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A Combined Analysis of North American Case-Control Studies of Residential Radon and Lung Cancer

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A COMBINED ANALYSIS OF NORTH AMERICAN CASE-CONTROL STUDIES OF RESIDENTIAL RADON AND LUNG CANCER

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Cohort studies have consistently shown underground miners exposed to high levels of radon to be at excess risk of lung cancer, and extrapolations based on those results indicate that residential radon may be responsible for nearly 10–15% of all lung cancer deaths per year in the United States. However, case-control studies of residential radon and lung cancer have provided ambiguous evidence of radon lung cancer risks. Regardless, alpha-particle emissions from the short-lived radioactive radon decay products can damage cellular DNA. The possibility that a demonstrated lung carcinogen may be present in large numbers of homes raises a serious public health concern. Thus, a systematic analysis of pooled data from all North American residential radon studies was undertaken to provide a more direct characterization of the public health risk posed by prolonged radon exposure. To evaluate the risk associated with prolonged residential radon exposure, a combined analysis of the primary data from seven large scale case-control studies of residential radon and lung cancer risk was conducted. The combined data set included a total of 4081 cases and 5281 controls, representing the largest aggregation of data on residential radon and lung cancer conducted to date. Residential radon concentrations were determined primarily by α-track detectors placed in the living areas of homes of the study subjects in order to obtain an integrated 1-yr average radon concentration in indoor air. Conditional likelihood regression was used to estimate the excess risk of lung cancer due to residential radon exposure, with adjustment for attained age, sex, study, smoking factors, residential mobility, and completeness of radon measurements. Although the main analyses were based on the combined data set as a whole, we also considered subsets of the data considered to have more accurate radon dosimetry. This included a subset of the data involving 3662 cases and 4966 controls with α-track radon measurements within the exposure time window (ETW) 5–30 yr prior to the index date considered previously by Krewski et al. (2005). Additional restrictions focused on subjects for which a greater proportion of the ETW was covered by measured rather than imputed radon concentrations, and on subjects who occupied at most two residences. The estimated odds ratio (OR) of lung cancer generally increased with radon concentration. The OR trend was consistent with linearity ($p = .10$), and the excess OR (EOR) was 0.10 per Bq/m^3 with 95% confidence limits (–0.01, 0.26). For the subset of the data considered previously by Krewski et al. (2005), the EOR was 0.11 (0.00, 0.28). Further limiting subjects based on our criteria (residential stability and completeness of radon monitoring) expected to improve radon dosimetry led to increased estimates of the EOR. For example, for subjects who had resided in only one or two houses in the 5–30 ETW and who had α-track radon measurements for at least 20 yr of this 25-yr period, the EOR was 0.18 (0.02, 0.43) per 100 Bq/m^3. Both estimates are compatible with the EOR of 0.12 (0.02, 0.25) per 100 Bq/m^3 predicted by downward extrapolation of the miner data. Collectively, these results provide direct evidence of an association between residential radon and lung cancer risk, a finding predicted by extrapolation of results from occupational studies of radon-exposed underground miners.

Radon-222 (denoted radon) is a noble gas with a half-life of 3.8 d. It is formed from radium-226, which is the fifth decay product of uranium-238. Uranium and radium occur naturally in soils and rocks, providing a continual source of radon. Radon can migrate from rocks and soils into enclosed areas, such as mine tunnels and houses. Radon is also present at very low levels in ambient air, although in certain circumstances, outdoor radon levels may exceed indoor air guidelines (Grasty, 1994; Steck et al., 1999). When inhaled into the lung, densely ionizing alpha particles emitted by deposited Po-218 and Po-214, short-lived decay products of radon, can interact with biological tissue leading to DNA damage. Cellular mutagenesis studies, experimental research in several animal species, and epidemiologic studies of underground miners have established radon as a human carcinogen (IARC, 1988).

These findings have led to concerns about the potential impact on lung cancer risk in the general population exposed to relatively low levels of radon in their homes. While dosimetric analysis suggests some radiation dose from inhaled radon impacts other organs, the estimated dose is extremely low, and there is no epidemiologic evidence supporting an association between inhaled radon and cancers in tissues other than the lungs (NRC, 1999).

In 1989, the U.S. Department of Energy (DOE) and the Commission on European Communities (CEC) sponsored a workshop in Arlington, VA, that brought together investigators who had ongoing or planned studies of lung cancer and residential radon to establish a common working framework for the pooling of radon data (DOE/CEC, 1989). Investigators recognized the excess risk due to radon would likely be small, and that because the characterization of historical exposure to radon is problematic and subject to misclassification, large sample sizes would be required to demonstrate a significant excess risk, evaluate subtle patterns of variation in radon risk, and verify extrapolations of risk from miner-based exposure-response models. In 1991 and 1995, the DOE and CEC sponsored subsequent workshops in Arlington and Baltimore to continue the process of harmonizing design protocols to facilitate the eventual pooling of data (DOE/CEC, 1991, 1995a, 1995b). Officials from Health Canada hosted a subsequent planning meeting in October 1995, including the principal investigators for all completed and ongoing North American case-control studies, invited scientists with expertise in radon risk assessment, and representatives from the U.S. DOE, the CEC, and the European pooling project.

These meetings encouraged a collaborative environment among investigators, and established a common set of variables and exposure assessment procedures that provided flexibility to the collaborating investigators to tailor a study design to the unique aspects of their study populations. The common data format was developed by the principal investigators (PIs) for the North American case-control studies at the working group meetings. Following a subsequent planning meeting hosted by Health Canada in June 1997, the data available from the three completed North American case-control studies were included in a pilot analysis (Catalan, 1998). A final data format for the analysis

included age, year of case and control ascertainment, source of information, sex, ethnicity, home sequence identifier, radon concentration in living areas and in basements, radon estimation method, proportion of time spent in the home, smoking, family income, and education (see Appendix). The values of some of these variables (such as education and income) were determined at the time of enrollment of the subjects; others (such as residential radon concentration) were determined on a year-by-year basis in each of the 50 yr prior to enrollment. Not all information was available for all subjects and all studies; however, this format served as the basis for merging of data and developing the analytic file that served as the basis for the combined analysis. Because the goal of the pooling was an analysis of data based on a common set of definitions for variables, results for individual studies using the pooled data may not correspond precisely to results in the original publications. However, there were no substantial differences between results from individual studies in the pooled data and the original published results.

At the time of the initial workshops, completed, ongoing, and planned epidemiologic studies of lung cancer and residential radon were being conducted primarily in the United States, Canada, and Europe. Thus, a natural grouping of studies from North America and from Europe emerged. Expected completion dates for the various studies, as well as the proximity of lead investigators, allowed pooling efforts to proceed on two parallel paths. In the mid-1990s, two collaborative working groups were established, one in North America and one in Europe, to monitor and direct pooling efforts within each region, with agreements to meet regularly to evaluate progress. The working groups functioned independently, but with frequent communication and information sharing. The current report, covering the pooling of data from residential radon studies carried out in North America, is the one of a series of three planned reports. Another describes the analysis of pooled data from European radon studies, while the third will be a world pooling that will combine European and North American studies, as well as any other available studies from other parts of the world. In a related effort Lubin et al. (2004) have analyzed data pooled from two Chinese studies.

Additional pooling studies of residential radon studies that incorporated new glass-based radon detectors are also currently underway in the United States (Iowa and Missouri), with a number of studies in Europe also using glass-based radon dosimetry. Thus, there exists the potential for an international pooling of studies employing this novel method of measuring residential radon exposures.

The North American pooling project included investigators from the seven primary North American case-control studies (denoted Iowa, Missouri-I, Missouri-II, New Jersey, Connecticut/Utah–South Idaho, and Winnipeg). While the Connecticut/Utah–South Idaho study was designed as a single study with common features, we included subjects for Connecticut and Utah-South Idaho separately in the pooled analysis and present results separately, effectively leading to seven studies in North America.

The North American pooling examines data on residential radon exposure and lung cancer for 4420 cases and 5707 controls included in the original publications. This extensive database permits a more detailed examination of radon and lung cancer risk and its potential modifiers than has previously been possible. The specific goals of the analysis of pooled data from studies of indoor radon and lung cancer are as follows:

1. To test the null hypothesis that residential radon does not increase risk of lung cancer.
2. If there is evidence of excess risk, to estimate precisely the effect across all studies.
3. To evaluate the consistency of radon effects among the different studies.
4. To evaluate variations in the exposure-response relationship with other lung cancer risk factors.
5. To compare risk estimates from the pooled residential data with extrapolations from miner-based risk models where typical exposures were higher.
6. To evaluate variations in the exposure-response by histologic type of lung cancer.

After consistently applying the inclusion criteria for the combined analysis, the present report is based on 4081 cases and 5281 controls. Krewski et al. (2005) previously reported results for a subset of 3662 cases and 4966 controls for which α-track measurements were available within the exposure time window (ETW) 5–30 yr prior to the index date. We also consider subsets of the data with additional restrictions focusing on subjects for which a greater proportion of the ETW was covered by measured rather than imputed radon concentrations, and on subjects who demonstrated limited mobility. These restrictions are considered to result in more accurate radon dosimetry.

EPIDEMIOLOGIC STUDIES OF RADON AND LUNG CANCER

Studies of Underground Miners

To date, 11 cohort studies of radon-exposed underground miners, which have included detailed yearly estimates of exposure, have been published. In each of these studies, exposure to radon was associated with an increased risk of lung cancer. A comprehensive analysis of the combined data from these studies revealed conclusively that exposure at high levels of radon is associated with increased risk of lung cancer (Lubin et al., 1994). Subsequently, the U.S. National Academy of Sciences Committee on the Biological Effects of Ionizing Radiation (the BEIR VI Committee) updated the data from those miner studies and extended earlier pooled analyses (NRC, 1988; Thomas & McNeill, 1982) to develop new miner-based risk models (NRC, 1999). In addition, the BEIR VI report outlined a molecular and radiobiological basis for a nonthreshold causal relationship between radon exposure and lung cancer. Using the miner-based

risk models, dosimetric comparisons between exposures in mines and houses, information on the radon concentration distribution in U.S. houses, results of molecular biological studies of radiation effects, and analyses of the physical properties of α-particles, the BEIR VI Committee estimated that 10–15% of the approximately 157,400 lung cancer deaths occurring annually in the United States may be attributable to residential radon, with about one-third of those deaths arising from houses above the action level of 148 Bq/m^3 set by the U.S. Environmental Protection Agency. A formal analysis of statistical variation and other sources of uncertainty suggested a wide range of 3300 to 32,000 lung cancer deaths in the United States per year attributable to residential radon (Krewski et al., 1999). A similar analysis conducted by Brand et al. (2005) using radon concentrations in Canadian homes and Canadian mortality patterns predicted a population attributable risk for lung cancer due to exposure to residential radon of 14%, with a 95% confidence interval of 7–29%. These results are of importance in establishing residential radon exposure guidelines (Spiegel & Krewski, 2002).

Extrapolation from occupationally to residentially exposed populations for radon-attributable lung cancer is subject to additional uncertainties due to differences between the mine and home environments, physical activity levels of miners as compared to the general population, and the absence of miner data for females and for children in studies of miners. The BEIR VI Committee observed that the applicability of the miner-based estimates for residential radon exposure is supported by consistency among three diverse analyses: (1) Mean cumulative radon exposure among miners in the 11 cohort mortality studies was about 20–30 times greater than the exposure received in 30 yr of occupancy in a typical house. The BEIR VI risk models, which reflected the full range of exposures in the miner data, provided an excellent fit to the data from very low exposed miners, in particular those under 50 WLM [1 WLM (working level month) indicates exposure to 1 WL (working level) for 170 h, where 1 WL is equal to approximately 3700 Bq/m^3], an exposure that may be experienced by long-term residents in high-radon houses. (2) A linear excess relative risk model developed from data on low-exposed miners and the miner-based risk model developed from data on all miners predicted comparable lung cancer risks for residential radon exposures (NRC, 1999; Lubin et al., 1997). (3) Comparisons of miner-based risk estimates per unit exposure with the results from a meta-analysis of published data from 13 residential radon studies also revealed compatible results (Lubin, 1999).

Studies of Lung Cancer and Residential Radon Exposure

While results of miner studies are unambiguous in demonstrating an excess risk from radon exposure, airborne contaminants in mines, differences in breathing characteristics of miners and residents at home, and other differences in the environments of mines and homes are substantial. As noted previously, the miner studies provide no direct information on radon lung cancer risks in females or children. Thus, it is important to evaluate directly whether

residential radon exposure is associated with lung cancer risk (Samet & Nero, 1989), and confirm the extent to which exposure-related risks in mines and homes are comparable.

To date, 20 case-control studies of residential radon and lung cancer with at least 200 cases and α-track radon measurements have been completed, including 7 studies in North America, 11 in Europe, and 2 in China (Table 1). Some of these studies reported a positive or weakly positive association between lung cancer risk and residential radon concentration, while others have reported results consistent with no association. To date, no case-control study has reported a statistically significant protective association. While risk estimates from meta-analyses of published residential studies are consistent with miner-based extrapolations, the meta-analyses also revealed significant heterogeneity of results across the residential studies. The reasons for this heterogeneity are not clear, but may relate to differences in study methodology, differences in the extent of exposure misclassification, or inadequate control of confounding (Catalan, 1998; Field et al., 2002).

TABLE 1. Case-Control Studies of Residential Radon and Lung Cancer[a]

Region	Number of cases	Number of controls	Average radon concentration (Bq/m^3)	Reference
North American				
New Jersey (NJ)	480	442	26	Schoenberg et al. (1992)
Winnipeg (Winn)	738	738	142	Létourneau et al. (1994)
Missouri-I (MO-I)	538	1183	63	Alavanja et al. (1994)
Missouri-II (MO-II)	512	553	56	Alavanja et al. (1999)
Iowa (IA)	413	614	127	Field et al. (2000a)
Connecticut (CT)	963	949	33	Sandler et al. (1999)
Utah–South Idaho (UT-ID)	511	862	57	Sandler et al. (1999)
Europe				
Sweden (Stockholm)	201	378	128	Pershagen et al. (1992)
Sweden (national)	1281	2576	107	Pershagen et al. (1994)
South Finland	291	495	213	Ruosteenoja et al. (1996)
Finland (national)	517	517	96	Auvinen et al. (1996)
Southwest England	982	3185	56	Darby et al. (1998)
Italy	387	406	94[a]	Bochicchio et al. (1998)
East Germany	1192	1640	74	Kreuzer et al. (2003)
West Germany	1449	2297	50	Krienbrock et al. (2001)
Sweden (non-smokers)	258	487	79	Lagarde et al. (2001)
France	552	1103	148	Baysson et al. (2002)
Czech Republic	210	12004[b]	519	Tomasek et al. (2001)
China				
Shenyang	308	356	85[c]	Blot et al. (1990)
Gansu	768	1659	223	Wang et al. (2002)

[a] Includes studies with at least 200 cases and α-track radon measurements.
[b] Study population.
[c] Median household radon level.

MATERIAL AND METHODS

For the current pooled analysis, we included data from seven case-control studies conducted in North America (Schoenberg et al., 1990; Létourneau et al., 1994; Alavanja et al., 1994, 1999; Field et al., 2000a; Sandler et al., this issue). A detailed summary of the results of each study is given in Appendix A. Tables 2 and 3 provide a brief description of the study designs, and the numbers of cases and controls available for pooling. Studies included in this pooling represent all studies satisfying the following criteria: a case-control design conducted in North America; ascertainment of at least 200 lung cancer cases with a majority histologically or cytologically confirmed; radon exposure estimates based primarily on long-term α-track detectors located in living areas of homes; and in-person or telephone interviews with subjects or next of kin to obtain data on a variety of demographic, socioeconomic, and smoking-related factors.

Source of Data

Characteristics of the subjects participating in the seven North American case-control studies that form the basis for the present combined analyses are given in Table 2. In all studies, cases were ascertained through state and provincial cancer registries and were histologically confirmed. New Jersey and Iowa identified cases through rigid reporting criteria based on hospital pathology records and death certificates as well as the state cancer registry (Schoenberg et al.,1990; Field et al., 2000a). In the Missouri and Iowa studies, the registry reported histologic type was independently verified by microscopic examination of the tissues by experienced pathologists (Field et al., 2004; Brownson et al., 1995).

In three of the seven studies (Connecticut, Utah-South Idaho, and Winnipeg), controls were selected by random digit dialing (Sandler et al., this issue; Létourneau et al., 1994). Driver's license and health care financing records were used to identify controls in Iowa (Field et al., 2000a), Missouri-I (Alavanja et al., 1994) and Missouri-II (Alavanja et al., 1999), New Jersey (Schoenberg et al., 1992), and for those 65 yr and older in Utah–South Idaho. Death certificates were used as the source of controls for proxy-interviewed cases in New Jersey.

All studies matched controls to cases on the basis of age (±5 yr) and sex (Iowa, Missouri-I, and New Jersey included only females). Race was used as a matching variable in New Jersey. Smoking status was used as a matching variable in Connecticut and Utah–South Idaho (based on smoking status 10 yr prior to interview) and in Missouri-II. Frequency matching or randomized recruitment was used for control selection, except in New Jersey and Winnipeg, where pair matching was used.

