Health Canada Santé Canada

University of Ottawa
Université d'Ottawa
uOttawa

Canada

Health Canada Santé Canada

University of Ottawa
Université d'Ottawa
uOttawa

Jan M. Zielinski

Bureau of Environmental Health Science, Health Canada

Department of Epidemiology and Community Medicine, University of Ottawa

RC-7 Epidemiological methods on residential radon and cancer risk

Buenos Aires, October 22, 2008

Canada

Outline

- What is radon?
- Reasons for pooling epidemiological studies
- US NRC BEIR VI Committee (1994-1999)
- Inventory of residential radon case-control studies
- Combined analysis of North American studies (1989-2004)
  - Winnipeg case-control study (1982-1994)
  - Protocol and results
  - Conclusions
- Comparison risk estimates from BEIR VI with results of pooled residential case-control studies

What is radon?

1550 Reports of Bergkrankheit or “mountain sickness” in Czech silver mines

1879 Illness recognized as lung cancer

1896 Discovery of radioactivity by Becquerel

1898 Isolation of radium by Marie & Pierre Curie

1900 Discovery of radon gas from the decay of radium

1924 Radon identified as the likely cause of Bergkrankheit

Radon in Environment

- **Radon-222 is a naturally occurring decay products of radium-226, the fifth daughter of uranium-238**
- **Both uranium-238 and radium-226 are present in most soils and rocks**
- **As radon gas forms from decay of radium-226, it can leave the rocks and enter surrounding air and water**
- **The distribution of radon in residences varies with the distribution of uranium in the soil, and building characteristics**
- **Radon concentrations can vary between countries, geographic areas within countries, and even between similar homes built at the same time on the same street**

Radon decay chain

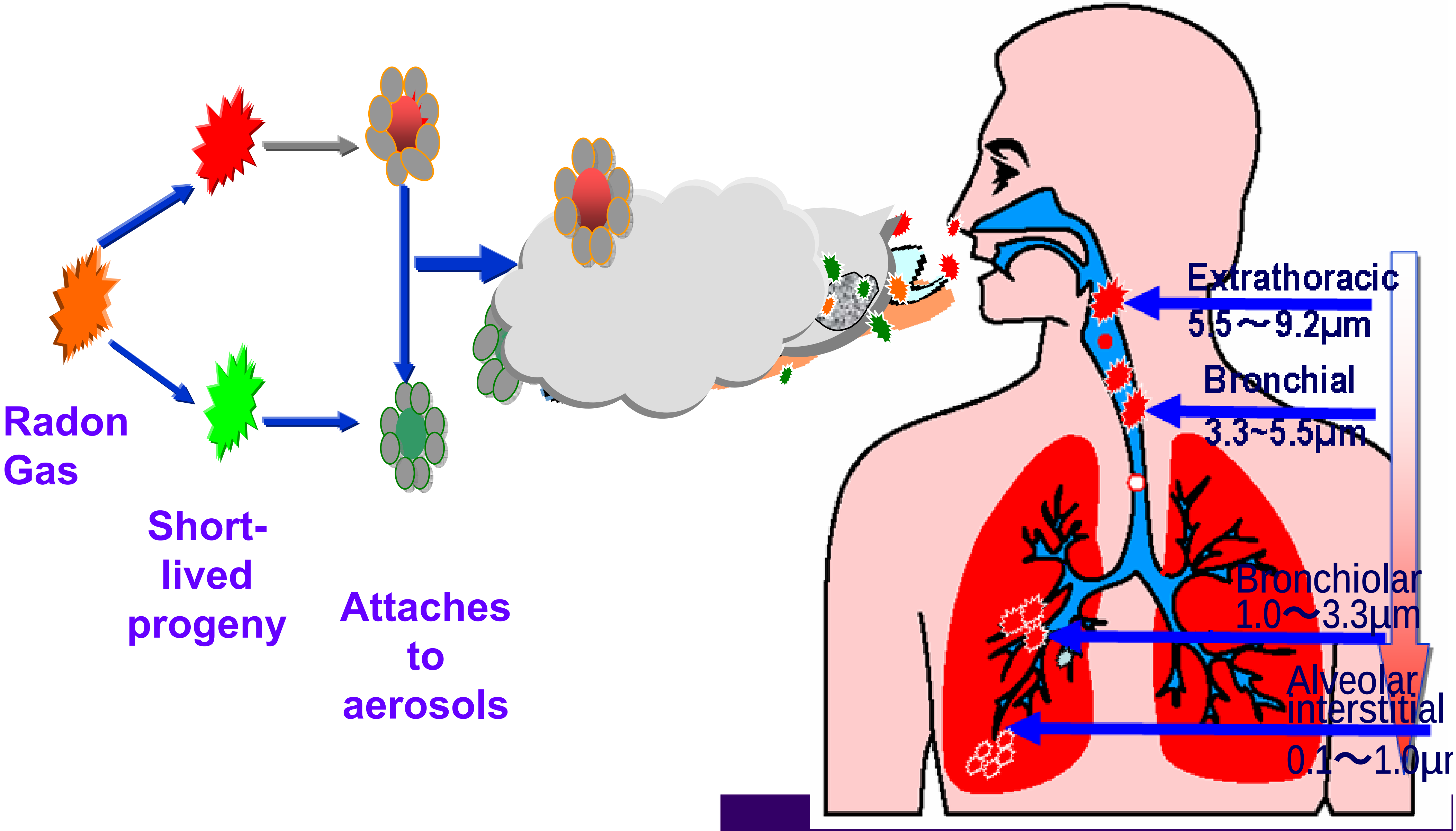
Nuclide	Decay	Half-life
Radon-222	α,γ	4 day
Polonium-218	α,γ	3 min
Lead-214	β,γ	27 min
Bismuth-214	β,γ	20 min
Polonium-214	α,γ	0.2 ms
Lead-210	β,γ	22 yrs
Bismuth-210	β,γ	5 day
Polonium-210	α,γ	138 day
Lead-206		Stable

^{218}Po and ^{214}Po deliver radiologically significant dose to the respiratory epithelium.

Long residency in glass (Lead-210)

Decay easy to measure (Polonium-210)

Radon Inhalation Hazard



Radon: Evidence of Carcinogenicity

- **In Vivo & In Vitro experimental Studies: inhalation studies in 3 species: rats, hamsters and dogs**
- **The International Agency for Research on Cancer (IARC 1988) has classified radon as a known human carcinogen (based on the strong evidence of lung cancers in underground miners exposed to high levels of radon.)**
- **A combined analysis of 11 cohorts of underground miners by Lubin (1994) and updated by the BEIR VI (1999).**
- **A combined analysis of 7 North American case-control studies of lung cancer and residential radon**
- **A combined analysis of 13 European case-control studies of lung cancer and residential radon**

Methods for Epidemiological Studies of Radon

Different types of studies:

- **Cohorts studies of underground miners**
- **Ecological studies of exposure to residential radon**
- **Case-control studies of lung cancer and residential radon**

Individual studies are usually too small to draw definite conclusions

Reasons for Pooling

- **Reduce uncertainty and obtain more precise estimates of risk than available from any single study (increase power for detecting risk)**
- **Allow more powerful exploration of modifying effects of factors such as smoking, sex, age at exposure**
- **Obtain the best overview or summary of studies**
- **Provides the best opportunity for developing an understanding of differences and similarities in studies and results (parallel analyses)**
- **Investigate the consistency of results from different studies**

Pooled Analyses - Descriptive statistics

Descriptive statistics are important. They allow to compare studies with respect to size, exposure distributions, and other characteristics calculated in the same manner with the same cutpoints, for each of the studies.

Pooled Analyses - Parallel Analyses

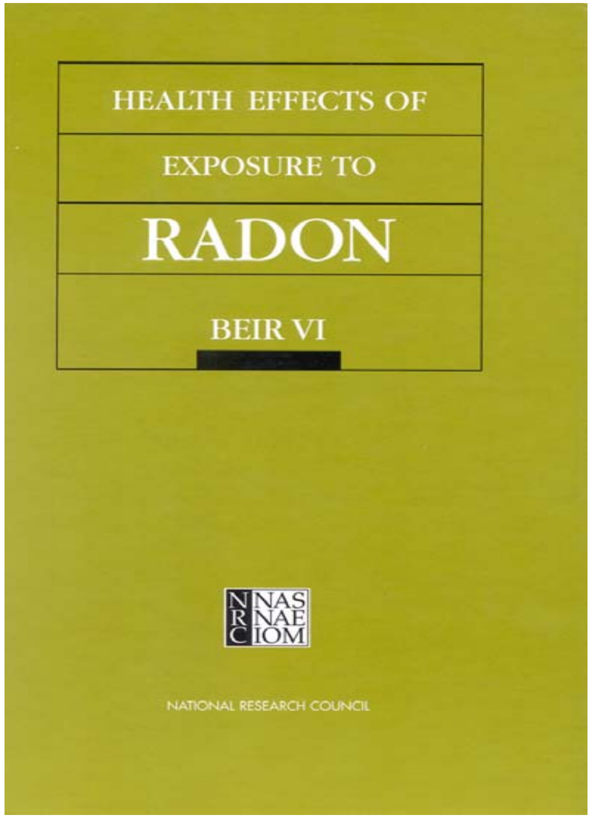
- **Similar methods applied to all studies**
- **First step in evaluating comparability of results**
- **Some sub-group analyses (male/female; only complete exposure histories)**
- **Certain aspects of methods may differ (e.g., methods for smoking adjustment)**

Pooled Analyses - Combined Analyses

- **Data from all studies considered as a single data set**
- **Evaluation of homogeneity across studies**
- **Subgroup analyses**
- **Overall estimate of risk with adequate evaluation of uncertainty**

BEIR VI: Health Risks of Radon

- **1994: Committee convened**
- **1999: Report released**



"Radon responsible for 10-15 % of all lung cancer deaths in the United States"

BEIR VI: Major Issues of Interest

- Animal Studies
- Cellular and molecular Studies
- Residential Studies
- Smoking and Radon-Smoking Interactions
- Miner Data Sets and Analysis
- Exposure and Dosimetry
- Risk Models and Uncertainties

BEIR VI: Miner Data Sets - 1

Location	Type of Mine	Number of Miners	Period of Follow-up	
China	Tin	17,143	1976-87	S
Czechoslovakia	Uranium	4,284	1952-90	
Colorado, U.S.A.	Uranium	3,347	1950-87	S
Ontario, Canada	Uranium	21,346	1955-86	
Newfoundland, Canada	Fluorspar	2,088	1950-84	S
Malmberget, Sweden	Iron	1,294	1951-91	
New Mexico, U.S.A.	Uranium	3,469	1943-85	S
Beaverlodge, Canada	Uranium	8,486	1950-80	
Port Radium, Canada	Uranium	2,103	1950-80	
Radium Hill, Australia	Uranium	2,516	1948-87	S
France	Uranium	1,785	1948-86	

S-some smoking data available

BEIR VI: Miner Data Sets - 2 Lung Cancer Deaths

Location	< 50 WLM	< 100 WLM	No restriction
China	77	116	980
Czechoslovakia	15	77	705
Colorado, U.S.A.	15	22	336
Ontario, Canada	180	231	291
Newfoundland, Canada	21	24	118
Malmberget, Sweden	17	36	79
New Mexico, U.S.A.	8	11	69
Beaverlodge, Canada	42	49	65
Port Radium, Canada	20	25	57
Radium Hill, Australia	52	53	54
France	22	33	45

BEIR VI: Miner Data Sets - 3 Summary

	< 50 WLM	< 100 WLM	No restriction
Lung Cancer deaths			
Non-exposed	**115**	**115**	**115**
Exposed	**353**	**562**	**2,674**
Person-years			
Non-exposed	**274,161**	**274,161**	**271,457**
Exposed	**454,159**	**564,772**	**883,996**

Excess Relative Risk Model (*Breslow and Day*)

$$E[Y_i] = t_i \lambda_i (1 + \beta D_i)$$

Stratify by age and calendar year

- Y_i = Poisson variable, number of deaths in i^{th} stratum
- t_i = number of person-years represented by i^{th} stratum
- λ_i = baseline mortality rate in i^{th} stratum
- D_i = average cumulative dose in i^{th} stratum
- β = excess risk associated with unit cumulative exposure

BEIR VI: Risk Modeling

The Excess Relative Risk $$ERR = \beta\,\gamma(\omega(t))$$

$\omega(t)$ - the cumulative radon exposure at age t

β - the potency of radon.

