and 25% of the controls >72 yr | Age-frequency matched by 5-yr age group | Yes | No | Type of variable/categories for adjustment not specified |
| Winn | Cases 35–80 yr of age | 1.6% of the cases and 4.7% of the controls >75 yr | Controls ±5 yr from case age | Yes | No | |
| MO-I | Controls 30–84 yr of age | 46% of the cases and 24% of the controls >80 yr | Age-frequency matched by 5-yr age groups | Yes in 6 categories | Yes in 3 age strata | Strongest trend, but nonsignificant, with increasing radon in <65 yr (youngest age group) |
| MO-II | Controls 30–84 yr of age | 21% of the cases and 20% of the controls >74 yr | Age-frequency matched by 5-yr age group | Yes in 5 categories | Yes in 3 age s trata | Statistically significant positive trend when glass-based retrospective surface monitor dosimetry used. |
| IA | Cases and controls 40–84 yr of age | 43% of the cases and 40% of the controls >70 yr | Age-frequency matched by 5-yr age group | Yes in 4 categories | Yes in 3 age strata | Excess risk heterogeneity test $p = .93$ (continuous) and $p = .79$ categorical |
| CT | Cases and controls 40–79 yr of age | 34% of cases and 20% of controls age 70–79 | Randomized recruitment within 16 age-gender strata | Yes in 8 categories | No | |
| UT/ID | Cases and controls 40–79 yr of age | 33% of cases and 31% of controls age 70–79 | Randomized recruitment within 16 age-gender strata | Yes in 5 categories | No | |

**TABLE 8.** Smoking-Specific Analyses

| Study | Proportion of smokers | Treatment of passive smoking | Model adjustment for confounding | Stratum-specific results for active smoking | | | Overall results |
|---|---|---|---|---|---|---|---|
| | | | | Current | Ex-smokers | Never-smokers | |
| NJ | Ever-smokers: cases: 86% controls: 47% | Taking spousal smoking into account did not change nonsmokers pattern of risk | Lifetime nonsmokers vs. ever-smokers (3 levels) adjusted for years since quit smoking | Yes: TWA Strongest exposure-response trend ($p$ = .01) occurred among light <15 cigs/day) smokers | No Consideration implicit by lifetime average cigs/day and years since quit but no results provided | Yes: TWA ORs 0.9, 1.2 Not statistically significant exposure-response trend ($p$ = .39 one-sided) | For continuous, cumulative radon exposure, OR greater for smokers than nonsmokers, especially among smokers of less than 15 cigs/day (significant exposure-response trend $p$ = .01). Trend not statistically significant for 15–24 and negative for 25+. |
| Winn | Ever-smokers: cases: 97% controls: 70% | No | Ever/never smoking status | No | No | No | Not tested |
| MO-I | All nonsmokers at the time of the study | Yes, OR 1.24 for highest radon exposure conc. Adjusted for age | Previous smoking (pack-years, previous smoker, years since cessation) | No | Yes: TWA OR 1.32 for highest radon exposure category. No exposure-response trend within group (b) | Yes: TWA OR 1.20 for highest radon exposure category. No exposure-response trend | Could not test since subjects were limited to current nonsmokers |

(*Continued*)

**TABLE 8.** (*Continued*)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| MO-II | Ever-smokers: cases: 92% controls: 87% | No | Smoking status: never, former, light/medium, heavy | Yes: TWA 3.5 OR for highest radon exposure category. Exposure response trend within group observed. | Yes: TWA OR 2.60 for highest radon exposure category. No significant exposure-response trend within group | Yes: TWA OR 1.35 for highest radon exposure category. No significant exposure-response trend | Positive exposure response was observed among heavy smokers, but the number of cases in each strata was relatively small, and the pattern of risk in heavy smokers was not statistically different from that in light to moderate smokers or those who did not smoke at all. |
| IA | Ever-smokers: cases: 86% controls: 33% | Yes, collected information on exposure to never-smoking subjects. | Cessation years; pack-year rate | Continuous: Excess risk = 0.33 (light smokers) Excess risk = 0.14 (heavy smokers) Categorical: Excess risk = 0.51 (light smokers) Excess risk = 0.20 (heavy smokers) | | Continuous analysis never-smoker excess risk = 0.22. Never smoker categorical excess risk = 0.88 | $p = .83$ (for continuous) and $p = .66$ (for categorical) for testing heterogeneity among the smoking categories fail to reject a multiplicative effect between radon and smoking on lung cancer risk |
| CT | Cases and controls: 94% | No | Average pack-years; adolescent indicator variable | No | No | No | Reported stratum-specific OR and ERR only for individuals who did not smoke during time window of interest. |
| UT/ID | Cases and controls: 90% | No | Average pack-years; adolescent indicator variable | No | No | No | Reported stratum-specific OR and ERR only for individuals who did not smoke during time window of interest. |