Principal investigators from the seven studies provided the analytic team with data on 10,127 subjects (Table 3). Of these, 686 subjects had no radon measurements, 30 subjects had no residence data within the 5–30 yr ETW, and 49 subjects had insufficient smoking information. These subjects were

TABLE 2. Characteristics of North American Case-Control Studies of Residential Radon and Lung Cancer

Study	Source of subjects		Years of ascertainment	Matching	Histologic diagnosis	Subjects selection	
	Cases	Controls				Cases	Controls
NJ	1. Rapid reporting system with hospital pathology departments 2. Hospital pathology records, state cancer registry, and death certificate files	Controls matched for live cases and matching of controls to cases for deceased cases. 1. Live cases: driver license (<65 yrs), Medicare files (65+) 2. Deceased cases: death certificates	Cases 1982–1984 Controls 1982–1983	Respondent type (P); 1. Live (Direct): age and race (FM) 2. Deceased (proxy): age, race, closest date of death (P)	Histologic type relied on outside pathology reports	480 Females = 48% of 994 interviewed, 37% of 1306 eligible No radon measurements were available for an additional 87 homes	442 Females = 44% of 995 interviewed 30% of 1449 eligible
Winn	Manitoba Registry	Phone directory	Cases 1983–1990 Controls 1983–1990	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	Missouri Cancer Registry	Driver licence (30–64 yr) Medicare files (65–84 yr)	Cases 1986–1991 Controls 1986–1991	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	Missouri Cancer Registry	Driver licence (30–64 yr) Medicare files (65–84 yr)	Cases 1993–1994 Controls 1993–1994	Two-stage randomized recruitment procedure; age, sex, smoking status (F)	Precise histologic confirmation by 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	Iowa SEER Cancer Registry with 90% of subjects rapidly reported	Driver licence (40–64 yr) Medicare files (65–84 yr)	Cases 1993–1996 Controls 1993–1996	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 46% of 1337 eligible completed questionnaires and had complete dosimetry

(Continued)

TABLE 2. *(Continued)*

Study	Source of subjects		Years of ascertainment	Matching	Histologic diagnosis	Subjects selection	
	Cases	Controls				Cases	Controls
CT	Cancer registries and medical record review	Random telephone screening	Cases 1989–1992 Controls 1990–1993	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	Cancer registries and medical record review	Random telephone screening	Cases 1989–1992 Controls 1989–1992	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 #'s 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. F, Female-restricted study; M & F, males and females included; FM, frequency matching; P, pairwise matching.

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

TABLE 3. Availability of Residential Radon Measurements and Smoking Information

	Number of subjects		Number of Subjects Excluded						Number of subjects retained for analysis	
			No smoking data		No radon data		No residence data[a]			
Study	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
NJ	480	442							480	442
Winn	738	738	9	4	1	2	20	10	708	722
MO-I	618	1402	7	1	81	224			530	1177
MO-IIa[b]	697	700	20	8	200	176			477	516
MO-IIg[b]	697	700	20	8	289	219			388	473
IA	413	614			1	1			412	613
CT	963	949							963	949
UT-ID	511	862							511	862
Subtotal	4,420	5707	36	13	283	403	20	10	4081	5281
Total[c]	10,127		49		686		30		9362	

[a] Within 5–30 yr exposure time window.
[b] Dosimetry based on air radon detectors (a) or CR-39 on glass artifact detectors (g).
[c] Total excludes MO-IIg data.

excluded from the pooled analyses. All analyses are based on the remaining 9362 subjects. This included a subset of the data involving 3662 cases and 4966 controls with α-track radon measurements within the exposure time window (ETW) 5–30 yr prior to the index date considered previously by Krewski et al. (2005).

Common Data Format for the Combined Analysis

The data have been submitted to the analytic team according to the format described in Appendix. The common format includes both fixed variables determined at the index date (the date of diagnosis for cases, and date of interview for controls) (see Appendix, Table A1) and year-by-year variables for up to 50 yr prior to the index date (Table A2).

Covariates included year of ascertainment or index date (year of diagnosis for cases and year of interview for controls), age at the index date, sex, source of information (subject or proxy), and number of hours worked per week at age 40 yr (Table A1). Education and income level were specified as three- and five-level categorical variables, respectively. In some cases, the optimum data set for each study could not be used in order to obtain a common data set. For example, the Iowa study assessed the retrospective within-home mobility of each subject, which was not used in the common data set.

The database included several smoking-related covariates, including smoking status (never-smoked, cigarettes only, pipe/cigar only, or mixed); number of cigarettes smoked on average per day during the entire interval when the person was an active smoker; age at start of cigarette smoking; age at cessation of smoking; and duration of cigarette smoking. Noncigarette smokers were those who smoked for less than 1 yr or less than 100 cigarettes in a lifetime; *mixed* refers to those smoking both cigarettes and pipes or cigars. Those subjects with no information on smoking status were eliminated from the database prior to analysis. Two additional variables, one that identified the phase of recruitment in the Connecticut/Utah-South Idaho study and another providing an offset based on the ratio of sampling probabilities for cases versus controls sampled under randomized recruitment, were used in the Connecticut/Utah–South Idaho and Missouri-II studies.

Year-by-year variables included the annual radon concentration in the living area (Bq/m^3) and the method of measurement. Although all studies used air-based radon dosimeters, radon measurements derived from glass artifacts were available only for the Missouri-II study. The Iowa study also estimated retrospective radon progeny by use of glass-based dosimeters (Field et al., 1999); however, those data were not available for this pooled analysis. Although the present combined analysis used only radon gas measurements, some limited comparisons between gas and glass-based radon dosimetry will be made using the data from Missouri-II. The Winnipeg, New Jersey, and Iowa studies included basement radon concentration measurements in order to monitor the generally higher radon concentrations in the basement as compared with the living area. As radon concentrations for prior houses were sometimes missing, imputed concentrations for missing houses were based on the best estimates derived by each PI.

Radon Dosimetry

All of the seven North American case control studies used alpha track detectors as the principal method to measure the concentration of radon progeny in indoor air (Table 4). Contemporaneous measurements were made in homes that the subjects had occupied or were currently occupying, and were used as an indicator of historical radon concentrations in those homes. Detectors were placed in the living area and bedroom areas of the home in which subjects were expected to spend the majority of their time. Although investigators in the Iowa study also incorporated estimates of nonresidential radon exposures (including both occupational and ambient exposures) into their overall radon exposure assessment, these nonresidential exposures were not included in the combined analysis in order to maintain comparability with the radon dosimetry in the remaining six studies. Ignoring nonresidential exposures will have some impact on the estimated lung cancer risk associated with residential radon exposures, although this effect is generally thought to be small (Lubin, 1998).

TABLE 4. Radon Dosimetry in the North American Case-Control Studies of Residential Radon and Lung Cancer

Study	Duration and method	Residence inclusion criteria	Location of dosimeter placement	Exposure time window	Exposure time window (ETW) coverage	Method of imputing missing data
NJ	1 yr ATD T, some short-term charcoal canister detectors	Last NJ residence of ≥10 years during the period 10–30 yr prior to dx or selection.	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 yr: 20 yr (cases) and 21 yr (controls); 82% cases and 79% controls resident >15 yr	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)	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: living cases: 78.5%; deceased cases: 76%; controls: 78.8%	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 (each other no differences for both method, but values by RSM significantly higher than that by ATD).	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.	Annual means were used for imputation of missing values for both measure methods

(Continued)

TABLE 4. *(Continued).*

Study	Duration and method	Residence inclusion criteria	Location of dosimeter placement	Exposure time window	Exposure time window (ETW) coverage	Method of imputing missing data
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.	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 years 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.	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.

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 most studies, an attempt was made to monitor all in-state homes occupied for a period of at least 1 yr within the ETW of interest. In Winnipeg, radon measurements were made in all homes occupied by study subjects within the Winnipeg metropolitan area. In New Jersey, only the last residence occupied for at least 10 yr during the period 10–30 yr prior to recruitment was monitored. A small number of measurements (8%) were made using charcoal canisters rather than track detectors in New Jersey. The Iowa study also measured only 1 home, but the participants were required to have occupied this home for at least 20 yr.

Radon Exposure Assessment

Although some investigators monitored radon in homes occupied by study subjects as much as 50 yr prior to recruitment (Létourneau et al., 1994), the combined analysis of the 7 North American case-control studies of residential radon and lung cancer focuses on the ETW 5–30 yr prior to the index date, the period identified by the National Research Council (1999) as being most relevant for lung cancer risk. Restriction of radon exposure assessment to this period presumes that neither radon exposure within 5 yr of lung cancer occurrence nor 30 yr or more prior to the index date contributes to lung cancer risk.

Average radon exposures in the 5–30 yr ETW are shown in Table 5 for cases, controls, and for cases and controls combined. Average radon exposures were calculated first by both treating all exposures occurring in the 5–30 yr ETW as equally important (time weighted average) and treating exposures occurring farther in the past as decreasing in importance (BEIR VI weighted average). In the latter case, exposures occurring 5–14, 15–24, and 25 yr or more prior to the index date were assigned weights of 1.0, 0.8, and 0.3, respectively (NRC, 1999).

TABLE 5. Estimated Average Radon Concentration in the 5–30 yr Exposure Time Window

	Time-weighted average[a] (Bq/m^3)			BEIR VI weighted average[b] (Bq/m^3)		
Study	Cases	Control	All subjects	Cases	Controls	All subjects
NJ	26.5	24.9	25.7	20.7	19.3	20.1
Winn	137.4	146.9	142.2	107.8	115.4	111.6
MO-I	62.2	62.9	62.7	48.6	49.2	49.0
MO-II	55.3	56.1	55.7	43.1	43.7	43.4
IA	136.2	121.3	127.3	106.4	94.5	99.3
CT	32.2	32.8	32.5	25.2	25.5	25.3
UT-ID	55.4	58.1	57.1	43.1	45.4	44.6

[a] Exposure determined using weights of 1.0 for exposures received in each year.

[b] Exposure determined using weights of 1.0, 0.8, and 0.3 for exposures received 5–14, 15–24, and 25 yr and more prior to the index date.

Statistical Methods

All analyses of the data were conducted using conditional likelihood regression for matched or stratified data (Breslow & Day, 1980). A preliminary analysis suggested that regression models for the evaluation of radon effects should include five covariates: sex, age at index date (under 50, 50–54, 55–59, 60–64, 65–69, 70–74, 75 yr and over), number of cigarettes smoked per day (nonsmoker, 1–9, 10–19, 20–29, and 30 cigarettes per day and more), duration of cigarette smoking (nonsmoker, 1–24, 25–34, 35–44, and 45 yr and longer), and an indicator variable for each study. We included these factors as stratification variables in the regression model to control for confounding. We also included an offset parameter to control for the randomized recruitment design in the Connecticut, Utah–South Idaho, and Missouri-II studies.

Further analysis revealed differences by cases and controls in numbers of residences and the number of years with alpha-track monitoring within the ETW, suggesting that number of residences and coverage could potentially confound the relationship between radon and lung cancer. The selected stratification factors were therefore enlarged to include categorical indicators of the number of residences and years with alpha-track measurements within the ETW, in addition to study, sex and categories of age, number of cigarettes smoked per day, and duration of cigarette smoking.

Analyses were based on a linear model for the odds ratio (OR) of the form

$$OR(x) = 1 + \beta x$$

where x is the radon concentration (Bq/m^3) and β is the excess odds ratio (EOR) for each unit increase in x. This model was fit using the PECAN module in the Epicure software package, which calculates parameter estimates under conditional analytic methodology (Preston et al., 2000). Results are based on the best estimates of radon concentrations, including both measured and imputed radon values supplied by the PIs. There was virtually no difference in the estimated EORs when the imputed values provided by the PIs were replaced with imputed values corresponding to the study-specific control means, as recommended by Weinberg et al. (1996).

Data Restrictions

Our main analyses are based on the full data set comprised of all 9362 subjects, including 4081 cases and 5281 controls. In addition, we also considered restricted data sets for which more accurate retrospective radon dosimetry was available. Specifically, we have examined the consequences of increasingly stringent restrictions on radon dosimetry, based on increasing the number of years in the ETW of interest for which actual (rather than imputed) radon measurements were available for a minimum of 1 yr, and increasing the number of years for which actual radon measurements were available using α-track air monitors. The latter restriction assumes that long-term α-track detectors provide a more accurate indicator of residential radon concentrations than

short-term charcoal canister detectors, which were used to a limited extent in New Jersey. Further restriction focusing on subjects who occupied at most two residences will offset both the reduction in the range of exposures conferred by population mobility (Lubin et al.1995; Field et al. 1996; Warner et al., 1996), and the increased exposure measurement error associated with the monitoring of previous residences. The restricted data sets necessarily involved fewer subjects than the main analysis, reflecting a trade-off between sample size and quality of radon dosimetry.

RESULTS

Characteristics of Study Subjects

Table 6 summarizes the key features of the data from the seven studies. Four studies, Iowa, Missouri-I, Missouri-II, and New Jersey, enrolled females only (1899 cases and 2748 controls), who have historically spent a greater proportion of their time in the home than men. The three remaining studies, Connecticut, Utah–South Idaho, and Winnipeg, contributed 867 female cases and 1031 female controls, for a total of 2766 female cases and 3779 female controls. The database also contains 1315 male cases and 1502 male controls. Information on 55.9% of the cases was collected through personal interviews; the remainder was ascertained from proxy respondents. The majority of the study subjects (86.5%) had some secondary education, 30% had postsecondary education, and 13% had at most elementary schooling. Among cases, 37.1% were diagnosed with adenocarcinoma, 22.4% with squamous-call carcinoma, and 16.3% with small-oat-cell carcinoma. The remaining 24.2% of cases lacked detailed histological information. Smoking status varied among the study participants. The Missouri-I study restricted its target population to former smokers and never smokers. The majority (96%) of cases in the Winnipeg study were ever smokers. Overall, 2925 subjects in the database never smoked tobacco.

Radon Dosimetry

Table 7 summarizes characteristics on the number of houses for which radon levels were measured or imputed. Investigators measured radon using α-track dosimeters in 12,058 residences in the 7 studies combined. The number of monitored residences per subject varied from 1 residence in Iowa to a maximum of 10 residences in Winnipeg; the mean number of α-track measured residences varied from 1 (Iowa) to 1.9 (Winnipeg). The amount of time within the ETW 5–30 yr prior to the index date covered by radon measurements ranged from 65.2% for the Missouri-II study to 92.4% for the Iowa study (Table 8).

Figure 1 shows the distribution of radon concentrations measured by α-track dosimeters in the living area in homes in the seven North American residential radon case-control studies. The mean radon concentrations were highest in Winnipeg (131.1 Bq/m^3) and Iowa (127.3 Bq/m^3), and lowest in Connecticut (32.9 Bq/m^3) and New Jersey (25.1 Bq/m^3). Missouri-I (60.4

TABLE 6. Distribution of Selected Covariates by Study and Sex

		Winn						CT			UT-ID		
Covariate	NJ, Female	Male	Female	Both	MO-I,Female	MO-II, female	IA, Female	Male	Female	Both	Male	Female	Both
Status													
Cases	480	469	239	708	530	477	412	527	436	963	319	192	511
Controls	442	473	249	722	1177	516	613	442	507	949	587	275	862
Histological Type													
Cases													
Squamous	124	180	44	224	21	88	81	157	71	228	114	34	148
Small/Oat Cell	108	70	42	112	10	108	74	72	86	158	57	37	94
Adenocarcinoma	143	130	103	233	259	162	175	187	193	380	86	76	162
Other	105	89	50	139	116	119	82	83	65	148	57	40	97
Uncertain					124			28	21	49	5	5	10
Controls	442	473	249	722	1177	516	613	442	507	949	587	275	862
Interview													
Subject	507	714	396	1110	1373	839	895	689	738	1427	727	378	1105
Proxy	415	228	92	320	334	154	130	280	205	485	179	89	268
Education													
Some elementary school	101	113	45	158	640	150	88	40	16	56	12	3	15
Some secondary school	558	422	242	664	655	609	523	664	666	1330	601	350	951
Some postsecondary	263	407	201	608	412	227	403	252	249	501	285	111	396
Unknown						7	11	13	12	25	8	3	11
Income													
<$10,000		42	39	81	564	284		32	50	82	43	54	97
$10,000–$20,000		200	125	325	585	229		119	148	267	195	133	328
$20,000–$30,000		281	142	423	299	153		201	196	397	249	114	363
$30,000–$40,000		299	127	426	164	124		295	231	526	265	84	349
>$50,000		120	55	175	95	82		242	222	464	113	52	165
Unknown	922					121	1025	80	96	176	41	30	71
Smoking type													
Never smokeed	301	89	157	246	1435	107	470	29	80	109	117	140	257
Cigarettes only	621	661	330	991	272	883	555	937	863	1800	789	327	1116
Pipe/cigar only		24	1	25				3		3			
Mixed		168		168		3							

TABLE 7. Characteristics of Radon Measurement Data in the Period 5–30 yr Prior to Index Date

	Number of residences Rn level measured or imputed			Number of residences Rn level α-track measured		
Study	Cases	Controls	All subjects	Cases	Controls	All subjects
NJ	570	518	1088	505	457	962
Winn	1924	1734	3658	1269	1297	2556
MO-I	808	1841	2649	808	1841	2649
MO-II	582	605	1187	582	605	1187
IA	412	613	1025	412	613	1025
CT	2054	2098	4152	917	997	1914
UT-ID	1430	2155	3585	643	1122	1765
Total	7780	9564	17,344	5136	6922	12,058

	Number of residences measured per subject					
	Cases		Controls		All subjects	
Study	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Range
NJ	1.2 ± 0.4	1–4	1.2 ± 0.4	1–4	1.2 ± 0.4	1–4
Winn	1.8 ± 1.2	0–8	1.8 ± 1.2	0–10	1.8 ± 1.2	0–10
MO-I	1.6 ± 0.8	1–5	1.6 ± 0.8	1–6	1.6 ± 0.8	1–6
MO-II	1.2 ± 0.5	1–4	1.2 ± 0.5	1–4	1.2 ± 0.5	1–4
IA	1.0 ± 0.0	1–1	1.0 ± 0.0	1–1	1.0 ± 0.0	1–1
CT	1.2 ± 0.8	0–5	1.3 ± 0.8	0–5	1.2 ± 0.8	0–5
UT-ID	1.5 ± 1.0	0–6	1.5 ± 0.9	0–6	1.5 ± 1.0	0–6
Total	1.4 ± 0.9	0–8	1.4 ± 0.8	0–10	1.4 ± 0.8	0–10

TABLE 8. Radon Measurement Coverage in the Period 5–30 yr Prior to Index Date

	Years monitored					
	Cases		Controls		All subjects	
Study	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Range
NJ	20.9 ± 4.5	9–25	21.1 ± 4.3	10–25	21.0 ± 4.4	9–25
Winn	16.6 ± 8.8	0–25	18.7 ± 7.8	0–25	17.7 ± 8.3	0–25
MO-I	19.1 ± 7.3	1–25	19.3 ± 7.4	1–25	19.3 ± 7.4	1–25
MO-II	16.1 ± 8.4	1–25	16.5 ± 8.4	1–25	16.3 ± 8.4	1–25
IA	23.3 ± 2.7	16–25	22.9 ± 2.9	16–25	23.1 ± 2.8	16–25
CT	18.4 ± 9.0	0–25	19.0 ± 8.3	0–25	18.7 ± 8.7	0–25
UT-ID	19.0 ± 7.9	0–25	20.1 ± 7.3	0–25	19.7 ± 7.6	0–25
Total	19.6 ± 7.3	0–25	18.8 ± 7.9	0–25	19.2 ± 7.6	0–25

Bq/m^3), Missouri-II (53.4 Bq/m^3), and Utah–South Idaho (58.6 Bq/m^3) demonstrated intermediate radon concentrations. Although glass-based radon measurements are not included in the formal combined analysis, the mean radon concentration based on glass surface monitors in living areas in the Missouri-II study (64.4 Bq/m^3) was somewhat higher than that based on alpha-track detectors.

