



Case-control studies on residential radon and lung cancer: A concise review

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The risk estimates for the general population extrapolated from the risk obtained from the miner studies led many national and international health organizations to estimate that residential exposure to radon and its decay products can be considered one of the main lung cancer risks after the tobacco smoking, which is responsible of a very large fraction of the total number of lung (and other) cancers. Due to this health relevance and to uncertainties in the extrapolation from studies on miners, many residential case-controls studies have been conducted in Europe, North America and China, are shortly reviewed in this paper. Most of these studies estimated an increased risk, proportional to the radon exposure, although a statistical significance of the estimated risk was reached only in few studies or restricted analyses, due to the low statistical power related to the relatively small study size and the presence of not negligible uncertainties in the evaluated radon exposure. The effects of these uncertainties were analyzed in some studies, and it was estimated to reduce the risk by 50% to 100%. Moreover, some restricted analyses showed that selecting subjects with a presumably better evaluation of radon exposure, for example with radon measurement covering all the exposure period of interest, the estimated risk increases by a factor of about two. The use of retrospective dosimetry compared with contemporary radon concentration measurements produce higher risks, too. In most of the studies a multiplicative interaction between tobacco smoking and radon is suggested, which implies that the lung cancer risk due to radon exposure is much higher for a smoker, compared with the risk for a never-smoker. More precise and definitive results are expected from pooled analysis. The just published pooled analyses of two Chinese studies and seven North American estimate a (slightly) significant excess odds ratio of 14% and 11% respectively. A more precise and comprehensive assessment is expected from the forthcoming results of the European pooling of 13 studies and the following pooling of all the studies. Other studies will be probably needed to answer some question on the risk for never-smokers and the interaction with passive smoking.

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KEY WORDS: Lung Neoplasms; Risk Factors; Radon; Smoking; Radiation Monitoring

INTRODUCTION

Several epidemiological studies on miner cohorts of underground mines have demonstrated that exposure to radon decay products increases the lung cancer risk of miners (1-4). On the basis of these studies, in 1988 radon decay products¹ were classified by the International Agency for Research on Cancer, of the World Health Organization, as Group 1 carcinogens, i.e., substances for which there is sufficient evidence of carcinogenicity based on human studies (5).

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The manuscript was received: 31.03.2004

Accepted for publication: 02.04.2004

The health impact of the risk extrapolated from miners to the general population was very high, due to the widespread presence of radon in indoor air of workplaces and dwellings, and many thousands of lung cancers were attributed to residential radon exposure (e.g. 6). As a consequence, many countries and international organizations introduced recommendations and regulations to limit radon exposure in workplaces and/or in dwellings (1,7-9). However, many uncertainties affected the extrapolation of the risk from miners to the general population, including the followings: i) the average radon concentration in mines were about 100 times higher than in dwellings, although the average exposure, which takes into account both radon concentration and the occupancy, were about 10 times more than in dwellings, due to the longer time spent at home; ii) the composition of the inhaled air in dwellings is quite different from that in mines, which contains also

other risk factors for lung cancer, such as arsenic; iii) the characteristics of the exposed groups are quite different, because miners are only men with strong constitution, whereas general population include both men and women of all ages and constitutions (3,4,10-11).

Therefore, epidemiological studies on residential exposure to radon and lung cancer risk, generally with a case-control design, were conducted in order to estimate the risk without the need of extrapolation. In this paper a concise review of these studies is presented.

SOME METHODOLOGICAL ISSUES

Effect of (and correction for) exposure uncertainty

Due to the relatively low radon concentration in dwellings, compared with values in mines, the residential radon health effects are more difficult to be highlighted. Exposure uncertainty (also called *error*) can affect very significantly the estimates of relative risks lower than 2. Being generally non-differential, exposure uncertainty not only adds an extra uncertainty in the estimated risk, but also introduces a bias, i.e. it produces an underestimate of the real risk and reduces the statistical power of the study (12-14). A differential bias was also attributed to measurement errors (15). Great efforts are needed in these studies to obtain high accuracy and precision of radon concentration measurements. However, only for few studies a detailed quality assurance program for radon measurements has been implemented (16,17). In some studies, the observed risks were corrected to take into account the estimated uncertainty on radon exposure. Such corrections increase the estimated risk compared to the observed one, but necessarily widen the confidence intervals (12,14).