Constant relative risk model (CRR model)

$$\gamma(\omega(t)) = \omega(t)$$

BEIR VI: Risk Modeling - Stratification

Attained age:

<55, 55-64, 65-74, 75+

Duration of exposure:

<5, 5-14, 15-24, 25-34, 35+

Exposure rate(WL):

<0.5, 0.5-1.0, 1-3, 3-5, 5-15, 15+

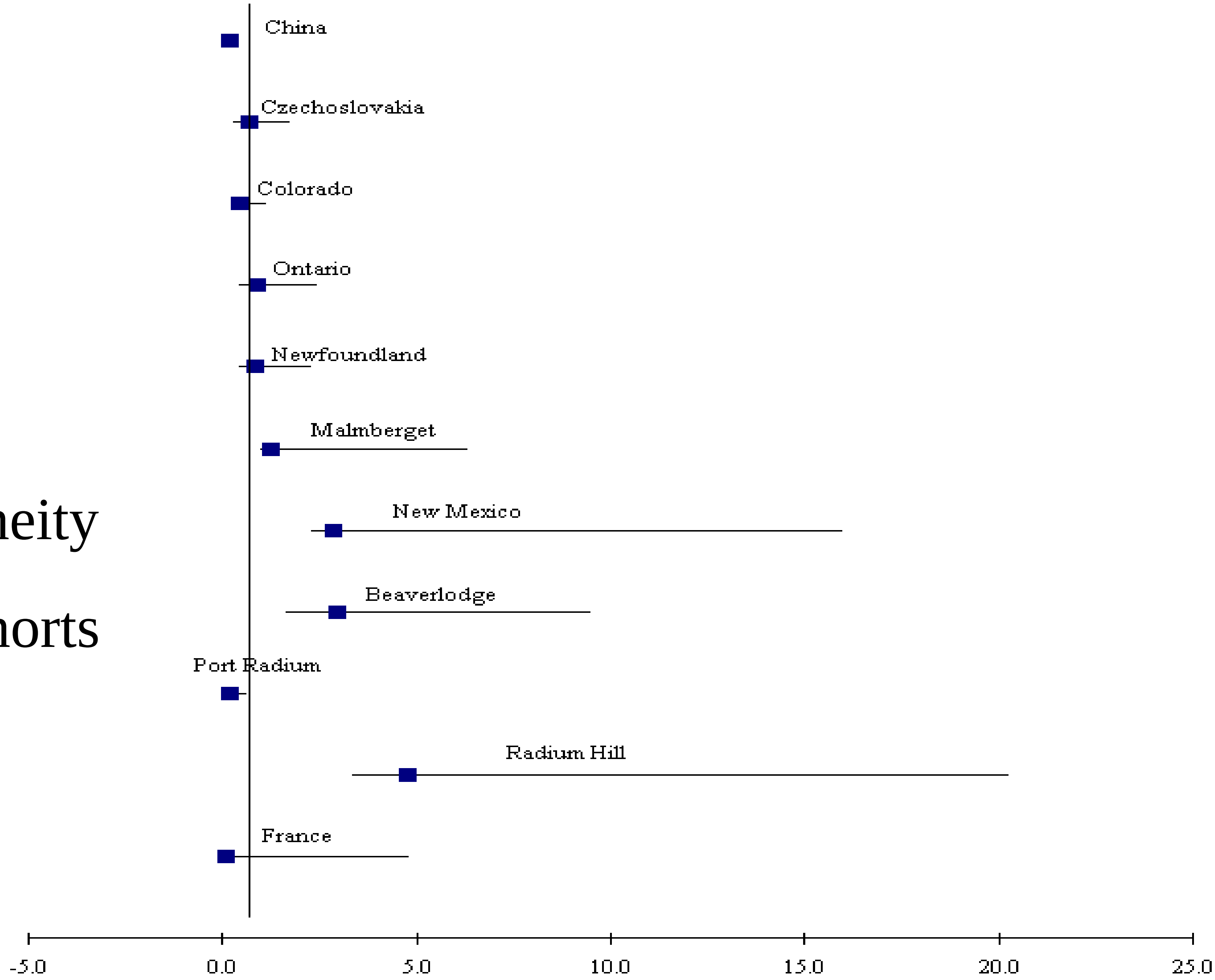
BEIR VI: Cohort-Specific Analysis

Constant Relative Risk Model	
Cohort	**β**
China	**0.17**
Czechoslovakia	**0.67**
Colorado, U.S.A.	**0.42**
Ontario, Canada	**0.89**
Newfoundland, Canada	**0.82**
Malmberget, Sweden	**1.25**
New Mexico, U.S.A.	**2.84**
Beaverlodge, Canada	**2.95**
Port Radium, Canada	**0.19**
Radium Hill, Australia	**4.76**
France	**0.09**

BEIR VI: Cohort-Specific Analysis

Heterogeneity

across cohorts



Combined Analysis: Random-Effects Model

The heterogeneity across cohorts is described by a random-effects model in which the overall effects and variation among individual cohorts are characterized by fixed and random regression coefficients

$$\beta_k = \beta + b_{\beta,k}$$

$b_{\beta,k}$ – random effect of kth cohort

β – fixed effect

Computationally difficult

Stage 1.

CRR model is fitted to each cohort

$\hat{\beta}_k -$ the estimate of model parameter β_k

$s_k -$ the estimated variance of $\hat{\beta}_k$

Stage 2.1

Combined Analysis: Two Stage Model

We Define $\bar{\beta} = \frac{\Sigma_k s_k^{-1} \hat{\beta}_k}{\Sigma_k s_k^{-1}}$; $\hat{\tau} = \frac{\Sigma_k s_k^{-1} (\hat{\beta}_k - \bar{\beta}_k)^2 - (K-1)}{\Sigma_k s_k^{-1} - \frac{\Sigma_k s_k^{-2}}{\Sigma_k s_k^{-1}}}$;

$$\omega_k = \frac{(\hat{\tau} + s_k)^{-1}}{\Sigma_k (\bar{\tau} + s_k)^{-1}}$$

Pooled estimate of the overall effect with

$$\hat{\beta} = \sum_k \omega_k \hat{\beta}_k$$

the variance

$$Var(\hat{\beta}) = (\sum_k (\hat{\tau} + s_k)^{-1})^{-1}$$

Stage 2.2

Combined Analysis: Two Stage Model

Test for homogeneity has a chi-square distribution with (K–1) df

$$\chi^2_{homog} = \sum_k s_k^{-1} (\hat{\beta}_k - \bar{\beta})^2$$

The shrinkage estimator of the cohort-specific effect with deviation from the overall estimate

$$\hat{\beta}_k^* = \frac{s_k \hat{\beta} + \hat{\tau} \hat{\beta}_k}{s_k + \hat{\tau}}$$

$$\hat{\delta}_k = \hat{\beta} - \hat{\beta}_k^* ;$$

$$Var(\hat{\delta}_k) = \frac{\hat{\tau}\, s_k}{\hat{\tau} + s_k}$$

Cohort Specific versus Combined Analysis

Location	Two Stage	Cohort Specific
Combined	0.76	
China	0.17	0.17
Czechoslovakia	0.67	0.67
Colorado, U.S.A.	0.44	0.42
Ontario, Canada	0.82	0.89
Newfoundland, Canada	0.82	0.82
Malmberget, Sweden	1.04	1.25
New Mexico, U.S.A.	1.58	2.84
Beaverlodge, Canada	2.33	2.95
Port Radium, Canada	0.24	0.19
Radium Hill, Australia	2.75	4.76
France	0.51	0.09

BEIR VI: Preferred Risk Models

Exposure-age-concentration model (EAC model)

$$\gamma(\omega(t)) = \omega(t) \times \phi(t) \times \gamma_{wl}(\omega) \times K \times \delta$$

Exposure-age-duration model (EAD model)

$$\gamma(\omega(t)) = \omega(t) \times \phi(t) \times \gamma_{dur}(\omega) \times K \times \delta$$

where $\phi(t)$ - the influence of attained age

K -the dosimetric factor

δ -the modified effect of smoking

γ_{wl} -the dose rate effect

γ_{dur} -the dose duration effect

$$\omega^{*}(t) \; = \; \omega_{[5-14]}(t) + \vartheta_2 \; \omega_{[15-24]}(t) + \vartheta_3 \, \omega_{[25^{+}]}(t).$$

BEIR VI: Preferred Risk Models Parameters

EAD Model		EAC Model	
$\beta \times 100$	0.55[a] (2.03)[b]	$\beta \times 100$	7.68[a] (1.94)[b]
Time since exposure windows			
θ_1	1.00	θ_1	1.00
θ_2	0.72	θ_2	0.78
θ_3	0.44	θ_3	0.51
Attained age			
$\phi_{<55}$	1.00	$\phi_{<55}$	1.00
ϕ_{55-64}	0.52	ϕ_{55-64}	0.57
ϕ_{65-74}	0.28	ϕ_{65-74}	0.29
ϕ_{75+}	0.13	ϕ_{75+}	0.09
Duration of exposure		Exposure rate (WL)	
$\gamma_{<5}$	1.00	$\gamma_{<0.5}$	1.00
γ_{5-14}	2.78	$\gamma_{0.5-1.0}$	0.49
γ_{15-24}	4.42	$\gamma_{1.0-3.0}$	0.37
γ_{25-34}	6.62	$\gamma_{3.0-5.0}$	0.32
γ_{35+}	10.20	$\gamma_{5.0-15.0}$	0.17
		γ_{15+}	0.11

BEIR VI: Influence Analysis (EAD Model)

Cohort Omitted	β – Exposure Age Duration Model	95% Confidence Interval	
None	0.55	0.27	1.12
China	0.71	0.40	1.28
Czechoslovakia	0.56	0.25	1.28
Colorado, U.S.A.	0.58	0.26	1.31
Ontario, Canada	0.55	0.25	1.24
Newfoundland, Canada	0.56	0.25	1.25
Malmberget, Sweden	0.55	0.26	1.19
New Mexico, U.S.A.	0.53	0.25	1.16
Beaverlodge, Canada	0.46	0.23	0.89
Port Radium, Canada	0.56	0.26	1.25
Radium Hill, Australia	0.44	0.23	0.85
France	0.60	0.29	1.24