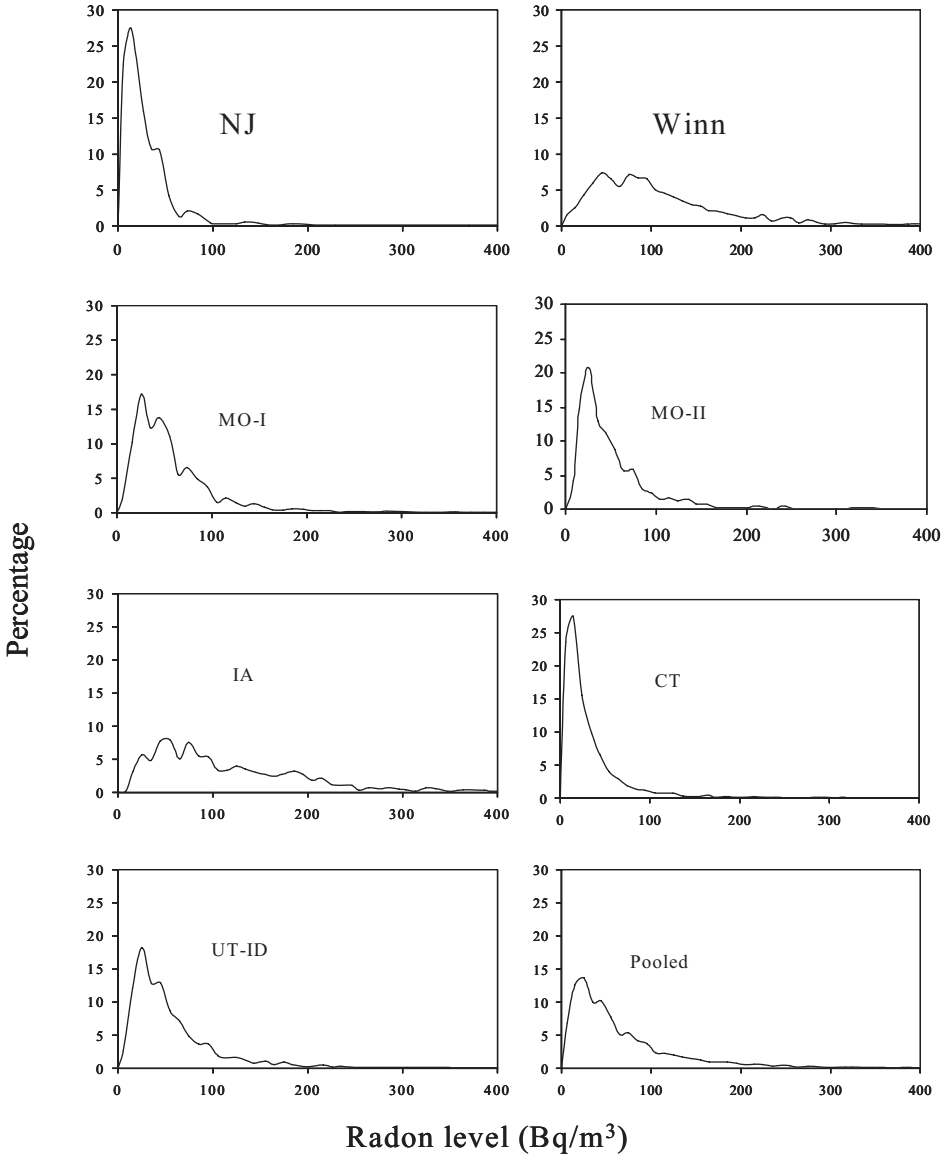

FIGURE 1. Distribution of measured radon levels in North American residential radon case-control studies.

Radon and Risk of Lung Cancer: Study-Specific Results

Table 9 shows ORs by categories of mean radon concentration for each of the 7 studies, 95% confidence intervals (CIs), and the estimated EORs at 100 Bq/m^3. These same results are also presented in Figure 2, where the

TABLE 9. Odds Ratio[a] (OR) of Lung Cancer, 95% Confidence Intervals (CI), and Number of Subjects by Mean Radon Level in the 5–30 yr Exposure Time Interval

		Radon concentration (Bq/m^3)								
Study		<25	25–49	50–74	75–99	100–149	150–199	≥200	Total	$\beta^b \times 100$
NJ	Cases	314	127	23	7	5	4		480	
	Controls	299	118	15	4	5	1		442	
	OR	1	1.14	1.21	1.81	0.49	6.98			0.56
	95% CI		(0.77, 1.68)	(0.49, 2.95)	(0.35, 9.40)	(0.11, 2.32)	(0.70, 70.06)			(–0.22, 2.97)
Winn	Cases		43	62	140	316	67	80	708	
	Controls		26	69	139	298	83	107	722	
	OR		1	0.53	0.74	0.73	0.71	0.77		0.02
	95% CI			(0.23, 1.25)	(0.34, 1.59)	(0.35, 1.53)	(0.31, 1.66)	(0.34, 1.73)		(–0.05, 0.25)
MO-I	Cases	34	189	189	56		62		530	
	Controls	81	411	450	119		116		1177	
	OR	1	0.96	0.86	1.02		1.16			0.01
	95% CI		(0.60, 1.53)	(0.53, 1.38)	(0.58, 1.76)		(0.67, 1.99)			(—, 0.42)
MO-IIa[c]	Cases	43	226	151	27		30		477	
	Controls	39	246	154	33		44		516	
	OR	1	0.84	0.93	1.00		0.99			0.27
	95% CI		(0.46, 1.56)	(0.49, 1.77)	(0.43, 2.28)		(0.44, 2.24)			(–0.12, 1.53)
MO-IIg[c]	Cases	33	113	132	59		51		387	
	Controls	44	131	170	71		57		473	
	OR	1	1.13	1.07	1.09		1.64			0.63
	95% CI		(0.57, 2.14)	(0.62, 1.89)	(0.63, 2.06)		(0.78, 3.34)			(0.02, 2.13)
IA	Cases		69	73	59	80	66	65	412	
	Controls		104	110	110	120	85	84	613	
	OR		1	1.56	1.31	1.79	2.06	1.93		0.44
	95% CI			(0.84, 2.91)	(0.69, 2.47)	(0.97, 3.31)	(1.07, 3.95)	(1.01, 3.68)		(0.05, 1.59)

(Continued)

TABLE 9. *(Continued).*

Study		Radon concentration (Bq/m^3)							Total	$\beta^b \times 100$
		<25	25–49	50–74	75–99	100–149	150–199	≥200		
CT	Cases	525	302	77	23		36		963	
	Controls	495	302	82	33		37		949	
	OR	1	1.11	0.97	0.62		0.92			0.02
	95% CI		(0.85, 1.43)	(0.63, 1.49)	(0.31, 1.24)		(0.51, 1.68)			(–0.21, 0.51)
UT-ID	Cases	66	225	129	44		47		511	
	Controls	109	374	207	69		103		862	
	OR	1	1.17	1.15	1.47		0.99			0.03
	95% CI		(0.74, 1.84)	(0.70, 1.89)	(0798, 2.75)		(0.55, 1.78)			(–0.20, 0.55)
Total[d]	Cases	994	1169	704	356	513	166	179	4081	
	Controls	1055	1549	1087	507	602	229	252	5281	
	OR	1	1.13	1.05	1.14	1.22	1.19	1.29		0.10
	95% CI		(0.94, 1.31)	(0.86, 1.27)	(0.90, 1.45)	(0.95, 1.56)	(0.86, 1.66)	(0.93, 1.80)		(–0.01, 0.26)

[a] ORs stratified by sex and categories of age, duration of smoking and number of cigarettes smoked per day, number of residences and years with α-track measurements in the exposure time window.

[b] Excess OR (β) based on the linear model: $OR(x) = 1 + \beta x$, where x is the mean radon concentration in the 5–30 yr exposure time window.

[c] Dosimetry based on air radon detectors (a) or CR-39 on glass artifact detectors (g).

[d] Totals and ORs exclude MO-IIg data.

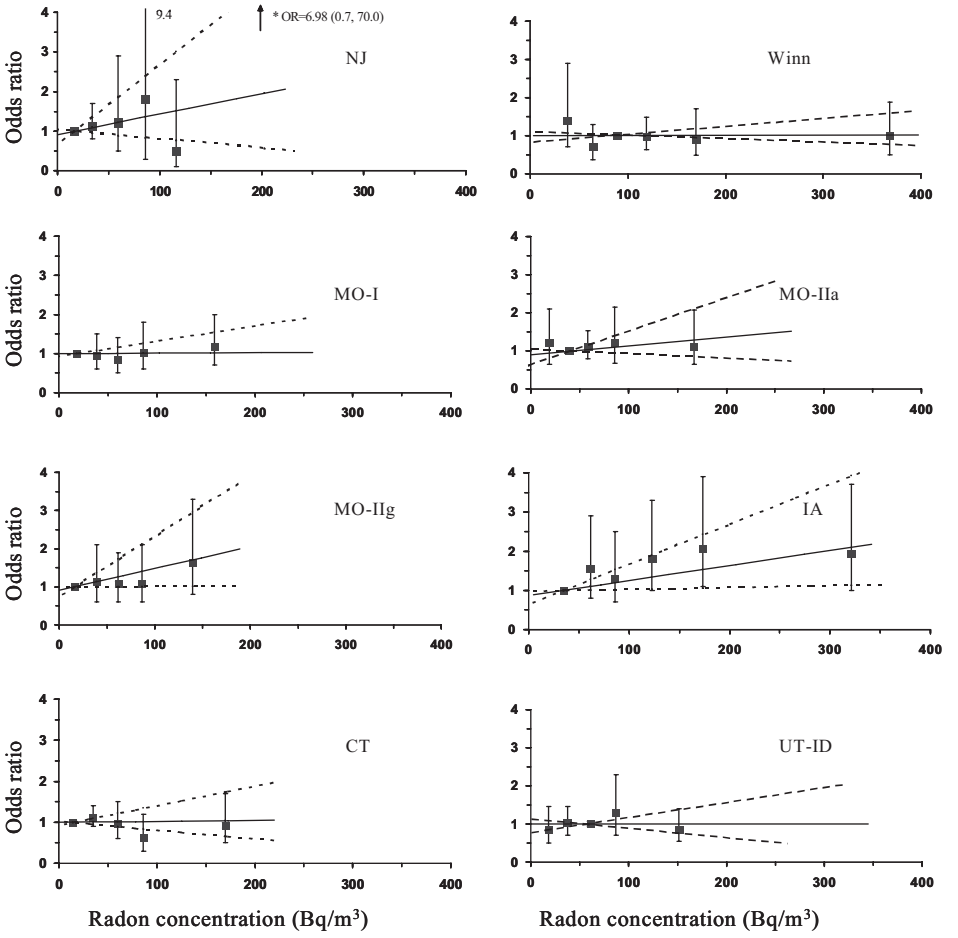

FIGURE 2. Odds ratios and 95% confidence intervals (CIs) for categories of mean radon concentration within 5–30 yr exposure time window, the fitted model for the linear excess odds ratio (solid line), and its 95% CI (dotted lines) for each study. Results for Missouri-II shown for dosimetry based on air radon monitors and on surface radon monitors.

abscissa of each category-specific OR is given by the mean radon concentration within its category. In general, the fitted exposure-response lines were adjusted to pass through the first (lowest) radon category to allow for a comparison of the fitted lines to the category-specific ORs. However, for the Winnipeg and Utah–South Idaho data, the fitted lines were adjusted to pass through the third radon category, while for Missouri-IIa (based on air rather than glass radon measurements), the fitted lines were adjusted to pass through the second category to show the general trend in the data. This adjustment did not impact the fitting of the exposure-response relationship, since the reference category is arbitrary and any baseline category is valid for comparative purposes.

Although some variability was observed among individual studies (Table 9, last column), differences in radon risk estimates were not statistically significant ($p = .44$). ORs increased significantly across radon exposure categories for the Iowa study and the Missouri-IIg study (based on glass α-track detectors). All other studies showed results consistent with no increased risk from residential radon exposure. None of the studies showed a significant decrease in lung cancer risk in relation to residential radon exposure.

Relative to the lowest category of radon, 15 of 31 ORs exceeded 1.0. These results provide no evidence of departures from the null hypothesis of no radon effect using a simple sign test to determine if there are more ORs exceeding unity than would be expected by chance under a binomial probability model ($p = .5$).

Misspecification of exposures generally (although not always) leads to bias in the exposure-response relationship toward a null association (Dosemeci et al., 1990; Wacholder et al., 1995; Field et al., 2002). As noted previously (Table 8), the proportion of the 5–30 yr ETW for which radon measurements were available varied appreciably among the 7 studies included in the combined analysis. It is reasonable to assume that the greater the proportion of the 5–30 yr ETW for which measured (as opposed to imputed) radon concentrations are available, the more accurate is the radon exposure ascertainment for study subjects. In addition, mobility will tend to reduce the range of radon exposures among the study subjects, and thereby decrease statistical power to detect an association between radon and lung cancer (Lubin et al., 1995; Field et al., 1996, 1998a). Examination of results for the restricted data sets provides an indication of the effects of improved radon dosimetry on radon risk estimates.

Table 10 and Figure 3 show results of analyses based on data restricted to subjects with radon measurements based on long-term alpha-track detectors for at least 20 of the 25 yr in the 5–30 yr ETW, and who had occupied a maximum of 2 residences during this period. Slopes for the linear EOR model in this restricted data set were positive for six studies (reaching the traditional 5% level of statistical significance in Iowa) and (nonsignificantly) negative in New Jersey. The observed differences in the EORs across studies (Table 10, last column) were not statistically significant ($p = .82$). Relative to the lowest category of radon, 18 of 30 ORs exceeded 1.0 ($p = .10$ for the sign test of no association between radon and lung cancer).

Radon and Risk of Lung Cancer: Pooled Results

Figure 4 shows category-specific ORs for each study and summary ORs (denoted by stars) for all studies combined. Using all of the available data (Table 9, last row), ORs exhibited marked variability, but tended to increase with increasing radon concentration. Based on a linear OR model, the EOR at 100 Bq/m^3 was 0.10 with 95% CI of (–0.01, 0.26) and did not reach the traditional level of statistical significant.

TABLE 10. Odds Ratio[a] (OR) of Lung Cancer, 95% Confidence Intervals (CI), and Number of Subjects by Mean Radon Level in the 5–30 yr Exposure Time Interval, with Data Restricted to Subjects Residing in 1 or 2 Houses in the Exposure Window and with 20 yr or More Covered by α-Track Air Monitors

		Radon concentration (Bq/m^3)								
Study		<25	25–49	50–74	75–99	100–149	150–199	≥200	Total	$\beta^b \times 100$
NJ	Cases	148	71	13	4	3	3[f]		242	
	Controls	134	68	10	3	5	—		221	
	OR	1	0.82	1.10	0.65	0.27	—			–0.11
	95% CI		(0.47, 1.46)	(0.34, 3.51)	(0.05, 7.87)	(0.04, 1.84)				(–0.41, 1.34)
Winn	Cases	31		30	43	55	33	48	240	
	Controls	21		36	53	78	42	69	299	
	OR	1		1.03	1.78	0.77	1.90	1.13		0.08
	95% CI			(0.33, 3.27)	(0.60, 5.27)	(0.29, 2.06)	(0.55, 6.56)	(0.40, 3.21)		(–0.04, 0.69)
MO-I	Cases	27	98	62	31		44		262	
	Controls	71	222	142	73		78		586	
	OR	1	1.01	1.00	0.99		1.35			0.07
	95% CI		(0.59, 1.72)	(0.57, 1.75)	(0.51, 1.92)		(0.72, 2.52)			(—, 0.66)
MO-IIa[c]	Cases	36	71	38	15		24		184	
	Controls	31	84	35	22		37		209	
	OR	1	0.43	1.02	0.71		0.57			0.07
	95% CI		(0.19, 0.98)	(0.41, 2.57)	(0.25, 1.98)		(0.21, 1.54)			(–0.34, 1.56)
MO-IIg[c,d]	Cases	31	90	91	44		43		298	
	Controls	43	113	131	56		51		394	
	OR	1	1.03	1.07	1.03		1.56			0.55
	95% CI		(0.45, 2.01)	(0.51, 1,97)	(0.54, 2.12)		(0.68, 3.26)			(0.00, 2.11)
IA	Cases	64		62	47	69	56	56	354	
	Controls	100		82	83	94	68	73	500	
	OR	1		2.10	1.68	2.02	2.43	1.90		0.33
	95% CI			(1.07, 4.11)	(0.84, 3.38)	(1.04, 3.92)	(1.21, 4.89)	(0.97, 3.72)		(–0.01, 1.34)
CT	Cases	240	96	37	13		30		416	
	Controls	248	98	39	19		21		425	
	OR	1	1.15	1.27	0.78		1.37			0.22
	95% CI		(0.73, 1.79)	(0.67, 2.39)	(0.31, 1.94)		(0.66, 2.81)			(–0.17, 1.13)

(Continued)

TABLE 10. *(Continued)*

Study		Radon concentration (Bq/m^3)							Total	$\beta^b \times 100$
		<25	25–49	50–74	75–99	100–149	150–199	≥200		
UT-ID	Cases	40	62	53	28		29		212	
	Controls	81	155	74	40		61		411	
	OR	1	1.00	1.58	1.62		1.44			0.57
	95% CI		(0.55, 1.84)	(0.79, 3.15)	(0.71, 3.70)		(0.67, 3.11)			(–0.08, 2.68)
Total[e]	Cases	503	481	295	181	202	115	133	1910	
	Controls	596	717	418	293	282	160	185	2651	
	OR	1	1.01	1.29	1.22	1.28	1.41	1.37		0.18
	95% CI		(0.80, 1.28)	(0.98, 1.70)	(0.88, 1.69)	(0.91, 17.8)	(0.93, 2.14)	(0.91, 2.06)		(0.02, 0.43)

[a] ORs stratified by sex and categories of age, duration of smoking, number of cigarettes smoked per day, number of residences and years with α-track measurements in the exposure time window.