Duration of radon concentration measurements

Radon concentration has significant time variations, and average values in winter are generally greater than in summer. For this reason, 12-month measurements have been adopted in most of the case-controls studies in order to average seasonal variations, while shorter (2-6 months) measurements are expected to be affected by larger errors. Seasonal correction factors have been applied in some studies to obtain unbiased yearly average radon concentration (18); however such correction factors take into account the average seasonal variations of radon concentration, which actually can be quite different from one house to another, depending on radon source behavior and living habits.

Statistical analysis

In residential case-control studies, average radon concentration in the period of interest (generally from 3-5 to 20-35 years before

the occurrence of lung cancer) is generally used as a measure of radon exposure. Most of the studies included both a categorical and a continuous analysis of data. In the categorical analysis, odds ratios (OR), which are a good approximation of relative risk, are related to radon concentrations grouped in categories, with the lowest category used as reference. With this approach, results are sensitive to the choice of both the reference and the other exposure categories, and extreme exposure values affect OR of the highest category only. In the continuous analysis, excess odds ratios (EOR) are calculated through regression with radon concentration as a continuous variable, generally using a linear function of exposure or of the logarithm of exposure. The results obtained with these two functions are very similar for radon concentrations up to about 400 Bq m⁻³. With this approach, results are more "objective" because they do not depend on the chosen categories, however they are quite sensitive to extreme high radon concentration values. Recently, more flexible analysis methods have been developed, in order to overcome the limits of the previous classical approaches, and a good review has recently been published (19). However, these modern methods are beyond the scope of this short review and have not been generally applied to the analysis of residential case-control studies, yet. For shortness purpose, only the results of continuous analyses, referred to a radon concentration of 100 Bq m⁻³, will be reported in this paper.

Retrospective dosimetry

In most studies the radon exposure in periods up to 35 years before the index year (i.e. the year of lung cancer diagnosis for cases or the year of enrollment for controls) is generally evaluated on the basis of contemporary measurements of radon concentration, assumed to be the equal to that one in the period of interest. This assumption is a potential major source of exposure uncertainty, because present (contemporary) radon concentration could be quite different from past values, due to changes of the building structure or of the living habits (especially in case of different inhabitants), which can affect radon entry and ventilation and therefore radon concentration values. In order to avoid this assumption, an alternative retrospective technique has been developed (20-21). This technique is based on the measurement of surface activity of ²¹⁰Po implanted in glass surfaces. The measured ²¹⁰Po activity comes from the deposition of radon decay products on such surfaces and the implantation due to the recoil energy of ²¹⁸Po or ²¹⁴Po. The following decay product, ²¹⁰Pb (with an half-life of 22.3 years), remains trapped in a thin layer due to the characteristics of glass, so that the alpha particle emitted from the following decay product, ²¹⁰Po, can escape the glass and be detected. In conclusion, the present measured ²¹⁰Po surface alpha activity is related to the past radon concentration in

the room integrated over many years. This retrospective technique was applied in three case-control studies (22-24), and in two ones the results have been published and were very interesting, as shown in the following section.

RESULTS AND DISCUSSION

The summary results of the main published case-control studies on residential radon exposure and lung cancer risk are reported in Table 1, and will be shortly discussed in the followings.

First group of studies with systematic measurement of residential radon concentration

The results of the first case-control studies with extensive and systematic experimental evaluation of radon exposure were quite different, from large EORs to negative EORs (see Table 1). Due to the large debate arisen from these controversial results more large studies were started with similar design in order to be easily pooled (55). Anyway, a meta-analysis of the first eight studies with more than 200 cases each (29-33,35-38) was published in

