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STUDIES OF RADON AND LUNG CANCER IN NORTH AMERICA AND CHINA

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INVITED PAPER

Abstract — Studies of radon-exposed underground miners indicate that residential radon is the second leading cause of lung cancer. Seven case–control studies of residential radon have been conducted in North America and two in China, and represent all studies in these areas which included 200 or more lung cancer cases and used long-term radon detectors. North American studies enrolled 4081 cases and 5281 controls, and Chinese studies enrolled 1076 cases and 2015 controls. Based on analyses of pooled data, odds ratios (ORs) and 95% confidence limits at 100 Bq m^{-3} were 1.106 (1.00,1.28) for the North American studies and 1.139 (1.01,1.37) for the Chinese studies. Tests of homogeneity of ORs within populations were not significant. Among subjects with complete dosimetry for the 5–30 y exposure period prior to interview, ORs at 100 Bq m^{-3} were 1.205 (1.03,1.50) for the North American studies and 1.279 (1.07,0.75) for the Chinese studies. Results are consistent with extrapolations from miners and indicate an excess lung cancer risk from residential radon.

INTRODUCTION

Radioactive radon (more precisely ^{222}Rn) derives from decay of ^{226}Rn, which is ubiquitous in the crustal rocks of the earth[1]. Because radon is an inert gas, it migrates along rock fissures and can accumulate in enclosed areas such as mine tunnels and residences. Radon and its decay products can be inhaled into the lung where alpha decay occurs. Extrapolations using models derived from studies of radon-exposed underground miners estimate that residential radon, for example, may be responsible for 7% of lung cancers in Germany[2], 4% in the Netherlands[3], 20% in Sweden[3] and 10–15% in the United States[1,4]. To confirm these predictions, investigators have conducted epidemiological studies of residential radon and lung cancer. While individual studies of residential radon and lung cancer have seemingly produced ambiguous evidence of an increased risk, meta-analyses have indicated a small but statistically significant excess risk from residential radon, although results were heterogeneous across studies[5,6]. However, this heterogeneity may have been due to incomplete adjustment for study differences, as recent analyses of pooled data from seven North American radon studies revealed no such heterogeneity[7,8].

There are inherent difficulties in identifying an association of residential radon and lung cancer risk due to a small expected risk from radon and substantial uncertainty in radon dosimetry[9,10]. Consequently, large numbers of subjects are needed, and the pooling of original data from multiple studies offers the best approach for addressing sample size limitations. Pooling also permits detailed assessment of radon effects, selection of adjustment factors and testing homogeneity of effects across study populations. Projects are under way to pool data from studies in Europe and in North America[11–14]. Results from the North American studies have recently been reported[7,8].

There have been seven case–control studies of lung cancer and residential radon conducted in North America[15–20] and two in China[21,22], representing all studies in these areas which included 200 or more lung cancer cases, used long-term radon detectors and collected data on smoking and other factors. The current report summarises results from these nine studies. European radon studies are discussed by Darby and Hill[23].

MATERIALS AND METHODS

The current paper reviews the published results from the North American pooling[7,8] and presents original analyses of combined data from studies in Shenyang[21] and Gansu provinces, China[22].

North American studies

Data from North American studies included 4081 lung cancer cases (2766 females and 1315 males) and 5281 controls (3779 females and 1502 males) (Table 1). For additional details see Field[24] and Krewski *et al*[7,8]. Four studies enrolled only females (New Jersey, Missouri-I, Missouri-II and Iowa studies), while three studies included both males and females (Winnipeg, Connecticut and Utah studies).

All studies used long-term alpha-track detectors as the principal measurement device, although specific details of the individual measurement protocols differed slightly. For the North American analysis, investigators characterised exposure within an exposure time window

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(ETW) defined as 5 to 30 y prior to study enrolment. This ETW is the period where radon is assumed to exert its most direct influence on lung cancer risk[1].

Chinese studies

The Shenyang case–control study included all incident female lung cancer cases identified through the Shenyang Cancer Registry and diagnosed between September 1985 and September 1987[21]. Investigators established a rapid reporting system, with nearly all cases interviewed within 1 month of diagnosis. Five per cent of cases were excluded because they were either too ill or had died prior to interview. Next-of-kin interviews were not carried out. Controls were age-matched to cases and sampled at random from the general population.

The radon component commenced 6 months after the start of the study. As a result not all females were included in the radon component. Radon was measured in one home for each subject. One-year alpha-track detectors were place in the current home, if the subject had resided there at least 5 y. Detectors were place in the previous residence if it was located in Shenyang, accessible and occupied for at least 5 y. A total of 301 cases and 355 controls were include in the radon study.