Influence Analysis Smoking Correction Factors

Cohort Omitted	β – ever-smoker/ β – overall	β – never-smoker/ β – overall
none	0.916	1.937
China	0.921	1.121
Colorado	0.929	1.220
Newfoundland	0.864	2.448
Malmberget, Sweden	0.952	2.584
New Mexico	0.897	2.651

The data for Radium Hill was too sparse to obtain useful estimate

BEIR VI: Assumptions for Extrapolation

Characteristic	**Assumption**
Shape of exposure-response function	Linear
Exposure rate	Risks at residential levels comparable with those in miners exposed at less than 0.5 WL (exposure-rate model) or for durations longer than 35 years (exposure-duration model)
Sex	***β*** **-** Ratio of ERR to exposure is the same for males and females
Age at exposure	***β*** **-** Ratio of ERR to exposure is the same for all ages at exposure
Tobacco smoking	Submulitiplicative interaction of smoking and radon; on basis of analyses of ever- and never-smoking miners, the ratio of ERR to exposure for never-smokers is about twice that for ever-smokers
Dosimetry of radon progeny in the lung	No modification of risk required, because dosimetric K factor estimated to be 1

BEIR VI: Residential Risk Extrapolation

Miner-Based Risk Model With Working Level Month 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 X 25 yr into residential WLM	
WL and Bq/m^3 at equilibrium	1 Bq/m^3 = 0.00027 WL
Equilibrium factor	= 0.40
Residential occupancy factor	= 0.70
Working months in 1 yr	365.25 X 24/170 = 51.6 Working months
Exposure to 100 Bq/m^3 for 25 yr	100 X 0.00027 X 0.40 x 0.70 X 51.6 X 25 = 10 WLM
Extrapolation of lung cancer risk to residential exposure	
Miner-based relative risk model	Excess relative risk = 0.0117/WLM
K-factor adjustment	1
Miner-based estimate of excess odds ratio for residential exposure	
Estimated excess odds ratio	0.0117 X 10 WLM = 0.117

Odds Ratio - 1.12 CI: (1.02 – 1.25)

Inventory of Case-control Studies

Region	Number of Studies	Number of Cases
Europe	13	7,148
North America	7	3,662
China	2	1,050

North American Pooling: Number of Subjects

Study		Cases	Controls
New Jersey	(NY)	480	442
Winnipeg	(Winn)	738	738
Missouri-I	(MO-I)	618	1,402
Missouri-II	(MO-II)	697	700
Iowa	(IA)	413	614
Connecticut	(CT)	963	949
Utah-South Idaho	(UT)	511	862
Total		**4,420**	**5,707**

Winnipeg Radon Case-control Study

American Journal of Epidemiology
Vol. 140, No. 4
Printed in U.S.A.

ORIGINAL CONTRIBUTIONS

Case-Control Study of Residential Radon and Lung Cancer in Winnipeg, Manitoba, Canada

E. G. Létourneau,[1] D. Krewski,[1,2] N. W. Choi,[3,4] M. J. Goddard,[1] R. G. McGregor,[1] J. M. Zielinski,[1] and J. Du[3]

Winnipeg Radon Case-control Study

1980: Cross-Canada radon survey of 18,000 homes
(average of 150 Bq/m3 in Winnipeg)

1982: First planning meeting for Winnipeg case-control study
(large scale, complete dosimetry)

1984: Case recruitment initiated

1992: Field work completed
(750 case-control pairs, 35,000+ dosimeters)

1993: Data analysis completed, manuscript written

1994: Publication in American Journal of Epidemiology
(Letourneau, Krewski, Zielinski et al., 140, pp. 310-322)
Overall odds ratio = 0.97 (0.81, 1.15) at 5,0000 Bq/m3-years

North American Pooling: Historical Milestones

- 1989: DOE/CEC Workshop (Arlington)
- 1995: DOE/CEC Workshop (Baltimore)
- 1995: Steering Committee Meeting (Ottawa)
- 1997: Pilot Analysis of 3 Studies (Ottawa)
- 1998: ASA Update (San Diego)
- 2000: All 7 Datasets Received (Ottawa)
- 2002: ASA Update (Deerfield Beach)
- 2003: Manuscript Submitted
- 2005: Manuscript Published!

Common Data Format

Year by Year Variables

- Home Sequence Identifier
- Smoking Intensity
- Living Area Radon Concentration
- Living Area Radon Estimation Method
- Proportion of Time Spent at Home

Static Variables

- Age & Year at Ascertainment
- Gender
- Smoking Status:

Ever/Never Smoker

Intensity *Duration*

Start Age

Stop Age

Years since Cessation

- Proxy Status
- Education
- Family Income
- Race

Study Designs

Study	Age / Control Selection	Gender
New Jersey	No restriction; Controls frequency matched to cases in 5-year age strata	Females
Winnipeg	Range 35 - 80 (cases); controls matched within +/- 5 years of case age	Females/Males
Missouri-I	Range 30 - 84; Controls frequency matched to cases in 5-year age strata	Females
Missouri-II	No restriction; Controls frequency matched to cases in 5-year age strata.	Females
Iowa	Range 40 - 84; Controls frequency matched to cases in 5-year age strata.	Females
Connecticut	Range 40 - 79; Controls frequency matched to cases.	Females/Males
Utah-South Idaho	Range 40 - 79; Controls frequency matched to cases.	Females/Males

Smoking Status of Subjects

Study	Smoking Status
New Jersey	Unrestricted
Winnipeg	Unrestricted
Missouri-I	Current Non-Smokers
Missouri-II	Unrestricted cases; Frequency matching of controls to cases by smoking status
Iowa	Unrestricted
Connecticut	Recruited all cases who had not smoked within the previous 10 years, and a random sample of half of the ever-smoking cases; Frequency matching of controls to cases by smoking status
Utah-South Idaho	Recruited all cases who had not smoked within the previous 10 years, and a random sample of half of the ever-smoking cases; Frequency matching of controls to cases by smoking status

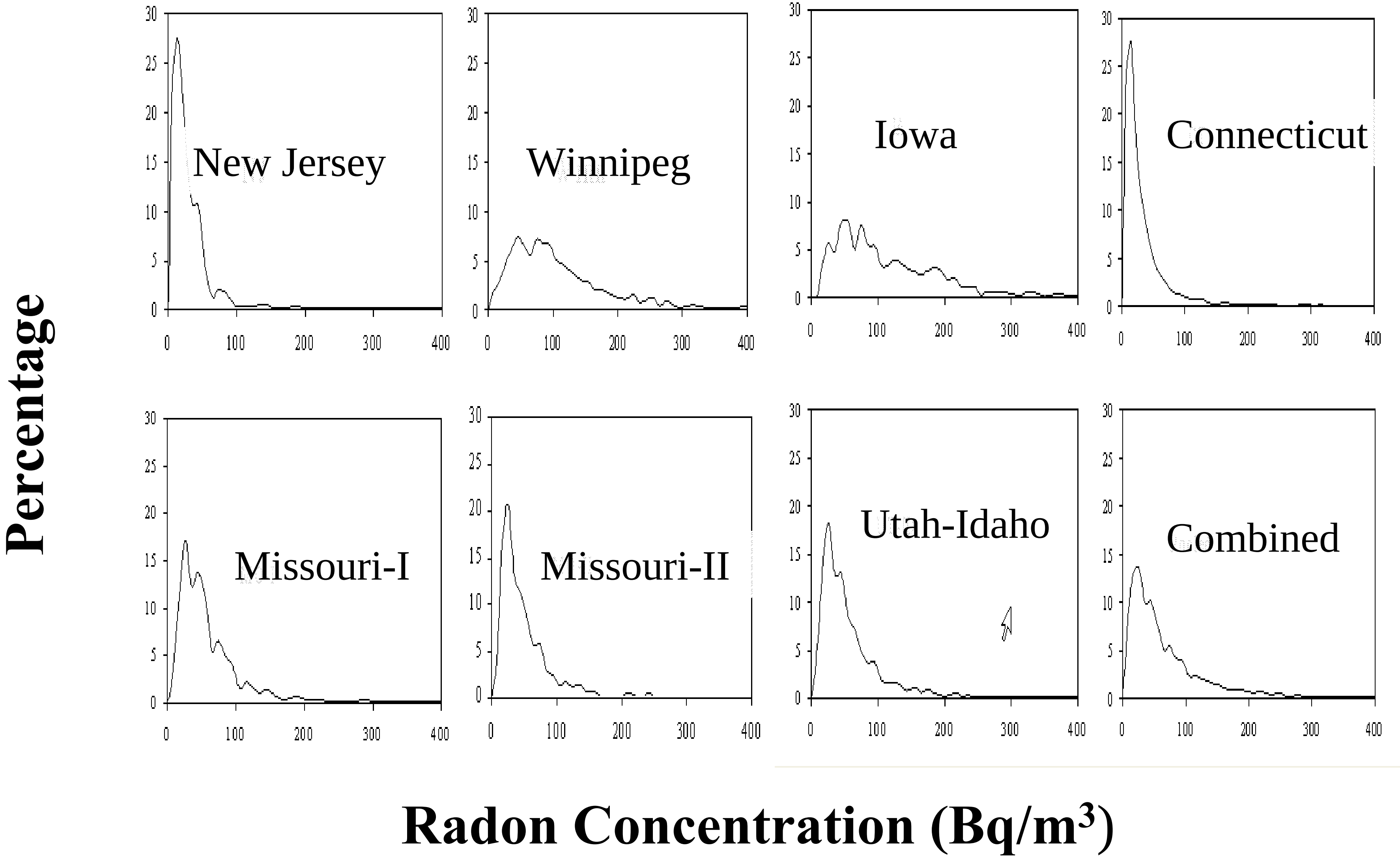
Radon Exposure Ascertainment I

Study	Residential Inclusion Criteria
New Jersey	All in-state homes (maximum 3 per subject) for subjects with a minimum of 8 potentially monitorable years of residency
Winnipeg	All city residences of at least one year residency
Missouri-I	All in-state residences
Missouri-II	All in-state residences
Iowa	Subject resided in their current home for 20 or more consecutive years; average residency 32 years
Connecticut	All homes of minimum 1 year residence from age 25 to ascertainment, and childhood home of longest residence Excluded subjects with highly mobile residential pattern
Utah-South Idaho	All homes of minimum 1 year residence from age 25 to ascertainment, and childhood home of longest residence Excluded subjects with highly mobile residential pattern

Radon Exposure Ascertainment II

Study	Targeted Exposure Time Window	Radon Exposure Estimation
New Jersey	5 - 30 years prior to diagnosis (cases) or selection (controls)	1 year ATD (92%) or 4 day charcoal canister (8%)
Winnipeg	5 - 30 years prior to interview	1 year ATD
Missouri-I	5 - 30 years prior to interview	1 year ATD
Missouri-II	25 years prior to ascertainment.	Two - 1 year ATD and CR-39 glass measurements.
Iowa	Temporal and spatial mobility information collected to allow for a variety of time windows	1 year ATD
Connecticut	Age 25 to 5 years prior to ascertainment.	1 year ATD
Utah-South Idaho	Age 25 to 5 years prior to ascertainment.	1 year ATD

Distribution of Radon Levels



Statistical Methods: Models

All analyses of the data were conducted using conditional likelihood regression for matched or stratified data. Analyses were based on a linear model for the odds ratio (OR) of the form.