[b] Excess OR (β) based on the linear model: $OR(x) = 1 + \beta x$, where x is the mean radon concentration in the 5–30 yr exposure time window.

[c] Dosimetry based on air radon detectors (a) or CR-39 on glass artifact detectors (g).

[d] Data restriction based on 20 yr or more coverage of exposure time window by CR-39 on glass artifact detectors.

[e] Totals and ORs exclude MO-IIg data.

[f] Odds ratio not reported because estimation algorithm did not converge.

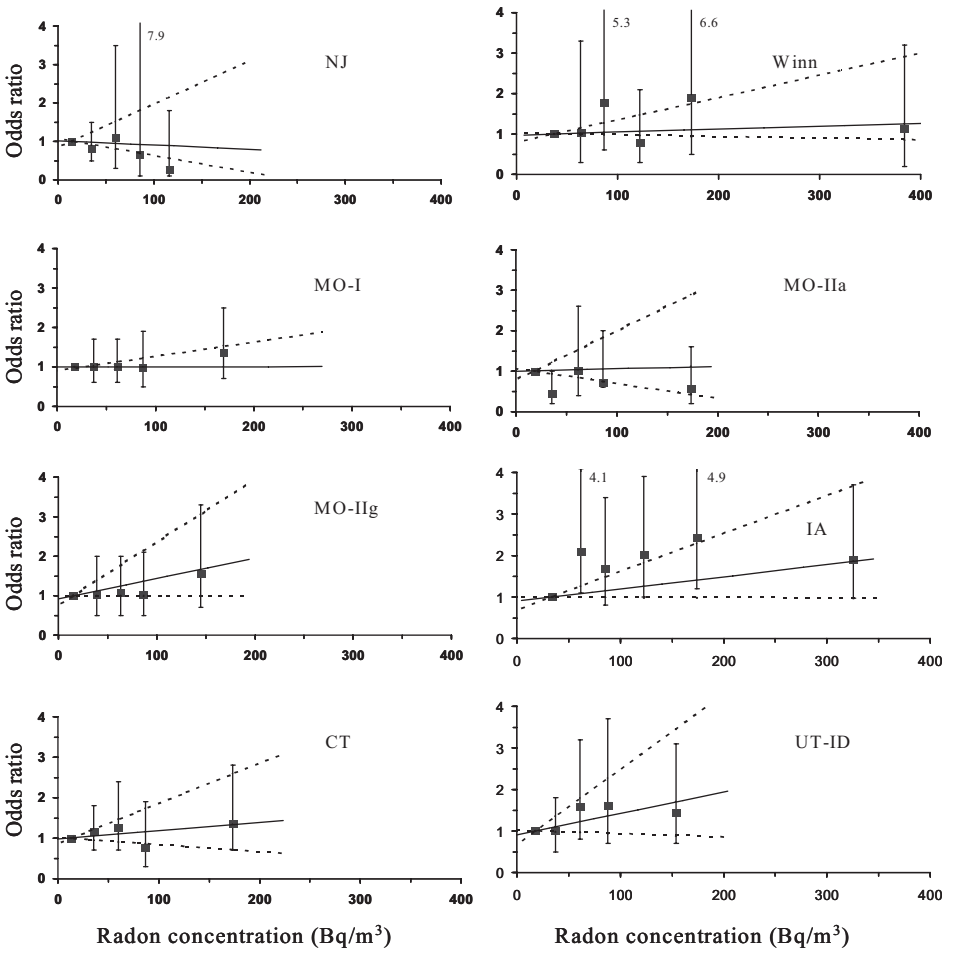

FIGURE 3. Odds ratios and 95% confidence intervals (CIs) for categories of mean radon concentration within 5–30 yr exposure time window, the fitted model for the linear excess odds ratio (solid line), and its 95% confidence limits (dotted lines) for each study. Results for Missouri-II shown for dosimetry based on air radon monitors and on surface radon monitors. Data limited to subjects residing in 1 or 2 residences during the exposure window, and at least 20 yr of coverage with α-track air monitors.

Table 11a illustrates the consequences of increasingly stringent restrictions on radon dosimetry, based on increasing the number of years in the ETW of interest for which actual (rather than imputed) radon measurements were available, and increasing the number of years for which actual radon measurements were available using α-track air monitors. The EOR was greater the more restrictive the criteria, both for an increasing number of years covered by actual radon measurements, and for the use of long-term alpha-track air monitors.

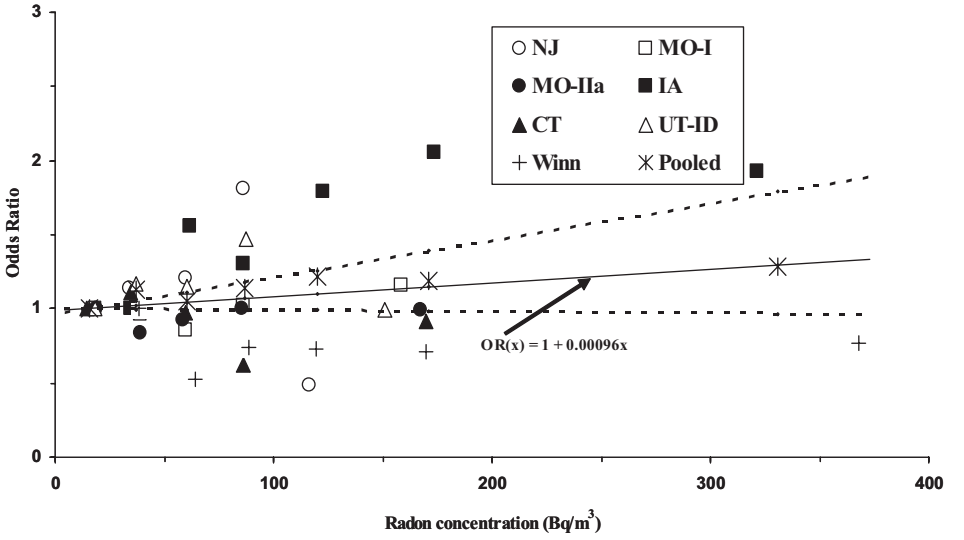

FIGURE 4. Odds ratios for categories of mean radon concentration within 5–30 yr exposure time window, and the fitted model for the linear excess odds ratio (solid line) and its 95% confidence limits (dotted lines) for all studies combined.

TABLE 11a. Excess Odds Ratio[a] (β) for Radon Concentration by Years in the 5–30 yr Exposure Window Covered by Air Radon Detectors

Restrictions	$\beta \times 100$	(95% CI)	Cases	Controls
Any radon estimate[b]	0.10	(–0.01, 0.26)	4081	5281
Years measured:				
>0	0.10	(–0.01, 0.26)	3883	5157
≥10	0.10	(–0.00, 0.27)	3427	4593
≥15	0.09	(–0.02, 0.25)	3032	4126
≥20	0.10	(–0.01, 0.28)	2489	3423
25	0.18	(0.01, 0.44)	1807	2517
Years measured with α-track air monitors				
>0	0.11	(0.00, 0.28)	3662	4966
≥10	0.13	(0.01, 0.32)	3148	4321
≥15	0.13	(0.00, 0.31)	2764	3857
≥20	0.14	(0.01, 0.35)	2263	3172
25	0.21	(0.03, 0.50)	1621	2323

[a] Based on the linear odds ratio model: $OR(x) = 1 + \beta x$, where x is the mean radon concentration in the 5–30 yr exposure time window. Models stratified by study, sex and categories of age, duration of smoking, number of cigarettes smoked per day, number of residences, and years with α-track measurements in the exposure time window.

[b] Includes 181 (Connecticut), 60 (Utah), and 81 (Winnipeg) subjects with no radon measurements within the 5–30 yr exposure time window.

To examine the possibility that the results in Table11a were the consequence of differentially increasing restrictions on negative studies showing no apparent association between radon and lung cancer, we calculated the proportions of cases and of controls from each study that contributed to the estimates in Table 11a. As seen in Table 11b and Figure 5, there were only minor changes in the relative contributions of each study with increasing restriction stringency, consisting of slightly larger proportions of subjects from Iowa (cases and controls) and Connecticut (cases only), smaller proportions from Missouri-II and Winnipeg, and similar proportions from Missouri-I, New Jersey, and Utah–South Idaho. Consequently, there was no indication that the increasing EORs seen in Table 11a with increasing restriction stringency were the result of differences in the relative contributions of the various studies to the combined database.

For subjects residing in 1 or 2 houses during the exposure window and with 20 yr or more covered with alpha-track air monitors, the EOR at 100 Bq/m^3 was 0.18 with 95% CI of (0.02, 0.43) (Table 12a and Figure 6). The analyses summarized in Tables 11a and Tables 11b and Figure 5 were repeated using data from subjects who resided in only 1 or 2 houses during the 5–30 yr ETW (Tables 12a and 12b, Figure 7). Comparing Tables 11a and 12a, EORs were uniformly larger when data were restricted to subjects living in one or two houses. Restrictions based on years measured or years measured with alpha-track air monitors resulted in similar patterns of increasing EORs with increasing restriction stringency. Again, there was no indication that differences in the EORs were the result of changes in the relative contributions of the various studies (Table 12b and Figure 7).

Application of BEIR VI Weights for Time Since Exposure

Using data from radon-exposed underground miners, the BEIR VI Committee developed two risk models for lung cancer from exposure to radon and radon progeny (NRC, 1999). In those models, risk of lung cancer from exposure to radon decreased with increasing time since the exposure occurred, with exposures 5–14 yr, 15–24 yr, and 25 yr and more prior to diagnosis of lung cancer estimated to have relative effects on radon lung cancer risk of 1.0, 0.8, and 0.3, respectively. Table 13 provides a comparison of both the EOR and model fit, as determined by the difference in the deviance between the fitted model and the null model (with $\beta = 0$), between the time-weighted mean radon concentrations and the BEIR VI-weighted radon concentrations. In the complete data, neither weighting scheme provided significant evidence of an association between radon and lung cancer. In the restricted data, the BEIR VI weights provided a slightly better fit than did equal weights. Using the BEIR VI weights, the EOR was 0.23 with a 95% CIof (0.03, 0.55).

Factors Modifying the Excess Odds Ratio

Tables 14a and 14b present EORs with stratification on a variety of demographic factors and cigarette smoking-related factors. In the complete data,

TABLE 11b. Proportions of Total Cases and of Total Controls by Number of Years in the 5–30 yr Exposure Window Covered by Radon Detector Measurements

	Study													
	NJ		Winn		MO-I		MO-II		IA		CT		UT-ID	
Restrictions	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Any radon estimate[a]														
	0.12	0.08	0.173	0.14	0.13	0.22	0.12	0.10	0.10	0.12	0.24	0.18	0.13	0.163
Years measured:														
>0	0.12	0.09	0.168	0.14	0.14	0.23	0.12	0.10	0.11	0.12	0.22	0.17	0.12	0.16
≥10	0.14	0.10	0.155	0.13	0.13	0.22	0.10	0.08	0.12	0.13	0.23	0.17	0.13	0.16
≥15	0.14	0.10	0.146	0.13	0.13	0.21	0.09	0.08	0.14	0.15	0.23	0.17	0.13	0.17
≥20	0.13	0.09	0.142	0.13	0.13	0.22	0.09	0.07	0.14	0.15	0.24	0.18	0.13	0.18
25	0.116	0.07	0.135	0.12	0.13	0.23	0.08	0.07	0.15	0.14	0.27	0.19	0.13	0.18
Years measured with α-track air monitors														
>0	0.12	0.08	0.177	0.14	0.15	0.24	0.13	0.10	0.11	0.12	0.20	0.16	0.12	0.16
≥10	0.13	0.09	0.165	0.14	0.14	0.23	0.11	0.09	0.13	0.14	0.20	0.15	0.12	0.16
≥15	0.14	0.09	0.157	0.14	0.14	0.23	0.10	0.08	0.15	0.16	0.20	0.15	0.12	0.16
≥20	0.12	0.08	0.153	0.14	0.15	0.23	0.10	0.08	0.16	0.16	0.21	0.16	0.12	0.16
25	0.10	0.07	0.147	0.13	0.14	0.25	0.09	0.08	0.17	0.15	0.23	0.16	0.12	0.17

[a] Includes 181 (CT), 60 (UT-ID), and 111 (Winn) subjects with no radon measurements within the 5–30 yr exposure time window.

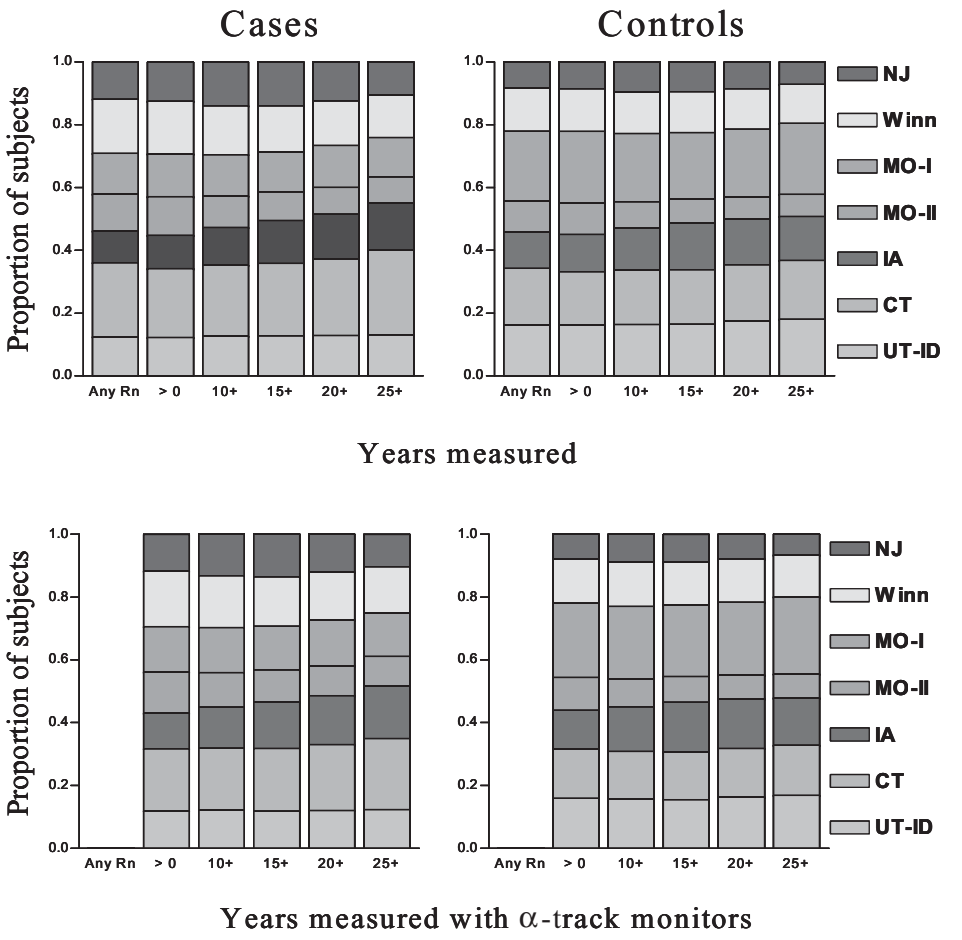

FIGURE 5. Proportions of cases and of controls from each study included in the analysis of the effects of dosimetry restrictions on the exposure-response relationship shown in Table 11a.

there was no significant heterogeneity in the EOR estimates by sex, age, or educational level, although there was a suggestion that the EORs were lower among subjects with less formal education (Table 14a). Respondents in the various studies were typically the subjects themselves. The percentage of case surrogate respondents ranged from 13% in Iowa to 45% in New Jersey. Overall, 44% of case information was derived from surrogates, while only 5% of control information was based on surrogates. The corresponding percentages in the restricted data were similar. There were no significant differences in the EOR by type of respondent, although there was some indication of a decreased EOR with surrogate-based information in the restricted data.

TABLE 12a. Excess Odds Ratio[a] (β) for Radon Concentration by Number of Years in the 5–30 yr Exposure Window Covered by Radon Detector Measurements, with Data Restricted to Subjects Residing in 1 or 2 Houses in the Exposure Time Window

Restrictions: ≤2 residences and	$\beta \times 100$	(95% CI)	Cases	Controls
Any radon estimate[b]	0.13	(0.00, 0.33)	2771	3656
Years measured:				
>0	0.13	(0.01, 0.34)	2642	3577
≥10	0.13	(0.00, 0.34)	2505	3366
≥15	0.14	(0.00, 0.35)	2361	3187
≥20	0.14	(0.00, 0.36)	2088	2832
25	0.18	(0.01, 0.46)	1724	2339
Years measured with α-track air monitors				
>0	0.15	(0.01, 0.37)	2467	3430
≥10	0.15	(0.00, 0.37)	2308	3194
≥15	0.17	(0.01, 0.41)	2171	3009
≥20	0.18	(0.02, 0.43)	1910	2651
25	0.21	(0.03, 0.52)	1552	2170

[a] Based on the linear odds ratio model: $OR(x) = 1 + \beta x$, where x is the mean radon concentration in the 5–30 yr exposure time window. Models stratified by study, sex and categories of age, duration of smoking, number of cigarettes smoked per day, number of residences, and years with α-track measurements in the exposure time window.

[b] Includes 113 (Connecticut), 40 (Utah), and 55 (Winnipeg) subjects with no radon measurement data within the 5–30 yr exposure time window.

Among cigarette-only smokers and never smokers, there were no significant differences in the EORs among categories representing cigarette smoking status, number of cigarettes smoked per day, duration of cigarette smoking, or time since quitting smoking (Table 14b).