Table 1. Summary of case-control studies on residential radon and lung cancer

Study area, year of publication	No. of cases	No. of controls	Gender	Smoking status	Duration of C_{Rn} meas. (months)	Average C_{Rn} ($Bq\ m^{-3}$)	EOR at 100 $Bq\ m^{-3}$	(95% CI)	Comment
New Jersey (USA), 1990 (29,32)	433	402	F	All	12	26	0.28	(-0.28, 0.97)	
Shenyang (China), 1990 (30,32)	308	356	F	All	12	118	-0.04	(-0.23, 0.19)	
Stockholm (Sweden), 1992 (31,32)	201	378	F	All	12	128	0.52	(-0.05, 1.54)	
Sweden-I, 1994 (33)	1,281	2,576	M,F	All	3	107	0.10	(0.01, 0.22)	
Sweden-I, 1997 (34)	1,281	2,576	M,F	All	3		0.17	(0.03, 0.37)	Adj. for measurement error
Missouri-I (USA), 1994 (35)	538	1,183	F	NS,ES	12	67	0.05	(-0.13, 0.24)	All subjects
	197	1,183	F	NS,ES			0.47	(0.03, 1.40)	Living subjects only
Winnipeg (Canada), 1994 (36)	738	738	M,F	All	6+6	120	-0.06	(-0.14, 0.05)	
South Finland, 1996 (37)	164	331	M	All	2	218	0.57	(0.27, 0.99)	
Finland, 1996,1998 (38)	517	517	M,F	All	12	96	0.11	(-0.06, 0.31)	
S-W England (UK), 1998 (39)	982	3,185	M,F	All	6 ^a	56	0.08	(-0.03, 0.20)	All subjects
	982	3,185	M,F	All		52	0.12	(-0.05, 0.33)	Adj. for measurement error
	484	1,637	M,F	All		55	0.14	(0.01, 0.29)	Complete Rn coverage
	484	1,637	M,F	All		48	0.24	(-0.01, 0.56)	Adj. for measurement error
Missouri-II (USA), 1999 (40)	247	299	F	All	12	59	0.04	(-0.13, 0.57)	Contemporary Rn meas.
	372	471	F	All		65	0.63	(0.07, 1.93)	Retrospective Rn meas.
Iowa (USA), 2000 (41)	413	614	F	All	12	89	0.16	(-0.03, 0.61)	All subjects
	283	614	F	All			0.33	(0.02, 1.23)	Living subjects only
Western Germany, 2001 (42)	1,449	2,297	M,F	All	12	50	-0.02	(-0.18, 0.17)	All subjects, current home
	365	595	M,F	All		60	0.13	(-0.12, 0.46)	Radon-prone areas
Sweden-II, 2001 (43)	258	487	M,F	NS	3 ^b	79	0.28	(-0.05, 1.05)	All subjects
Sweden-II, 2002 (44)	109	229	M,F	NS	3 ^b	90	0.33	(-0.12, 2.00)	Contemporary Rn meas.
	109	229	M,F	NS		83	0.75	(-0.04, 4.30)	Retrospective Rn meas.
Trentino (Italy), 2001 (45)	138	210	M,F	All	12	130	0.40	(-0.70, 5.60)	
Pluton (Czech Rep.), 2001 (46)	210	12,004	M,F	All	12	509	0.09	(0.02, 0.21)	Cohort study
Imst (Austria), 2002 (47)	194	198	M,F	All	12	200	0.25	(0.08, 0.43)	
North-West Spain, 2002 (48)	163	241	M,F	All	3-8	130	1.48	(0.12, 4.48)	
Gansu (China), 2002 (49,50)	768	1,659	M,F	All	12	228	0.16	(0.03, 0.40)	All subjects
	768	1,659	M,F	All			0.29	(0.03, 1.04)	Adj. for measurement error
	463	1,143	M,F	All			0.23	(0.06, 0.57)	>70% Rn coverage only
	463	1,143	M,F	All			0.65	(0.16, 3.04)	Adj. for measurement error
France, 2002 (51)	552	1,103	M,F	All	6	148	0.05	(-0.01, 0.12)	
Eastern Germany, 2003 (52)	1,192	1,640	M,F	All	12	74	0.08	(-0.03, 0.20)	All subjects
	427	536	M,F	All			0.09	(-0.06, 0.27)	Complete Rn coverage
Lazio (Italy), 2003 (53,54)	384	404	M,F	All	6+6	107	0.10	(-0.14, 0.41)	

Av. C_{Rn} =Average radon concentration; EOR=excess odds ratio; CI=confidence interval; ES=Ex-smoker; NS=Never-smoker.

^a Seasonal correction factors were applied to obtain an estimate of 12-month average

^b All radon detectors were exposed during heating season

Early studies on residential radon and lung cancer

Early studies on residential radon and lung cancer, e.g. those carried out in Sweden and Canada (25-28), were generally of small size and mostly based on proxy of radon exposure, such as the type of dwelling, building materials and the soil characteristics. Due to these characteristics these studies have not been included in meta-analyses or pooled-analyses and their results are not reported in Table 1. Nevertheless, these studies were very useful to highlight the radon issue and to improve the design of following studies.