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

x **- Average Radon Concentration (Bq/m^3) in 5 – 30 year Exposure Time Window (ETW)**

β – Excess Odds Ratio (EOR) for each unit increase in *x*

Statistical Methods: Stratification

The analyses ware stratified by:

- **Sex**
- **Age**
- **Number of cigarettes smoked per day**
- **Duration of cigarette smoking**
- **Number of residences occupied: 1, 2+**
- **Years of coverage by ATD measurements < 25, 25+**

Odds Ratio[a] (95% CI) for Lung Cancers

Study	Radon concentration (Bq/m^3)							ß×100
	<25	25-49	50-74	75-99	100-149	150-199	≥ 200	
NJ	1	1.14 (0.8,1.7)	1.21 (0.5,2.9)	1.81 (0.3,9.4)	0.49 (0.1,2.3)	6.98 (0.7,70.0)		0.558 (-0.22,2.97)
Winn	1		0.53 (0.2,1.3)	0.74 (0.3,1.6)	0.73 (03,1.5)	0.71 (0.3,1.7)	0.77 (0.3,1.7)	0.017 (-0.05,0.25)
MO-I	1	0.96 (0.6,15)	0.86 (0.5,1.4)	1.02 (0.6,1.8)		1.16 (0.7,2.0)		0.01 (- -,0.42)
MO-II	1	0.84 (0.5,1.5)	0.93 (0.5,1.8)	1.00 (0.4,2.3)		0.99 (0.4,2.2)		0.269 (-0.13,1.53)
IA	1		1.56 (0.8,2.9)	1.31 (0.7,2.5)	1.79 (1.0,3.3)	2.06 (1.1,3.3)	1.93 (1.0,3.7)	0.442 (0.05,1.59)
CT	1	1.11 (0.9,1.4)	0.97 (0.6,1.5)	0.62 (0.3,1.2)		0.92 (0.5,1.7)		0.024 (-0.21,0.51)
UT-ID	1	1.17 (0.7,1.8)	1.15 (0.7,1.9)	1.47 (0.8,2.7)		0.99 (0.5,1.8)		0.027 (-0.20,0.55)
Total	*1*	*1.13 (0.9,1.3)*	*1.05 (0.9,1.3)*	*1.14 (0.9,1.4)*	*1.22 (1.0,1.6)*	*1.19 (0.9,1.7)*	*1.29 (0.9,1.8)*	*0.096 (-0.01,0.26)*

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

Completeness of Monitoring

- **At least one year monitored in 5 – 30 year ETW**
- **At least 20 Years monitored with α-track monitors in ETW**

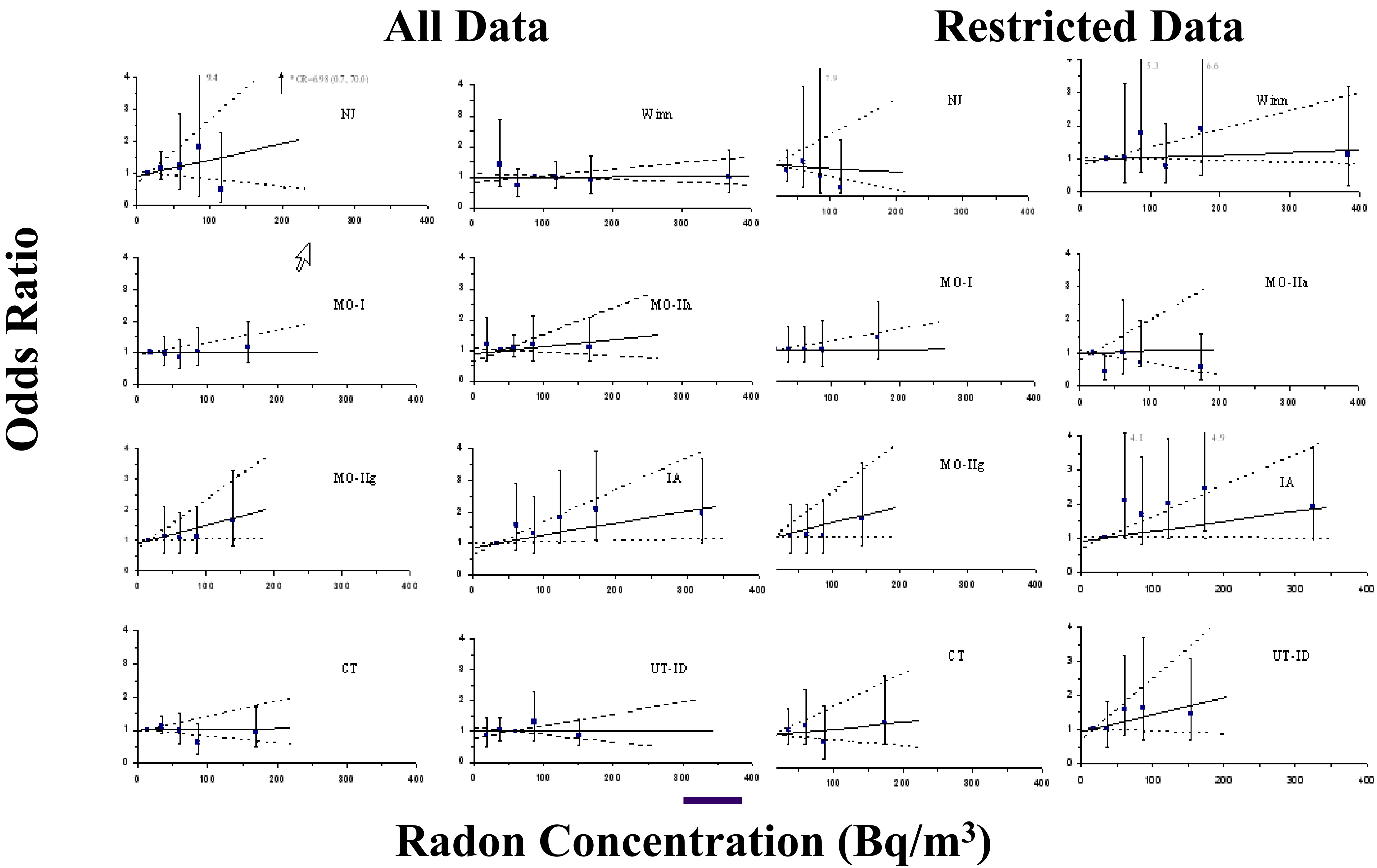
Residential Mobility

- **Occupied only 1 or 2 residences in ETW**

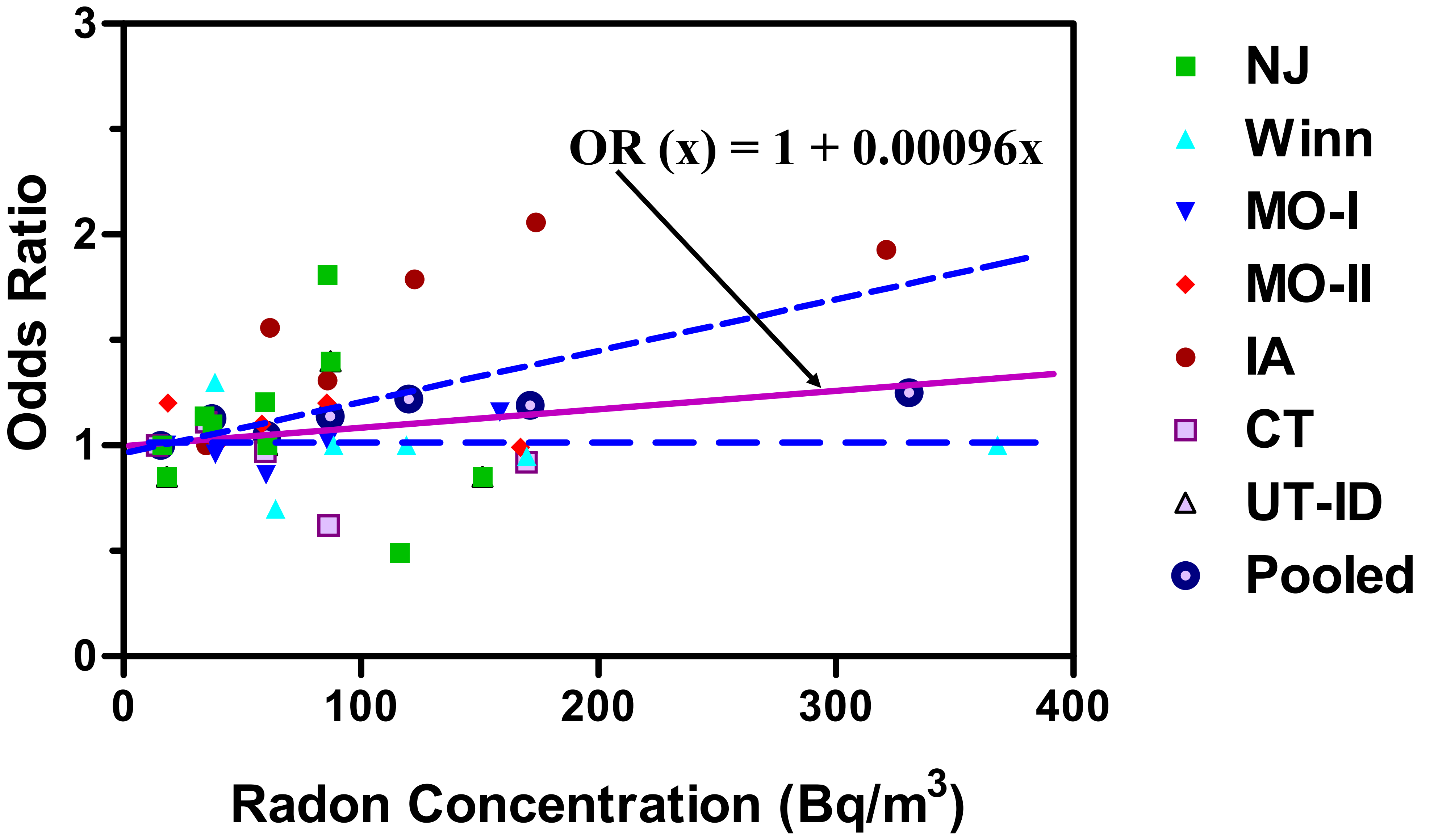
Odds Ratio (95% CI) for Lung Cancers: <u>Restricted Data</u>