Radon Risks by Histological Type of Lung Cancer

The histological type of lung cancer was available on all but 183 lung cancer cases. Table 15 shows the EOR at 100 Bq/m^3 for each histological type of lung cancer (using the same controls for each histologic subtype). Similar results were obtained when cases were restricted to females only or to males only. The preponderance of adenocarcinomas in the complete data set (1514 of 4081 cases) is due to the emphasis on females and (current) nonsmokers in several of the case series. The largest EOR (0.23 per 100 Bq/m^3) was observed for small-cell carcinoma, although the confidence limits overlapped the EORs for other histologic types of lung cancer. Only lesions of unknown histology failed to demonstrate a positive EOR (–0.17 per 100 Bq/m^3). Because of the reduced number of subjects, all of the confidence limits for the EORs for specific histologic types of lung cancer included zero. Using lung cancer cases only, we conducted a normal linear least-squares regression of the natural logarithm of radon concentration on study, age, sex, and histological type of lung cancer. Radon concentrations were not statistically different by histological type, suggesting that differences in Table 15 may be due to

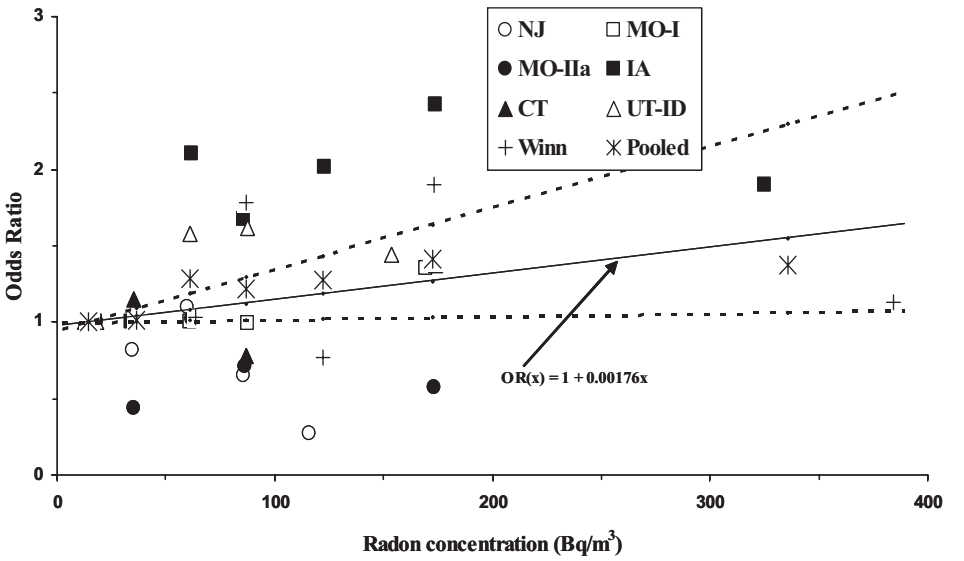

FIGURE 6. Odds ratios for categories of mean radon concentration within 5–30 yr exposure time window, the fitted model for the linear excess odds ratio (solid line) and its 95% confidence limits (dotted lines) for all studies combined. Data limited to subjects residing in 1 or 2 residences during the exposure window, and at least 20 yr of coverage with α-track air monitors.

chance. In contrast to the full data set, the largest EOR (0.27 per 100 Bq/m^3) was for adenocarcinoma with data restricted to at most 2 residences and at least 20 yr of α-track monitoring within the 5–30 yr ETW.

Nonlinearity of the Exposure-Response Relationship

Figure 2 provides no evidence of a deviation from linearity in the EOR. However, using the complete data and data restricted to those with 1 or 2 houses and 20 yr or more coverage with alpha-track air detectors, we fited various models to evaluate more formally the possibility of nonlinearity in the exposure-response relationship. Specifically, the following models (with stratification on study, sex and categories of age, cigarettes smoked per day, and duration of cigarette smoking) were fited to the data:

$$\mathrm{OR}(x) = 1 + \beta x e^{\gamma x} \quad \text{(linear-exponential model)}$$

$$\mathrm{OR}(x) = 1 + \beta x^{\gamma} \quad \text{(power model)}$$

and

$$\mathrm{OR}(x) = 1 + \beta x + \gamma x^2 \quad \text{(quadratic model).}$$

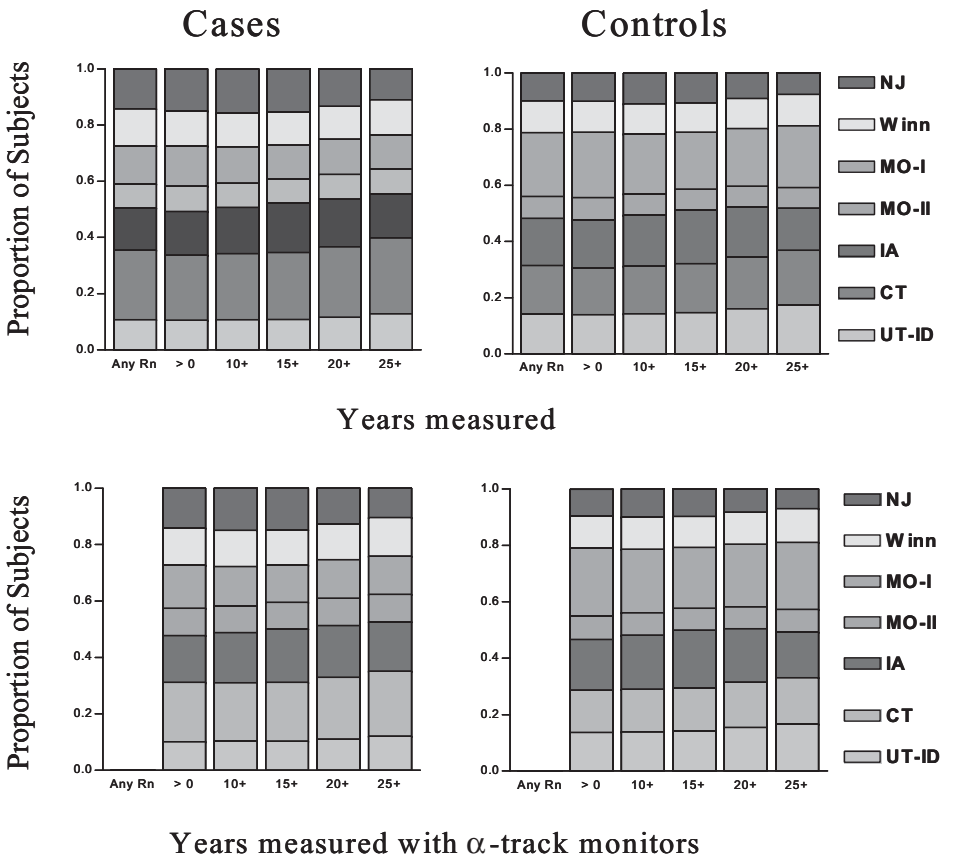

FIGURE 7. Proportions of cases and of controls from each study included in the analysis of the effects of dosimetry restrictions on the exposure-response relationship shown in Table 12a. Data from subjects residing in one or two houses during the 5–30 yr exposure period.

None of these models offered a significantly improved fit compared to the linear model.

Random versus Fixed Effects Models

Estimates of the slope of the exposure-response relationship were calculated under a fixed-effects regression model (Pinheiro & Bates, 2000). As noted previously, there were no significant differences in the estimated EORs among studies in either the full or restricted (1 or 2 residences with at least 20 yr of coverage with alpha-track air monitors in the ETW) data sets, precluding the need for a random effects model (Laird & Mosteller, 1990; Whitehead & Whitehead, 1991) to accommodate heterogeneity among studies.

Heterogeneity in radon lung cancer risk estimates can also be displayed in a radial plot, where the standardized score (the ratio of the estimate to its

TABLE 12b. Proportions of Total Cases and of Total Controls by Number of Years in the 5–30 yr Exposure Window Covered by Radon Detector Measurements, with Data Restricted to Subjects Residing in 1 or 2 Houses in the Exposure Time Window

	Study													
	NJ		Winn		MO-I		MO-II		IA		CT		UT-ID	
Restrictions: ≤2 residences	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
Any radon estimate[a]														
	0.14	0.10	0.13	0.11	0.14	0.23	0.086	0.078	0.15	0.17	0.25	0.17	0.11	0.14
Years measured:														
>0	0.15	0.10	0.13	0.11	0.14	0.23	0.09	0.08	0.16	0.17	0.23	0.17	0.11	0.14
≥10	0.16	0.11	0.12	0.11	0.13	0.21	0.09	0.08	0.16	0.18	0.24	0.17	0.11	0.14
≥15	0.15	0.11	0.12	0.11	0.12	0.20	0.09	0.07	0.18	0.19	0.24	0.17	0.11	0.15
≥20	0.13	0.09	0.12	0.11	0.13	0.21	0.09	0.07	0.17	0.18	0.25	0.18	0.12	0.16
25	0.11	0.08	0.13	0.11	0.12	0.22	0.09	0.07	0.16	0.15	0.27	0.19	0.13	0.17
Years measured with α-track air monitors														
>0	0.14	0.09	0.13	0.11	0.15	0.24	0.10	0.08	0.17	0.18	0.21	0.15	0.10	0.14
≥10	0.15	0.10	0.13	0.11	0.14	0.22	0.09	0.08	0.18	0.19	0.21	0.15	0.10	0.14
≥15	0.15	0.10	0.13	0.11	0.13	0.22	0.09	0.08	0.19	0.20	0.21	0.15	0.10	0.14
≥20	0.13	0.08	0.13	0.11	0.14	0.22	0.10	0.08	0.19	0.19	0.22	0.16	0.11	0.16
25	0.11	0.07	0.14	0.12	0.14	0.24	0.10	0.08	0.18	0.16	0.23	0.16	0.12	0.17

[a] Includes 113 (CT), 40 (UT-ID), and 55 (Winn) subjects with no radon measurement data within the 5–30 yr exposure time window.

TABLE 13. Excess Odds Ratio[a] (β) for Lung Cancer for Time-Weighted Radon Expesure in the 5–30 yr. Interval Prior to the Index Date

	All data		Subjects with ≤2 residences and ≥20 yr with α-track air monitors	
Weights for exposure	β × 100	Reduction in deviance[b]	β × 100	Reduction in deviance[b]
Equal	0.10 (–0.01, 0.26)	2.97	0.18 (0.02, 0.43)	5.28
BEIR VI[c]	0.12 (–0.01, 0.33)	3.14	0.23 (0.03, 0.55)	5.53

[a] Based on the linear OR model: $OR(x) = 1 + \beta x$, where x is the mean radon concentration in the 5–30 yr exposure time window. Models stratified by study, sex and categories of age, sex, duration of smoking number cigarenes smoked per day, number of residences, and years with α-track measurements in the exposure time window.

[b] Reduction in deviance compared to model with $\beta = 0$.

[c] Exposure determined using weights of 1.0, 0.8, and 0.3 for exposures received 5–14, 15–24, and 25 yr and more prior to the index date.

TABLE 14a. Excess Odds Ratio[a] (β) for Lung Cancer and 95% Confidence Interval (CI) for Time-Weighted Radon Concentration in the 5–30 yr Interval Prior to the Index Date by Categories of Demographic Factors

	All data				Subjects with ≤2 residences and ≥20 yr with α-track air monitors			
Category	Cases	Controls	β × 100	P^b	Cases	Controls	β × 100	P^b
Overall (95% CI)	4081	5281	0.10 (–0.01, 0.26)		1910	2651	0.18 (0.02, 0.43)	
Sex								
Females	2766	3779	0.17		1373	1956	0.18	
Males	1315	1502	0.03	0.27	537	695	0.16	0.97
Age at disease occurrence								
<60	1028	1481	0.02		270	398	0.16	
60–64	703	811	0.70		331	428	1.27	
65–69	836	1066	0.32		461	640	0.12	
70–74	758	894	0.01		410	560	0.30	
≥75	756	1030	–0.02	0.10	438	625	–0.05	0.09
Highest grade level of education								
0–7	534	674	–0.04		248	347	–0.00	
8–13	2476	2814	0.22		1157	1472	0.23	
≥14	1025	1785	0.01	0.32	485	826	0.17	0.47
Type of respondent								
Subject	2280	4976	0.16		1081	2483	0.29	
Surrogate	1801	305	–0.05	0.47	829	168	–0.20	0.09

[a] Based on the linear OR model: $OR(x) = 1 + \beta x$, where x is mean radon concentration within 5–30 yr exposure time window. Models stratified by study, sex, categories of age, duration of smoking and number cigarettes smoked per day, number of residences, years with α-track measurements in the exposure time window, and, when assessed, education and type of respondent. Combined estimates based on fixed effects modeling. Numbers of cases and controls vary due to missing data.

[b] Test of homogeneity of β.

TABLE 14b. Excess Odds Ratio[a] (β) for Lung Cancer and 95% Confidence Interval (CI) for Time-Weighted Radon Concentration in the 5–30 yr Interval Prior to the Index Date by Categories of Cigarette Smoking-Related Factors, with Data Limited to Never and Cigarette-Only Smokers

	All data				Subjects with ≤2 residences and ≥20 yr with α-track air Monitors			
Category	Cases	Controls	β × 100	P^b	Cases	Controls	β × 100	P^b
Overall	4004	5155	0.09		1885	2588	0.16	
(95% CI)			(–0.01, 0.26)				(0.01, 0.41)	
Cigarette smoking status								
Never smoker	690	2235	0.09		359	1266	0.22	
Ever smoker	3314	2920	0.09	0.97	1526	1322	0.13	0.64
Number of cigarettes smoked per day								
1–9	313	576	0.42		170	300	0.02	
10–19	1158	1213	0.11		589	562	0.29	
20–29	1111	729	0.04		472	302	0.05	
≥30	732	402	0.11	0.80	295	158	0.26	0.81
Duration of cigarette smoking (yr)								
1–24	307	767	0.06		123	329	0.05	
25–34	558	627	–0.03		189	216	–0.02	
35–44	1084	746	0.28		500	338	0.23	
≥45	1365	780	0.11	0.69	714	439	0.20	0.83
Years since stopping cigarette smoking[c]								
0	1830	1,150	0.07		805	478	0.13	
1–9	750	679	0.07		356	305	0.15	
10–19	380	405	0.26		189	168	0.15	
≥20	354	686	0.16	0.96	176	371	0.11	0.99

[a] Based on the linear OR model: $OR(x) = 1 + \beta x$, where x is mean radon concentration within 5–30 yr exposure time window. Models stratified by study, sex, categories of age, duration of smoking and number cigarettes smoked per day, and number of residences and years with α-track measurements in the exposure time window. Combined estimates based on fixed effects modeling. Numbers of cases and controls vary due to missing data.

[b] Test of homogeneity of β for never smokers and levels of cigarette smoking variables.

[c] Estimates and tests of homogeneity include additional adjustment for years since stopping cigarette smoking.

standard error) is plotted against the inverse of its standard error (Figure 8). The slope of a line from the origin to any point (the tangent of the subtended angle, or the ratio of the ordinate to the abscissa values) is the estimated EOR per Bq/m^3 for that study. The summary EOR and its 95% CI are displayed as the solid and dotted lines, respectively. Note that points more distant from the origin represent studies where the EORs are estimated with greater precision (larger inverse standard error), while points closer to the origin represent less precision (smaller inverse standard error). In the full data, the New Jersey estimate appeared the most discrepant, although studies tended to be grouped along the line representing the overall EOR estimate. In the restricted data, the Utah–South Idaho estimate was the most discrepant. In neither panel was any study markedly different from the others.

TABLE 15. Excess Odds Ratio[a] (β) by Histological Type of Lung Cancer and 95% Confidence Interval (CI) for Time-Weighted Radon Concentration in the 5–30 yr Interval Prior to the Index Date

	All data			Subjects with ≤2 residences and ≥20 yr with α-track air monitors		
Histologic type	Cases	$\beta^b \times 100$	(95% CI)	Cases	$\beta \times 100$	(95% CI)
Adenocarcinoma	1514	0.09	(–0.05, 0.33)	704	0.27	(0.02, 0.73)
Squamous cell	914	0.05	(–0.04, 0.33)	427	0.13	(–0.04, 0.62)
Small/Oat cell	664	0.23	(–0.08, 0.85)	301	0.20	(–0.11, 1.00)
Other	806	0.16	(–0.03, 0.55)	383	0.22	(–0.04, 0.84)
Unknown	183	–0.17	(—, 0.07)	95	–0.16	(—, 0.19)
All	4081	0.10	(–0.01, 0.26)	1910	0.18	(0.02, 0.43)

[a] Based on fiting the linear OR model: $OR(x) = 1 + \beta x$, where x is mean radon concentration within 5–30 yr exposure time window. Models stratified by study, sex, categories of age, duration of smoking and number cigarettes smoked per day, and number of residences and years with α-track measurements in the exposure time window.

[b] Combined estimate based on fixed effects modeling.

TABLE 16. Influence Analysis for Excess Odds Ratio[a] (β) and 95% Confidence Interval (CI) by Sequentially Omitting One Study

	All data		Subjects with ≤2 residences and ≥20 yr with α-track air monitors	
Omitted study	$\beta \times 100$	(95% CI)	$\beta \times 100$	95% CI
None	0.10	(–0.01, 0.26)	0.18	(0.02, 0.43)
NJ	0.09	(–0.02, 0.25)	0.19	(0.02, 0.46)
Winn	0.15	(0.01, 0.36)	0.22	(0.02, 0.51)
MO-I	0.11	(–0.01, 0.31)	0.20	(0.02, 0.52)
MO-II	0.09	(–0.02, 0.25)	0.18	(0.02, 0.45)
IA	0.04	(–0.04, 0.19)	0.13	(–0.02, 0.41)
CT	0.11	(–0.01, 0.29)	0.17	(0.01, 0.45)
UT-ID	0.11	(–0.01, 0.29)	0.14	(0.00, 0.39)

[a]Based on fitting linear OR model: $OR(x) = 1 + \beta x$, where x is total cumulative radon exposure in the 5–30 yr exposure time window. Models stratified by study, sex, categories of age, duration of smoking and number cigarettes smoked per day, and number of residences and years with α-track measurements in the exposure time window.