*Note*. Conc, radon concentration category; TWA, time-weighted average concentration; OR, odds ratio.

strongest trend was observed among subjects who smoked <15 cigarettes/day ($p = .01$). Among New Jersey never-smokers, the exposure-response trend was non-significant. Field et al. (2000a) found no evidence of heterogeneity in excess risks estimates obtained from a linear excess odds model across categories of smoking (never, light, heavy), regardless of whether cumulative radon exposure was analyzed as a categorical or continuous variable. Sandler et al. (this issue) found similar risk estimates among the various subgroups based on smoking status.

### Analyses by Histologic Type of Lung Cancer

All of the North American studies investigated the possible heterogeneity of radon effect by histologic type of lung cancer. In the New Jersey study, exposure-response trends were observed among all histologic types with the exception of squamous-cell carcinoma. Significant trends among radon exposure categories were observed for small-cell carcinoma (when radon exposure was estimated cumulatively) and for large-cell carcinoma (when radon exposure was estimated based on radon concentration in the one monitored home). The absence of uniform pathology slide review and possibility of misclassification by histologic type were a limitation of the interpretation of the analyses stratified by histologic type in this study (Schoenberg et al., 1990).

The most significant dose response trends in the Iowa study were observed for large-cell carcinoma. Although the OR for the highest exposure category was 3.42 in the large-cell cancer stratum, the 95% confidence limits were large (0.93–14.53), due in part to the small number of cases ($n = 32$). A particular strength of the Iowa study was the consensus histologic diagnosis provided by two surgical pathologists for 96% of the lung cancer cases (Field et al., 2004). Nevertheless, differences in the linear excess odds between the various histologic types were not statistically significant (continuous $p = .58$, categorical $p = .65$).

An association between radon exposure and adenocarcinoma among nonsmoking women was the single significant result within histologic type in the Missouri-I study. However, statistical power was also greatest within this cell type since adenocarcinoma was the most common histologic type of lung cancer reported among former smokers and lifetime nonsmokers (Brownson et al., 1995). In the Missouri-II study, which included both "smokers" and "nonsmokers," significant $p$ values for trend (based on a continuous exposure variable from retrospective surface monitor measurements) were observed in the squamous-cell and "other" histologic types. Neither adenocarcinoma nor small-cell histologic types demonstrated significant dose-response trends in the Missouri-II analyses. No histologic specificity was observed in either the Winnipeg, Connecticut, or Utah/southern Idaho studies, which is consistent with their lack of finding an overall significant main effect of radon on lung cancer for all histologic types.

As is evident from both Table 9 and the foregoing discussion, no consistent pattern can be discerned among the histologic analyses in the seven included studies, each of which demonstrated some "significant pattern." The evidence

**TABLE 9.** Histologic Analyses

| Study | Overall results | Small cell | Large cell | Squamous cell | Adenocarcinoma | Other/unknown type |
|---|---|---|---|---|---|---|
| NJ | All showed an ER trend except squamous-cell carcinoma | Most significant CUM result ($p$ = .079) | Most significant CONC result ($p$ = .027) | No ER trend | NS ER trend | — |
| Winn[a] | All point estimates >1 but none significant | OR = 1.35 (0.44–4.11) | — | OR = 1.19 (0.9–1.56) | OR = 1.33 (0.83–2.13) | OR = 1.35 (0.16–1.53) |
| MO-I | Significant trend[b] ($p$ < .05) | — | — | — | Significant ER trend[c] 49% of tumors | Other = 28% of all tumors Unknown = the 24% not typed |
| MO-II | Significant trend ($P$ = .02) (CR-39 dosimetry) | OR = 2.2 | — | OR = 2.3 | OR = 1.9 | OR = 2.2 |
| IA | Linear excess odds differences between histologic types was not statistically significant (continuous $p$ = .58, categorical $p$ = .65) | OR = 1.44 (0.47–4.35) for 5th exposure category; no dose-response trend observed | Significant trend observed: continuous $p$ = .04, categorical $p$ = .03 | OR = 3.17 (1.08–10.06) for 5th exposure category; suggestive dose-response trend observed: categorical $p$ = .06 | OR = 1.35 (0.64–2.83) for 5th exposure category; no dose-response trend observed | OR = 2.95 (0.96–9.82) for 5th exposure category; no dose-response trend observed |
| CT, UT/ID | All showed a positive nonsignificant point estimate except squamous-cell carcinoma | ERR = 0.165 (–0.35–0.69) | — | ERR = -0.176 (–0.39–0.37) | ERR = 0.202 (–0.19–0.59) | ERR = 0.212 (–0.35–0.78) for other non-small-cell carcinoma |