Study	Radon Concentration (Bq/m^3) <25	25-49	50-74	75-99	100-149	150-199	≥ 200	ß×100
NJ	1	0.82 (0.5,1.5)	1.10 (0.3,3.5)	0.65 (0.1,7.9)	0.27 (0.1,1.8)	--		-0.11 (-0.41,1.34)
Winn	1		1.03 (0.3,3.3)	1.78 (0.6,5.3)	0.77 (03,2.1)	1.9 (0.5,6.6)	1.13 (0.4,3.2)	0.076 (-0.04,0.69)
MO-I	1	1.00 (0.6,17)	1 (0.6,1.7)	0.99 (0.5,1.9)		1.35 (0.7,2.5)		0.069 (- -,0.66)
MO-II	1	0.44 (0.5,1.5)	1.02 (0.5,1.8)	0.71 (0.4,2.3)		0.57 (0.4,2.2)		0.069 (-0.34,1.56)
IA	1		2.1 (1.1,4.1)	1.68 (08,3.4)	2.02 (1.0,3.9)	2.43 (1.2,4.9)	1.90 (1.0,3.7)	0.327 (-0.01,1.37)
CT	1	1.15 (0.7,1.8)	1.27 (0.7,2.4)	0.78 (0.3,1.9)		1.37 (0.5,1.7)		0.215 (-0.21,0.51)
UT-ID	1	1 (0.5,1.8)	1.58 (0.8,3.2)	1.62 (0.7,3.7)		1.44 (0.7,3.1)		0.568 (-0.08,2.68)
Total	*1*	*1.01* *(0.8,1.3)*	*1.29* *(1.0,1.7)*	*1.22* *(0.9,1.7)*	*1.28* *(0.9,1.8)*	*1.41* *(0.9,2.1)*	*1.37* *(0.9,2.1)*	*0.176* *(0.02,0.43)*

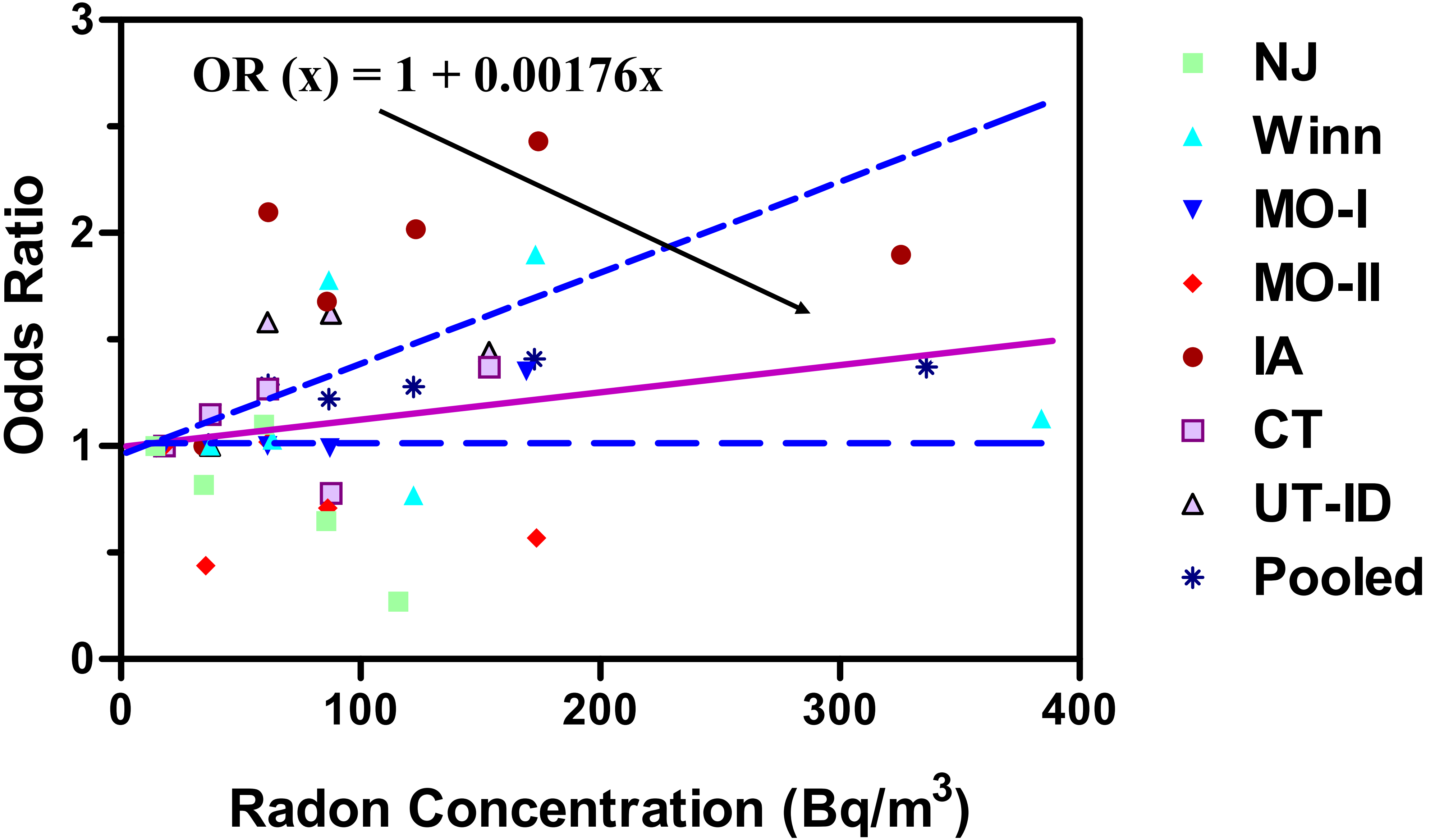
Odds Ratio and 95% Confidence Limits



Odds Ratio for All Data



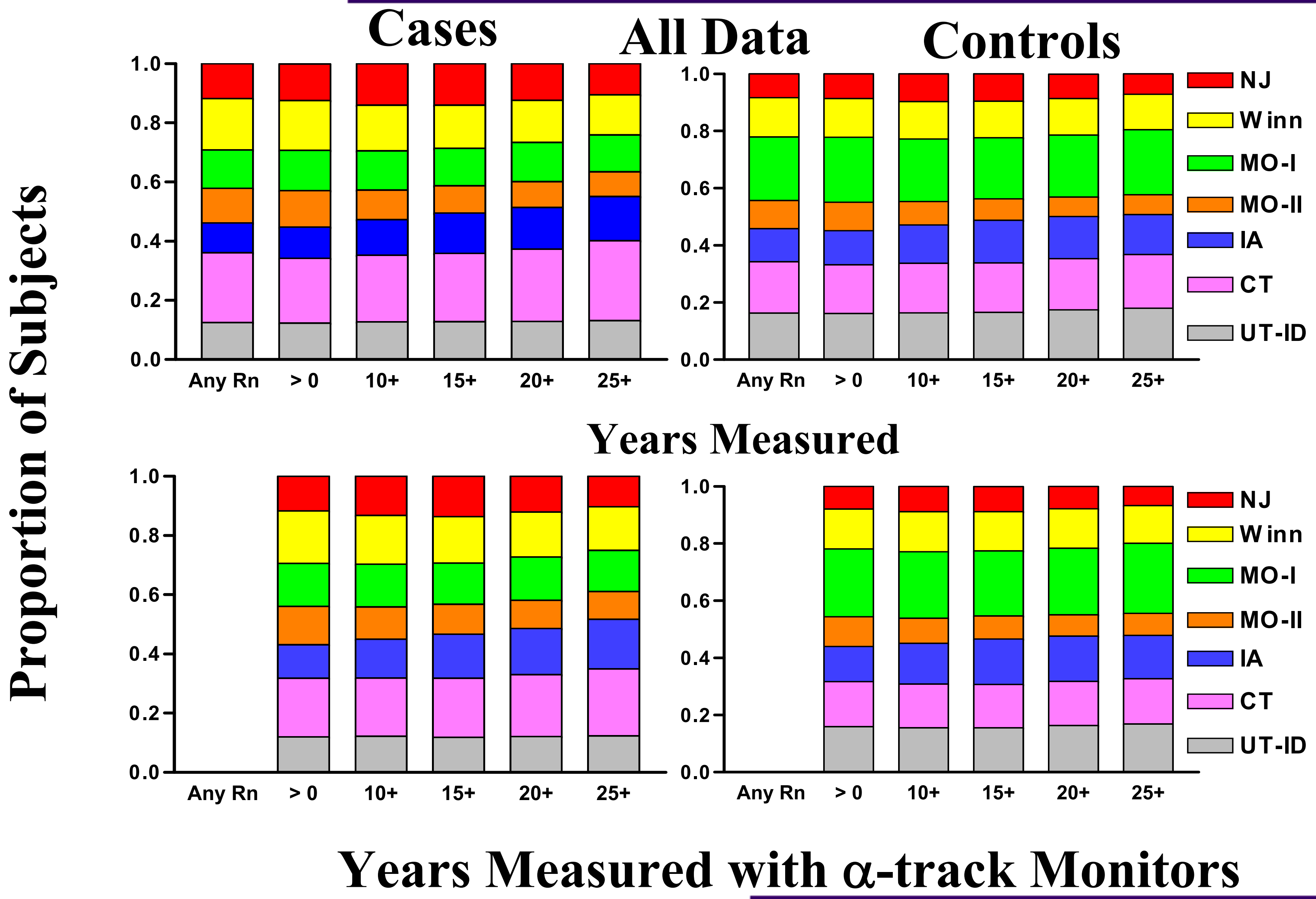
Odds Ratio for Restricted Data



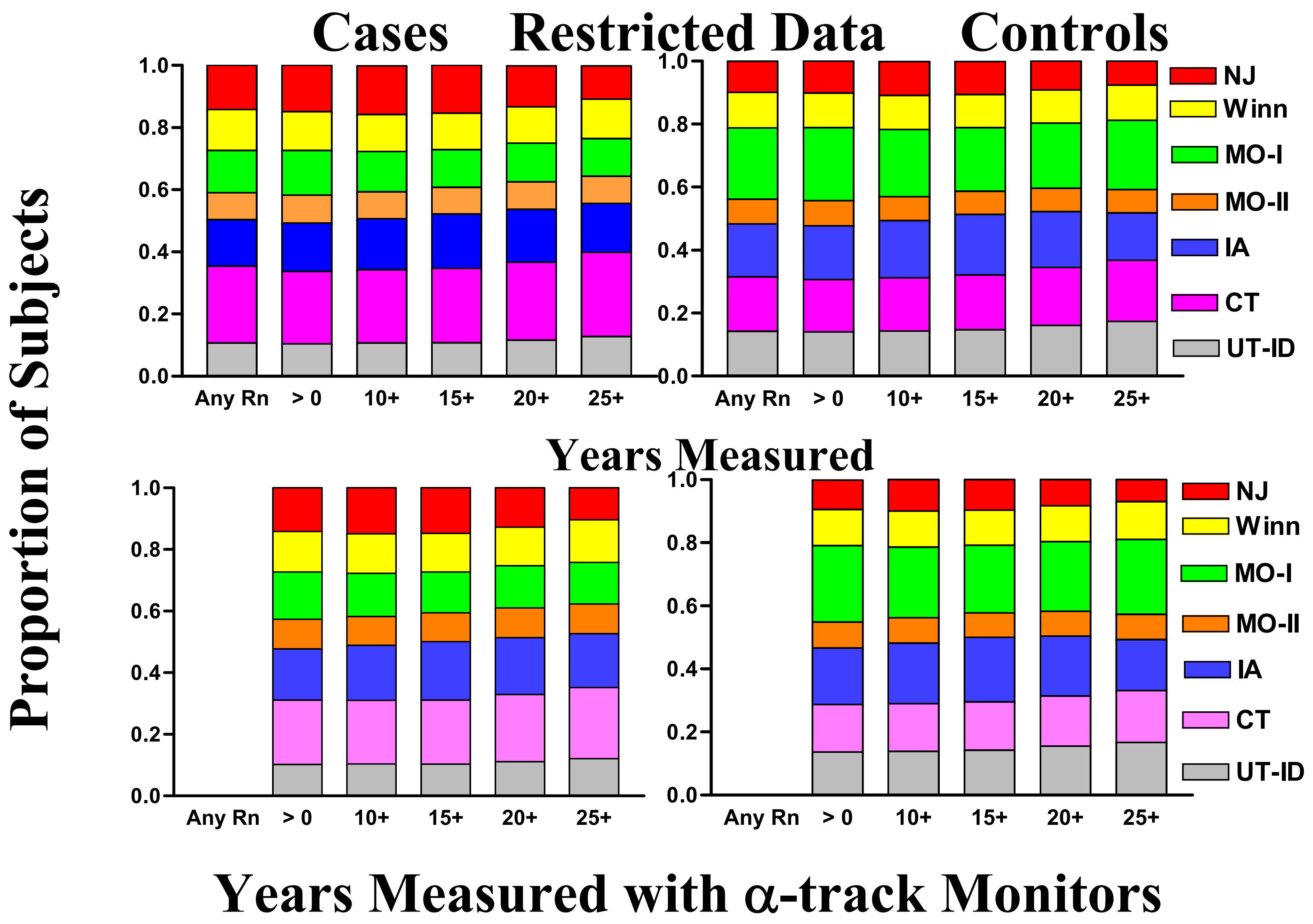
Combined Excess Odds Ratio (ß) in the 5 – 30 Year ETW