Influence Analysis of Radon Effects

Summary estimates of the EOR at 100 Bq/m^3 reflect the radon-lung cancer association from the seven studies using either the complete data or the restricted data with subjects residing in one or two houses within the 5–30 year ETW and with 20 years or more covered by alpha-track air monitors. Table 16 and Figure 9 illustrate the influence of each study on the overall estimate for the complete and restricted data. The EOR estimates were computed

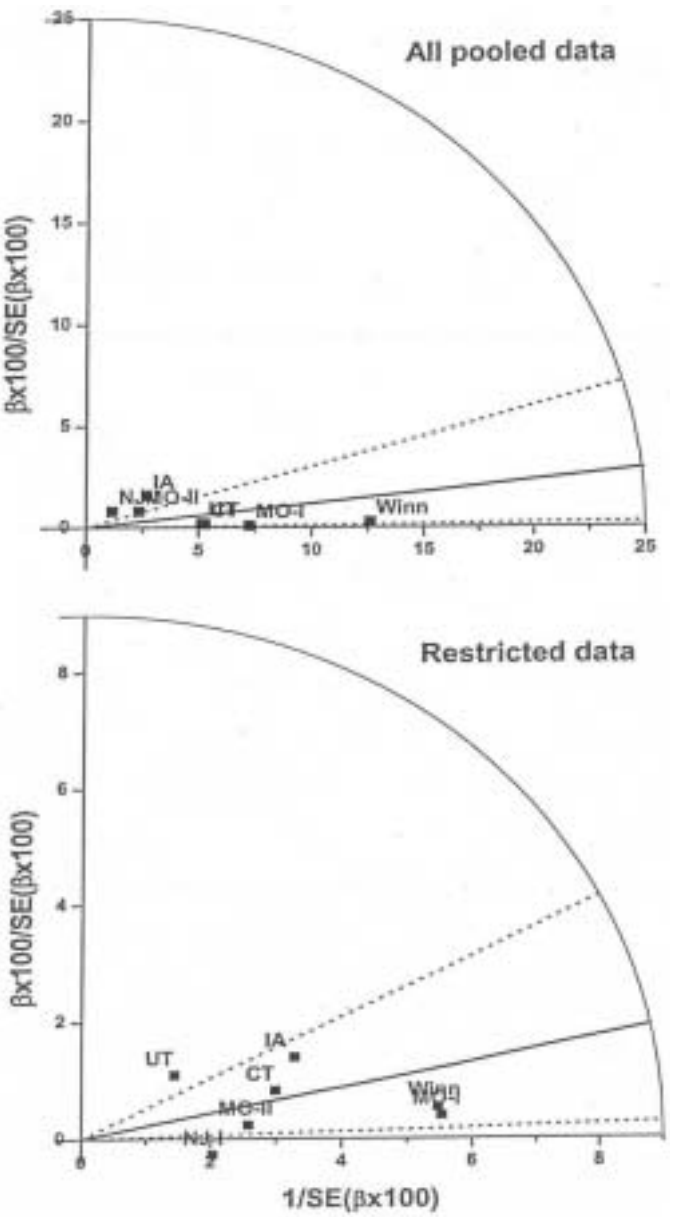

FIGURE 8. Radial plot based on the estimated excess odds ratio (EOR) at 100 Bq/m^3 and its standard error (SE). Solid line and dotted lines are the EOR at 100 Bq/m^3 and its 95% confidence interval.

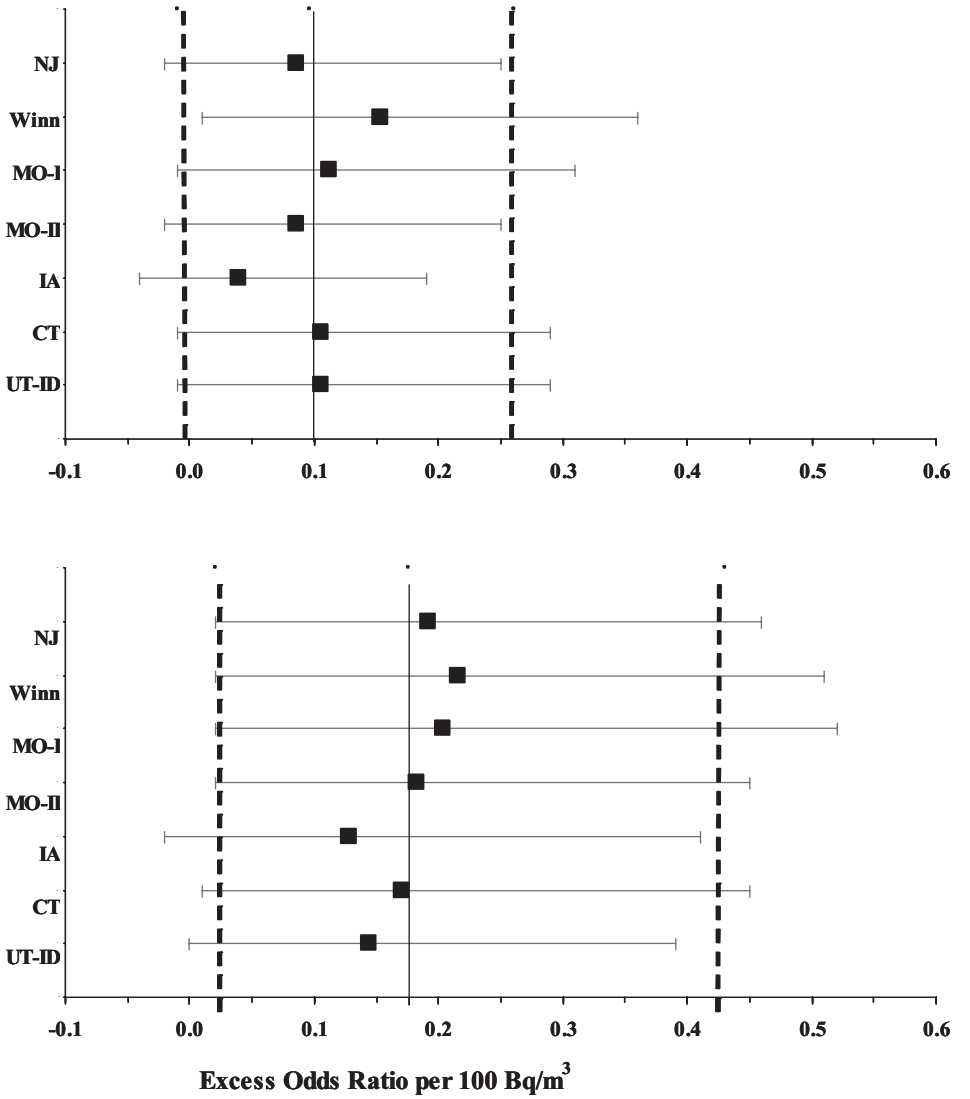

FIGURE 9. Results from influence analysis comparing the excess odds ratio at 100 Bq/m^3 (solid line) and its 95% confidence interval (CI) (dotted lines) for all studies combined with estimates when one study is omitted. Estimates using all data [top, summary EOR and 95% CI at 100 Bq/m^3, 0.096 (–0.01,0.26)] and data restricted to subjects residing in 1 or 2 houses in the 5–30 yr exposure time window and with 20 yr or more covered by α-track air monitors [bottom, summary EOR and 95% CI at 100 Bq/m^3, 0.18 (0.02,0.43)].

by omitting each study in sequence. In the complete data, Iowa and Winnipeg had the most influence on the overall EOR estimate. In the restricted data, omitting Iowa resulted in a reduction of the EOR by about 20%, whereas omitting either Winnipeg or Missouri-I increased the EOR.

Adjustment for Potential Confounding

There were 28 subjects (three from the Connecticut study and 25 from the Winnipeg study) who smoked cigars/pipes only, including five cases and 23 controls, with 15 subjects (3 cases and 12 controls) in the restricted data. The ORs for use of cigars/pipes relative to never smokers were 0.89 (0.3, 2.6) and 0.91 (0.2, 4.2) in the full and restricted data, respectively. Unless otherwise noted, these people were consequently included in the never smoker group. Preliminary analysis, along with consideration of the design features of the seven case-control studies included in the present combined analysis, suggested that regression models for the evaluation of radon effects should include covariates for study, sex, and categories of age at index date, number of cigarettes smoked per day, duration of cigarette smoking, and number of residences and years with alpha-track measurements in the 5–30 yr ETW. Our a priori approach for the control of these potentially confounding factors involved a conditional likelihood approach with matched sets based on the cross-classification of all factors. This stratification approach contrasts with an alternative that includes each covariate (or more precisely indicator variables for levels of a covariate) as a main effect in the overall regression model. The latter approach assumes that each covariate separately multiplies the odds of disease, although this modeling strategy can be expanded by including some higher order interactions among the covariates. Stratification requires minimal assumptions on the joint patterns of risk among the five factors, thereby allowing maximum control of the factors across study populations. Stratification by the seven previously identified factors resulted in 2053 strata with at least 1 case or 1 control. With the large number of matched strata, we used a conditional likelihood, since an unconditional likelihood can be biased if the number of cases and controls within individual stratum are small (Breslow & Day, 1980).

Control of potentially confounding factors can be accomplished using models that include these factors as stratification variables, confounders as main effects variables, or a combination in which models include main effects and some higher order interactions. Table 17 shows estimates of the EOR per100 Bq/m^3 for the complete and restricted data and restricted data for a variety of models. Data were further limited to never smokers and cigarette-only smokers. Stratification on the 7 variables discussed previously led to an EOR per100 Bq/m^3 of 0.09 in the complete data and 0.16 in the restricted data. Use of other smoking-related variables (cessation of smoking and age at start of smoking) resulted in slightly larger EORs.

We further considered differences between models that stratified on study, age, sex, number of cigarettes smoked per day, duration of cigarette use, levels of number of residences, years with α-track measurements in the 5–30 yr ETW, and models that included main effects and some higher order interactions. One consequence of stratification was that a greater number of strata had no cases or no controls, and thus provided no information for

TABLE 17. Control for Cigarette Smoking Variables and the Effect on the Linear Excess Odds Ratio (β) Model for Lung Cancer and Mean Radon Concentration in the 5–30 yr Exposure Time Window, with Data Limited to Never and Cigarette-Only Smokers

Additional stratification variables[a]	Main effects variables[b]	All data, $\beta \times 100$	Subjects with ≤2 residences and ≥20 yr with α-track air monitors, $\beta \times 100$
Study, age, sex, cigarettes/day, duration of smoking[c]		0.09	0.16
Age, sex, cigarettes/day, duration of smoking	Study	0.03	0.10
Study, sex, cigarettes/day, duration of smoking	Age	0.02	0.06
Study, sex, cigarettes/day, duration of smoking	Age × study	0.02	0.05
Study, age, cigarettes/day, duration of smoking	Sex	0.07	0.13
Study, age, cigarettes/day, duration of smoking	Sex × study	0.08	0.13
Study, age, sex, cigarettes/day	Duration of smoking	0.04	0.07
Study, age, sex, cigarettes/day	Duration × study	0.02	0.05
Study, age, sex, duration of smoking	Cigarettes/day	0.03	0.06
Study, age, sex, duration of smoking	Cigarettes/day × study	0.02	0.05
Study, age, sex, cigarettes/day, duration of smoking, years cessation		0.08	0.14
Study, age, sex, cigarettes/day, duration of smoking	Years cessation	0.10	0.17
Study, age, sex, cigarettes/day, duration of smoking	Years cessation × study	0.09	0.16
Study, age, sex, cigarettes/day, duration of smoking, age first smoked		0.10	0.18
Study, age, sex, cigarettes/day, duration of smoking	Age first smoked	0.09	0.16
Study, age, sex, cigarettes/day, duration of smoking	Age first smoked × study	0.09	0.19

[a] Model based on a conditional likelihood with strata defined by levels of number of residences, years with α-track measurements in the 5–30 yr exposure time window, and the listed factors.

[b] For two variables, model includes indicator variables for main effects and the one-way interaction.

[c] A priori model for control of smoking-related factors.

estimation of lung cancer risk associated with radon exposure. In the full data set, a total of 1151 strata with 875 cases and 1065 controls contributed no information. This included 18% of subjects in Iowa, 29% in Utah–South Idaho, 34% in Winnipeg, 20% in New Jersey, 29% in Connecticut, 6% in Missouri-I, and 17% in Missouri-II. In the restricted data, 899 strata with 452 cases and 597 controls contributed no information to the radon analysis. Due to the fact of their exclusion, the noninformative group represented relatively extreme

TABLE 18. Comparison of Subjects Who Did and Did Not Contribute Information on Risk With Radon Exposure in Stratified Analysis.

	Cases			Controls		
Category	No information[a]	Information	*p* Value[b]	No information	Information	*p* Value[b]
			All data			
Number of subjects	875	3206		1065	4216	
Average age (never smokers)	67.1	69.6	.32	61.6	68.5	<.01
Average age (ever smokers)	65.6	64.5	<.01	63.3	63.1	.7
Percent ever smokers	97.7	78.7	<.01	79.5	51	<.01
Average cigarettes/day	24.6	22.3	<.01	16.1	19.7	<.01
Average years smoked	38.2	41.3	<.01	25.5	36.7	<.01
Average radon (never smokers) (Bq/m^3)	35	64.9	<.01	97.59	74.1	.11
Average radon (ever smokers) (Bq/m^3)	74.2	68.2	.45	74.2	59.6	<.01
	Subjects with ≤2 residences and ≥20 yr with α-track air monitors					
Number of subjects	452	1458		597	2054	
Average age (never smokers)	63.6	72.6	<.01	62.6	71	<.01
Average Age (ever smokers)	66.4	67.6	.01	65.5	66.9	<.01
Percent ever smokers	97.8	75.7	<.01	78.9	43.3	<.01
Average cigarettes/day	23.9	21.1	<.01	16.1	19	<.01
Average years smoked	39.2	43.3	<.01	26.1	39.7	<.01
Average radon (never smokers) (Bq/m^3)	38.5	72.7	<.01	100.9	79.5	.11
Average radon (even smokers) (Bq/m^3)	83.4	79.0	.24	84.6	63.1	<.01

[a] In conditional likelihood analysis, entries for subjects who provided no information for estimation of radon risk, i.e., stratum included only cases or only controls. Stratification based on study, sex, categories of age, duration of smoking and number cigarettes smoked per day, number of residences, and years with α-track measurements in the exposure time window.

[b] *p* Value based on one-way ANOVA by availability of information.

individuals (Table 18). For example, in the restricted data, individuals in the noninformative group smoked for fewer years, but consumed more cigarettes per day for cases and were slightly younger. Radon concentrations were higher in the noninformative group, with the difference varying by case status. In the noninformative group, 98% of cases and 79% of controls ever smoked cigarettes, compared to 76% of cases and 43% of controls in the informative group.

DISCUSSION

The broad objective of the analysis was to evaluate the association between radon exposure and lung cancer risk under residential exposure conditions. Such direct residential observations eliminate the need to extrapolate from occupational exposure conditions, and avoid uncertain adjustments for differences in physiological, dosimetric, and other differences between underground miners and the general population (Krewski et al., 1999; NRC, 1999). The specific goals of the combined analysis were to test the null hypothesis that prolonged residential radon exposure is not associated with increased lung cancer risk, obtain a precise estimate of the excess odds ratio for lung cancer in relation exposure, evaluate the consistency of the exposure-response relationships observed in different studies, identify demographic and socioeconomic factors that may modify the association between residential radon and lung cancer risk, and compare the overall estimate of residential radon lung cancer risk with extrapolations based on radon-exposed underground miners.

The scope of the combined analysis included all published North American case-control studies completed to date that fulfilled the criteria for inclusion. In particular, the combined analysis included seven such studies conducted in New Jersey (Schoenberg et al., 1992), Winnipeg, Canada (Létourneau et al., 1994), Missouri (Alavanja et al., 1994, 1999), Iowa (Field et al., 2000a), Connecticut (Sandler et al., this issue), and Utah–South Idaho (Sandler et al., this issue). These large-scale epidemiologic studies involved a minimum of 413 cases, and relied primarily on 1-yr integrated α-track measurements for radon dosimetry. Each of the investigators sought to obtain comprehensive indications of historical radon exposures, either by monitoring as many of the homes that the study subjects had occupied as possible, or by focusing on homes that subjects had occupied for an extended period of time. The combined data on 4081 cases and 5281 controls represent the largest lung cancer case series analyzed to date and exceed the 2787 lung cancer cases in the combined analysis of 11 cohort studies of underground miners (NRC, 1999).

Average radon gas concentrations varied substantially among the seven studies included in the combined analysis. The highest exposures occurred in Winnipeg, Canada, where the average radon concentration in the living area was 131 Bq/m^3, and in Iowa, with an average level of 127 Bq/m^3. The lowest radon levels were recorded in New Jersey, with the average radon concentration being 25 Bq/m^3, and Connecticut, with a mean level of 33 Bq/m^3. Radon concentrations in individual homes varied substantially in all studies, with almost 2% of the measurements in Winnipeg being above 800 Bq/m^3. Winnipeg was selected as the site for the Canadian case-control study because it has the highest average radon concentrations of any large urban center in Canada (McGregor et al., 1980).

Because four of the seven studies (Iowa, Missouri-I, Missouri-II, and New Jersey) focused exclusively on females, there were more female (2766) than male (1315) lung cancer cases in the combined data set. Age restrictions for

cases varied from a minimum of 30–40 yr of age to a maximum of 70–84 yr in Winnipeg, Missouri-I, Missouri-II, Iowa, Connecticut, and Utah–South Idaho, with no age restriction in New Jersey. The average age of the lung cancer cases was 65.6 yr. Of the 4081 cases included in the full combined analysis, a minority (1025 cases) had some postsecondary education, with the remainder (3010 cases) having at most high school education, and 46 cases having no education information.

Although most interviews (2280) were conducted with the cases themselves, questionnaires for many cases (1801) were completed by proxies. (Of the 5281 control interviews, only 305 involved proxies.) Although Missouri-I included only current nonsmokers, and Connecticut and Utah–South Idaho oversampled cases who had not smoked within the last 10 yr, only 690 cases were never smokers. However, the combined case series included a total of 734 former smokers defined as people who had quit smoking for at least 10 yr.

The combined analysis proceeded in two phases, the first being a parallel analysis (top eight rows of Table 9 and Table 10) of each of the seven studies using a common analytic approach to establish consistency with the results reported by the original investigators. Since our common analytic approach based on the estimation of odds ratios within common radon exposure categories for all seven studies and the application of a linear excess odds ratio model to evaluate trends in risk with increasing radon exposure did not necessarily conform exactly to the analytic methods employed by the original investigators, precise numerical agreement with the originally reported results was not obtained. However, our parallel analyses led to the same general conclusions as those obtained by the original investigators.