1997, estimating an overall EOR=0.09, at 100 $Bq\ m^{-3}$, which was slightly statistically significant (95%CI=0.01,0.19) (56). Moreover, the results obtained analyzing the subset of miners exposed at radon exposure levels comparable to residential ones were very similar (57). However, the meta-analysis confirmed the heterogeneity among the studies, which was possibly due to the different adjustment for confounding factors, which cannot be resolved in a meta-analysis, but only with a pooled analysis. Therefore these results could not be considered conclusive.

The second group of case-control studies

The case-control studies published after the meta-analysis of Lubin and Boice gave generally results more homogeneous. Both the design and the analysis of most of these studies were largely discussed in international meetings and in international collaborations, in order to make easier a comparison and to prepare a large data pooling. Only in the large study in Western Germany an $EOR < 0$ was estimated, but this was probably due to the concomitance of some specific factors, such as: the low radon concentration; the low number of years of interest covered by measurements, because only the current dwelling was measured; the presence of a non-differential bias (42,15). On the other extreme of the range, in the small sized N-W Spain study a risk much higher than in the other studies was estimated, however the value reported in Table 1 was actually derived from the published categorical analysis results, which were driven by the chosen reference category (48). A real continuous analysis, which was not included in the published paper, would probably give quite different results.

In some studies (Sweden-I, S-W England, Gansu), radon exposure uncertainty was evaluated and the observed EOR was corrected to take into account such uncertainty (34,39,50). The corrected EOR increased by a factor in the range 50% to 100% (see Table1). The uncertainty evaluations were generally quite approximate, but the significant increase of the risk estimates underlines the importance to take into account exposure uncertainty for a correct evaluation of the radon health impact.

Restricted analyses

Besides the results with all the subjects, some results with restricted data set are also reported in Table 1. In two studies, Missouri-I and Iowa (35, 41), a higher risk was estimated for live subjects: whereas in the Missouri-I no clear explanation was given, in the second study this results was attributed to the better memory of subjects (compared with their next-of-skin) regarding the time spent in the different floors of their home, where the measured radon concentration resulted quite different. In other words, a more accurate exposure evaluation for the living subjects was given as explanation of their higher risk.

Another important restricted analysis is related to the measurement coverage of the period of interest (see Table 1). In fact, some studies (showed that when subjects with a high or complete coverage are selected, a quite higher risk is obtained. This result demonstrates again the effect of exposure uncertainty on the risk estimates. The results obtained with radon retrospective dosimetry represent another demonstration of the importance of the exposure evaluation. In fact, in two studies (Missouri-II and Sweden-II) the EOR estimated on the basis of radon exposure

evaluated with retrospective techniques was quite higher than that one obtained with contemporary radon concentration measurements (see Table 1), suggesting that the former evaluation is more accurate (40,44).

Radon-smoking interaction

The statistical power for evaluating the radon-smoking interaction was generally low for these studies. However, in many of them the OR, or the EOR, for never-smokers were similar to that for smokers, suggesting a multiplicative interaction (e.g.33). This result is somewhat different from that derived from the miner studies, where a less-than-multiplicative interaction was estimated, with a relative risk for never-smokers equal to about 2 to 3 higher than that for smokers (3,4). However, these miner study results were based on few subjects with adequate smoking data (3,4). A multiplicative interaction has a very important consequence: due to the high lung cancer risk of a smoker compared to that one of a never-smoker, the absolute increase of risk due to the same radon exposure is much higher for a smoker than for a never-smoker. Moreover, the results of the recent Swedish-II study on never-smokers suggest that a synergistic interaction could exist between radon and passive smoking, too (43); however, larger studies are necessary to confirm this conclusion.

CONCLUSIONS AND PERSPECTIVES

Most of the case-control studies estimate an increased risk due to residential radon exposure, although the increase is generally not statistically significant. The estimated risk is generally higher when exposure uncertainties are reduced or taken into account.