Years measured with α-track air monitors	All Homes		Restricted (1 or 2 Homes)	
	ß × 100	(95% CI)	ß × 100	(95% CI)
> 0	0.106	(0.00, 0.28)	0.147	(0.01, 0.37)
³ 10	0.134	(0.01, 0.32)	0.145	(0.00, 0.37)
³ 15	0.125	0.00, 0.31)	0.167	(0.00, 0.41)
³ 20	0.142	(0.01, 0.35)	0.176	(0.02, 0.43)
25 +	0.205	(0.03, 0.50)	0.212	(0.03, 0.52)

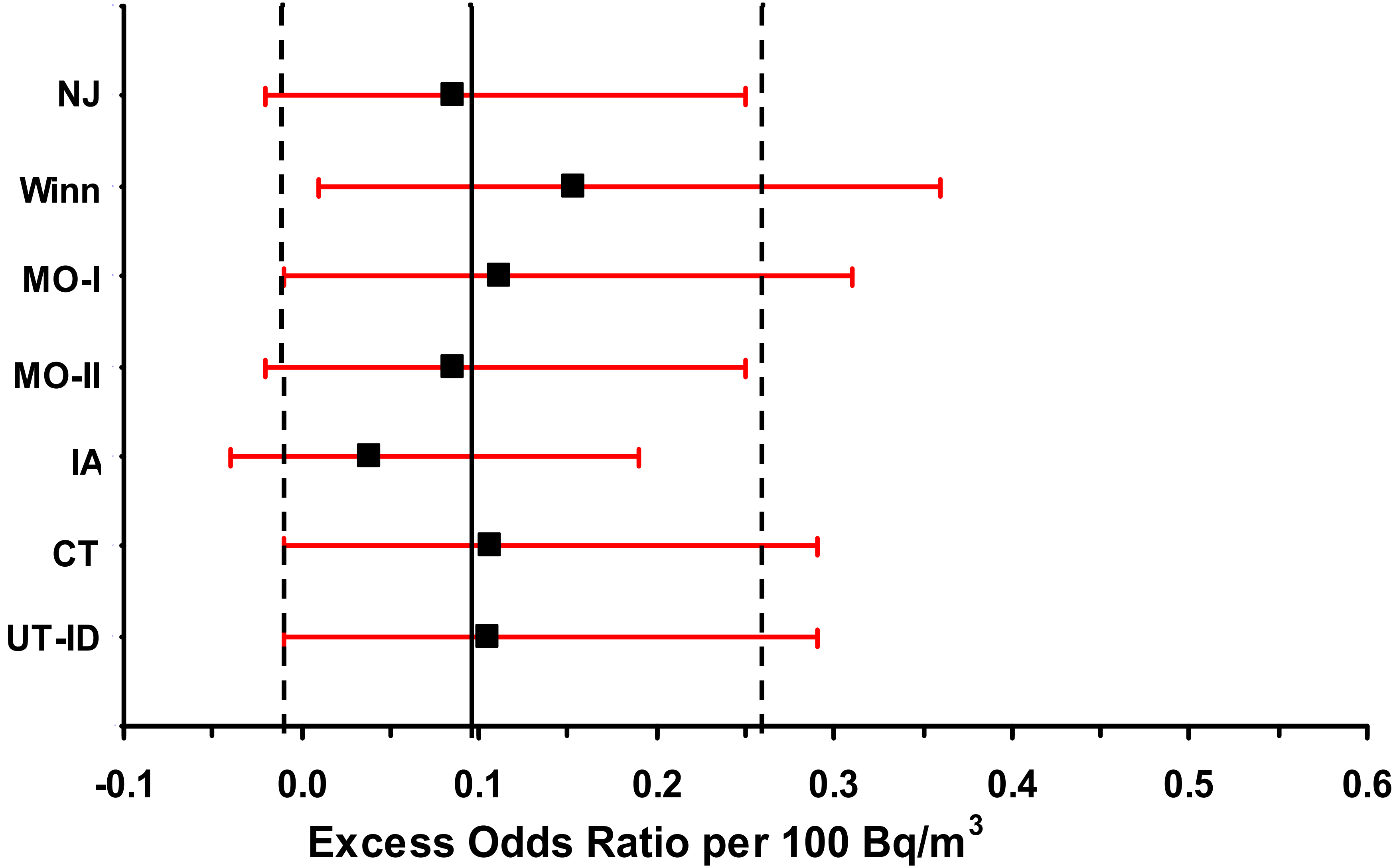
Contribution of Subjects from Different Studies



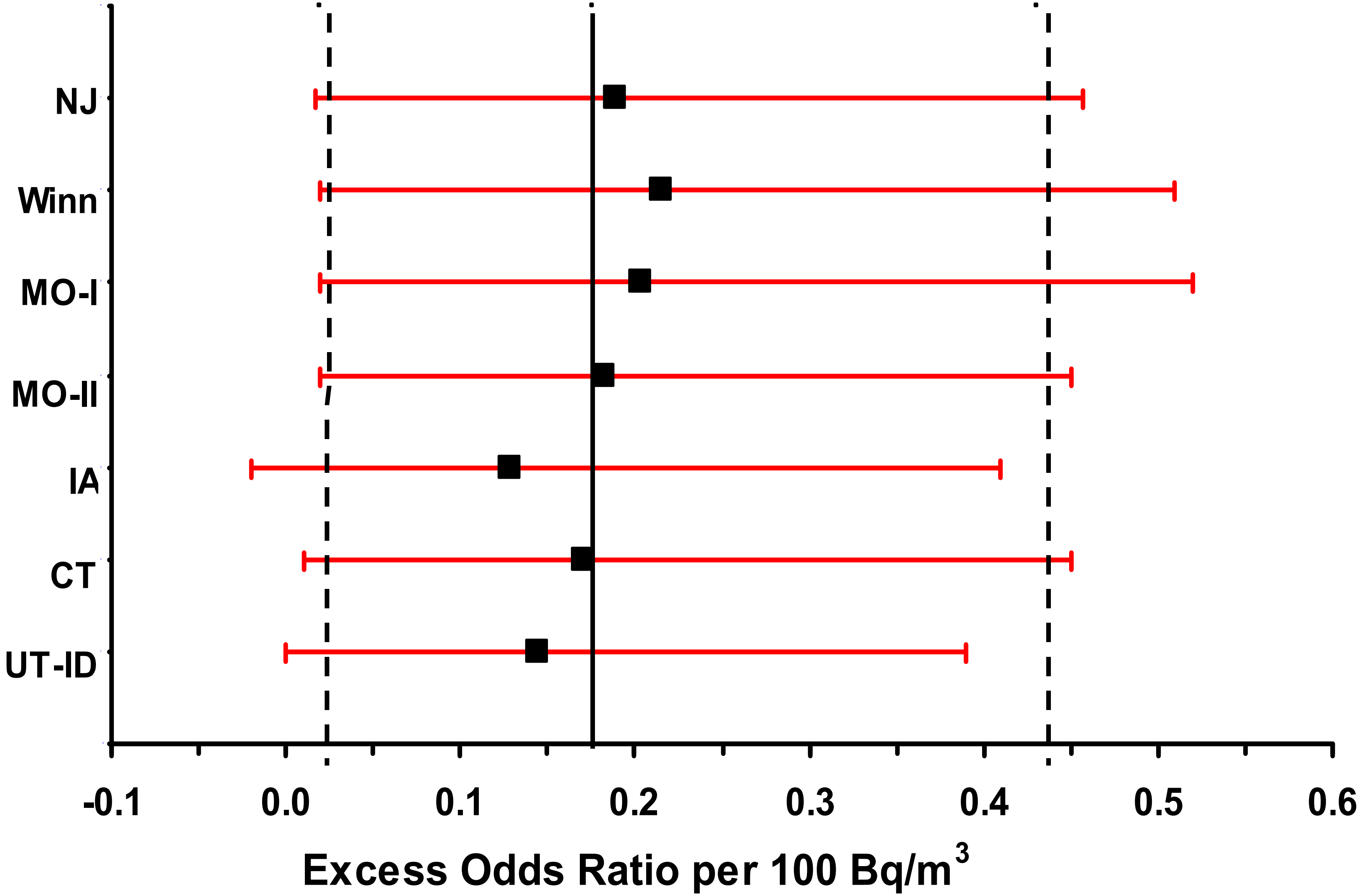
Contribution of Subjects from Different Studies



Influence Analysis : All Data



Influence Analysis : Restricted Data



Excess Odds Ratio (ß) for Lung Cancer

Category	All Data		Restricted Data	
	ß × 100	P-Value	ß × 100	P-Value
Sex				
Females	0.17		0.18	
Males	0.03	**0.27**	0.16	**0.97**
Age at Disease Occurrence				
<60	0.02		0.16	
60-64	0.70		1.27	
65-69	0.32		0.12	
70-74	0.01		0.30	
≥75	-0.02	**0.10**	-0.05	**0.09**
Highest Grade Level of Education				
0-7	-0.04		-0.00	
8-13	0.22		0.23	
≥14	0.01	**0.32**	0.17	**0.47**
Type of Respondent				
Subject	0.16		0.29	
Surrogate	-0.05	**0.47**	-0.20	**0.09**

Excess Odds Ratio (ß) for Lung Cancer

Smoking Category	All Data		Restricted Data	
	ß × 100	P-Value	ß × 100	P-Value
Never-smoker	0.068		0.223	
Ever-smoker	0.094	**0.97**	0.125	0.64
Number of Cigarettes Smoked per Day				
1-9	0.417		0.023	
10-19	0.105		0.289	
20-29	0.044		0.045	
> 29	0.108	**0.80**	0.263	**0.81**
Duration of Cigarette Smoking				
1-24	0.058		0.050	
25-34	-0.031		-0.018	
35-44	0.283		0.234	
> 44	0.114	**0.11**	0.198	**0.83**
Years since Stopping Cigarette Smoking				
0	0.071		0.127	
1-9	0.071		0.146	
10-19	0.264		0.148	
>19	0.163	**0.96**	0.111	**0.99**