*Note*. CI: confidence interval; CUM: analysis of cumulative radon exposure; ER: exposure response; NS: not statistically significant; OR: odds ratio; ERR: excess relative risk; TWA: analysis of time-weighted (by residence duration) in monitored homes only; (–) 95% confidence interval.

[a]Analysis of cumulative radon (bedroom measures) analyzed as a continuous variable (OR per 3750 Bq/m$^3$-years), and restricted to subjects with minimum 75% coverage of the 5–30 yr ETW.

[b]Significant trend limited to the log-transformed cumulative radon exposure data, analyzed as a continuous variable; $p$ value ranged from .01 to .04 depending on the model covariates.

[c]Significant trend was observed for adenocarcinoma when continuous results were adjusted for saturated fat and age ($p$ = .04), and when categorical results adjusted for age and one of several other variables: previous smoking ($p$ = 0.04); smoking pack-years + years since cessation ($p$ = .01); previous lung disease ($p$ = .05); education ($p$ = .4); saturated fat intake ($p$ = .01).

for histologic specificity even in studies among miners is weak (Samet, 1989) and the potential for misclassification of histologies is significant (Steinhausler, 1998; Thomas et al., 1993). Brownson et al. (1995) observed overall agreement rates of only 65.6% between original diagnoses of histologic type of lung cancer and a consensus review of tissue slides by three pathologists. Among the lung cancer histologic types in Iowa, small-cell carcinoma had the highest percent exact agreement (98.0%, 95% CI = 96.6% to 99.4%), while adenocarcinoma had the lowest percent exact agreement (82.9%, 95% CI = 79.2% to 86.6%) (Field et al., 2004). Field et al. (2004) further reported that samples collected by cytologic examination (OR = 2.4, 95% CI = 1.1 to 5.2) or biopsy examination (OR = 2.2, 95% CI = 1.1 to 4.2) were more likely to be misclassified than samples obtained via resection.

The data presented in this report do not indicate that a particular lung cancer histologic type is associated with radon-induced lung cancer. This finding is in agreement with the findings from occupationally radon-exposed miners (NRC, 1999).

## SUMMARY OF FINDINGS

The major study findings for each of the five published studies of residential radon exposure are summarized in Table 10. The highest statistically significant (90% CI) upper categorical odds ratio of 8.7 (90% CI 1.3–57.8) was observed in the New Jersey study. The test for trend was also significant at the 90% confidence level, $p = .04$. As suggested by the authors of this study, the New Jersey results must be interpreted cautiously, since the upper exposure category contained a very limited number of subjects. The Winnipeg study, which benefited from the highest radon exposure levels, and examined risk for both the interval 5–15 and 5–30 yr before subject ascertainment, observed no increased risk for either the basement or the bedroom measurements. Consistent with the Winnipeg findings were those in the Missouri-I study of nonsmoking women, in which neither the categorical odds ratios nor the test for trend was statistically significant.

The Missouri-II study observed contrasting results based on type of radon exposure method used for analyses. When the analyses were limited to alpha-track radon gas measurements, no statistically significant categorical odds ratios or dose response trends were noted. When analyses were based on glass-based retrospective surface monitors, however, a statistically significant upper exposure categorical odds ratio of 3.3 (95% CI 1.5–3.3) and a statistically significant trend with increasing retrospective radon exposure ($p = .02$) were observed.