More precise results and a better comparison of different studies can be obtained from pooled analyses of groups of studies. Two very recent pooled analyses have been published: i) the pooling of two Chinese studies, which included the published Shenyang and Gansu studies, with a total of 1076 cases and 2015 controls (58-59); ii) the pooling of seven North-American studies, which included the following studies: New Jersey, Missouri-I, Winnipeg, Missouri-II, Iowa, Connecticut, Utah-South Idaho, with a total of 4081 cases and 5281 controls (58,60). The estimated EOR at 100 Bq m⁻³ were 0.14 (95% CI=0.01,0.37) and 0.11 (95% CI=0.00,0.28) for and the Chinese and the North American studies, respectively, and no statistically significant difference among studies was observed. The restricted analysis on subjects with complete dosimetry for the 5-30 y exposure period prior to interview showed higher risks, with EOR= 0.28 (95% CI=0.07,0.75) and EOR=0.21 (95% CI=0.03,0.50). These results were consistent with extrapolations from miner studies. Other excellent reviews of residential case-control studies were recently published (61-63), containing additional information compared to

present review.

The perspectives include the followings: i) the publication of the pooled results of 13 European studies, with a total of about 7000 cases and 14000 controls, expected in 2004; ii) the pooled analysis of all the available case-control studies, which is expected to be concluded in the 2005 or 2006; iii) the conclusion (probably in the 2005) of a collaborative European study with the use of retrospective dosimetry on a sub-sample of subjects enrolled in previous studies, with a total of about 700 cases and 900 controls; iv) the realization of new studies specifically addressed to the risk of never-smokers and the interaction between radon and passive smoking, and two such studies have been planned in USA and in Italy.

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Footnote

'The health effects of radon are actually due to the inhalation of its decay products, however, in this paper as well as in many other ones, we will refer to radon instead of radon decay products for shortness purpose.

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Case-control studies of lung cancer have now been carried out in a number of different countries. In these studies radon concentrations have been measured in both current and former homes of the study subjects and detailed smoking histories have also been collected. None of these studies is large enough on its own to assess the risks with sufficient precision to provide useful estimates, or to assess satisfactorily the way in which radon and the smoking can act together to cause lung cancer. The results of this collaborative analysis will provide more precise estimates of the lung cancer risk that can be attributed to residential radon exposure, which will help in formulating appropriate public health strategies. Our team. Sarah Darby. Objective To determine the risk of lung cancer associated with exposure at home to the radioactive disintegration products of naturally occurring radon gas. Design Collaborative analysis of individual data from 13 case-control studies of residential radon and lung cancer. Setting Nine European countries. Subjects 7148 cases of lung cancer and 14 208 controls. Main outcome measures Relative risks of lung cancer and radon gas concentrations in homes inhabited during the previous 5-34 years measured in becquerels (radon disintegrations per second) per cubic metre (Bq/m³) of household air. Results A study of lung cancer risk from residential radon exposure and its radioactive progeny was performed with 200 cases (58% male, 42% female) and 397 controls matched on age and sex, all from the same health maintenance organization. That analysis produces AORs that are substantially less than 1.0 with borderline statistical significance ($0.048 < \text{or} = p < \text{or} = 0.05$) between approximately 85 and 123 Bq m. College-educated subjects in comparison to high-school dropouts have a significant reduction in cancer risk after controlling for smoking, years of residency, and job exposures with AOR = 0.30 (95% CI: 0.13 The risk of lung cancer posed by residential exposure to radon has been studied in epidemiologic investigations using ecologic, cohort, and case-control designs.⁷⁻¹³ Positive trends were observed in some studies but not in others, and there has been no consistent pattern to the interaction between radon exposure and smoking in relation to lung cancer. The primary aim of this study was to narrow the uncertainty in the estimation of the risk of residential exposure to radon, which necessitated a study considerably larger than any of the earlier investigations. A further aim was to assess the int Epidemiological studies on residential radon exposure and the risk of histological types of lung cancer have yielded inconsistent results. We conducted a meta-analysis on this topic and updated previous related meta-analyses. We searched the databases of Cochrane Library, Embase, PubMed, Web of Science and Chinese National Knowledge Infrastructure for papers published up to 13 November 2018. The pooled odds ratio (OR) and 95% confidence interval (CI) were calculated using fixed and random effects models. Residential Radon and Histological Types of Lung Cancer: A Meta-Analysis of Case-Control Studies. by Cong Li 1,2, Chunhong Wang 2, Jun Yu 2, Yongsheng Fan 2, Duanya Liu 2, Wenshan Zhou 1,* and Tingming Shi 1,* 1.