Excess Odds Ratio (ß) (95% CI) for Lung Cancers by Histological Type

Histological Type	All Homes		Restricted Data	
	ß × 100	(95% CI)	ß × 100	(95% CI)
Adenocarcinoma	0.088	(-0.05,0.33)	0.267	(0.02,0.73)
Squamous cell	0.048	(-0.04,0.33)	0.126	(-0.04,0.62)
Small/oat cell	0.232	(-0.08,0.85)	0.204	(-0.11,1.00)
Other	0.159	(-0.03,0.55)	0.224	(-0.04,0.84)
Unknown	-0.169	(- -,0.07)	-0.161	(- -,0.19)
All	**0.096**	**(-0.01,0.26)**	**0.176**	**(0.02,0.43)**

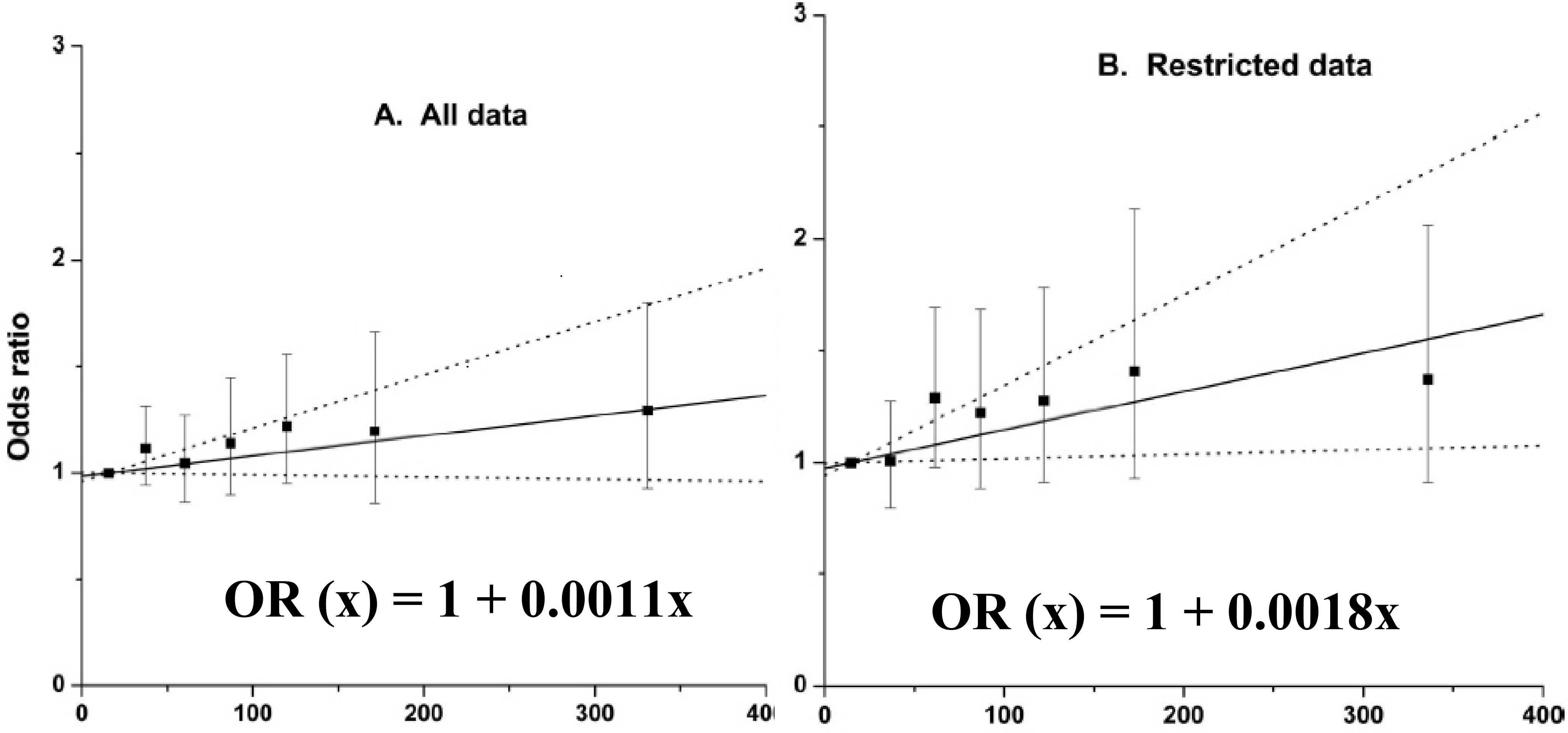
Summary and Conclusions - 1

- **Combined analysis of 7 North American residential radon case-control studies involving 4,081 cases and 5,281 controls**
- **Several studies focused on females (IA, MO-I, MO-II, NJ) because of their generally lower baseline lung cancer risk**
- **Several studies focused on current nonsmokers (MO-I) or former smokers (CT, UT-ID)**
- **Nearly all measurements were based on 1 year air ATD**
- **Average living area radon levels ranged from 26 Bq/m3 in New Jersey to 150 Bq/m3 in Winnipeg**
- **Overall average radon level about 70 Bq/m3**

Summary and Conclusions - 2

- **Analysis of all data revealed positive, but not-significant, association between residential radon and lung cancer risk (only IA showed a significant positive association)**
- **Analysis of restricted data indicated a significant positive association**
- **Odds ratio increased with completeness of monitoring in the 5 - 30 year ETW**
- **No effect ever/never smoking, duration or intensity of smoking, or smoking cessation on odds ratios**
- **No significant effect of educational attainment on odds ratios**

North American Pooling: Results



Radon Concentration (Bq/m^3)

Epidemiology, 2005, Vol. 16, pp. 137- 145

ORIGINAL ARTICLE

Residential Radon and Risk of Lung Cancer

A Combined Analysis of 7 North American Case-Control Studies

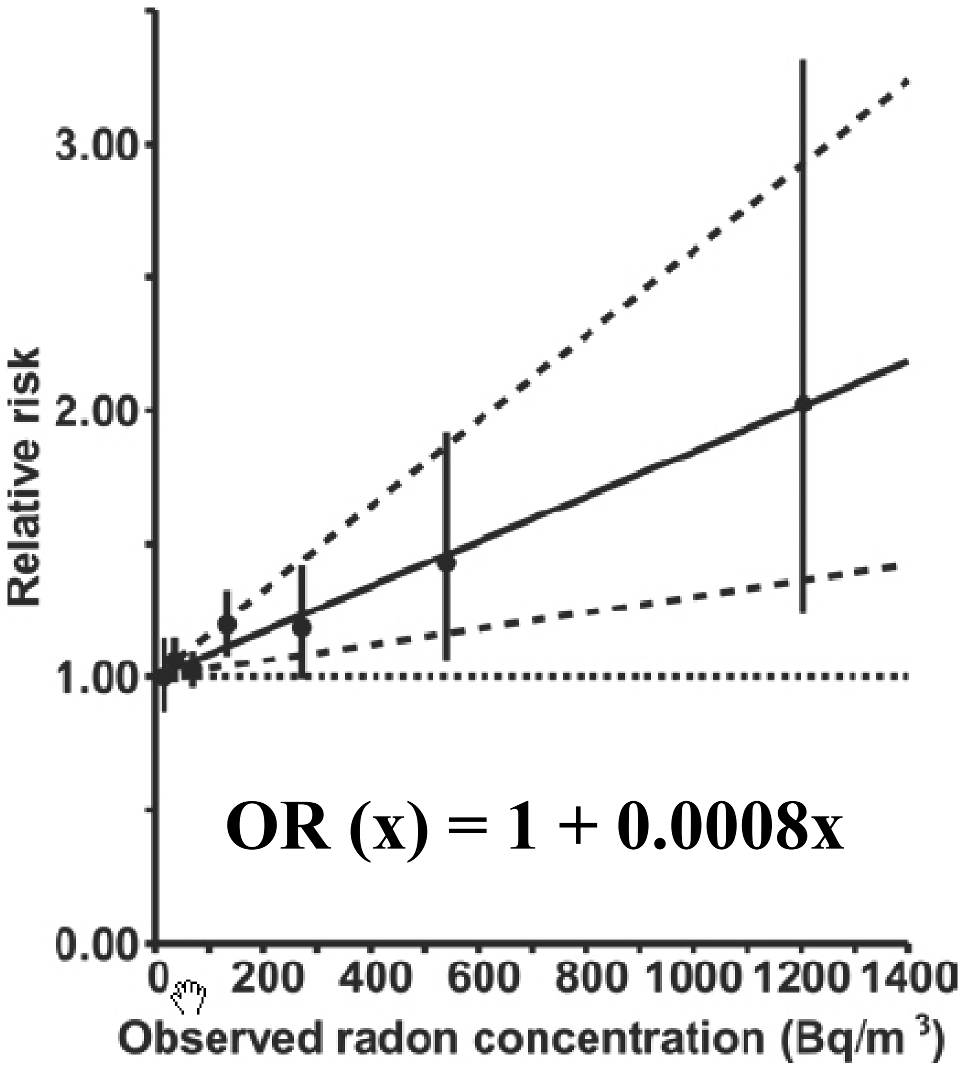
Daniel Krewski,[*] Jay H. Lubin,[†] Jan M. Zielinski,[‡] Michael Alavanja,[§] Vanessa S. Catalan,[‖] R. William Field,[**¶] Judith B. Klotz,[††] Ernest G. Létourneau,[‡‡] Charles F. Lynch,[¶] Joseph I. Lyon,[§§] Dale P. Sandler,[‖‖] Janet B. Schoenberg,[††] Daniel J. Steck,[¶¶] Jan A. Stolwijk,[***] Clarice Weinberg,[†††] and Homer B. Wilcox[††]*