The Gansu study case–control study enrolled all incident cases of lung cancer in two prefectures of Gansu Province between June 1994 and April 1998. Controls were randomly selected from population census lists and matched to cases by age, sex and prefecture[22].

For each subject, 1 y alpha-track detectors were placed in each house occupied for 2 or more years during the previous 30 y and located within the two prefectures. A total of 88% of cases and 95% of controls had at least one measurement in the 5–30 y ETW. A total of 768 cases and 1795 controls were used in the radon analysis.

Radon exposure

All studies had gaps within the ETW from unmeasured homes. For the North American pooling and for the Gansu study, investigators inserted the mean radon levels for control homes for the unmeasured periods for calculation of time-weighted average radon concentration[25]. For comparability, radon exposure was computed within the 5–30 y ETW for the Shenyang data using a similar approach for gaps. This resulted in the exclusion of 16 cases and 15 controls from the original Shenyang data since radon measurements did not include years within the ETW. We also omitted two subjects (controls) with extreme radon values (1219 and 1659 Bq m^{-3}) that were more than 50% greater than the next largest value.

Modelling the odds ratio

A linear excess odds ratio (EOR) model of the form $OR = 1 + \beta x$, where x is the time weighted radon concentration and β is the EOR parameter for 1 Bq m^{-3}), was fitted to the data. The North American data were adjusted for study, sex, age, duration of smoking, number of cigarettes smoked per day, number of residences and years of the ETW covered with alpha-track measurements[8]. The Chinese studies were adjusted for age, smoking risk, number of residences and coverage, and for the Gansu study, town, sex and socioeconomic factors. The smoking risk variable had four levels: smoked 20 or more cigarettes per day for 40 or more years; smoked 10 or more cigarettes per day for 30 or more years; other smokers; and never smoked. Subjects

Table 1. Numbers of cases and controls, time-weighted average radon concentrations (Bq m^{-3}) and per cent coverage of the 5–30 year exposure-time window in lung cancer studies in China and North America.

Study	Cases		Controls		Radon concentration (Bq m^{-3})	Per cent coverage
	Female	Male	Female	Male		
China						
Shenyang[21]	285		338		127	67.5
Gansu[22]	205	563	427	1232	226	76.8
North America*						
New Jersey[16]	480		442		29	84
Winnipeg[26]	239	469	249	473	142	75.2
Missouri-I[17]	530		1177		63	77.2
Missouri-II[18]	477		516		56	65.2
Iowa[19]	412		613		127	92.4
Connecticut[20]	436	527	507	442	33	82.8
Utah–South Idaho[20]	192	319	275	587	57	82.8
Total	3272	1878	4561	2734		

*Data for North American studies extracted from Krewski *et al*[8].

were assigned to the most exposed category. The smoking adjustment in the Chinese studies differed from the adjustment in the North American studies, but this difference had minimal impact.

RESULTS

Coverage by radon measurements of the ETW varied from 65% in the Missouri-II study to 92% in the Iowa study. The high coverage in the Iowa study was due to study design which included only enrolled subjects who were resident in their current house for 20 y or more[19]. Coverage in the Missouri-II study was lower due to the use of air radon detectors only in the current house, since investigators relied on an alternative dosemeter that measures alpha decay from glass artefacts to represent cumulative radon exposure over time[18]. For comparability, the North American analysis used only the air radon measurements for the Missouri-II data.

Table 2 shows estimates of the EOR at 100 Bq m^{-3} for the pooled North American and Chinese studies, the Shenyang study and the Gansu study. For subjects with some radon measurements within the ETW, the EORs and 95% confidence intervals for the North American and Chinese studies are 0.106 (0.00,0.28) and 0.133 (0.01,0.36) respectively. The test of homogeneity of EORs in the Chinese studies was not significant ($p = 0.31$). The Shenyang study exhibited no dose–response relationship for the complete data, while there was a significant radon risk in the Gansu study.

Increasing the number of years within the ETW covered by radon measurements is expected to reduce uncertainty and improve the accuracy of exposure assessment. Table 2 shows the impact on the EORs for subjects with increased coverage of the ETW. EORs generally increased with greater coverage of the ETW. Results for the combined North American studies and for the Chinese studies are very similar. In the restricted analyses, there was no significant heterogeneity.

Table 3 shows EORs for all data and for subjects with coverage restrictions. For the North American studies, Krewski *et al* present EORs for subjects with one or two residences and 20 y or more coverage of the ETW[8]. This limitation was problematic for the Shenyang data since only one house was measured. We therefore present the Chinese results for those with complete coverage. The North American data and the Chinese data show no significant difference in radon effects by sex, age at disease or smoking status. In both populations, there was a reduced effect for radon among surrogate responders.