The second phase was the combined analysis (bottom row of Tables 9 and 10) of all seven datasets. Using α-track detectors to measure radon concentrations in residences in these studies, the estimated excess odds ratio was significantly greater than zero in Iowa, but not in any of the other six case-control studies. (Although a significant effect was found in Missouri-II using glass-based α-track detectors, glass artifact radon measurements were not included in the combined analysis because of their availability only in Missouri-II.) Overall, odds ratios stratified by sex and categories of age as well as duration and intensity of smoking tended to increase with increasing categories of radon exposures, with the odds ratio for exposures in excess of 200 Bq/m^3 being 1.29 (95%CI: 0.93–1.80). Although the overall estimate of the excess odds ratio for lung cancer was positive, 0.10 per 100 Bq/m^3 with a 95% CI of (–0.01–0.26), and did not reach the traditional level of statistical significance.

The overall EOR for lung cancer in relation to residential radon exposure was estimated to be 0.03 per 100 Bq/m^3 among males and 0.17 per 100 Bq/m^3 among females, although this difference was not statistically significant (p = .27). There was some evidence of heterogeneity (p = .10) in the EOR depending on the age at ascertainment, although no clear trend with age was apparent. There was no difference in EORs with increasing educational attainment (p = .32). The EOR was higher, although not significantly (p = .47), among

subjects who completed the study questionnaires themselves (EOR = 0.16 per 100 Bq/m^3) than among subjects for whom this information was obtained from proxies (EOR = –0.05 per 100 Bq/m^3). No significant differences in the overall EOR were noted with smoking status (ever/never), duration or intensity of smoking, or time since smoking cessation.

Although our primary focus in the present analysis is on all types of lung cancer combined, we also conducted analyses by histological subtypes of lung cancer. Of the 4081 cases in the full data set, the predominant subtype was adenocarcinoma (1514 cases), followed by squamous-cell carcinomas (914), and small-/oat-cell carcinomas (664); other (806 cases) and unknown (183) subtypes account for the remaining cases. This pattern was also apparent among the 1910 cases included in the restricted data set. The preponderance of adenocarcinomas is likely due to the emphasis on females and on nonsmokers within several of the case series included in the North American combined analysis. Within the restricted data set, the largest EOR was noted for adenocarcinomas (EOR = 0.27 per 100 Bq/m^3, with 95% CI: 0.02–0.73). The EORs for squamous-cell carcinomas (0.13 per 100 Bq/m^3), small-/oat-cell carcinomas (0.20 per 100 Bq/m^3), and other malignant lung lesions (0.22 per 100 Bq/m^3) were all close to that (0.18 per 100 Bq/m^3) for lung cancer as a whole based on the restricted data set. Only lesions of unknown histology (EOR = –0.16 per 100 Bq/m^3) failed to demonstrate a positive excess odds ratio. The larger EOR per unit exposure for adenocarcinoma agrees with residential case-control studies (Missouri-I) and with the case-control study carried out in Chinese tin miners (Yao et al., 1994), which also observed a greater excess odds ratio among subjects with adenocarcinoma. The next largest risk occurred among subjects with small-cell carcinoma. The comparison of histologic types requires cautious interpretation since only the Iowa and Missouri studies verified the registry-reported histologic type through independent pathologists led microscopic review and examination of actual tissue samples. Previous studies have shown significant misclassification of some histologic types reported by state cancer registries (Brownson et al., 1995).

In order to determine if any one of the seven case-control studies had a dominant effect on the results of the combined analysis, we conducted an influence analysis in which the overall EOR was recalculated after removing one of the seven studies from the combined analysis. Exclusion of the Winnipeg data, a large study in which no evidence of an association between residential radon and lung cancer was observed, resulted in an increase in the estimated EOR from 0.10 (95% CI: –0.01, 0.26) to 0.15 (0.01, 0.36) per 100 Bq/m^3. Conversely, exclusion of the data from Iowa, the only one of the seven studies involved in the present combined analysis that demonstrated a clear positive association between radon and lung cancer risk, resulted in a decrease in the overall estimated EOR to 0.04 (–0.04, 0.19) per 100 Bq/m^3. Only Iowa demonstrated important effects in the influence analysis conducted using the restricted data. Exclusion of Iowa decreased the EOR from 0.18 (0.02, 0.43) to 0.13 (–0.02, 0.41) per 100 Bq/m^3, with the confidence interval for the EOR now including the null value of zero.

The BEIR VI Committee suggested that the apparent inconsistency in findings among residential radon case-control studies was largely a consequence of errors in dosimetry (NRC, 1999). Accurate ascertainment of exposure is critical in most epidemiologic investigations, particularly those focusing on environmental health hazards such as radon. A strength of the present combined analysis is the large number of subjects for which comprehensive reliable radon dosimetry data are available, permitting a more detailed assessment of the exposure-response relationship for radon and lung cancer. Our analyses support the homogeneity of results for the various North American radon studies. Thus, the "inconsistency" of results observed by the BEIR VI Committee may simply be due to random variation. Restricting data based on coverage of the ETW with alpha-track detector measurements very likely resulted in decreased uncertainty in retrospective radon exposures. There was a general pattern of increasing estimates of the excess odds ratios with increasing coverage of the ETW. The additional restrictions based on limiting the number of residences to one or two houses within the ETW further reduced uncertainties due to differences that arise between the living patterns of study subjects during their residence in prior houses and the living patterns of current residents of past houses. These restrictions again led to a monotonic pattern of increasing risk estimates. In particular, restriction to those subjects with at least 20 yr covered by α-track monitors led to an increase of the EOR at 100 Bq/m^3 from 0.10 (–0.01, 0.26) to 0.18 (0.02, 0.43).

The EOR of 0.10 (–0.01, 0.26) based on the full data compares well with the meta-analytic estimates of 1.12 (1.0, 1.3) and 1.22 (1.1, 1.3) reported by Lubin and Boice (1997) and Lubin (1999) based on data from North American and European residential radon case-control studies. Unlike the present combined analysis, which makes use of the primary raw data from the case-control studies included in the analysis, the meta-analysis is based on summary odds ratios within categories of radon exposure as reported in the original analyses. Consequently, there is no opportunity to explore the effects of restriction with the abbreviated meta-analytic approach to the pooling of information from different studies.

The results of the restricted analysis reported here represent our best estimate of residential radon lung cancer risks based on the seven case-control studies included in the present combined analysis. The restricted analysis, which focused on subjects with exposure assessment based on long-term alpha-track detectors covering at least 20 yr, likely contributed to the higher risk estimates by reducing exposure misclassification. While it is conceivable that the increased risks observed in the subset analyses may be attributable to some unidentified systematic or differential bias, no such sources of bias were identified in the analyses. In most case-control studies, nondifferential misclassification of exposure results in a bias towards the null (Kelsey et al., 1986; Lubin et al., 1990; Pierce et al., 1990). In fact, Field and colleagues (2002) have demonstrated in the Iowa study population that improved retrospective radon exposure estimates increase our ability to detect an association between prolonged residential radon exposure and lung cancer.

The increase in the estimated excess relative risk for women can be seen as possibly reflecting a similar phenomenon. The radon exposures of women, who have typically spent more of their time at home, may be more accurately represented by the residential measurements than are those of men.

Although imputation of missing values using the observed control mean imputation (OCMI) method discussed by Weinberg et al. (1996) (the imputation methods used by most of the collaborating investigators in the present combined analysis) leads to Berkson rather than classical exposure measurement error and is not expected to bias the estimates of risk, such imputation increases the uncertainty of risk estimates (Fung & Krewski, 1999a). Perhaps more importantly, the presence of classical measurement error has the effect of biasing estimates of the excess odds ratio toward the null value of zero, and overstating the precision of such estimates (Fung & Krewski, 1999a, 1999b). Radon concentrations are known to exhibit seasonal variation (Pinel et al., 1995; Krewski et al., 2004), with radon concentrations generally higher in the winter as compared to the summer months, as well as annual variation (Létourneau et al., 1992). Of particular importance is year-to-year variation in annual average radon levels, which cannot be gauged in the majority of the present studies that involve integrated α-track measurements over a single year in any given home. Darby et al. (1998) estimated the coefficient of variation of the classical measurement error distribution to be about 50%. Using methods specifically developed to account appropriately for both Berkson and classical measurement error, Darby and colleagues found that the excess relative risk based on a case-control study of residential radon and lung cancer in southwest England increased from 0.15 to 0.22 per 100 Bq/m^3, an increase of about 50%. The Gansu study conducted by Lubin et al. (2004) included a substudy that estimated variability of radon measurements within rooms and houses and between houses and also found a coefficient of variation of about 50%, which in turn increased the EOR per Bq/m^3 by about 50%. Similar results have been reported by Lagarde et al. (1997), Heid et al. (this issue), and Schaffrath-Rosario et al. (this issue). The Iowa investigators are currently performing repeat measurements at several hundred study homes in Iowa to assess the degree of residential radon gas variation over time.

Population mobility also contributes to uncertainty about cumulative radon exposure and subsequently to uncertainty about residential radon lung cancer risks (Lubin et al., 1995; Warner et al., 1996; Field et al., 1996). As individuals move from home to home, the difficulty in tracing and monitoring multiple residences increases. Further, since historical exposure concentrations are inferred from contemporaneous radon measurements, exposure measurement error compounds as the number of homes occupied by the study subjects increases. This may explain the lack of association between residential radon and lung cancer risk found in the Winnipeg study conducted by Létourneau et al. (1994). Although a design objective of this study was to trace and monitor all residences occupied by the study subjects within the Winnipeg metropolitan area throughout their entire lifetimes, the appreciable mobility among the study

subjects (who occupied over the lifetime an average of over four homes) may have resulted in increased measurement error and a corresponding downward bias in the estimate of radon lung cancer risk. This concern supports our preference for risk estimates based on our restricted data set, which focuses on subjects with limited mobility and near complete monitoring in the period 5–30 yr prior to recruitment. Although the restricted data set is preferred over the full data set on the grounds that radon dosimetry is expected to be more reliable in terms of accuracy and precision, the properties of this restriction strategy warrant further investigation. As noted previously, restricting the number of homes occupied to a maximum of two can be expected to reduce random exposure measurement error, which in turn will mitigate the well-known bias in estimates of risk toward the null value of zero. In contrast, the Berkson errors induced by OCMI are expected to induce only minimal bias in the present analysis. However, the observation of increasing EORs with increasing years of monitoring within the ETW of interest, which was also noted by Lubin et al. (2004) in a case-control study in Gansu, China, suggests that the mean radon level among the control homes monitored (which serves as the imputed radon level for unmeasured homes) may differ from the mean radon level in unmonitored homes. This could occur in the present combined analysis if unmonitored homes tended to be older and more difficult to trace, and subject to greater ventilation, and hence lower radon concentrations, as compared to newer, more energy-efficient homes. In this case, OCMI would lead to overestimation of the radon levels in unmonitored homes, and hence underestimation of lung risk. Correction for such a systematic effect by restriction to subjects with more complete radon monitoring data would produce the observed pattern of increasing lung cancer risk with increasing years of monitoring.

In the combined analysis reported here, we focused on cumulative radon exposure occurring in the 5–30 yr period prior to case recruitment based on our presumption that this is the exposure period of most relevance for radon-induced lung cancer. Not all temporal exposures may be of equal importance with respect to lung cancer induction (Goddard et al., 1995). The National Research Council (1999) estimated the relative weights appropriate to exposures occurring 5–15 yr, 15–25 yr, and more than 25 yr prior to disease diagnosis to be 1.0, 0.8, and 0.3, respectively, based on their combined analysis of the 11 miner cohorts. Applying the BEIR VI weights to the full data set leads to an EOR of 0.12 (–0.01, 0.33) per 100 Bq/m^3, as compared to 0.10 (–0.01, 0.26) per 100 Bq/m^3 based on equal weighting. In the restricted data, the EOR is 0.23 (0.03, 0.55) per 100 Bq/m^3, somewhat greater than the EOR of 0.18 (0.02, 0.43) per 100 Bq/m^3 based on equal weighting of exposures.

Radon is one of the most extensively investigated human carcinogens (IARC, 1988; NRC, 1999), and one of the few for which there is demonstrable epidemiologic evidence of carcinogenic potential (Moolgavkar et al., 1999). Underground miners exposed to high levels of radon gas in the past have clearly shown an increase in risk of lung cancer. Lubin et al. (1994) conducted a combined analysis of over 60,000 miners from 11 cohort mortality studies of

occupational exposure to radon in uranium and other underground miners, demonstrating a clear exposure-response relationship between radon and lung cancer. Lubin and Boice (1997) subsequently conducted a meta-analysis of eight published case-control studies that suggested a positive association between residential radon association and lung cancer risk. An updated meta-analysis by Lubin (1998) based on 13 studies provided stronger evidence of an association between residential radon and lung cancer. The National Research Council (1999) showed that extrapolation of the miner data to residential exposure levels produced estimates of risk compatible with those from the first meta-analysis reported by Lubin and Boice (1997).

The main results from the pooled analysis are shown in Tables 11a and 12a in terms of estimates of the EOR at 100 Bq/m^3, overall and within subgroups, based on restrictions believed linked to improved dosimetry conditions. Based on results from the restricted data (Table 12a), residing in a home with a mean radon concentration of 100 Bq/m^3 for 25 yr (the ETW utilized in our analyses) resulted in an EOR of 0.18, including both charcoal cannister and alpha-track radon measurements, with an EOR of 0.21 for alpha-track measurements alone. We compare those results to estimates derived from miner-based risk models with the *K*-factor adjustment by computing the EOR for 25 yr of residential exposure at 100 Bq/m^3 under standard assumptions for residency patterns and equilibrium levels for radon and its short-lived decay products (Table 19). The *K* factor is a dimensionless factor that characterizes the dose to lung cells for exposures in homes compared to similar exposures in mines and is approximately equal to 1 (NRC, 1988, 1991, 1999; Krewski et al., 2002). Using the simple linear excess relative risk model for miners exposed to less than 50 WLM developed by the National Research Council (1999) BEIR VI Committee leads to an estimated EOR of 0.12 (0.02, 0.25) per 100 Bq/m^3. (Similar predictions are obtained using other BEIR VI risk projections models that make use of all of the available miner data.) The fact that the BEIR VI residential risk projections are close to the risk estimates from the full combined analysis and lower than the restricted risk estimates from the combined analysis may reflect exposure measurement error in the miner data, error that has not been addressed through restriction as in the combined analysis.

The seven case-control residential epidemiologic radon studies presented in this report have estimated past residential radon concentrations, as a proxy for exposure, primarily by year-long α-track detector measurements in each current and some former homes. Alpha-track detectors can provide accurate and precise measurements (Field et al., 1998b) of the average radon gas concentration over the time they are in place, and provide estimates of exposure levels retrospectively by assuming constant radon concentrations during each interval of occupancy in a single residence. However, historical exposure reconstruction can be problematic since many houses may no longer exist, others may have a current occupant who refuses entry, and still others may have current radon concentrations that differ from the concentrations that were typically found in the home when the study subject lived there. Missing

TABLE 19. Assumptions and Factors Using a Miner-Based Risk Model With Working Level Month[a] as the Unit of Exposure, and the Estimated Odds Ratio of Lung Cancer from Residing Under Standard Living Conditions for 25 yr in a Home With a Constant Radon Concentration of 100 Bq/m^3

Component	Assumption/relationship
Translating 100 Bq/m^3 × 25 yr into "residential" WLM	
WL and Bq/m^3 at equilibrium[a]	1 Bq/m^3 = 0.00027 WL
Equilibrium factor	≈0.40
Residential occupancy factor	≈0.70
"Working months" in 1 yr	365.25 × 24/170 = 51.6 Working months
Exposure to 100 Bq/m^3 for 25 yr	100 × 0.00027 × 0.40 × 0.70 × 51.6 × 25 ≈ 10 WLM
Extrapolation of lung cancer risk to residential exposure	
Miner-based relative risk model[b]	Excess relative risk = 0.0117/WLM
K-factor adjustment[c]	1
Miner-based estimate of excess odds ratio for residential exposure	
Estimated excess odds ratio[d]	0.0117 × 10 WLM ≈ 0.117

[a] Working level (WL) is a measure of exposure rate, where 1 WL is equivalent to any combination of the short-lived progeny of radon in 1 L of air, under ambient temperature and pressure, that results in the ultimate emission of 1.3×10^5 MeV of alpha energy, 1WL = $2.08/10^5$ Jh/m^3. Working level month (WLM) is a measure of cumulative exposure to radon and its short-lived progeny, where 1 WLM is equivalent to exposure to one working level for 1 working month (170 h), 1 WLM = $2/10^5$ Jh/m^3 × 170 h = $3.5/10^3$ Jh/m^3 (NRC, 1999).

[b] Miner-based relative risk model approximated using a linear relative risk (RR) model for low-exposed miners (<50 WLM) as RR(WLM) = 1 + β × WLM, where β is the excess relative risk parameter (NRC 1999).

[c] A dimensionless factor that characterizes the dose to lung cells for exposures in homes compared to similar exposures in mines (NRC, 1999).

[d] Since lung cancer is a rare disease, the odds ratio closely approximates the relative risk.

data from homes that cannot be measured for radon and significant variations between the current radon concentrations and historical radon concentrations (Steck, 1992) reduce a study's power to detect an association (Lubin et al., 1990; Field et al., 1996; Weinberg et al., 1996).

The Iowa study (Field et al., 2000a) restricted its inclusion criteria to subjects who lived in their current home for more than 20 yr to reduce the amount of missing data, decrease temporal variation, and optimize power by increasing the variation in cumulative exposures across subjects. Another method used by Alavanja et al. (1999) and Field et al. (1999) to improve retrospective exposure assessment was the use of glass-based alpha-track detectors. The glass-based findings of Alavanja et al. (1999) are presented in this report, while the glass-based findings in Iowa (Field et al., 2000a) have not yet been formally published. This highly innovative alternative glass-based dosimetry approach (Lively & Ney, 1987; Samuelsson, 1988) measures the accumulation of a long-lived radon decay product, ^{210}Pb, in glass items through alpha-particle emissions of a subsequent decay product, ^{210}Po. This alpha emission is measured by a specially designed detector that can be affixed to a glass surface.