In the Iowa study, a suggestive odds ratio of 1.8 (95% CI 0.99–3.26) was noted for the upper category of the overall analysis of radon concentration, and a statistically significant upper exposure category odds ratio of 2.1 (95% CI 1.1–4.2) was observed when analyses were restricted to live cases. Within the analyses of cumulative radon exposure, statistically significant tests for trend in odds ratios were also noted among all study subjects, and in an analysis restricted to live cases. Field et al. (2000b) and Alavanja et al. (2000) have

**TABLE 10.** Major Findings for American Residential Radon Studies[a]

| Study | Highest exposure group and risk estimate (CI) | Comments |
|---|---|---|
| NJ | 148 Bq $m^{-3}$ –418 Bq $m^{-3}$ OR 8.7 (1.3–57.8)[b] | Exposure based on time weighted average radon concentration. Test for trend in odds ratios with increasing cumulative radon ($p$ = .04). |
| Winn | >7,201 Bq/$m^3$-years, OR 1.6 (0.9–2.7)[c] | Bedroom measurement with at least 75% of the 25-yr ETW. |
| | >11,201 Bq/$m^3$-years, OR 1.0 (0.7–1.6)[c] | Basement measurement with at least 75% of the 25-yr ETW. |
| MO-I | 91.0 Bq $m^{-3}$-566.1 Bq $m^{-3}$, OR 1.2 (0.9–1.7)[c] | Exposure based on time weighted average radon concentration. Test for trend in odds ratios with increasing radon concentration (continuous $p$ = .99; categorical $p$ = .19). |
| MO-II | >148 Bq $m^{-3}$, OR 0.71 (0.3–1.3)[c] | Exposure based on time-weighted indoor radon gas alpha-track detectors. Test for trend in odds ratios with increasing radon concentration (continuous $p$ = .79) |
| | >148 Bq $m^{-3}$, OR 3.33 (1.5–7.5)[c] | Exposure basedon time-weighted-average indoor exposure CR-39 surface measurements. Test for trend in odds ratios with increasing radon concentration (continuous $p$ = .02) |
| IA | | Eleven $WLM_{5-19}$ is approximately equal to a 15-yr exposure at 150 $Bqm^{-3}$. |
| | >16.95 $WLM_{5-19}$, OR 1.79 (0.99–3.26)[c] | Exposure for all cases and controls based on cumulative radon exposures using a complex retrospective exposure algorithm Test for trend in odds ratios with increasing radon concentration (continuous $p$ = .14; categorical $p$ = .05). |
| | >16.95 $WLM_{5-19}$, OR 2.14 (1.12–4.15)[c] | Exposure for all live cases and controls based on cumulative radon exposures using a complex retrospective exposure algorithm Test for trend in odds ratios with increasing radon concentration (continuous $p$ = .03; categorical $p$ = .01). |
| CT | >53 $Bqm^{-3}$, ERR 0.12 (–0.07–0.55) | Overall ERR for the combined states study was 0.24 (–0.07–0.55). |
| UT | >53 $Bqm^{-3}$, ERR 0.44 (–0.47–1.36) | |

*Note*. CI: confidence Interval; ERR: excess relative risk; $WLM_{5-19}$: working level month 5–19 yr prior to diagnosis for cases or interview for controls.
[a] Adapted from Field (2001).
[b] 90% Confidence interval.
[c] 95% Confidence interval.

suggested that the inability to detect an association in residential radon studies relates to various factors (Field et al., 1996), including poor retrospective radon exposure assessment. In fact, Field et al. (2002) have shown that the power of an epidemiologic study to detect an excess risk from residential radon exposure is enhanced by linking spatially disparate radon concentrations with the subject's retrospective mobility to obtain a true estimate of exposure. Additional information concerning factors affecting retrospective radon exposure estimates for residential radon studies can be found elsewhere (Steck & Field, this issue).

Detailed information on each of the studies just described can be found elsewhere: New Jersey (NJSDH, 1989; Schoenberg et al., 1989a, 1989b, 1990, 1992; Klotz et al., 1993), Winnipeg (Létourneau et al., 1992, 1994, 1995), Missouri-I (Alavanja et al., 1993, 1994, 1995, 1996; Bennett et al., 1999; Brownson et al., 1993, 1995, 1997), Missouri-II (Alavanja et al., 1999; Brownson & Alavanja, 2000; Mahaffey et al., 1993, 1996, 1999; Sinha et al., 1998, 2000), Iowa (Alavanja et al., 2001; Field, 2001; Field et al., 1996, 1998a, 1998b, 1999, 2000a, 2000b, 2001, 2002; Fisher et al., 1998; Smith, 2001; Steck & Field, 1999; this issue; Steck et al., 1993, 1999, 2002), and the Connecticut and Utah/Southern Idaho studies (Sandler et al., this issue; Weinberg et al., 1996). A pooled analysis of the residential radon studies described in this article is available elsewhere (Krewski et al., 2005, and this issue).

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