The EORs based on both the complete and restricted data in the combined analysis are similar to the downward extrapolation of miner data, with miner analyses estimating an EOR of 0.117 (0.02, 0.25) per 100 Bq m^{-3}[1].

SUMMARY

The pooled North American data showed a small but consistent excess risk of lung cancer with increased residential radon concentration. Restrictions suggestive of improved accuracy of exposure assessment resulted in increased, and statistically significant, excess radon risks. The combined Chinese data showed increased risks with radon concentration, and no significant differences in study-specific EORs. Risk estimates from the pooled Chinese studies, and the pooled North American studies were consistent with each other and with miner-based extrapolations. All results point to a small excess risk of lung cancer from residential radon.

Table 2. Excess odds ratio[a] (β) and 95% confidence interval (CI) for radon concentration by years in the 5–30 y exposure window covered by alpha tract radon detectors.

Coverage	North American studies[b]			Combined Chinese studies			Shenyang study			Gansu study		
	Cases	$\beta \times 100$	(95% CI)	$\beta \times 100$	(95% CI)	*P* value[c]	Cases	$\beta \times 100$	(95% CI)	Cases	$\beta \times 100$	(95% CI)
>0[d]	3662	0.106	(0.00,0.28)	0.133	(0.01,0.36)	0.31	275	−0.019	(−0.13,0.43)	753	0.175	(0.02,0.049)
≥10	3148	0.134	(0.01,0.32)	0.140	(0.01,0.38)	0.28	194	−0.021	(− ,0.45)	578	0.186	(0.02,0.53)
≥15	2764	0.125	(0.00,0.31)	0.121	(0.00,0.35)	0.15	171	−0.064	(− ,0.30)	484	0.178	(0.02,0.52)
≥20	2263	0.142	(0.01,0.35)	0.163	(0.02,0.44)	0.13	145	−0.059	(− ,0.35)	432	0.234	(0.05,0.66)
25	1621	0.205	(0.03,0.50)	0.319	(0.09,0.88)	0.70	106	0.177	(−0.12,2.04)	358	0.355	(0.09,1.08)

[a]Based on the linear odds ratio model: $OR(x) = 1 + \beta x$, where x is the mean radon concentration in the 5–30 y exposure time window. See text for adjustment factors.
[b]Results for North American studies extracted from Krewski *et al*[8].
[c]*P* value for likelihood ratio test of homogeneity of estimates of β for Chinese studies.
[d]Includes subjects with long-term radon measurements within the 5–30 y exposure time window.

Table 3. Excess odds ratio[a] (β) for lung cancer and 95% confidence interval (CI) for time-weighted radon concentration in the 5–30 year interval prior to the index date.

Variable	All data						Restricted data[b]					
	North American studies[c]			Chinese studies			North American studies[c]			Chinese studies		
	Cases	β × 100	P[d]	Cases	β × 100	P[d]	Cases	β × 100	P[d]	Cases	β × 100	P[d]
Overall	4081	0.096		1028	0.133		1910	0.176		464	0.319	
(95% CI)		(−0.01,0.26)			(0.01,0.36)			(0.02,0.43)			(0.08,0.88)	
Sex												
Females	2766	0.167		477	0.101		1373	0.183		191	0.331	
Males	1315	0.028	0.26	549	0.161	0.24	537	0.157	0.97	273	0.239	0.78
Age (years) at disease occurrence[e]												
<50				229	0.333					87	0.495	
50–54				211	0.173					90	0.167	
55–59	1028	0.016		223	0.089		270	0.165		110	0.322	
60–64	703	0.704		210	0.275		331	1.274		95	0.330	
65–69	836	0.321		155	−0.090	0.34	461	0.121		82	0.051	0.23
70–74	758	0.321					410	0.303				
≤75	756	−0.021	0.11				438	−0.052	0.09			
Type of respondent												
Subject	2280	0.160		644	0.089		1081	0.287		278	0.298	
Surrogate	1801	−0.050	0.44	384	−0.090	0.01	829	−0.201	0.09	186	−0.090	0.01
Cigarette smoking status												
Never-smoker	690	0.086		322	0.124		359	0.223		119	0.556	
Ever-smoker	3331	0.094	0.99	706	0.144	0.89	1526	0.125	0.64	345	0.212	0.42

[a]Based on the linear OR model: $OR(x) = 1 + \beta x$, where x is mean radon concentration within the 5–30 y exposure time window. See text for adjustment. Number of subjects varies due to missing data.
[b]For North American studies, data include subjects with residence in one or two houses and ≥20 y coverage of ETW. For Chinese studies, data include subjects with complete coverage of the ETW.
[c]Results for North American studies extracted from Krewski *et al*[8].
[d]Test of homogeneity of β.
[e]Youngest age category for North American studies is <60 y, and oldest age category for Chinese studies is ≤65 y.

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