Long-owned glass items, such as a beloved baby picture, are identified by study subjects. The mean radon exposure of the glass (and presumably of its owner) over its lifetime can be calculated from the known decay properties of radon and the deposition of its progeny.

Previous laboratory experiments (Lively & Steck, 1993) have demonstrated a high correlation between cumulative radon exposure and implanted ^{210}Po activity for glass surfaces. Additional studies of this relationship in samples of homes have also shown moderate to good correlation between contemporary year-long radon gas concentrations and historically derived radon gas concentrations using glass-based α-track detectors (Samuelsson et al., 1992; Lively & Steck, 1993; Steck et al., 1993; Mahaffey et al., 1993). Field studies have documented excellent agreement between the surface activity measurements from the two different glass-based detectors used in Missouri (Alavanja et al., 1999) and Iowa (Field et al., 1999). In fact, a recent field study has shown a strong correlation between the historically measured cumulative radon gas exposure and the measured glass surface activity, providing further support for the use of glass-implanted ^{210}Po to estimate historical radon gas exposure (Field et al., 1999; Steck et al., 2002).

Limitations of the glass-based exposure method include the requirement that suitable pieces of glass exist in the home. The study subject must know that the glass was new when bought and must be able to recall the age of the glass with a reasonable accuracy. Differences in deposition conditions can lower the correlation between actual cumulative radon exposure and implanted activity in the glass. The reconstruction of historic radon concentrations may be less accurate if other factors such as cigarette smoke or particulate air pollution are present in the home (Weinberg, 1995; Field et al., 1999). However, a stronger relationship between historical radon exposure and implanted glass activity can be achieved when adjustments are made for the deposition environment of the surface (Steck & Field, 1999; Steck et al., 2002; Fitzgerald & Hopke, 2000; Walsh & McLaughlin, 2001). Studies are currently underway to further validate the glass-based detectors and pool the glass-based results from the Iowa and Missouri II residential radon studies (Field et al., 2000b).

A combined analysis of 13 European case-control studies involving over 7000 cases of lung cancer and 14,000 controls is currently underway within the European Union (Darby & Hill, 2003). This ongoing analysis will include completed case-control studies in Sweden (Pershagen et al., 1994), Finland (Auvinen et al., 1996), southwest England (Darby et al., 1998), and Germany (Kreienbrock et al., 2001; Kreuzer et al., 2003). This important analysis will contribute greatly to the database on residential radon and lung cancer risk because of the large number of cases involved and the higher average radon concentrations observed in the 13 European studies as compared to the 7 North American studies reported here.

Once the European investigators completes its combined analysis, a combined analysis of the North American and European data is planned. This global pooling of residential radon studies will also include additional data from New

Jersey (H. B. Wilcox, personal communication, 2004), which are currently undergoing independent analysis, as well as studies in China conducted by Blot et al. (1990) and Wang et al. (2002). The global analysis will include over 12,000 cases, and will provide the most definitive direct statement about the risk of lung cancer associated with the presence of radon gas in homes worldwide.

Pooling has its inherent limitations, including the inability to improve the quality or reporting of the original residential radon studies. In addition, because of the diversity of the various study methods and the need for a common data format, it was not always possible to use the best exposure data for each residential radon study. For example, the Iowa study (Field et al., 2000a) linked radon measurements in various locations including inside and outside the house with the retrospective mobility of the subjects. In addition, the findings for the histologic types require cautious interpretation since only the Missouri and Iowa studies obtained more precise consensus diagnoses performed by a panel of blinded expert pathologists (Field et al., 2004). 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. Therefore, the results of this combined analysis should be interpreted in light of the strengths and limitations of each of the individual residential radon studies and within the contexts of results from occupational, animal, and molecular radon-related studies.

In conclusion, the aggregated data from the North American residential radon studies included a large number of cases and controls and represented a broad range of residential radon concentrations. The overall estimate of the EOR for lung cancer was estimated to be 0.10 (–0.01, 0.26) per 100 Bq/m^3. Restrictions that increased coverage of the ETW resulted in increasing EORs. For example, those subjects (comprised of 1910 cases and 2651 controls) who had resided in at most 2 residences with at least 20 yr coverage in the ETW 5–25 yr prior to the index date had an EOR of 0.18 (0.02, 0.43).

Collectively, our results provide direct evidence of an association between residential radon exposure and lung cancer, a finding predicted by downward extrapolation of epidemiological data on underground miners exposed to higher levels of radon, and consistent with toxicological results from animal and in vitro studies. This conclusion is supported by a combined analysis of the two Chinese case-control studies, involving a total of 1050 cases and 1996 controls (Lubin et al., 2004). Further information on residential radon lung cancer risks will be provided by the global combined analysis of all residential radon case-control studies.

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APPENDIX: DATA FORMAT FOR COMBINED ANALYSIS

The data received from each site were combined into two separate records: (1) fixed variables for general information, and (2) year-by-year variables, including those related to radon exposure. Tables A1 and A2 outline each record has been coded and formatted. For all variables, missing values have been set to –999. Note, however, that missing values may occur as a consequence of one of several distinct conditions specific to the variable of interest (Table A3, Table A4).

TABLE A1. Data Format for Record 1—Fixed Variables

Variable name	Description	Column start in ASCII File	Column width in ASCII File	Coded values	
ID	Study-defined unique subject identifier	1	9.	Integer	
SET_NO	Pair-matched set number or frequency-matched stratum number	11	4.	NA (sequential)	
STATUS	Subject status (type)	16	1.	Case	1
				Control	0
HISTO	Histological type	18	1.	Control	0
				Squamous	1
				Small/oat cell	2
				Other	3
				Adenocarcinoma	4
				Uncertain	5
AGE_ASC	Age at diagnosis for cases; age at interview for controls	20	2.	Integer value between 30 and 84	
YR_ASC	Last two digits of calendar year of ascertainment defined as year of diagnosis for cases and interview for controls	23	2.	Numeric 19_ where _ values can range from 82 to 91 for cases	
INTERV	Interview type (source of information) self (subject) or proxy (spouse or other surrogate) respondent	26	1.	Subject	1
				Proxy	2
SEX	Subject sex	28	1.	Females	1
				Males	2
EDU_CAT	Highest level of education undertaken (but not necessarily completed) by subject.	30	4.	Some elementary school (grades 0–7)	1
				Some secondary school (grades 8–13)	2
				Some postsecondary education	3
				Unknown	–999
INCOME	Average annual family income in Canadian or U.S. dollars (respectively). (Note that income was not ascertained in the New Jersey-I study).	35	4.	<$10,000	1
				$10,000–$20,000	2
				$20,000–$30,000	3
				$30,000–$50,000	4
				≥$50,000	5
				Unknown	–999

TABLE A1. *(Continued)*

Variable name	Description	Column start in ASCII File	Column width in ASCII File	Coded values	
SM_TYPE	Smoking category of subject. "Never" smokers include those who smoked <1 yr or <100 cigs. (original category 5 for Missouri); *mixed* refers to those smoking both cigarettes and pipes or cigars. Those subjects with missing values are eliminated from the data set.	40	4	Never smoked Cigarettes only Pipe/cigar only Mixed Unknown	1 2 3 4 –999
SM_RATE	Smoking rate as average number of cigarettes smoked/day during the active smoking period. Defined as 0 for non or pipe/cigar smokers.	45	5.2	Numeric with 2 digits before the 2 decimal places Unknown	 –999
SM_START	Age started smoking. Defined as missing (·) for non or pipe/cigar smokers.	51	4.	Positive integer value Unknown	 –999
SM_STOP	Age stopped smoking. Defined as missing (·) for non or pipe/cigar smokers.	56	4	Positive integer value Unknown	 –999
SM_DUR	Net years of cigarette smoking adjusted for periods of cessation intermediate between start and stop age. Defined as 0 for non or pipe/cigar smokers.	61	4.1	Numeric with 2 digits before the single decimal place Unknown	 –999
SM_LAG	Number of years prior to ascertainment since the subject last smoked cigarettes. Defined as missing (·) for non or pipe/cigar smokers.	66	4.	Positive integer value Unknown	 –999
ETHNIC	Race (New Jersey and Missouri) or country of origin (Winnipeg). Missouri study was restricted to subjects of "white" race (all coded as 1).	76	4.	New Jersey: White/Hispanic Black/Native/Asian or Pacific islander/Other Winnipeg Canadian birth Non-Canadian birth Connecticut and Utah-South Idaho: White	 1 2 1 2 1

TABLE A1. *(Continued)*

Variable name	Description	Column start in ASCII File	Column width in ASCII File	Coded values	
				Asian	1
				Native/	2
				American	3
				Black	4
				Missing (unknown)	–999
STUDY	Study identifier	81	1.	Integer value from 1 to 7	
PIPE	"Have you EVER smoked as much as 12 ounces or 100 pipefuls of tobacco in your lifetime?"	83	4.	Yes	1
				No	2
				Missing (unknown)	–999
CIGARS	"Have you EVER smoked as many as 1 cigar a week for a year or 52 cigars in your lifetime?"	88	4.	Yes	1
				No	2
				Missing (unknown)	–999
STATE	State code for study site	93	4.	UT-ID	1
				CT	2
				Others	–999
WORK_40	Hours per week subject worked at age 40	98	4.	Ranges from 0 to 120 hours per week	
				Missing	–999
PHASE	Phase of recruitment; recruitment probabilities were changed midstream to deal with greater than expected smoking associated risk.	103	4.	1 or 2	
				Missing	–999
OFFSET	Offset based on sampling probabilities	108	7.3	Calculated: (Ca_AS*Ca_SM)/(Co_AS*Co_SM) where: Ca_AS = case age/sex probability CA_SM = case smoking probability Co_AS = control age/sex probability Co_SM = control smoking probability	
				Missing	–999

Note. In Missouri and New Jersey data sets, home identification numbers were available only for homes with complete measurement. In these data sets, therefore, a missing (·) value can denote either that the relevant home was not identified, or measurement was incomplete (refusal, loss of dosimeter, less than a year of measurement). The Winnipeg file contains home numbers every home identified in the housing history whether measured or not. In Winnipeg, missing values indicate lack of identification. The availability of a complete house history with identification numbers is important, as errors in estimated duration of residence in a home will be correlated for adjacent homes. Such information will be considered in an uncertainty analysis during the final (Phase II) analysis.

TABLE A2. Data Format For Record 2—Year-by-Year Variables

Variable name	Description	Column start in ASCII file	Column width in ASCII file	Coded values	
ID	Study-defined subject identification number	1	9.	Positive integer value	
STATUS	Subject status	11	1	Case	1
				Control	0
TIME	Index variable for the following variables, which take on unique values for each of 50 yr prior to ascertainment	13	2.	Sequential positive integer from 1 to 50	
HOME	Sequential number starting at 1 for the most recent, increasing as time prior to ascertainment increases.	16	4.	Positive integer value Missing	–999
CONC	Average annual radon concentration in living area in bequerels per cubic meter	21	6.1	Numeric value with 3 digits prior to a single decimal place	
				Missing	–999
ES_TYP	Estimation type for living area radon concentration during indexed year.	28	4.	Regression from basement	1
				OCMI	2
				1 yr α-track measure	3
				Canister Measure	4
				Not an applicable time period for subject	6
				A-track + regression	7
				OCMI + regression	8
				Mixed (more than one house per year and method used to estimate radon for each house differs)	9
				Missing (no estimation)	–999

TABLE A2. *(Continued)*

Variable name	Description	Column start in ASCII file	Column width in ASCII file	Coded values	
CONC_G	Average annual radon concentration in living area in bequerels per cubic meter by glass measure.	33	6.1	Numeric value with 3 digits prior to a single decimal place	
				Missing	–999
ES_TYP_G	Estimation type for living area radon concentration during indexed year.	40	4.	Glass measure	5
				Missing (no estimation)	–999
CONCB	Average annual radon concentration in basement in becquerels per cubic meter (only routinely available in Winnipeg data set) during indexed year.	45	6.1	Numeric value with 3 digits prior to a single decimal place	
				Missing (no estimation)	–999
ES_TYB	Estimation type for basement radon concentration during indexed year.	52	4.	Regression from basement	1
				Imputation by OCMI	2
				1 year alpha track meas.	3
				Canister	4
				Not an applicable time period for subject	6
				Missing (no estimation)	–999
OCCUP	Estimated fraction of the average 24-h period that the subject occupied the home (direct information available only in Missouri data set) during indexed year.	57	4.2	Numeric value (a proportion between 0.0 and 1.0)	
				Unknown	–999
S_CIGS	Number of cigarettes smoked/day by the subject in indexed year.	72	4	Positive integer value	
				Unknown	–999
STUDY	Study identifier	77	1.	Integer value from 1 to 7	

Note. OCMI refers to the Observed Control Mean Imputation method (Weinberg et al. 1996).

TABLE A3. Data Availability—Fixed Variables

Variable	Description	Availability						
		NJ	Winn	MO-I	MO-II	IA	CT	UT-ID
ID	Study-defined unique subject identifier	X	X	X′	X	X	X	X
SET_NO	Pair-matched set number or frequency-matched stratum number		X					
STATUS	Subject status (type)	X	X	X	X	X	X	X
HISTO	Histological type	X	X	X	X	X	X	X
AGE_ASC	Age at diagnosis for cases; age at interview for controls	X	X	X	X	X	X	X
YR_ASC	Last two digits of calendar year of ascertainment defined as year of diagnosis for cases and interview for controls	X	X	X	X	X	X	X
INTERV	Interview type (source of information) self (subject) or proxy (spouse or other surrogate) respondent	X	X	X	X	X	X	X
SEX	Subject sex	X	X	X	X	X	X	X
EDU_CAT	Highest level of education undertaken (but not necessarily completed) by subject	X	X	X	X	X	X	X
INCOME	Average annual family income in Canadian or U.S. dollars (respectively). (Note that income was not ascertained in the New Jersey study).		X	X	X		X	X
SM_TYPE	Smoking category of subject. "Never" smokers include those who smoked <1 yr or <100 cigs. (original category 5 for Missouri); *mixed* refers to those smoking both cigarette and pipes or cigars.	X	X	X	X	X	X	X
SM_RATE	Smoking rate as average number of cigarettes smoked/day during the active smoking period. Defined as 0 for non or pipe/cigar smokers.	X	X	X	X	X	X	X
SM_START	Age started smoking. Defined as missing (·) for non or pipe/cigar smokers	X	X	X	X	X	X	X
SM_STOP	Age stopped smoking. Defined as missing (·) for non or pipe/cigar smokers	X	X	X	X	X	X	X
SM_DUR	Net years of cigarette smoking adjusted for periods of cessation intermediate between start and stop age. Defined as 0 for non or pipe/cigar smokers	X	X	X	X	X	X	X
SM_LAG	Number of years prior to ascertainment since the subject last smoked cigarettes. Defined as missing (·) for non or pipe/cigar smokers	X	X	X	X	X	X	X
ETHNIC	Race (New Jersey and Missour) or country of origin (Winnipeg). Missouri study was restricted to subjects of "white" race (all coded as 1).	X	X	X	X	X	X	X
PIPE	"Have you EVER smoked as much as 12 ounces or 100 pipefuls of tobacco in your lifetime?"						X	X
CIGARS	"Have you EVER smoked as many as 1 cigar a week for a year or 52 cigars in your lifetime?"						X	X
STATE	State code for study site						X	X
WORK_40	Hours per week subject worked at age 40						X	X

TABLE A3. *(Continued)*

Variable	Description	Availability						
		NJ	Winn	MO-I	MO-II	IA	CT	UT-ID
PHASE	Phase of recruitment. Recruitment probabilities were changed midstream to deal with greater than expected smoking associated risk.						X	X
OFFSET	Offset based on sampling probabilities (see Dr. Weinberg for discussion on how to use offsets in analysis)						X	X
STUDY	Study identifier	X	X	X	X	X	X	X

TABLE A4. Data Availability—Year-by-Year Variables

Variable	Description	Availability						
		NJ	Winn	MO-I	MO-II	IA	CT	UT-UT
ID	Study-defined subject identification number	X	X	X	X	X	X	X
STATUS	Subject status	X	X	X	X	X	X	X
TIME	Index variable for the following variables which take on unique values for each of 50 years prior to ascertainment	X	X	X	X	X	X	X
HOME	Sequential number starting at 1 for the most recent, increasing as time prior to ascertainment increases	X	X	X	X	X	X	X
CONC	Average annual radon concentration in living area in Bequerels/cubic meter	X	X	X	X	X	X	X
ES_TYP	Estimation type for living area radon concentration during indexed year (upper—arithmetric means, lower—geometric means)	X	X	X	X	X	X	X
	1. Regression from basement	18.8	110					
		14.9	91.4					
	2. OCMI		120				28	41.9
			120				26.2	38.3
	3. 1 yr alpha-track measure	30.1	151.8	63.6	57	127.8	34.3	59.9
		20.7	106.6	48.1	41.9	93.3	20.5	44.1
	4. Canister measure	44.4						
		44.4						
	5. Glass measure				66.7			
					54.2			
	6. Not an applicable time period for subject—percentage					7.6%		
	7. Alpha track + regression						31.8	54.4
							20.7	42.0
	8. OCMI + regression						28.0	47.9
							24.4	44.6

TABLE A4. *(Continued)*

Variable	Description	Availability						
		NJ	Winn	MO-I	MO-II	IA	CT	UT-UT
	9. Mixed						29.2	51.8
							23	45.0
CONCB	Average annual radon concentration in basement in becquerels per cubic meter (only routinely available in winnipeg data set) during indexed year	X	X			X		
ES_TYB	Estimation type for basement radon concentration during indexed year (upper—arithmetric menas, lower—geometric means)	X	X			X		
	1. Regression from basement		76.3					
			57.8					
	2. OCMI		177.3					
			177.3					
	3. 1-yr alpha-track measure	18.8	226.5			227.7		
		14.9	170.5			170.6		
	4. Canister measure							
	5. Glass measure							
	6. Not an applicable time period for subject—percentage					7.6%		
	7. Alpha track + regression							
	8. OCMI + regression							
	9. Mixed							
OCCUP	Estimated fraction of the average 24-h period that the subject occupied the home (direct information available only in Missouri data set) during indexed year	X	X	X	X			
S_CIGS	Number of cigarettes smoked/day by the subject in indexed year	X	X	X	X	X	X	X
STUDY	Study identifier	X	X	X	X	X	X	X