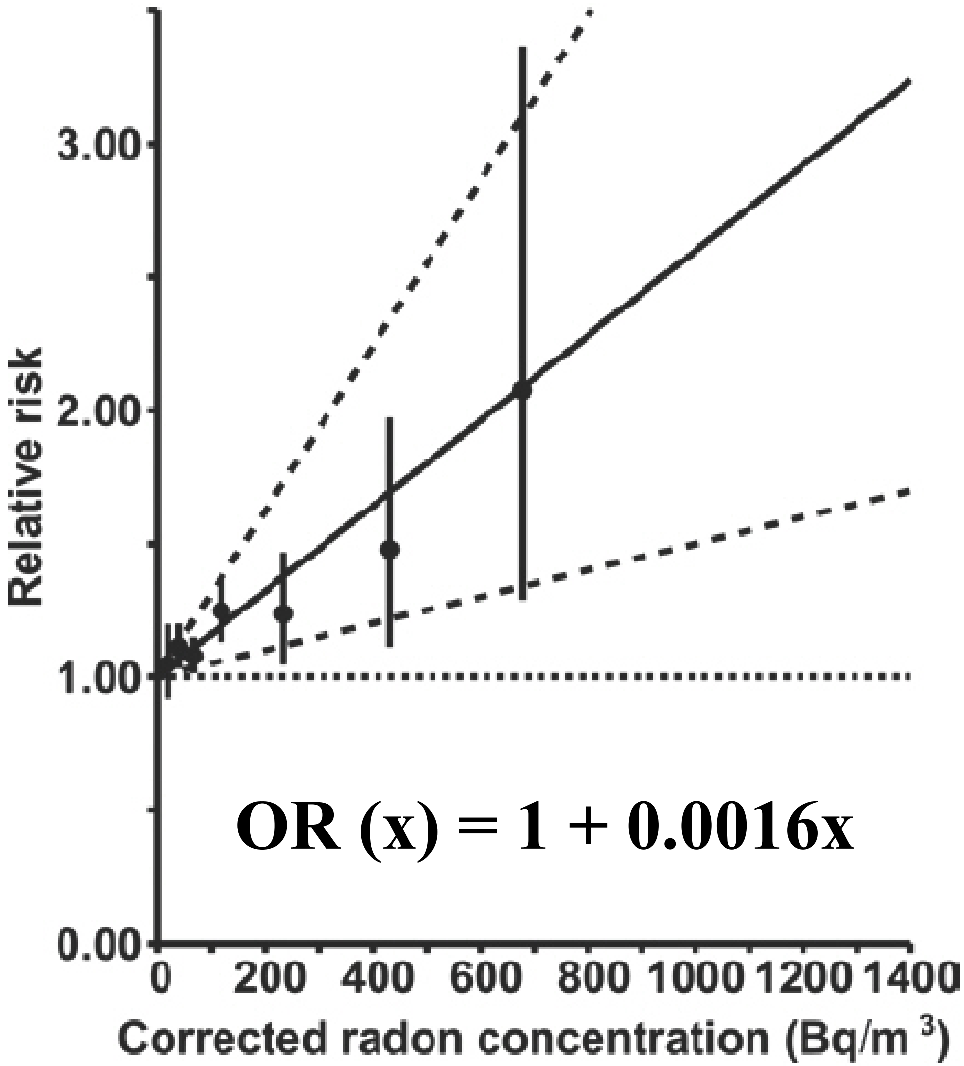
Odds Ratio - 1.11 CI: (1.00 – 1.28)

European Pooling: Number of Subjects

Study	Cases (N)			Controls (N)		
	Men	Women	Total	Men	Women	Total
Austria	161	22	183	164	24	188
Czech Republic	159	12	171	657	56	713
Finland nationwide	798	83	881	1 277	158	1 435
Finland southern	160	.	160	328	.	328
France	509	62	571	1 080	129	1 209
Germany eastern	833	112	945	1 322	194	1 516
Germany western	1117	206	1323	1 741	405	2 146
Italy	325	59	384	296	109	405
Spain	145	11	156	213	22	235
Sweden nationwide	546	414	960	1 017	1028	2 045
Sweden never-smokers	114	144	258	220	267	487
Sweden Stockholm	.	196	196	.	375	375
United Kingdom	654	306	960	2 073	1053	3 126
Total	**5,521**	**1,627**	**7,148**	**10, 388**	**3,820**	**14 ,208**

European Pooling: Results





BMJ, December 2004

Cite this article as: BMJ, doi:10.1136/bmj.38308.477650.63 (published 21 December 2004)

Papers

Radon in homes and risk of lung cancer: collaborative analysis of individual data from 13 European case-control studies

S Darby, D Hill, A Auvinen, J M Barros-Dios, H Baysson, F Bochicchio, H Deo, R Falk, F Forastiere, M Hakama, I Heid, L Kreienbrock, M Kreuzer, F Lagarde, I Mäkeläinen, C Muirhead, W Oberaigner, G Pershagen, A Ruano-Ravina, E Ruosteenoja, A Schaffrath Rosario, M Tirmarche, L Tomášek, E Whitley, H E Wichmann, R Doll

Odds Ratio - 1.08 CI: (1.03 – 1.16)

International Journal of Cancer, March 10, 2004

RISK OF LUNG CANCER AND RESIDENTIAL RADON IN CHINA: POOLED RESULTS OF TWO STUDIES

Jay H. LUBIN[1,*] Zuo Yuan WANG[2], John D. BOICE JR[4], Zhao Yi XU[5], William J. BLOT[4], Long De WANG[3] and Ruth A. KLEINERMAN[1]

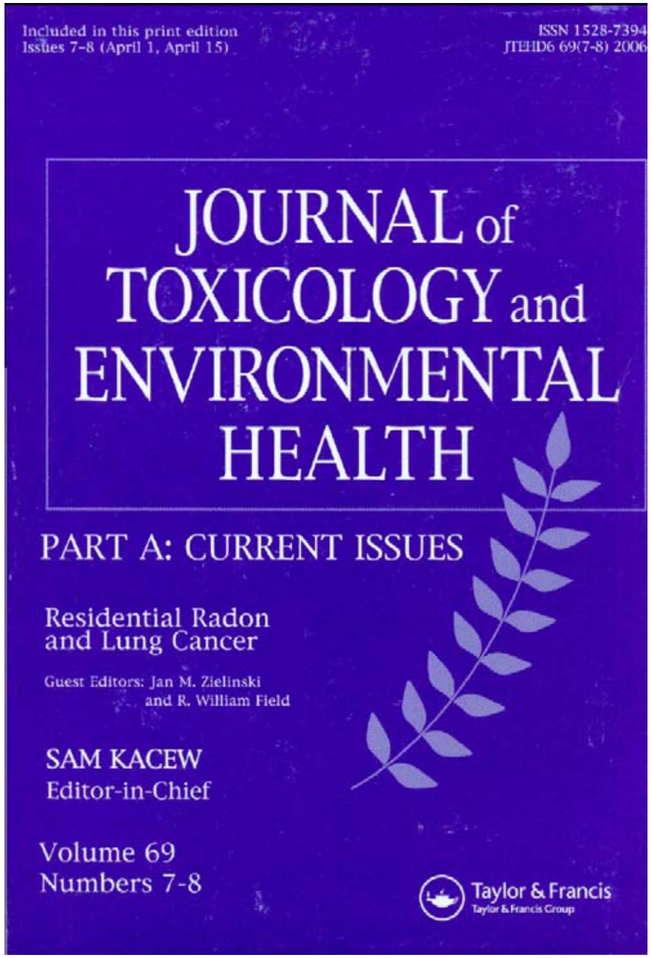
[1]*Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, Maryland, USA*
[2]*Laboratory of Industrial Hygiene, Ministry of Health, Beijing, China*
[3]*Ministry of Health, Beijing, China*
[4]*International Epidemiology Institute*
[5]*Liaoning Center for Disease Control and Prevention, Shenyang, China*

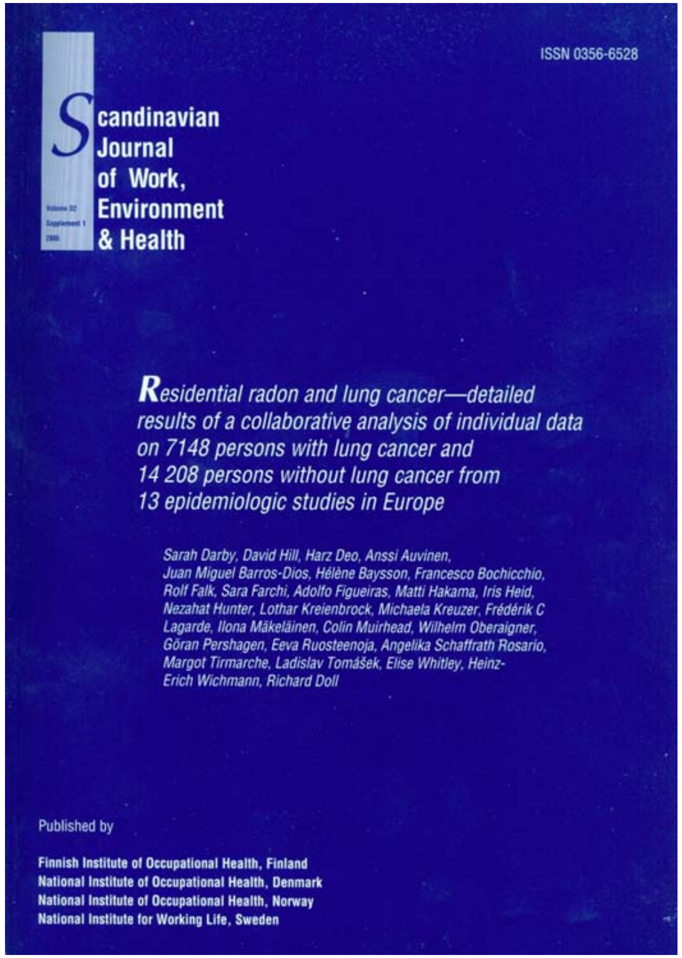
Odds Ratio - 1.33 CI: (1.01 – 1.36)

Consistency of the Odds Ratios at 100 Bq/m^3

Study	Odds ratio	95 % CI
BEIR VI (CRR model)	1.12	1.02 – 1.25
European pooling	1.08	1.03 – 1.16
North American pooling	1.11	1.00 – 1.28
Chinese pooling	1.33	1.01 – 1.36

Extended Pooling Reports





References I

Case-Control Studies:

Breslow, N. E. and Day, N. E. 1980. Statistical methods in cancer research. Volume I. The analysis of case-control studies. IARC Scientific Publications No. 32. Lyon: International Agency for Research on Cancer.

Cohort Studies

Breslow, N. E., and N. E. Day. 1987. Statistical Methods in Cancer Research. Volume II. The Design and Analysis of Cohort Studies. IARC Scientific Publications No. 82.Lyon: International Agency for Research on Cancer.

Epidemiology:

Rothman, K., Greenland, S., Lash, T.L. . 2008. Modern Epidemiology. Lippincott Williams & Wilkins.

Random-Effects models:

Rutter, C. M., and R. M. Elashoff. 1994. Analysis of Longitudinal Data: Random Coefficient Regression Modeling. Statistics in Medicine. 13:1211-1231.

Two Stage Regression:

Whitehead, A., and J Whiehead J. 1991. A general parametric approach to the meta-analysis of randomized clinical trial. Statistics in Medicine. 10:1665-1677.

Modeling Software:

Preston, D. L., Lubin, J. H., Pierce, D. A. and McConney, M. 1993. Epicure User's Guide. Seattle,Washington: Hirosoft International Corporation.

References II

Web Links:

National Research Council (NRC). Committee on the Health Risks of Exposure to Radon (BEIR VI). Health Effects of Exposure to Radon. Committee on the biological effects of ionizing radiations, board of radiation effects research, Committee on Life Sciences, National Research Council (Washington, DC: National Academy Press) (1999)

http://www.nap.edu/catalog.php?record_id=5499

Hirosoft International Corporation

http://www.hirosoft.com/

Special Issue of Journal of Toxicology and Environmental Health (Part A Current Issues, Volume 69 Issue 7 & 8 2006) on "Residential Radon and Lung Cancer"

http://www.informaworld.com/smpp/title~content=g742096493~db=all

Contact: Jan_Zielinski@hc-sc.gc.ca